Richard J. Martin
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Michele C. Walsh

Fanaroff & Martin's

NEONATAL-PERINATAL MEDICINE

Diseases of the Fetus and Infant



ELEVENTH EDITION

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Fanaroff and Martin's Neonatal-Perinatal Medicine

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Fanaroff and Martin's Neonatal-Perinatal Medicine

Diseases of the Fetus and Infant

11th Edition

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To our spouses

Patricia Martin and Roslyn Fanaroff

to the Martin children and grandchildren

Scott, Molly, William, and Adelaide Martin;
Sonya Martin; and Peter, Mateo, and Soren Graif

to the Fanaroff children and grandchildren

Jonathan, Kristy, Mason, Cole, and Brooke Fanaroff;
Jodi, Peter, Austin, and Morgan Tucker;
and Amanda, Jason, Jackson, and Raya Hirsh

to the Walsh children

Sean and Tiffany Sukys
and Ryan Sukys

with love, admiration, and deep appreciation
for their continued support and inspiration

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Preface

Together with my colleague Avroy A. Fanaroff (and more recently, Michele C. Walsh), we have been privileged to transform the third edition (1983) of this text into its 11th edition over a span of 35 years. This has been a great honor and an enormous learning experience. Over this time, although neonatal survival rates may give reason to rejoice, the persistent respiratory and neurodevelopmental problems observed in former preterm infants remain cause for concern. Fortunately, we have made great strides in our ability to control nosocomial infections in preterm infants, and both target and achieve the intrauterine rate of growth through improved nutritional support. Meanwhile, the complex, ever-expanding genetic disorders and birth defects now loom as major problems in the neonatal intensive care unit and as leading causes of neonatal mortality.

The field of Neonatal-Perinatal Medicine has transitioned from anecdotal medicine to evidence-based medicine. The problem is that evidence-based medicine predicts outcomes for groups but not individuals. The next frontier, individualized or personalized medicine, requires application of the human genome project to the individual patient. That frontier may be rapidly approaching with the acquisition and application of new knowledge and technology. Over the last decades, translation of bench research to bedside innovation has proceeded remarkably as has understanding of the underlying mechanisms of many complex disorders. Advances in genetics have provided insight into the etiology of many disorders, and many previously mysterious diseases can now be attributed to single gene defects or mitochondrial disorders accompanied by cellular energy failure. We have attempted to address and incorporate these advances into the body of the text.

For this 11th edition, we have added several new sections and multiple new authors, notably expanding our international contributors, hence providing a truly global perspective. Many sections have been completely reorganized, and a large number of chapters have been rewritten or updated. We remain exceedingly grateful to our accomplished authors who have responded enthusiastically and maintained our need for a rapid timeline in this electronic era. As with prior editions, the 11th edition is available both in print and as an e-book on the Expert Consult platform, in a fully searchable and portable format.

This book would not exist without the remarkable clinical and intellectual environment that constitutes Rainbow Babies & Children's Hospital in Cleveland. On a daily basis, we gain knowledge from our faculty colleagues and fellows, and wisdom from our nursing staff who are so committed to their young patients. Once again, we have been blessed with an in-house editor, Bonnie Siner, to whom we cannot adequately express our thanks. She is the glue behind the binding in the book, and she has worked tirelessly with Elsevier staff members to bring this project to fruition. Elsevier has, once again, provided the resources to accomplish this mammoth task.

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1

Growth of Neonatal Perinatal Medicine—A Historical Perspective

TONSE N. K. RAJU

We trust we have been forgiven for coining the words, "neonatology" and "neonatologist." We do not recall ever having seen them in print. The one designates the art and science of diagnosis and treatment of disorders of the newborn infant, the other the physician whose primary concern lies in the specialty. … We are not advocating now that a new subspecialty be lopped from pediatrics … yet such a subdivision … [has] as much merit as does pediatric hematology.

—A. J. Schaffer, 1960[75]

The terms *neonatology* and *neonatologist* were not in general use until the mid-1960s. In the preface to the first edition of his monograph *Diseases of the Newborn*, Dr. Alexander Schaffer christened the new specialty and its practitioners, asking our "forgiveness" for doing so.[75] An apology was not needed, because time has proven him to be immensely prophetic. In 1975, the first neonatal-perinatal medicine subspecialty examination was offered by the American Board of Pediatrics, and 355 were certified as the country's first neonatologists. After the 2012 certifying examination, 5552 individuals have been certified by the Board as neonatologists, and several hundred more since then. This phenomenal growth has been matched by an increasing fund of knowledge. Today a cursory search using the subject heading "newborn" in the National Library of Medicine's PubMed database yields nearly 60,000 citations.[59] Thus at the beginning of the twenty-first century, neonatology stands tall and strong as a specialty, carving a unique niche, bridging obstetrics with pediatrics and intensive care with primary care.

Although the formal naming of our specialty appears to be recent, its roots extend into the nineteenth century, when systematic and organized care for premature infants began in earnest. This chapter traces the origins and growth of modern perinatal and neonatal medicine, with a brief perspective on its promises and failures. The reader may consult scholarly monographs and review articles on specific topics for in-depth analyses.[6,7,24,31,79,80]

Perinatal Pioneers

Many scientists played strategic roles in developing the basic concepts in neonatal-perinatal medicine that helped to formalize the scientific basis for neonatal clinical care. Their work and teachings inspired generations of further researchers advancing the field. For brevity's sake, only a few are shown in Fig. 1.1.

Medicinal chemistry (later called biochemistry) and classic physiology gained popularity and acceptance toward the end of the nineteenth century, inaugurating studies on biochemical and physiologic problems in the fetus and newborn. Some leading scientists in the early twentieth century, making fundamental contributions and training scores of scientists from around world, included Barcroft[8,34] and his mentee Dawes in England (gas exchange and nutritional transfer across the placenta and oxygen carrying in fetal and adult hemoglobin); Ylppö in Finland (neonatal nutrition, jaundice, and thermoregulation); Lind in Sweden (circulatory physiology); Smith in Boston[81] (fetal and neonatal respiratory physiology); DeLee in Chicago[26,27] (leading researcher on incubators and in high-risk obstetric topics, he also founded the first US "incubator station" at the Chicago Lying-in Hospital); Day in New York (temperature regulation, retinopathy of prematurity, and jaundice); and Gordon[38] in Denver (nutrition). Although no formal curriculum existed, all these centers offered rigorous training in perinatal physiology and clinical medicine. Smith once said, "If you were interested in babies and liked Boston, I was the only wheel in town!"[60] Table 1.1 highlights some milestones in perinatal medicine.

The High-Risk Fetus and Perinatal Obstetrics

Because so many deaths occurred in early infancy in times past, many cultures adopted remarkably innovative methods to deal with such tragedies. According to a Jewish tradition, full, year-long mourning is not required for infants who die

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Abstract

Emerging from centuries of humble origins, the field of maternal and newborn care has matured into a robust medical specialty. This growth, however, has not been smooth. Along with spectacular advances in physiology, clinical sciences, and technological innovations over the decades, humbling setbacks have led to course corrections in our collective historic march. This chapter attempts to provide a historical perspective, highlighting important milestones, on the growth of neonatal perinatal medicine.

Keywords

Apgar
oxygen therapy
cesarean birth
retinopathy of prematurity
premature baby side shows
assisted ventilation
neonatal resuscitation

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• **Fig. 1.1** Pioneers in perinatal and neonatal physiology and medicine. **A,** Joseph Barcroft. **B,** Arvo Ylppö. **C,** John Lind. **D,** William Liley. **E,** Joseph DeLee. **F,** Richard Day. **G,** Clement Smith. **H,** Harry Gordon. (**A,** From Barcroft J. *Research on Pre-natal Life.* Vol 1. Oxford: Blackwell Scientific; 1977, courtesy of Blackwell Scientific; **B-D** and **F-H,** from Smith GF, Vidyasagar D, eds. *Historical Review and Recent Advances in Neonatal and Perinatal Medicine: Neonatal Medicine.* Vol 1. Evansville, IN: Ross Publication; 1984, pp ix [**B**], xix [**C**], xxii [**D**], xvi [**F**], xii [**G**], xiv [**H**], courtesy of Mead Johnson Nutritional; **E,** Courtesy of Mrs. Nancy DeLee Frank, Chicago.)

before 30 days of age.[40] In some Asian ethnic groups, infant-naming ceremonies are held only after several months, until which time the infant is simply called "it." In India, an odd or coarse-sounding name is given to the first surviving infant after the death of a previous sibling; this is aimed at deflecting evil spirits. In her book on the history of the Middle Ages, Tuchman notes that infants were seldom depicted in medieval artworks.[89] When they were drawn (e.g., the infant Jesus), women in the pictures looked away from the infant, ostensibly conveying respect but perhaps because of fearful aloofness.

Since antiquity, the care of pregnant women has been the purview of midwives, grandmothers, and experienced female elders in the community. Wet nurses helped when mothers were unavailable or unwilling to nurse their infants. Little or no assistance was needed for normal or uncomplicated labor and delivery. For complicated deliveries, male physicians had to be summoned, but they could do little because many of them lacked expertise or interest in treating women. Disasters during labor and delivery were common, rendering this phase in their lives the most dreaded for women.[43] In the early 1900s unexpected intrapartum complications accounted for 50% to 70% of all maternal deaths in England and Wales.[17,56] Because the immediate concern during most high-risk deliveries was to save the mother, sick newborns were not given substantial attention; their death rates remained very high.

Occasionally, happy outcomes of high-risk deliveries did occur. In one of the oldest works of art depicting labor and delivery (Fig. 1.2*A*), a bearded man and his assistant are standing behind a woman in labor, holding devices remarkably similar to the modern obstetric forceps. The midwife has delivered an evidently live infant. In Fig. 1.2*B*, three infants from a set of quadruplets, nicely swaddled, have been placed on the mother, as the unwrapped fourth infant is being handed to her for nursing. A divine figure in the background is blessing the newcomers.

Cesarean sections were seldom performed on living women before the thirteenth century. Even subsequently, the procedure was performed only as a final act of desperation. Contrary to popular belief, Julius Caesar's birth was not likely by cesarean section. Because Caesar's mother was alive during his reign, historians believe that she probably delivered him vaginally. The term *cesarean* probably originated from *lex caesarea*, in turn from *lex regia*, the "royal law" prohibiting burial of corpses of pregnant women without removal of their fetuses.[11,94] The procedure allowed for baptism (or a similar blessing) if the child was alive or burial otherwise. Infants surviving the ordeal of cesarean birth were assumed to possess special powers, as supposedly

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TABLE 1.1 Selected Milestones in Perinatal Medicine

Category	Year(s)	Description
Antenatal aspects	1752	Queen Charlotte's Hospital, the world's first maternity hospital, is founded in London.[57]
	1915-1924	Campbell introduces outlines of regular prenatal visits, which become a standard.
	1923-1925	Estrogen and progesterone are discovered.
	1928	First pregnancy test is described, in which women's urine is shown to cause changes in mouse ovaries.
Fetal assessment	1543	Vesalius observes fetal breathing movements in pigs.
	1634	Paré teaches that absence of movement suggests a dead fetus.
	1819, 1821	Laënnec introduces the stethoscope in 1819, and his friend Kergaradec shows that fetal heart sounds can be heard using it.
	1866	Forceps are recommended when there is "weakening of the fetal heart rate."
	1903	Einthoven publishes his work on the ECG.
	1906	The first recording of fetal heart ECG is made.
	1908	The term *fetal distress* is introduced.
	1948-1953	There are developments in the external tocodynamometer.
	1953	Apgar describes her scoring system.[3]
	1957-1963	Systematic studies are conducted on fetal heart rate monitoring.
	1970	Dawes reports studies on breathing movement in fetal lambs.
	1980	Fetal Doppler studies begin.
	1981	Nelson and Ellenberg report that Apgar scores are poor predictors of neurologic outcome.
Labor and delivery	ca. 1000–500 BC	In Ayurveda, the ancient Hindu medical system, physicians describe obstetric instruments.
	98-138	Soranus develops the birthing stool and other instruments.
	1500s	There are isolated reports of cesarean sections on living women.
	1610	The first intentional cesarean section is documented.
	1700s	The Chamberlen forceps are kept as a family secret for three generations.
	1921	Lower uterine segment cesarean section is reported.
	1953	The modern vacuum extractor is introduced.
Fetal physiology	1900-1950	Barcroft, Dawes, Lind, Liley, and others study physiologic principles of placental gas exchange and fetal circulation.

ECG, Electrocardiogram.
See references 41, 43, 60-62, 70-72, 82, 83.

did Shakespeare's Macduff—"not of a woman born," but of a corpse, and able to slay Macbeth.[54]

Soranus of Ephesus (circa 38-138 AD) influenced obstetric practice for 1400 years. His *Gynecology* can be regarded as the first formal "textbook" of perinatal medicine. Initially extant, it was rediscovered in 1870 and translated into English for the first time in 1956.[88] Soranus wrote superbly about podalic version, obstructed labor, multiple gestations, fetal malformations, and numerous other maternal and fetal disorders. In an age of belief in magic and the occult, he insisted that midwives should be educated and free from superstitions. He forbade wet nurses from drinking alcohol lest it render the infant "excessively sleepy." His chapter, "How to Recognize the Newborn That Is Worth Rearing," remains one of the earliest accounts on assessing viability of sick newborns—a topic of great concern even today.

Midwives and Perinatal Care

Although occasionally caricatured (Fig. 1.3), midwives were responsible for delivering obstetric care for thousands of years. Men disliked obstetrics, and women were too shy to let male physicians handle them. Good midwives were always in great demand, and many of them held important social and political positions in European courts.[43,61,91]

The emergence of man-midwives (Fig. 1.4) in England had a major effect on high-risk obstetric practice. Chamberlen the Elder (1575-1628) is usually credited for inventing the modern obstetric forceps.[43,61,63] For 150 years, through three generations of Chamberlens, the instrument remained a trade secret. By then, others had developed similar devices, and patients began associating good obstetric outcomes with male physicians—a strategic factor in transforming midwifery to a male-dominated craft.[43] The shift from women-midwifery to men-midwifery might also have been caused by changing social values and gender relationships in which women voluntarily began making choices about their bodies.[91] Today's increasing roles for female midwives and the higher proportion of women choosing specific birth practices (e.g., home versus hospital delivery, "underwater births," cesarean delivery on request) offer interesting contrasts and perspectives to eighteenth century obstetrics.

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• **Fig. 1.2** High-risk deliveries. **A,** Marble relief of uncertain date depicting a high-risk delivery. The physician and his assistant in the background are holding devices similar to modern obstetric forceps. A midwife has just helped deliver a live infant while two people are looking through the window. **B,** Delivery of quadruplets. (From Graham H. *Eternal Eve: The History of Gynecology and Obstetrics.* New York: Doubleday; 1951, pp 68, 172.)



• **Fig. 1.3** On call. "A Midwife Going to a Labour," caricature by Thomas Rowlandson, 1811. (Courtesy of The British Museum, London.)



• **Fig. 1.4** Man-midwife. (Courtesy of Clements C. Fry Print Collections, Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, CT.)

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Neonatal Resuscitation: Tales of Heroism and Desperation

Popular artworks and ancient medical writings provide accounts of miraculous revivals of apparently dead adults and children.[66] These are tales of successes only, for the failures were buried and rarely reported. Attempts to "stimulate" and revive apparently dead newborns included beating, shaking, yelling, fumigating, dipping in ice-cold water, and dilating and blowing smoke into the rectum and other techniques.[25,30,66,93] Oxygen administration through an orogastric tube to revive asphyxiated infants persisted well into the mid-1950s, when James and Apgar showed conclusively that the therapy was useless.[1,52]

Apgar and the Language of Asphyxia

Few scientists in the twentieth century influenced the practice of neonatal resuscitation as profoundly as Apgar (1909-1974). A surgeon, she chose obstetric anesthesia for her career. Her simple scoring system inaugurated the modern era of assessing infants at birth on the basis of simple clinical examination.[3] Right or wrong, the Apgar score became the language of asphyxia. It is often said that the first words heard by a newborn infant are "What's the Apgar score?" Although "giving an Apgar" has become a ritual, its profound effect has been on formalizing the process of observing, assessing, and communicating the infant status at birth in a consistent and uniform manner. This process eventually led to the formal steps of resuscitation at birth using the score. Few people know that it was also Apgar who was the first to catheterize the umbilical artery in a newborn.[16] A woman of enormous energy, talent, and compassion, Apgar was honored with her depiction on a 1994 US postage stamp (Fig. 1.5).

Foundling Asylums and Infant Care

In its early days, the Roman Empire experienced decreasing population growth. The emperors taxed bachelors and rewarded married couples to encourage procreation.[82] In 315 AD, Emperor Constantine, hoping to curb infanticide and encourage the adoption of orphans, decreed that all "foundlings" would become slaves of those who adopted them. Similar humanitarian efforts by kings and the Council of the Roman Church led to the institutionalization of infant care by establishing foundling asylums for abandoned infants,[82] also called "Hospitals for the Innocent"—the first children's hospitals. Parents of unwanted infants "dropped off" their infants in a revolving receptacle at the door of such asylums, rang the doorbells, and disappeared into the night (Fig. 1.6). Sadly, such incidences occur even in modern times.[73]

Foundling asylums adopted pragmatic techniques for fundraising. In eighteenth century France, lotteries were held, and souvenirs were sold. In May 1749, Handel gave a concert to support London's "Hospital for the Maintenance and Education of Exposed and Deserted Young Children." The final item of the program was the playing of "The Foundling Hymn."[82]



• **Fig. 1.5** Virginia Apgar, US postage stamp. (Courtesy of the US Postal Service.)

Saving Infants to Man the Army

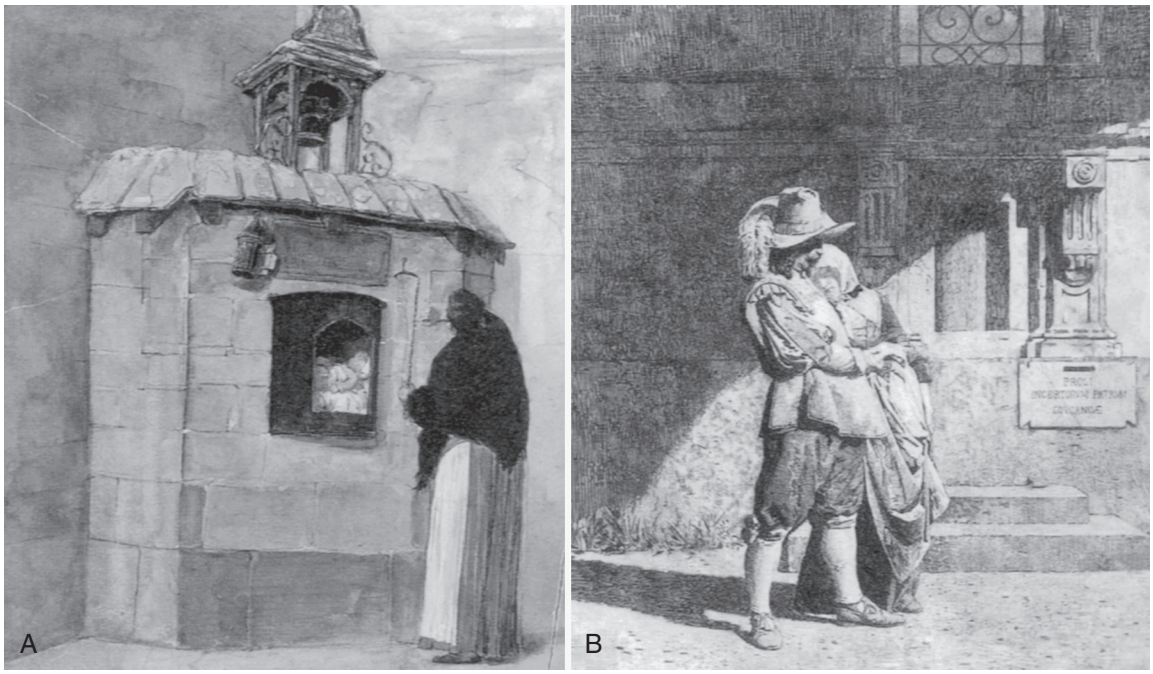
During the French Revolution, France faced appalling rates of infant mortality. With rates greater than 50%, the Revolutionary Council in 1789 enacted a decree proclaiming that working-class parents "have a right to the nation's succors at all times."[82] The post-revolutionary euphoria about equality and fraternity among men stimulated reforms, heralding an idealistic welfare state, leading to collecting and maintaining valid statistics about children. The world's first national databases began in France in the late eighteenth century.[82]

Over the next century, France faced a population problem similar to that of ancient Rome—a negative population growth. The birth rate had declined, and infant mortality remained high. Fearing future shortages of troops, the military leaders, deeply engaged in battles with Prussia, were naturally alarmed. Commissions were set up to study the depopulation problem and develop remedial actions. A series of measures began to improve maternal and neonatal care.[6,7,22,24,82,83] Young parents were encouraged to uphold their patriotism and bear more children to "man the future armies." It is the irony of our times that such noble intentions as saving infants were motivated by brutal needs for enhancing military might.

An Ingenious Contrivance, the *Couveuse*, and Premature Baby Stations

A popular story of the origin of modern incubator technology is that upon seeing the poultry section during a casual visit to the Paris Zoo in 1878, Tarnier (1828-1897), a

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• **Fig. 1.6** Foundling homes. **A,** *Le Tour*—revolving receptacle. Mother ringing a bell to notify those within that she is leaving her baby in the foundling home (watercolor by Herman Vogel, France, 1889). **B,** *Remorce* ("Remorse")—parents after placing their infant in a foundling home (engraving and etching by Alberto Maso Gilli, France, 1875). (**A** and **B,** Courtesy of the Museum of the History of Medicine, Academy of Medicine, Toronto, Ontario, Canada; from Spaulding M, Welch P. *Nurturing Yesterday's Child: A Portrayal of the Drake Collection of Pediatric History.* Philadelphia: Decker; 1991, p 110 [**A**] and p 119 [**B**].)

renowned obstetrician, conceived the idea of "incubators" similar to the "brooding hen" or *couveuse*.[6,7,22,24] He asked an instrument maker, Martin, to construct similar equipment for infants. With a "thermo-syphon" method to heat the outside with an alcohol lamp, Martin devised a sufficiently ventilated, 1 m^3 double-walled metal cage, spacious enough to hold two premature infants. The first *couveuses* were installed at the Paris Maternity Hospital in 1880. Tarnier's efforts led to dramatic improvements in survival rates for preterm infants.

Although a few others had developed incubators before Tarnier,[7] it was he and his students, Budin (1846-1907) and Auvard (1855-1941), who are largely responsible for institutionalizing preterm infant care. They placed several incubators side by side, promoting the concept of caring for groups of sick preterm infants in geographically separate regions within their hospital.[6,7,69,86] Budin and Auvard improved the original *couveuse* by replacing its walls with glass and using simpler methods for heating. Their efforts greatly influenced incubator technology during the first half of the twentieth century in Europe and the United States (Fig. 1.7 and Table 1.2).

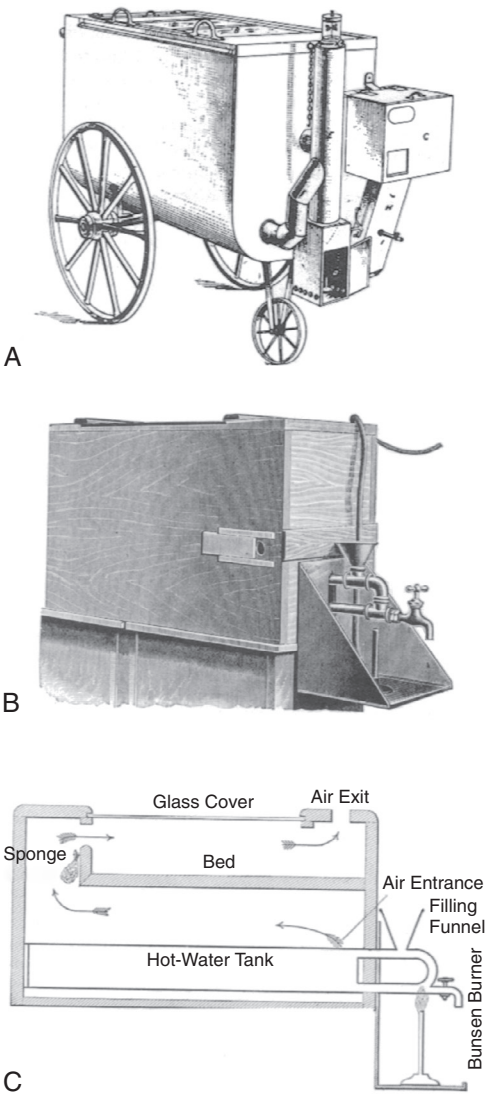
In 1884, Tarnier made another important contribution; he invented a small, flexible rubber tube for introduction through the mouth into the stomach of preterm infants. With this tube, he could drip milk directly into the stomach. This method of nutritional support he called "gavage feeding." Gavage feeding plus keeping infants in relatively constant and warm temperatures had a dramatic impact on improving survival rates.[15,21] Tarnier also recommended that the legal definition of viability should be 180 days of gestation, which was opposed by contemporary obstetricians, who thought that the concept was "therapeutic nihilism."[7] Defining *viability* remains a highly emotional and contentious issue in contemporary neonatal-perinatal practice.

Incubators, Baby Shows, and Origins of Neonatal Intensive Care Units

Almost two decades after its debut in France, incubator technology appeared in the United States, heralding organized newborn intensive care. As in France, it was an obstetrician who spearheaded the movement. In 1898, DeLee established the first "Premature Baby Incubator Station" at the Sara Morris Hospital in Chicago. During the early 1900s, as academic obstetricians and pediatricians were organizing specialized care for premature infants, an interesting, if bizarre, set of events led to the era of "premature baby shows," which began in Europe and continued in the United States, lasting well into the 1940s.[6,7,78]

Couney, a Budin associate of doubtful medical credentials, wished to popularize the French technology abroad and show the value of "conserving" premature infants. (This account has been doubted.[7]) Couney obtained six incubators, probably from the French innovator Lion. Initially, Couney wanted to exhibit only the incubators as a technology of hope for saving infants. To add drama, however, he brought six preterm infants from Virchow's maternity unit in Berlin and exhibited them inside the incubators at the

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• **Fig. 1.7** Early incubators. **A,** Rotch incubator, circa 1893. **B,** Holt incubator. **C,** Schematics of the Holt incubator. (**A**, From Cone TE Jr. *History of American Pediatrics.* Boston: Little Brown; 1979, pp 57 and 58, courtesy of Little Brown; **B** and **C**, from Holt LE. *The Diseases of Infants and Children.* New York: Appleton; 1897, pp 12 and 13, courtesy of Appleton.)

1896 Berlin Exposition. He coined a catchy phrase for the show—*kinderbrutanstalt* or "child hatchery"—igniting the imagination of a public thirsty for sensational scientific breakthroughs.

Couney's Berlin exhibit was an astounding success. One such show was at Great Britain's Victorian Era Exhibition in 1897. The show was praised by *Lancet* in an editorial that recommended that large "incubator stations" be established similar to fire stations, where parents could borrow incubators.[36] This was the origin of the phrase "premature baby incubator stations," which became part of the medical lexicon. In a later editorial, *Lancet* also criticized the "danger of making a public show of incubator for babies."[37] Couney sailed to the United States and, beginning in 1898, started premature infant exhibitions at many state fairs, traveling circuses, and science expositions, and finally settled in New York City to organize annual incubator baby shows in Coney Island. The last infant show was held during the 1939 to 1940 season in Atlantic City.[78]

In 1914, Hess of Chicago started a Premature Infant Station at the Sarah Morris Children's Hospital (of the Michael Reese Medical Center). With great attention to environmental control and aseptic practices and a regimental approach to feeding, Hess and his head nurse, Evelyn Lundeen (Fig. 1.8), achieved spectacular survival rates.[47,68] Hess also developed an incubator built on the concept of a double-walled metallic "cage" with warm water circulating between the walls. He used electric current for heating and devised a system to administer free-flow oxygen (Fig. 1.9). Only a few Hess incubators are known to have survived to this day. Hess's premature unit outlasted the DeLee Premature Station. In December 2008, the Michael Reese Medical Center closed, however, declaring bankruptcy.

The story of development of incubators and their impact on pediatrics is a tale of the success of technology and that of the perils technology might beget (see later section on the relationship of improved incubator care and the retinopathy of prematurity [ROP] epidemic). In the heroic age of the mechanical revolution, the notion that machines could solve all human problems was all too appealing. The incubator stands as the most enduring symbol of the spectacular success of modern intensive care and (paradoxically) some of its failures.[79,80]

Supportive Care and Oxygen Therapy

In a single-page note in 1891, Bonnaire referred to Tarnier's use of oxygen in treating "debilitated" premature infants 2 years earlier[14]; this was the first published reference to the administration of supplemental oxygen in premature infants for a purpose other than resuscitation. The use of oxygen in premature infants did not become routine, however, until the 1920s. Initially, a mixture of oxygen and carbon dioxide—instead of oxygen alone—was employed to treat asphyxia-induced narcosis. It was argued that oxygen relieved hypoxia, whereas carbon dioxide stimulated the respiratory center.[85] Oxygen alone was reserved for "pure asphyxia" (whatever that meant). The advent of mobile oxygen tanks and their easy availability in the mid-1940s enabled the use of oxygen for resuscitation.[51,53,79]

The success of incubator care brought new and unexpected challenges.[68,69] Innovative methods had to be developed to feed the increasing number of premature infants who were surviving for longer periods than ever before. Their growth needed to be monitored, and illnesses related to prematurity, such as sepsis, apnea, anemia, jaundice, and respiratory distress, had to be studied and treated. Another completely unexpected peril from "improved" incubator technology was the epidemic of blindness from ROP (then called retrolental fibroplasia), documented in vivid detail elsewhere.[79,80] The apparent culprit in cases of ROP was the "leakproof" incubator that led to a great increase in the inspired oxygen concentrations (piped in free-flow manner),

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TABLE 1.2 Evolution of Incubators

Year(s)	Developer/Product	Comments
1835, ca. 1850	von Ruehl (1769-1846)	A physician to Czarina Feodorovna, wife of Czar Paul I, von Ruehl develops the first known incubator for the Imperial Foundling Hospital in St. Petersburg. About 40 of these "warming tubs" are installed in the Moscow Foundling Hospital in 1850.
1857	Denucé (1824-1889)	The first published account of introducing an incubator is a 400-word report by Denucé. This is a "double-walled" cradle.
1880-1883	Tarnier (1828-1897)	Tarnier incubator is developed by Martin and installed in 1880 at the Port-Royal Maternité.
1884	Credé (1819-1892)	Credé reports the results of 647 infants treated over 20 years using an incubator similar to that of Denucé.
1887	Bartlett	Bartlett reads a paper on a "warming crib" based on Tarnier's concept but uses a "thermo-syphon."
1893	Budin (1846-1907)	Budin popularizes the Tarnier incubator and establishes the world's first "special care unit for premature infants" at Maternité and Clinique Tarnier in Paris.
1893	Rotch (1849-1914)	The first American incubator with a built-in scale, wheels, and fresh-air delivery system is developed; the equipment is very expensive and elaborate.
1897	Holt incubator	A simplified version of the Rotch incubator is developed. In this double-walled wooden box, hot water circulates between the walls.
1897-1920s	Brown, Lyons, DeLee, Allin	Many modifications are made to the early American and European incubators by physicians. These are called baby-tents, baby boxes, warming beds, and other names.
1922	Hess	Hess introduces his famous incubator with an electric heating system. For transportation, he develops special boxes that can be plugged into the cigarette lighters in Chicago's taxi cabs.
1930-1950s	Large-scale commercial incubators	There is worldwide distribution of Air-Shields and other commercial ventilators.
1970-1980	Modern incubators	Transport incubators with built-in ventilators and monitoring equipment are developed—mobile intensive care units.

See references 6, 7, 21-24, 77-80 for primary citations.



• **Fig. 1.8** Hess and Lundeen medallions at the Michael Reese Hospital, Chicago. (Photo courtesy of Tonse N. K. Raju.)

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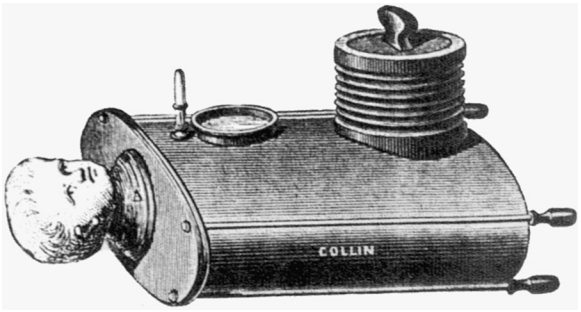
• **Fig. 1.9** A Hess incubator on display at the Spertus Museum in Chicago. (From the International Museum of Surgical Sciences, Chicago.)

coupled with the belief that oxygen was innocuous and that if a little bit could save lives, a lot could save even more lives. Because more and more sick and small preterm infants began to survive with incubator care, providing ventilatory assistance became an urgent necessity.

Ventilatory Care: "Extended Resuscitation"

The first mechanical instrument used for intermittent positive pressure ventilation in newborns was the *aerophore pulmonaire*, a simple device developed by the French obstetrician Gairal.[65,66] It was a rubber bulb attached to a J-shaped tube. By placing the bent end of the tube into the infant's upper airway, one could pump air into the lungs. Holt recommended its use for resuscitation in his influential 1897 book.[48]

Before starting mechanical ventilation, one needed to cannulate the airway, a task nearly impossible without a laryngoscope and an endotracheal tube. Blundell (1790-1878), a Scottish obstetrician, was the first to use a mechanical device for tracheal intubation in living newborns.[13,32] Introducing two fingers of his left hand over the infant's tongue, he would feel the epiglottis and then guide a silver pipe into the trachea with his right hand. His tracheal pipe had a blunt distal end and two side holes. By blowing air into the tube about 30 times a minute until the heartbeat began, Blundell saved hundreds of infants with birth asphyxia and infants with laryngeal diphtheria. His method of tracheal intubation is practiced in many countries today.[90] In the



• **Fig. 1.10** The Man-Can, circa 1873 to 1875. A handheld, negative-pressure ventilatory device for which a patent was applied in 1876.[19,20] (From DeBono E. *Eureka! How and When the Greatest Inventions Were Made: An Illustrated History of Inventions from the Wheel to the Computer*. New York: Holt, Rinehart & Winston; 1974, p 159.)

late nineteenth century, a wide array of instruments evolved to provide longer periods of augmented or extended ventilation for infants who had been resuscitated in the labor room. Most of the early instruments were designed for use in adults, however, and were used later in newborns and infants, particularly to treat paralytic polio and laryngeal diphtheria.[39,45,81,85]

The iron lung (or "man-can") was one of the earliest mechanical ventilatory devices (Fig. 1.10), and a US patent was issued for it in 1876.[19,20,42] In other ventilatory equipment, varying methods for rhythmic inflation and deflation of the lungs were used for prolonged ventilation. Among those, the Fell-O'Dwyer apparatus used a unique foot-operated bellows system connected to an implement similar to the aerophore bulb.[25,65,66]

Between 1930 and 1950, there were sporadic but important reports of prolonged assisted ventilation provided to newborns.[12,62,84,85] Beginning in the late 1950s and through the 1960s, more neonatal intensive care units (NICUs) began providing ventilatory assistance regularly (Table 1.3). Ventilatory care did not become predictably successful, however, until the early 1970s, when continuous positive pressure was incorporated into ventilatory devices.[44,58,62,84]

Supportive Care: Intravenous Fluid and Blood Transfusions

When it comes to intravenous therapy, our legacy is one of bloodletting, not of transfusing. Blundell (of intubation fame) also made a major contribution to transfusion science. Believing that "only human blood should be employed for humans," he developed instruments, syringes, and funnels for this purpose. In 1818, Blundell carried out the first direct transfusion from a healthy donor into a recipient; 5 of his first 10 patients survived.

Human-to-human transfusions gradually became accepted, but physicians in the nineteenth century were puzzled about unexpected disasters among blood transfusion recipients. It took 15 years after Landsteiner's discovery of blood groups in 1901 for the general acceptance

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TABLE 1.3 Ventilatory Care, Respiratory Disorders, and Intensive Care

Category	Approximate Time Span	Procedures and Techniques
Resuscitation and oxygen	From antiquity to early 1970s	Mouth-to-mouth breathing (although it fell from favor in the late eighteenth century because many influential physicians declared it a "vulgar method" of revival)
	1878	Tarnier uses oxygen in debilitated premature infants.
	1900-1930s	Schultz, Sylvester, and Laborde methods of resuscitation involve various forms of swinging infants (Schultz), traction of the tongue (Sylvester), and compression of the chest (Laborde).
	1930-1960s	Oxygen administration to the oral cavity through a rubber catheter
	1930s-1940s	Tight-fitting tracheal tube and direct tracheal oxygen administration
	1913-1920s	Byrd-Dew method: immersion in warm water, with alternate flexing and extending of the pelvis to help the "lungs open"
	1850-1930s	Dilation of the rectum
	1930-1950s	Inhalation of oxygen and 7% CO_2 mixture (for morphine-induced narcosis)
	1940-1950s	Positive-pressure air-lock (Bloxsom method)
	1940 to late 1950s	Concept that "air in the digestive tract is good for survival" is promoted—administration of oxygen to the stomach
	1950 to late 1960s	Hyperbaric oxygen in Vickers pressure chamber
	1950-1960s	Mouth-to-mouth or mouth-to-endotracheal tube breathing
Assisted ventilation	1930s-1980s	Bell develops a negative-pressure jacket
	1930-1950	Negative-pressure ventilators and iron lungs, used rarely in infants
	1960s	Positive-pressure respirators used for prolonged ventilatory support
	1971	Continuous positive airway pressure introduced for use in newborns
	1973	Intermittent mandatory ventilator
	1970-1980s	High-frequency ventilators; continuous monitoring of pulmonary function
Surfactant	1903	Hochheim reports "hyaline membranes" noted in the lungs of infants with RDS
	1940-1950s	Clinical descriptions and pathology studied
	1955–1956	Pattle discovers surfactant in pulmonary edema foam and lung extracts.
	1959	Avery and Mead show absence of surfactant in infants with hyaline membrane disease.[4]
	1971	Gluck introduces lecithin/sphingomyelin ratio.
	1973	Liggins suggests that antenatal steroids help mature the pulmonary surfactant system.
	1980	First effective clinical trial of postnatal surfactant therapy (bovine, Fujiwara)
	1989-1991	Commercial surfactants become available.
	1995	Widespread antenatal steroid use leads to declines in rates for RDS and improves survival rates for infants with birth weight <1000 g, heralding a new era of epidemics of bronchopulmonary dysplasia and retinopathy of prematurity.
Education research and patient care	1950 and beyond	Era of controlled clinical trials in neonatal medicine begins
	1970s	Regionalization of neonatal-perinatal care
	1990s	Evidence-based medicine, systematic reviews
		Large perinatal networks for research (self-funded and federally funded)
	2005	Hypothermia for perinatal hypoxic-ischemic encephalopathy
Border of viability debates	2005	Improved survival rates for infants between 22 and 26 weeks' gestation raise questions about the definition of border of viability and the ethics of intensive care for such infants. Debates and dilemma continue.
Adults born preterm	2008–2017	Large population-based national cohorts and longitudinal studies are beginning to report health and social well-being of adults born at preterm gestation.[67]

RDS, Respiratory distress syndrome.
See references 2, 4, 5, 18, 25, 46, 49, 58, 61, 92.

and understanding of the scientific basis for blood group incompatibility.[92]

Adult transfusions were rare, but newborn transfusions were rarer still. On March 8, 1908, a 4-day-old term infant who had hemorrhagic disease of the newborn made history. "As the child's skin became waxen white and mucous membranes without color, it was decided to attempt transfusion of blood obtained from the infant's father," wrote Lambert from New York.[55] Carrel, a surgeon from Rockefeller University Hospital, performed an end-to-end anastomosis of

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the right popliteal vein of the infant with the left radial artery of the father. No anesthetic was given to either patient. "The amount of blood transfused could not be measured, but enough blood was allowed to flow into the baby to change her color from pale transparent whiteness to brilliant red…[and] as soon as the wound was sutured, the infant fed ravenously and immediately went to sleep," according to Lambert. Incidentally, Carrel was the first surgeon to develop innovative methods of suturing blood vessels—a contribution for which he received the 1912 Nobel Prize.

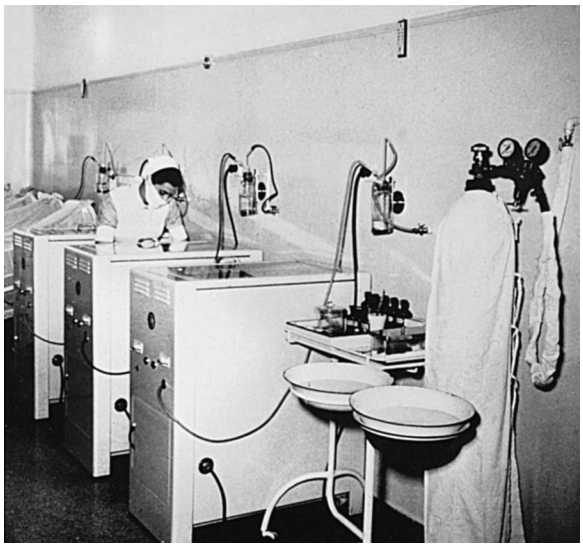
Despite Lambert's dramatic report, direct father-to-infant transfusion did not become routine. Because of unexpected reactions among the recipients, blood transfusions continued to be risky, despite proper matching of the donors' blood for major blood types. The mystery was understood only after the discovery of Rh subtypes by Landsteiner and Wiener in 1940.[92,95]

The discovery of the Rh blood types, leading to the conquest of erythroblastosis fetalis, remains an unparalleled triumph in pediatric medicine. This is an example of an orderly progression of accumulating knowledge leading to the near-eradication of a disease. First, there were the clinical descriptions of the disease (erythroblastosis); then there was a revolutionary, if symptomatic, therapy for it (exchange transfusion); then in utero transfusions; and finally, successful efforts to prevent it (RhoGAM). The enthralling story of the conquest of erythroblastosis has been described superbly in many monographs and comprehensive review articles.[28,29,92,95]

Tools and Supplies for Neonatal Intensive Care Units

It may be impossible for us to realize the hardship of performing such simple and mundane chores as the collection of blood from or insertion of catheters into the veins of preterm infants before the advent of ultrasmall needles, pumps, and tubing. These were not available until the 1930s. In 1912, Blackfan (1883-1941) developed an ingenious suction device for blood collection.[9] Obtaining blood was done by puncturing the sagittal sinus or femoral or carotid veins; the latter sometimes led to accidental puncture of the nearby arteries. Well into the early 1970s, only a handful of laboratories could perform arterial blood gas analyses with less than 5 mL of blood.

Using the intraperitoneal route for treating dehydration or hypovolemic shock was common. Electrolyte solutions and blood were being administered directly into the peritoneal cavity with the expectation that its large absorptive surface allowed for rapid absorption.[10,95] In 1923, Sidbury introduced umbilical venous catheterization for neonatal blood transfusions,[77] and in the 1950s, Diamond and colleagues began using this route for exchange transfusions.[28,29] Indwelling polyethylene tubes were not introduced for gastric feeding until 1951.[74,95,96]



• **Fig. 1.11** The first preterm infant unit in Athens, Greece, using incubators with oxygen flowing into them (circa 1947). (Courtesy of John Sofatzis, MD, Athens, Greece.)

Pediatric Surgery: Not for Rabbits Anymore

As the trend of specialization among surgical subspecialties became popular, generalist surgeons resisted the change. Churchill, a famous surgeon, once remarked that his surgical residents at Massachusetts General Hospital "were quite proficient at operating on rabbits," and there was no need for a subspecialty in pediatric surgery.[35] Despite those objections, Harvard Medical School founded the first department of pediatric surgery in 1941 and named Ladd as its chair.

Global Neonatal Care

By the middle of the twentieth century, scores of neonatal units based on the Hess model were built in many European countries (Fig. 1.11) and the United Kingdom.[33,61] During the final decades of the twentieth century, in many Asian countries, indigenous instruments and devices were being developed to improve neonatal resuscitation and intensive care for sick newborns.

Medical Errors and "Patient Safety" as a New Discipline

It appears that the flip side of the well-known adage *to err is human* is the saying that *truth is a corrected error*. . . . In a series of papers, Robertson provides a breakdown of errors in neonatal medical practice in the twentieth century.[70-72] He defined years 1920 to 1950 as the *hands-off years*, 1950 to 1970 as the *heroic years*, and 1970 to 2000 as the *experienced years*. An astounding range of errors has affected our

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field: from iatrogenic hypothermia of preterm infants to aniline dye–contaminated diapers leading to epidemics of methemoglobinemia; chloramphenicol causing shocklike syndromes; sulfisoxazole causing kernicterus; and infant formulas causing metabolic alkalosis and lactobezoars.

As technological advances bring new modes of diagnostic methods and treatments, there are risks for also bringing new types of errors. We regret errors, and we learn a great deal by understanding the causes and consequences of errors and by developing effective means of preventing them. Toward this end it is gratifying to note that *patient safety* has evolved as a new discipline.[76]

Controlled Clinical Trials, Evidence-Based Medicine, and Research Networks

The modern era of controlled clinical trials evolved in the second half of the twentieth century. The first randomized controlled clinical trial (RCT) in the United States was on a neonatal topic.[79,80] In 1949, in their newly established "infant station" at the Babies Hospital, New York, Silverman and colleagues saw an infant with a severe stage of ROP. This 1200 g infant was the son of a biochemistry professor. Desperate to do "anything" to prevent the infant becoming totally blind, Silverman's group decided to administer adrenocorticotropic hormone (ACTH). The infant made a dramatic recovery. This gave them the inspiration to "try" to design a placebo-controlled randomized trial using ACTH for ROP.

The results were disappointing. In addition to causing steroid-related side effects, ACTH was no more effective than the placebo in reducing ROP severity. The experience of organizing this trial led Silverman to develop additional RCTs in neonatal medicine; the most famous of which is the multicenter trial of curtailed or liberal use of oxygen to prevent ROP.[79,80]

With RCT as the backbone, advances in statistical methods and computer sciences gave rise to the science of systematic analyses, culminating in the founding of the Cochrane Collaboration in 1993, named after the British epidemiologist Cochrane. The Collaboration produces and disseminates systematic reviews on therapies in all of medicine.

Another welcome trend of the 1980s was the development of cooperative clinical and research networks. Examples of these include the self-funded Vermont Oxford Network and the federally funded Maternal-Fetal Medicine Units and the Neonatal Research Networks. Such cooperative networks have also been organized in the United Kingdom and European countries. These networks have conducted many highly successful collaborative clinical trials. With common protocols and shared resources, they have managed to enroll and study large numbers of research subjects within short time spans. The generic database maintained in these networks has become an invaluable resource for observational research. From the perspective of a historian, however, the long-term impact of these developments on the neonatal practice at the community (or practitioner) level and their overall impact on neonatal outcomes need to be studied systematically.

Future of Neonatal Research, Education, and Databases in the Internet Era

Of all the advances in the twentieth century, none has made a greater impact on our lives than computers, the Internet, and information technology. The Internet and information technology opened new avenues for dissemination of research information and helped the development of clinical research databases. These resources need to give way for creative means pooling our collective experiences in patient care in a prospective manner.

Although today's NICU is a technological marvel, conceptually it remains a miniaturized version of the adult intensive care unit. Knowledge about the environmental influences on growth and development may change the shape of future NICUs. Although the immediate and long-term adverse effects of excessive noise, light, handling, and pain on infant growth are being studied, attempts are being made to transform the impersonal intensive care environment into an infant-friendly experience. Many ultramodern NICUs have now been built on the concepts of environmental care. Such "kind and gentle" NICUs may be what Tarnier, Budin, Hess, and others conceived of some 100 years ago.

Despite incredible advances in the care of premature infants, today's scientists are facing many unresolved issues, including limits of viability, cost of care, quality of life for intensive care "graduates" (into their adult lives), and an ever-increasing battle against opportunistic nosocomial microorganisms. A major concern is the definition of border of viability and the ethics of providing intensive or palliative care for infants born between 22 and 25 weeks' gestation. To the long list of new problems, one might add the growing realization that many adult-onset disorders may have developmental origins.

These and similar concerns also vexed the early pioneers of our subspecialty. Future historians may assess this century of neonatal medicine with the same sense of surprised wonder and awe that we now feel when remembering the days of infant hatcheries and baby incubator shows.

Some Famous High-Risk Infants

Shakespeare's King Henry VI offers one of the most poignant musings on the burdens of disability and the difficult birth (owing to footling presentation) of his brother, the Duke of Gloucester, who later became Richard III. Henry says to the Duke,[54] who was supposedly born premature (although not confirmed by other historians), "Thy mother felt more than a mother's pain, yet brought forth less than

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TABLE 1.4 Ominous Beginnings for Some Famous Historical and Fictional Personalities

Category	Name	Description*
Religious	Moses	Jewish tradition holds that Moses was born "6 months and 1 day" after he was conceived; thus, he could be hidden for 3 months from Pharaoh's soldiers who were looking to find and kill the liberator of Jews.[50,60]
Historical personalities and characters	Duke of Gloucester (later Richard III) (1452-1485)	Footling presentation, possibly premature; might have had cerebral palsy (hemiplegia?)[54]
	Macduff (Scottish nobleman in Shakespeare's *Macbeth*)	Delivered by cesarean section after his mother's death—"not of a woman born" but of a corpse[54]
Artists and writers	Jonathan Swift (1667-1745)	Mentioned by Cone[24]
	Licetus Fortunio (1577-1657)	"A fetus no more than five and one-half inches" at birth[86]
	Pablo Picasso (1881-1973)	Left on the table as a stillbirth; his uncle, Don Salvador, a physician, resuscitated him
	Voltaire (1694-1778)	Premature and asphyxiated, the "puny little boy" was not expected to live and was hurriedly baptized; he was raised in the attic to keep him warm
	Samuel Johnson (1709-1784)	A huge baby, he was "strangely inert" at birth, requiring slapping and shaking. With persuasion, he made a few whimpers and lived.
	Johann Wolfgang von Goethe (1749-1823)	After 3 days of labor, his mother delivered him; he was "lifeless and miserable" and thought to be stillborn at birth.
	Anna Pavlova (1882-1931)	"A premature, so puny and weak," she was wrapped in cotton wool for 3 months.
	Thomas Hardy (1840-1928)	He was thrown aside as dead at birth. "A good slapping" from the midwife revived him.
	Sidney Poitier (born 1927)	Being 3 months premature, he was so small that his father "could place him in a shoebox." His grandmother said that despite prematurity, he would "walk with the kings." He did, when he became Bahamian ambassador to Japan in the 1990s.†
Scientists	Johannes Kepler (1571-1630)	A "seven-month" baby; estimated IQ, 161
	Christopher Wren (1632-1723)	Mentioned by Cone[24]
	Isaac Newton (1642-1727)	Thought to be "as good as dead" at birth. He was such a "tiny mite" that he could be placed in a quart mug.
Politicians	Franklin D. Roosevelt (1882-1945)	Weighed 10 lb at birth but was "blue and limp with a deathlike respiratory standstill" from too much chloroform given to his mother, Sara Roosevelt
	Winston Churchill (1874-1965)	His early birth "upset the ball." Later a duchess remarked that the baby had such a lusty "earth-shaking" cry as she had ever heard. Recent historians doubt his premature birth.

*The biographical notes are derived mostly from anecdotal statements of historians or family members or are from later recollection by the individuals themselves; we cannot be certain of the scientific validity of these stories.
†Quoted by Sidney Poitier in the television show *Biography,* CNN, Spring 2000.
See references 54, 64, 87.

a mother's hope." King Richard himself in a different Shakespearean play bemoans his misfortune[54]: "Deformed, unfinish'd, sent before my time/Into this breathing world, scarce half made up."

Did King Richard have hemiplegic cerebral palsy as a consequence of prematurity? We cannot be sure. The list of leaders, celebrities, and famous individuals supposed to have been regarded as being at high risk at birth (Table 1.4) is impressive,[64] although the authenticity of the stories is difficult to confirm because most of them were derived from anecdotal statements.

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Key Points

- The past: Neonatology has a rich history focused largely on basic supportive care until the 1970s.
- The present: The last 40 to 50 years have seen the advent of significant innovative interventions and changed from anecdotal to evidence-based care, with many randomized clinical trials enabled by the establishment of cooperative clinical and research networks.
- The future: Challenges include optimizing the NICU environment, data collection and its dissemination in the digital age, defining limits of viability, introducing precision medicine, and optimizing quality of life for NICU graduates.

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2

Epidemiology for Neonatologists

ANDREA N. TREMBATH

Introduction

Epidemiology is the study of health and disease and the associated causes.[9,23] The role of epidemiology in neonatal-perinatal medicine is to define the prevalence and causes of illness in women and children by exploring risk factors and their associations. Specifically, maternal and infant mortality rates are used to assess the levels of health, access to needed health care, and quality of health care provided by a region or country.

Common Epidemiologic Concepts

In epidemiology, risk describes the probability of disease occurrence; however, it may represent a wide variety of statistical measures that include incidence, prevalence, rate, or odds. A risk factor often implies an increase in the outcome of interest with exposure, although risk measures may also represent protective effects. Risks are often compared using relative measures such as the risk ratio, odds ratio, and rate ratio (Table 2.1). Relative measures are helpful in the identification of risk factors but can be misleading if not accompanied by absolute measures such as the risk difference. For example, a relative risk of 2.0 indicates that the exposed group is twice as likely to develop the disease as the unexposed group. However, twice as likely may represent an absolute change in risk from 0.2 (20%) to 0.1 (10%; risk difference of 0.1 or 10%) or may represent an absolute change in risk from 0.002 (0.2%) to 0.001 (0.1%; risk difference of 0.001 or 0.1%). A small change in absolute risk, therefore, may have little to no clinical impact.

In neonatology, the impact of single risk factors on outcomes is generally small, and caution should be used when inferring causality. Most diseases such as intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD) have many component causes, some of which remain either unknown or unmeasurable. These component causes can occur at different times, and the sequence of their occurrence may be important in the development of the disease.

Health Statistics and Data Sources

A clear understanding of the definitions used to calculate the epidemiologic data for health statistics is essential. In the United States, population-level health data is primarily derived from birth and death certificates submitted to the National Vital Statistics System (NVSS) by individual states and territories.[11] The standardized terminology and definitions allow direct comparison of important population-level health markers such as birth, death, and outcome rates[21] (Table 2.2). A standard set of reporting measures are reported to the NVSS; however, individual states may choose to collect additional data of importance to their specific population. In the United States, completion of a birth certificate form is required for all births regardless of length of gestation or weight and uses uniform definitions[4,11,21] (Table 2.3). Fetal death reporting requirements, however, vary by state and may be based on gestational age or birth weight criteria.

The ability to make inferences based on health statistics relies on the availability of large datasets such as those found through the NVSS. However, many of the important questions regarding survival and neurodevelopmental outcomes of the smallest and sickest infants in neonatology represent only a small total number nationwide. Single centers often do not have large enough populations of neonates to have the statistical power to determine clinically important differences in outcomes. To meet this need, several networks of neonatal and maternal centers have been established.

The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN), established in 1986 to improve the medical care for newborns and their families, is a consortium of US neonatal intensive care units (NICUs) that conducts multicenter clinical trials and observational trials on infants.[8] Among the ongoing observational trials, the Generic Database Study (GDB) has been collecting information on very low birth rate (VLBW) infants since 1987, including data on hospital admission as well as follow-up data that includes standardized neurodevelopmental assessments. In addition, the NRN designs and executes high-quality clinical trials

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Abstract

Perinatal epidemiology aims to define the prevalence and causes of health and disease in women and children. Health statistics derived from national databases including the National Vital Statistics System provide information on birth and death rates and include information on neonatal and maternal morbidities. Specifically, information on maternal and infant mortality rates are critical indicators of a population's health and wellness.

Keywords

epidemiology
infant mortality
pregnancy-related death
prematurity
health disparities

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TABLE 2.1 Common Measures and Definitions

Risk ratio	Ratio of the incidence of risk in an exposed group to the incidence risk in the unexposed group
Odds ratio	Ratio of the odds of an event in the exposed group to the odds of an event in the unexposed group
Incidence	Proportion of individuals who are initially free of an outcome who subsequently develop the outcome over a specified period of time
Prevalence	Proportion of individuals who have a specific outcome at a given time

TABLE 2.2 Commonly Reported Rates

Perinatal mortality (PMR)*	Infant deaths under 7 days of age and fetal deaths ≥28 weeks' gestation per 1000 live births plus fetal deaths
Infant mortality rate (IMR)	Deaths prior to 1 year of life per 1000 live births
Neonatal mortality	Deaths prior to 28 days of life per 1000 live births
Post-neonatal mortality	Deaths from 28 days to <365 days per 1000 live births

*PMR definition I is used for international and state-specific comparisons because of differences among countries and states in the completeness of reporting of fetal deaths prior to 28 weeks' gestation.

TABLE 2.3 Vital Statistics Definitions

Live birth	The complete expulsion or extraction from the mother of a product of human conception, irrespective of the duration of the pregnancy, which, after such expulsion or extraction, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, regardless of whether the umbilical cord has been cut or the placenta is attached. Heartbeats are to be distinguished from transient cardiac contractions; respirations are to be distinguished from fleeting respiratory efforts or gasps.
Fetal death	Death before the complete expulsion or extraction from the mother of a product of human conception, irrespective of the duration of pregnancy that is not an induced termination of pregnancy. The death is indicated by the fact that, after such expulsion or extraction, the fetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Heartbeats are to be distinguished from transient cardiac contractions; respirations are to be distinguished from fleeting respiratory efforts or gasps.
Infant death	Live birth (as above) that results in death prior to 1 year of life (<365 days).
Neonatal death	Death before 28 days of life
Post-neonatal death	Death at 28 days to 364 days of life

that provide epidemiologic data on subset populations and specific neonatal diseases.

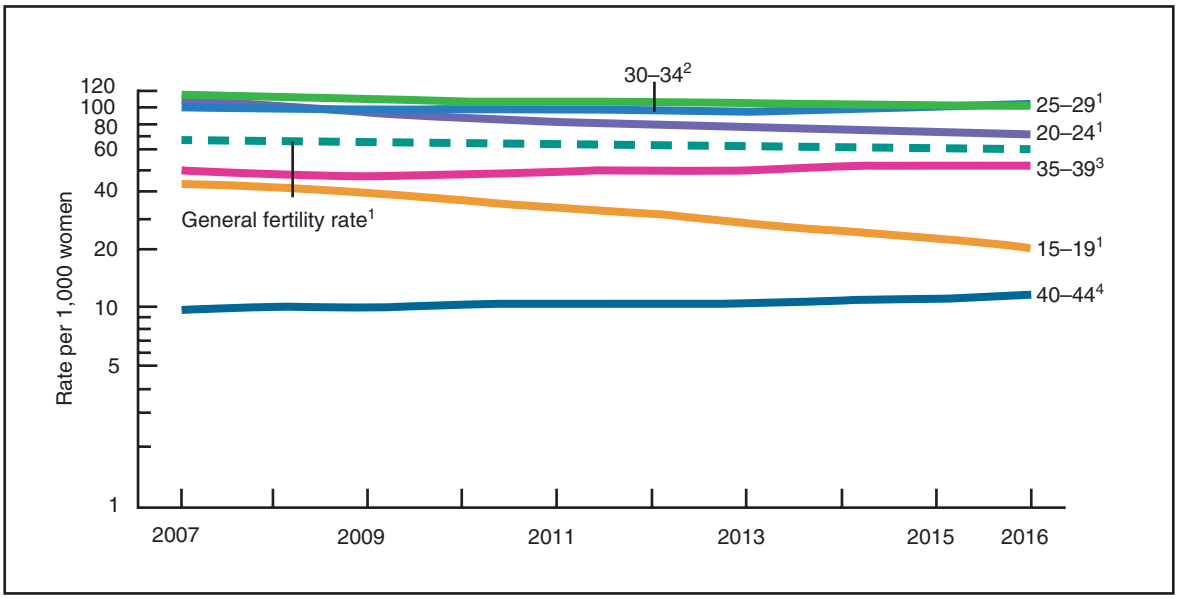
The Vermont Oxford Network (VON) is an international collaborative of more than 1000 NICU and medical centers established in 1988.[24] The mission of VON is "to improve the quality and safety of medical care for newborn infants and their families through a coordinated program of research, education, and quality improvement projects." VON maintains a database of inpatient hospital information on VLBW infants using standardized measures. In total, more than 2.2 million infants are represented in this database, providing a rich resource for information on the care and hospital outcomes of high-risk infants.

National and international quality collaboratives are filling an important role in neonatology by providing a platform to gather information on maternal child health as well as improving the care delivered to newborns. While the scope and direction of the quality initiatives vary, several perinatal state collaboratives, such as California Perinatal Quality Care Collaborative, the Ohio Perinatal Quality Collaborative, the Perinatal Quality Collaborative of North Carolina, and Tennessee Initiative for Perinatal Quality Care, have contributed valuable data on rates of late onset sepsis, nonindicated cesarean section, antenatal corticosteroid use, and narcotic abstinence syndrome.[10,15]

Birth Data

There were 3,978,497 births in the United States in 2015, a number that has remained fairly stable for nearly a decade.[12,19] The mean age of a mother at first birth has risen to 26.3 years in the United States and 28 in the United Kingdom.[20,22] The increase in maternal age at first birth is reflected in a steady rise in the birth rate for women in their thirties and forties, 101.5 per 1000 births for women age 30-44.[20] The teenage birth rate (ages 15-19), however, has

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[1]Significant decreasing trend for 2007–2016 ($p < 0.05$).
[2]Significant decreasing trend for 2007–2011; significant increasing trend for 2011–2016 ($p < 0.05$).
[3]Significant decreasing trend for 2007–2010; significant increasing trend for 2010–2016 ($p < 0.05$).
[4]Significant increasing trend for 2007–2016 ($p < 0.05$).
NOTES: Rates are plotted on a logarithmic scale. The general fertility rate is the number of births per 1,000 women aged 15–44; the age-specific birth rate is the number of births per 1,000 women in the specified age group. Access data table for Figure 1 at https://www.cdc.gov/nchs/data/databriefs/db287_table.pdf#1.
SOURCE: NCHS, National Vital Statistics System, Natality.

• **Fig. 2.1** General fertility rate and age-specific fertility rates, 2007-2016. (Source: NCHS, National Vital Statistics System, https://cdc.gov/nchs/data/databriefs/db287_table.pdf#1.)

continued to decline to 22.3 per 1000 live births—an over 60% reduction from its peak in 1991[19] (Fig. 2.1).

In the United States, the overwhelming majority of births occur in a hospital (98.5%) and are attended by an allopathic doctor of medicine (84%). Nurse midwives attended 8% of deliveries in 2015.[19] Among out-of-hospital deliveries, 63% occurred at home and 30.9% occurred at a birthing center. The rate of delivery by cesarean section in the United States remains around 32% overall; however, rates among all age groups have continued to decrease since 2009. Among women younger than 25 years, the rate of cesarean section has had the most significant declines. However, the rate of cesarean section delivery is nearly double among women age 40 and over.[5,12,19]

In 2015, 133,155 infants were born as twins in the United States, a rate of 33.5 per 1000 births. The twin birth rate increased steadily by 76% between 1980 and 2009. The increase has slowed since the mid-2000s; however, the peak rate was in 2014 at 33.9 per 1000 births.[5,19] The increases in twinning rates have been associated with increased use of assistive reproductive therapies (ART) such as fertility-enhancing drugs and are reflected by the increasing mean maternal age. In contrast, the rate of higher-order multiples has decreased dramatically (103.6/100,000) since the 1998 peak of 193.5 per 100,000 births. The reduction in higher-order births has been associated with more conservative use of ART, such as limiting the numbers of implanted embryos during in vitro fertilization.

Fetal Deaths

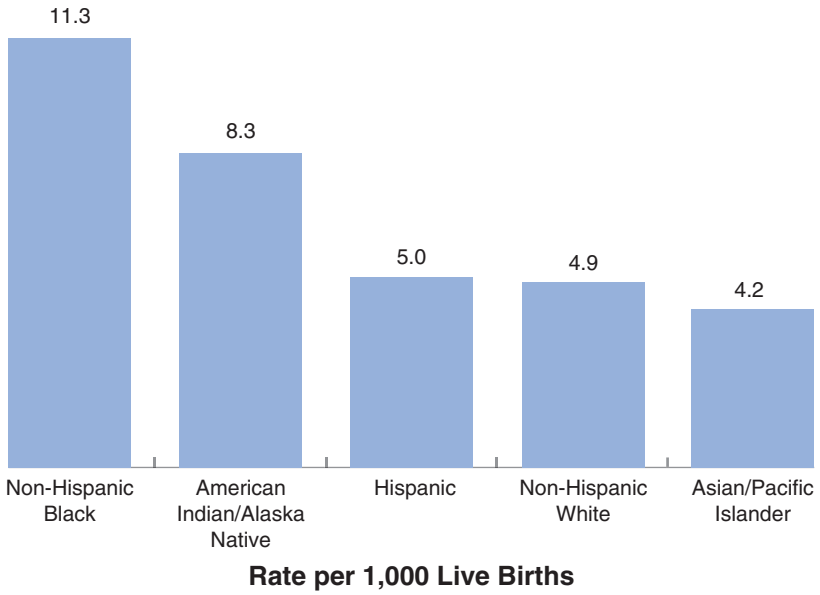
Rates of fetal death are the most difficult-to-interpret statistic because of inconsistencies in reporting. For statistical purposes, the fetal period is defined as the in utero period from 8 weeks after conception until term. A fetal death is commonly referred to as a miscarriage if it occurs at less than 20 weeks' gestation and a stillbirth if it occurs after 20 weeks' gestation.

Infant Deaths

Infant mortality (IM) is a critical measure of the health and welfare of a population. In 2015, 26,000 infants died before reaching age 1, resulting in an infant mortality rate of 5.9 deaths per 1000 live births.[14] This rate achieved the Health People 2020 IM goal of 6 per 1000 live births, and overall, the rates of IM in the United States have been declining steadily for at least 40 years.[13] Despite reaching the Health People 2020 goal, the United States ranks 32nd in infant mortality when compared to other developed countries, well behind Sweden, Japan, Singapore, and Hong Kong. Six countries had an infant mortality rate less than half the US rate.

The leading causes of infant mortality in the United States include premature birth and low birth weight (which accounts for nearly half of infant mortality), congenital defects, sleep-related deaths, pregnancy-related

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• **Fig. 2.2** Infant mortality rates by race, 2016. (Source: NCHS, National Vital Statistics System, www.cdc.gov/reproductivehealth/maternalinfanthealth/infantmortality.htm.)

complications, and injuries.[18,19] While these are primarily medical diagnoses, they are highly influenced by the social determinants of health. Social determinants of health are defined as those "nonmedical factors that influence health, including health-related knowledge, attitudes, beliefs, or behaviors."[6] These include socioeconomic factors such as education, employment, and neighborhoods, as well as health behaviors such as tobacco use and diet/exercise. The impact of these social determinants of health can be seen in the marked health disparities that exist in IM rates by race. The rate of IM among black infants is more than 2 times the rate of that for non-Hispanic white infants[19] (Fig. 2.2).

Pregnancy-Related Deaths

Pregnancy-related deaths, also known as maternal mortality, is defined as death of a woman either during pregnancy or in the 1 year following the end of pregnancy and is related to pregnancy or its management, excluding those caused by accidents or incidental causes. In 1983 the CDC began surveillance of pregnancy-related deaths using death certificates voluntarily submitted by the 50 states, New York City, and the District of Columbia.[7] From 1987 to 2013, the rate of pregnancy-related deaths has increased from 7.2 to 17.3 per 100,000 live births[5,7] (Fig. 2.3). The reasons for the increased rates of mortality are unclear, although may be due in part to increased reporting. However, it is well recognized that there has been an increase in the number of pregnant women with chronic health conditions such as obesity, hypertension, diabetes mellitus, and cardiovascular disease.[1,17] These conditions place a pregnant woman at a higher risk of adverse outcomes (Fig. 2.4).

In addition, significant disparities in rates of pregnancy-related deaths occur according to race and sociodemographic levels. Black women experience pregnancy-related mortality rates nearly 3.5 times higher than those of white women or other races (43.5 vs 12.7 and 14.4 per 100,000 live births).[7]

Maternal Morbidity

Severe maternal morbidity is any unexpected outcome of the pregnancy or labor and delivery process that results in short- and long-term impacts on a woman's health. The rate of severe maternal morbidity has increased in recent years, affecting approximately 50,000 women in 2013 and 2014.[5] The increase is likely due to an overall increase in the rates of maternal chronic conditions that predispose to higher rates of complications, such as the need for blood transfusions or hysterectomy (Fig. 2.5).

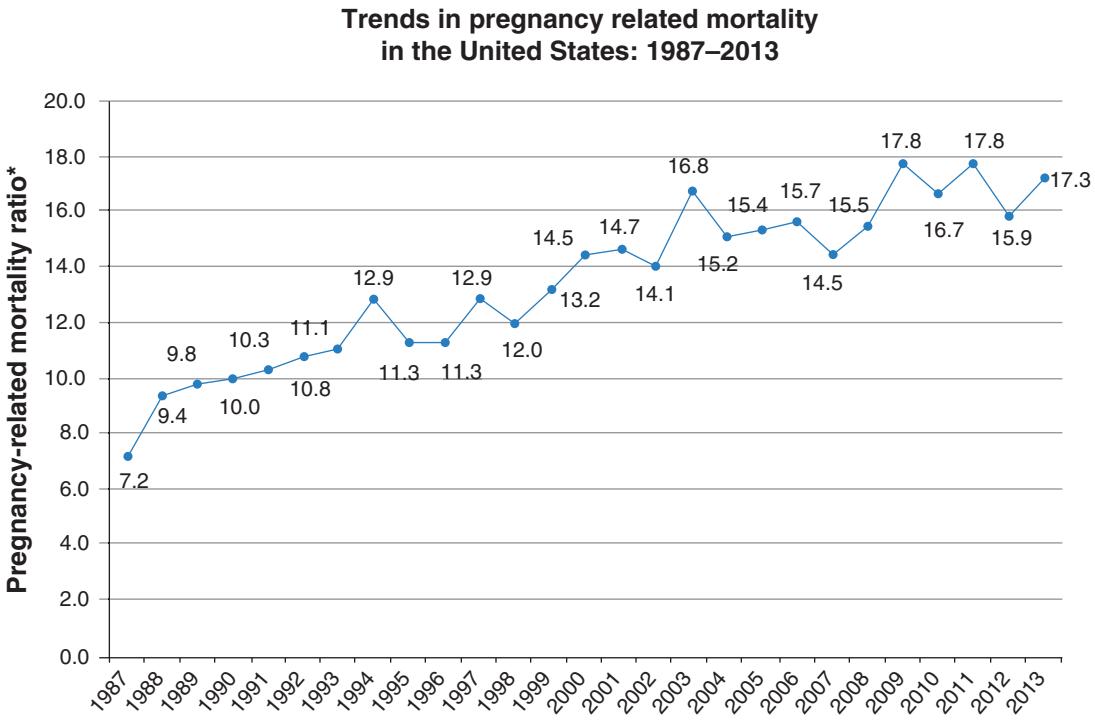
Neonatal Morbidity

Prematurity and Low Birth Weight

Prematurity and low birth weight are the leading causes of infant mortality and the primary driver of serious neonatal morbidity. In total, 382,786 preterm births occurred in the United States in 2015, and the rate of low birth weight (defined as <2500 g) infants was 8.16%—a number that has continued to rise nearly 2% from 2014.[18,19]

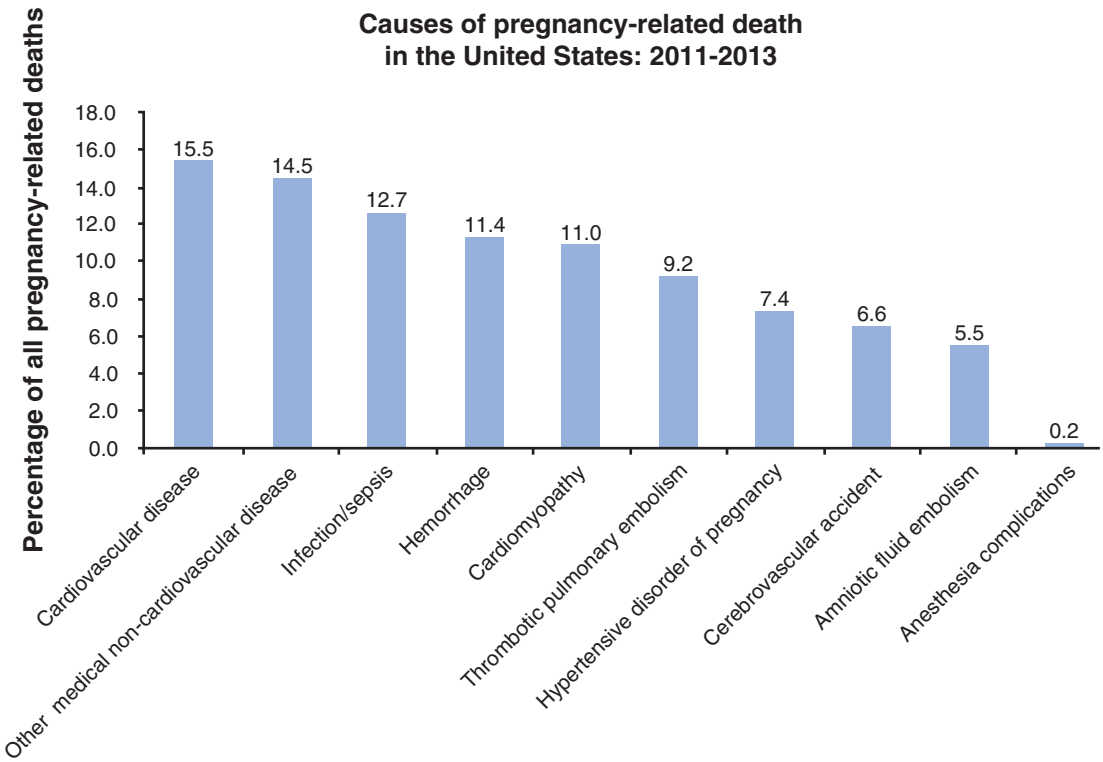
Traditionally, prematurity has been defined as birth prior to 37 weeks' gestation and is still the primary definition used in most national health statistics. However, in 2013, the American College of Obstetrics and Gynecology (ACOG) recognized the role that a few weeks makes in the risk for morbidity or mortality in the preterm infant by reclassifying full-term delivery as 39 0/7 weeks through 40 6/7 weeks' gestation[2] (Table 2.4). The change in terminology

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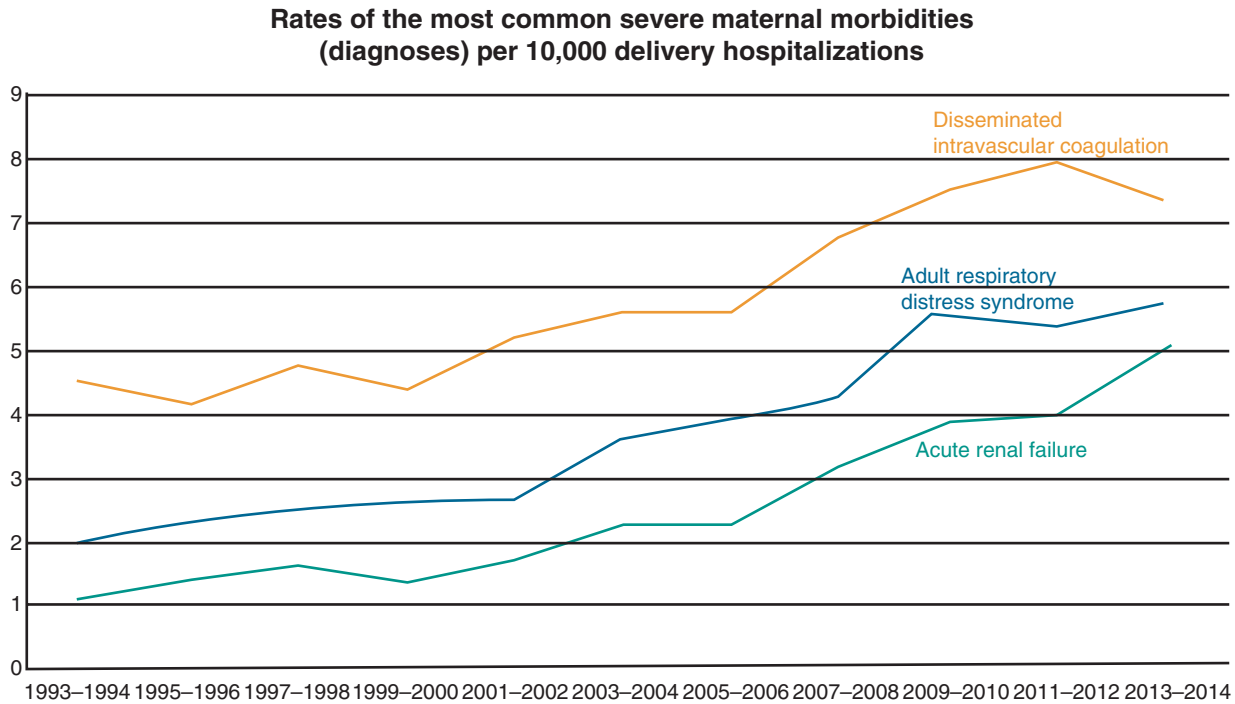
Note: Number of pregnancy-related deaths per 100,000 live births per year.

• **Fig. 2.3** Pregnancy-related mortality trends, 1987-2013. (Source: NCHS, National Vital Statistics System, Reproductive Health, www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-relatedmortality.htm.)



• **Fig. 2.4** Causes of pregnancy-related death, 2011-2013. (Source: NCHS, National Vital Statistics System, Reproductive Health, www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-related-mortality.htm.)

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• **Fig. 2.5** Rates of the most common severe maternal morbidities per 100,000 delivery hospitalizations. (Source: NCHS, National Vital Statistics System, Reproductive Health, www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-relatedmortality.htm.)

TABLE 2.4 Definitions of Premature and Term Gestation

Extremely preterm	<28 weeks
Very preterm	28 0/7 to 31 6/7 weeks
Moderate preterm	32 0/7 to 33 6/7 weeks
Late preterm*	34 0/7 to 36 6/7 weeks
Early term*	37 0/7 to 38 6/7 weeks
Full term*	39 0/7 to 40 6/7 weeks
Late term*	41 0/7 to 41 6/7 weeks
Post term*	42 0/7 weeks or beyond

*Based on American College of Obstetrician Gynecologists definition of term pregnancy.

acknowledges that the morbidity and mortality due to prematurity does not abruptly cease after 37 weeks. Rather, infants born at 37-38 weeks' gestation have an infant mortality rate nearly double that of infants born at 38-39 weeks (3.01 vs 1.85).[19] Infants delivered by elective cesarean section at 37-38 weeks' gestation are twice as likely to have adverse respiratory outcomes and require intensive care unit admission compared with infants delivered at 39 completed weeks of gestation.[2] In addition to the medical morbidity and mortality, prematurity comes with a significant cost to the health care system as the average first year cost of caring for a preterm infant (<37 weeks) was nearly 10 times that of caring for a term infant (37 weeks and greater) and costs the US health care system approximately $26 billion dollars annually.[16]

Multiple perinatal quality collaborative organizations nationwide, the March of Dimes, and other national organizations including the American Academy of Pediatrics have campaigns to educate the public about these increased risks and to encourage delays in delivery until 39 completed weeks of gestation.[3] In 2010, the Joint Commission on Hospital Accreditation established a perinatal core measure requiring the reporting of rates of nonmedically indicated deliveries performed between 37 and 39 weeks' gestational age.

Because of these initiatives and many others, the rate of preterm birth in the United States declined to 12.3% in 2008 following three decades of increases, and by 2011, the rate dropped further to 11.72%.[19] In 2016 the percentage of preterm births was 9.84%, based on best obstetrical estimate of delivery prior to 37 weeks' gestation.[12] Infants in multiple gestation pregnancies are more likely to be born prematurely and are more likely to be low birth weight than those in singleton pregnancies. Thus they are at a greater risk of early death—with twins 5 times (and triplets 10 times) as likely to die in infancy. In addition, rates of preterm birth demonstrate marked health disparities with the highest rates of prematurity among non-Hispanic black births, as compared to non-Hispanic white births (13% vs 9%).[14]

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Key Points

- Birth rates in the United States have remained stable for nearly a decade.
- Pregnancy-related deaths and maternal morbidity rates continue to rise.
- The US infant mortality rate was 5.9 deaths per 1000 live births.
- Prematurity and low birth weight are the leading causes of infant mortality and demonstrate significant health disparities.

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3

Medical Ethics in Neonatal Care

NAOMI T. LAVENTHAL AND JONATHAN M. FANAROFF

This chapter explores the complexity of moral problem solving in neonatal medicine. First, principles of medical ethics and key terms and concepts are defined, followed by the application of these concepts in specific moral problems that arise (1) when a pregnant patient refuses treatment, (2) in the prenatal consultation at the limits of gestational viability, and (3) when withholding and withdrawing life-sustaining medical treatment in the neonatal intensive care unit (NICU) is undertaken. This list is not an exhaustive representation of ethical challenges facing NICU providers but rather highlights some that are frequently encountered, and the principles offered to address them are applicable to many other situations. A collaborative, procedural framework for consensual end-of-life decision making is described, and specific ethical issues that may arise in end-of-life care are discussed, including the use of analgesic agents, brain death and organ donation, palliative care, and the withdrawal or withholding of artificial nutrition and hydration. This chapter includes guidelines for ethical conflict resolution and an approach to the conduct of clinical research. Finally, a brief summary of ethical responsibilities of neonatal physicians is presented.

Three elements characterize the practice of medicine that are timeless, universal, and irrefutably true: (1) the *fact* of illness and the vulnerability it creates, (2) the *act* of the profession (the use of medical skills for the benefit of the patient), and (3) the *practice* of medicine itself—that which physicians and patients do together in the clinical encounter, characterized by mutual intentionality.[112] These three elements are well exemplified in the care of sick neonates, in which the vulnerability of anxious parents is manifest, the clinical competence and moral discretion of health professionals are used for the benefit of newborn patients and their parents, and the practice is carried out in a patient-parent-physician relationship characterized by mutual trust and pursuit of the neonatal patient's and parents' good.

Medical ethics involves the systematic, reasoned evaluation and justification of the "right" action in pursuit of human good or well-being in the context of medical practice. It involves a critical examination of the concepts and assumptions underlying medical and moral decision making, and it may include a critical examination of the kind of person a physician should be.[118] Medical ethics has become a central focus in the practice of neonatal intensive care, because it contains all the elements of moral discourse but without clear-cut "right" answers expected in routine clinical practice. Numerous ethical issues arise as physicians attempt to determine how best to use technology in pursuit of what is right and good for the patient, in consideration of the values parents place on different outcomes.

These issues are compounded by several limitations on NICU providers' ability to elicit and understand parents' values; these can be pragmatic, related to patient and professional time limitations, but may also result from limitations in the provider's knowledge and expertise of how best to have these difficult conversations.[10,14,75,80,132] Care is also complicated by the medical uncertainty surrounding accurate outcome prediction of potentially adverse findings and by the very nature of many decisions in which quality of life and life *itself* may be under consideration.[74,100] All these issues make the NICU a challenging, highly scrutinized environment in how ethical issues are examined, reasoned, and justified, and raise fundamental questions about what the responsibilities of neonatal health care providers should be.

Ethical issues may be experienced as moral dilemmas, moral uncertainty, or moral distress. A *moral dilemma* is present when the physician believes there is an obligation to pursue two (or more) conflicting courses of action. Because only one of these courses can be pursued, the physician has to make a value-based choice that compromises one of these obligations. Conflict between respect for parental authority and professional duty to provide recommended medical care is a frequently encountered example of a moral dilemma.

Moral uncertainty arises when the presenting issue is unclear. This is commonly manifest as ambivalence on the part of parents who might struggle with a concomitant desire to prolong the life of their infant and wish to avoid burdensome procedures or impaired survival. On the part of physicians, moral uncertainty might arise when treatments are readily available, but with a low likelihood of success.

Moral distress arises when the decision maker feels certain about the morally right thing to do, but this perceived "right" course of action is precluded for numerous reasons,

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Abstract

This chapter explores the complexity of moral problem solving in neonatal medicine. First, principles of medical ethics and key terms and concepts are defined, followed by the application of these concepts in specific moral problems that arise (1) when a pregnant patient refuses treatment, (2) in the prenatal consultation at the limits of gestational viability, and (3) when withholding and withdrawing life-sustaining medical treatment in the neonatal intensive care unit (NICU) is undertaken. This list is not an exhaustive representation of ethical challenges facing NICU providers but rather highlights some that are frequently encountered, and the principles offered to address them are applicable to many other situations. A collaborative, procedural framework for consensual end-of-life decision making is described, and specific ethical issues that may arise in end-of-life care are discussed, including the use of analgesic agents, brain death and organ donation, palliative care, and the withdrawal or withholding of artificial nutrition and hydration. This chapter includes guidelines for ethical conflict resolution and an approach to the conduct of clinical research. Finally, a brief summary of ethical responsibilities of neonatal physicians is presented.

Keywords

ethics
bioethics
viability
antenatal consultation
shared decision-making

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including the caregiver's lack of decision-making authority or institutional or financial constraints. This phenomenon has been most extensively described among nurses but is also experienced by other NICU providers, including physicians, and involves a sense of powerlessness, frustration, physical symptoms, and ultimately professional "burnout."[15,37,56,115,137] Although unprocessed moral distress can result in maladaptive "moral residue,"[37,123,133] contemporary explorations of this topic have focused on constructive approaches to building moral resilience[116,150] and directing moral distress toward positive actions to improve patient care.[115]

Principles in Medical Ethics

Ethical reasoning requires an understanding of the fundamental principles that define a domain (Box 3.1). Beauchamp and Childress have described four core bioethical principles: autonomy, beneficence, nonmaleficence, and justice. Consideration of a real time ethical conflict or dilemma in the context of these principles can be a useful starting point and can be particularly helpful in articulating the ethical questions, uniting a struggling team by use of commonly held, noninflammatory language. However, a principles-based approach is of limited value when the problem revolves around a conflict between the principles themselves, as is often the case in the NICU. In many cases, a "principalis" paradigm may not do justice to the nature or complexity of the moral problem. In addition, in a purely principle-based approach, the role of the neonatal health care provider as *moral agent* (i.e., someone with personal virtues and values and the opportunity to take action that comports with that judgment of morality) is de-emphasized. This chapter does not prescribe adherence to any particular ethical theory but aims to enhance appreciation of the language of ethical discourse to enable nuanced reflection, reasoning, and ethical decision making, and to underline the role of the health care provider in these situations.

Autonomy

The principle of autonomy supports the right of competent patients to make their own health care choices. An individual who makes an autonomous choice acts intentionally, with understanding and without external controlling influences.[12] An idealized expression of autonomy occurs when a competent adult chooses voluntarily and intelligently from among various options whose relative risks and benefits have been fully explained to him or her by the physicians (i.e., via a truly informed consent process).

The term *parental autonomy* is often used interchangeably with *parental authority*, although most argue that autonomy can strictly be used only when making decisions for oneself. *Parental authority* is the more correct term when referring to the role of parents in decision making for their newborn infants.

Neonatal health care professionals should show respect for parental authority/autonomy: (1) because of the presumption that parents will make decisions that are in their child's best interests (parents are often described as the "natural surrogate decision makers" for children)[41] and (2) as a means of promoting shared decision making with physicians. Parents are not uniform in their desire to direct or even participate in medical decision making for their children.[9,61,81,96,143] However, physicians must be conscious of the impact of *their* authority, the power that derives from expertise and confidence, as well as limitations in their own ability to determine how directive parents wish for them to be in preference-sensitive decisions.[10,50,51,120]

In the second half of the 20th century, there was a shift away from a paternalistic approach to information sharing and medical decision making toward empowerment of the patient to make autonomous choices.[35] This condemnation of paternalism has more recently been viewed as excessively burdening some patients with weighty decisions that they do not wish to make alone.[110] There is a body of evidence that the prevailing bioethics emphasis on autonomy and self-determination can be overwhelming to parents,[108,151] and numerous studies show that respect for parental authority does not require physician adherence to a strict informed consent interaction. A more nuanced application of this respect can be satisfactorily achieved by including parents in decision making within a trusting parent–physician relationship.[64,107] Parental insistence on their right and role as final decision maker should be addressed carefully and viewed as a warning signal that there has been a degradation of the quality of communication with the medical team, or a sense that their authority as parents has been denigrated.

Too rigid or simplistic an interpretation and application of respect for parental autonomy by physicians is also problematic, such as when agreeing to a parental statement that "we want everything done." Without exploring what underlies this declaration, physicians may neglect the complexity of the situation and the underlying parental fear of "abandonment."[43] Finding the right balance between respect for parental autonomy and the physician's role and responsibility in any decision-making process requires

• BOX 3.1 Key Concepts Underlying Ethical Care in the Neonatal Intensive Care Unit

- Respecting parental authority/autonomy
- Applying the best interests of the infant standard of judgment
- Minimizing harm to the newborn
- Developing sound parent-physician relationships
- Empowering and informing parents
- Applying family-centered care principles
- Respecting parents' values and cultural and religious beliefs
- Sharing decision making
- Developing respectful interprofessional (moral) teamwork

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insight, empathy, and great analytical and communication skills.

Beneficence

Beneficence is the obligation to "do good," that is, to promote the best interests of their patients. In newborns, this obligation is embodied in the concept of the "best interests of the newborn." This is a moral and legal *standard of judgment* that helps to establish the primacy of duties to infants, ensuring they be regarded as fully human individuals with interests, even when clearly unable to express their own value system. Pursuing a course of action in the best interests of an infant implies determining what treatment course has a more favorable benefit-to-harm ratio than other possible options. Interpretation of the meaning of "benefit" can vary between infants and between stakeholders (parents, relatives, health care providers) for the same infant. Interpretations of what it means for a treatment to be beneficial include improvement in the infant's condition, stabilization of the infant's condition, or delaying the onset of clinical deterioration. Amelioration of clinical symptoms, or avoidance of complications of treatment, might also be construed as benefit. Benefit can also be achieved by identifying a less restrictive or intrusive treatment.

Determination of best interests requires an assessment of the child's potential *quality of life*. Quality-of-life considerations encompass the predicted cognitive and neurodevelopmental outcome, the potential for motor disability or other physical handicap (e.g., vision, hearing), and longer-term concerns such as behavioral and learning difficulties or school problems. It also considers the requirements for repeated or prolonged hospitalization, surgery, or medication; technology dependence; and the potential for pain and suffering to be endured. Quality-of-life considerations may also include less concrete medical states, such as the capacity for meaningful and potentially enjoyable interaction with other people and the environment. Some of the most ferocious disagreements between and within NICU teams relate to the inherently subjective nature of quality of life. Contemporary clinical ethicists have moved away from seemingly quantifiable assessments of quality of life, related to measurable outcomes, toward a more subjective interpretation, informed largely by the parents' expressed values.[75] Physicians and other care providers in the NICU must exercise caution not to misidentify expressions of hope, such as descriptions of future milestones and achievements, as manifestations of maladaptive denial of likely outcomes, particularly given that parents have been shown to identify with providers who express hope and compassion in their communication.[14,18,68,96] Although well-intentioned providers might seek to "correct" parents' interpretation of the quality of an anticipated outcome, recognition that some families might see more value in survival with neurodevelopmental disability or technology dependence than others is crucial to family-centered care and shared decision making.

The standard of best interests of the newborn acts as a threshold for judgment, yet the subjective nature of this assessment and the fact that the assessment is being done by surrogate decision makers must always be recognized. Additionally, it is imperative for clinicians to be aware of their limited powers of prognostication. Repeated studies by Meadow and colleagues have shown that when health care professionals predict that an infant will not survive to discharge, they are incorrect relatively frequently.[76,97,98] However, there are circumstances in which the best interest standard can be very helpful to medical teams, such as when urgent decisions must be made in the absence of parental input or when parents refuse clearly life-saving interventions. For the latter, best interest serves as a standard for overriding parental decisions.

Diekema has suggested that the more conservative "harm" principle be applied in overriding parental wishes. By this principle, rather than determine the "best interests," a harm threshold will be determined below which the parents' decision will be overruled.[29] Although invocation of the harm principle can be quite helpful, stakeholders for sick neonates must be careful to apply it in the context of illness severity, urgency, and maintenance of professional standards and integrity.[106,110]

Despite these definitional difficulties and suggested alternative standards such as the "harm" principle, "best interests of the newborn" is accepted as a guiding principle for decision makers because it unites different meanings under one standard and exhibits reasonableness, given the prevailing conditions.[73] Properly understood, the concept can serve as a powerful tool in settling disputes about how to make good decisions for individuals who cannot decide for themselves.

Nonmaleficence

The principle of *nonmaleficence* implies an obligation not to inflict *harm* on others. It has been closely associated with the maxim *primum non nocere* (first do no harm).[12] Although beneficence incorporates preventing and removing harm as part of promoting "the good" of a patient, the injunction not to *inflict* harm remains a distinct principle and requires intentionally refraining from actions that cause harm. Such harm is generally interpreted as *physical harm*, especially pain, disability, or death. Nonmaleficence requires that no initiation or continuation of treatment be considered without consideration of whether the treatment is overly burdensome or harmful. This is especially relevant given a historical context in which attention to pain in neonates has been sorely disregarded, to the degree in which surgeries were performed without anesthesia. However, as for benefit, defining events and interventions that are harmful to the event can be subjective. For some, harm is narrowly defined as pain or anxiety related to the condition or its treatment; assessment of this kind of harm can be aided by the use of bedside pain scores and other objective measures. For

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others, any intervention that does not change the ultimate outcome for the infant imparts undue burden. Providers and parents may differ about whether hospitalization in an intensive care unit, without the promise of recovery or discharge home, is harmful to the infant.

Justice

Justice is the dominant principle relating to *social cooperation*. Justice is the framework by which we determine how social benefits, such as health care, and burdens, such as research risks, are distributed. Although justice is regarded as a guiding principle for any health care system, no single, simple, ideal implementation adequately addresses the priorities of all relevant stakeholders. Generally, concepts of justice range from the broader utilitarian calculus to promote the greatest good for the greatest number in underwriting the *distribution of resources* (*macroallocation*) to a more narrowly focused equality of opportunity for each individual (*microallocation*). Justice in the distribution of resources requires that (1) patients in similar situations have access to the same health care, and (2) the level of health care available for one set of patients takes into account the effect of such a use of resources on other patients. Contemporary interpretations of resource allocation have focused on disparities,[1] both on equality in access to care, upstream from provision of the medical intervention itself, and emphasized the principle of *equity* over *equality*. This distinction is important in emphasizing the equality of health *outcome* rather than equality in provision of any specific resource.

Reasoning in the context of allocation of resources for the individual patient allows that fairness is an important consideration but is not the fundamental standard in this interaction. Microallocation issues are very rarely appropriate at the bedside; individual providers caring for individual patients are poorly suited to make decisions about whether one patient, or another, is more deserving of a limited resource, or to make *ad hoc* institutional-level decisions about how limited resources will be distributed. First, there is an inherent conflict of interest, in which the provider might rightly prioritize the immediate needs of the patient she is caring for over larger, systems-level considerations. Second, rationing and allocation schemes depend on economic and public health expertise beyond that possessed by most providers. However, individual providers *do* have a moral obligation to judiciously use medical resources for individual patients and ought not use unnecessarily expensive treatments or treatments that will not effectively promote the patient's health. The conventional ethical prohibition of bedside rationing is also complicated by daily realities of medical care in which time, ICU beds, and limited-quantity equipment are tacitly managed as a matter of routine.[127]

In every system, the provision of neonatal services requires guidelines to be developed for determining appropriate use of these costly and often limited resources. Priorities must be set and justified by organizational leaders. Any changes in the way neonatal care is delivered also need to be fair and accessible, as well as open and challengeable. Disputes should be addressed based on the acceptance of objective measures and trust in the integrity and fairness of the process and the individuals responsible for management of the process. With greater attention being paid to escalating health care costs, there is little question that how resources for sick newborns are used and justified may become more critically and ethically questioned. However, neonatal intensive care has been shown via a number of approaches to be remarkably cost effective,[146] particularly relative to the care of other patient populations.[55,99]

Key Terms and Concepts

Communication With Parents

Parents require complete and truthful information about their infant—the diagnosis and prognosis, the available treatment options (including, where relevant, the option of no treatment), the benefits and harms associated with each option, and the limits of available technology. The manner in which this information is communicated influences parents' understanding of the situation,[65,89] their ability to discuss moral issues and values openly, and their ability to participate effectively in a decision-making process (Box 3.2). Information communicated in an honest and respectful manner is likely to foster trust; information that is confusing, incomplete, evasive, or conveyed in a hurried or dismissive way will engender mistrust. *Transparency* in communication is crucial: It emphasizes the physician's reasoning, builds an understanding of the illness, makes the connection between data and their implications, and tempers unrealistic parental expectations.[66]

As medicine advances, physicians and parents must sometimes struggle with information that is at the limits of medical knowledge and in which the implications of findings are uncertain. The manner in which *medical uncertainty*, specifically *prognostic uncertainty*, is (or is not) communicated is extremely important and influences subsequent decision making. Individual practitioners and neonatology groups may espouse different strategies to dealing with prognostic uncertainty. One is to examine outcome data and identify thresholds below which intensive care will not be offered because outcomes are unacceptably poor and thresholds above which intensive care is insisted upon because outcomes are reasonably good. In isolation, this strategy often fails (1) because one or more stakeholders cannot accept the possibility of foregoing a chance of survival for statistical outliers, (2) because of limitations to available outcome data, or (3) because statistical information is not viewed as helpful to decision making.[28,75] This approach has been increasingly subject to criticism.[33]

A more *wait-until-certainty approach* begins with treatment for almost every infant with any chance of survival. It establishes momentum in favor of continuing treatment

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• BOX 3.2 Guidelines for Respectful Communication With Parents

- Create an environment for communication that encourages parents' participation and their becoming as fully informed as possible.
- Identify and remove barriers that limit parents' role in communication (e.g., language, physical distance).
- Communicate with parents: at the time of admission, at any crisis point in their child's NICU course, via periodic reviews of longer stay patients, and other unstructured opportunities.
- Encourage parents to seek clarification of information at any point by requesting an appointment with the child's responsible physician.
- Provide open, truthful communication at all times.
- Provide information as accurately as possible and with as much certainty of diagnosis and prognosis as is possible in each clinical situation.
- Identify areas of medical uncertainty.
- Use easily understandable language, and pay attention to health care "literacy" issues.
- Assess family communication preferences, and attempt to communicate within those parameters.
- Be pre-emptive in communication (i.e., foresee what problems or issues may arise in the child's course).
- Be proactive in communication in any clinical situation in which a poor outcome is predicted.
- Convene meetings with both parents when important decisions need to be made.
- Keep parents informed of any special investigations/tests that are planned in the course of management of their child.
- Recognize the need for time to process and absorb information.
- Promote consistency and continuity of communication in the face of medical staff changes and handovers.
- Practice open, honest, and timely disclosure regarding medical error.

NICU, Neonatal intensive care unit.

as long as the medical course remains relatively uneventful. The possibility of withdrawal or discontinuation of life-sustaining medical treatment is considered only when severe, adverse medical findings become unequivocally evident. A problem with this strategy is the often false promise that certainty will, at some point, exist, and potentially relegates parents and other members of the health care team to the role of bystanders as the medical course unfolds.

Contemporary approaches to decision making have focused on individualization within consistently and fairly applied institutional guidelines, in which available population-based epidemiology, individual factors not accounted for by large studies, and parental values are all considered, using the language of *trial of therapy*,[100] to emphasize the remaining prognostic uncertainty, even for families requesting that "everything be done." Ongoing moral responsibility of the decision makers is emphasized in an effort to involve parents and the health care team in navigating the ensuing prognostic uncertainty.

The *timing* of any communication with parents is crucial. Ideally parents' readiness to receive information and their coping resources should be ascertained so that appropriate information is shared with consideration of their adaptation to the medical setting. In acute situations, if an urgent decision is required, the physician needs to move the relationship rapidly, however, from one of "moral strangers" to one in which moral issues can be openly discussed.

Obtaining *parental consent* for each planned intervention for the infant is often the prompt for communicating with parents in the neonatal intensive care unit (NICU). Some authorities may regard that obtaining formal, informed consent from parents for virtually every neonatal test or procedure is a means of maintaining a high standard of ethical care. Ensuring that parents are kept up to date and advised of treatment plans is important; however, information gathered from an ethnographic study showed that parents did *not* want to be asked to consent to every procedure.[2] They often felt overwhelmed when asked to consent for routine and minor procedures and felt they were given the illusion that they could or should say stop when there was no real choice and no time to learn more about each procedure. It was also clear that the more the staff offered information and time to listen to parents when *not* driven by a consent process, the easier it was for parents to discuss questions and dilemmas on fairly equal terms. When consent was required, parents emphasized the need for a two-way informed agreement between fairly equal partners with established mutual trust and respect.

A sound *patient-physician relationship* is a *sine qua non* of good medicine, for it is within this relationship that physicians exercise their humanity, understanding, and respect for the values of others. Every communication interaction with parents is an opportunity for relationship building. The ideal model in *adult* patient-physician relationships is considered to be the *deliberative-interactive model*, wherein physicians not only help the patient with clarification of his or her values but also strive to make their own reasoning transparent for the patient to appreciate the many factors that inform their professional recommendation.[35] In neonatal medicine, the physician's communication relationship is with the parents (or legal guardians) of the newborn, and the optimal parent-physician relationship aims to mirror the deliberative-interactive model, wherein physicians provide parents with accurate and timely information (with as much medical certainty as possible) and encourage and empower them to identify their values and treatment preferences. This model of relationship respects parental authority, encourages the physician's expression of his or her own clinical judgment, and, in so doing, promotes the best interests of the newborn and the family. A family-centered approach to daily rounds, in which parents are invited to actively engage in the exchange of information and formulation of the daily plan, can be facilitative toward building relationships and obviate the need for extensive and granular medical updates to precede substantive exploration of the prognosis or the goals of care. However, providers must be cognizant of barriers to daytime parental presence at the bedside, such as responsibilities to other children and

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family members, costs of transportation to and from the hospital, and the need for one or both parents to return to work. Physicians might also face barriers to spending time with parents at the bedside, such as competing patient care, as well as administrative and academic obligations. There may also be personal *physician-related factors* that need to be overcome, such as physicians' reluctance to express their views, a focus on short-term goals, an inherent avoidance of prognostication and discussion about outcomes, and a fear of damaging the relationship by being the bearer of bad news. Nevertheless, it is incumbent on physicians to attempt to develop a *therapeutic alliance* with parents and to engage in relationship building with them. The responsibility for a parent-physician relationship always rests with the physician.

Teams and Communication

Although it is important that the responsible physician attempt to integrate all of the important information and maintain a consistent relationship and pattern of communication with parents, neonatal intensive care is provided by many clinicians with expertise in different fields. This requires an understanding among the team members of the differences in responsibility in communication with parents, such as when conveying day-to-day quantifiable, objective information, or when communicating severe diagnoses or the more speculative, prognostic significance of specific findings. Although the responsibilities of each discipline are generally known, in certain situations communication boundaries may need to be defined to minimize fragmented and inconsistent information. Interdisciplinary meetings, in which all the practitioners involved with the patient share their findings and perspective, are crucial in ensuring that consistent patterns of communication are maintained. It is sometimes said that the ability to communicate is innate. This is not, however, borne out in the literature. For both family and team interactions, "relational competence" is a primary skill that can and should be improved and developed throughout one's career.[130]

Family-Centered Neonatal Intensive Care

Family-centered care is a philosophy that acknowledges the sick newborn infant's place within the social unit of the family. It also acknowledges that cultural, emotional, and social support by the family is an integral component of the infant's care. Family-centered care shapes policies, programs, facility design, and day-to-day interactions but should reflect values and attitudes just as equally as protocols. The potential benefits of a family-oriented approach include improved parental satisfaction with care and decision making, decreased parental stress, greater parental ability to cope with their infant's appearance and behavior, improved success with breastfeeding, and increased parental comfort and competence for post-discharge care.[31] The role of the parent perspective is increasingly highlighted in every step of NICU care, including unit design, development of rules and policies, and even in quality improvement initiatives.[32] In addition, many NICUs have begun to engage "resource" or "veteran" parents into their daily activities.[16]

Recognition of the child's place within the family highlights the cultural, religious, and spiritual dimensions of families' lives and may bring to light significant diversity within these domains. In a pluralistic society, parents and physicians are unlikely to share the same values, cultural systems, personal histories, and experiences, and at times of stress these differences may present health care providers with significant challenges.

The first challenge is to recognize, understand, and respect the cultural, religious, and spiritual views and values of parents and families. Misperceptions caused by a lack of sensitivity can lead to inappropriate care or poor clinical outcomes. *Cultural competence* is more than acknowledgement of cultural norms different from one's own. Rather, cultural competence is an ability to interact effectively with people of different cultures and comprises four components: (1) the individual's awareness of his or her own cultural worldview, (2) the individual's attitude toward cultural differences, (3) the individual's knowledge of different cultural practices and worldviews, and (4) the individual's cross-cultural skills.[91] Developing cultural competence results in an ability to understand, communicate with, and interact effectively with people across cultures.

The second challenge for neonatal health care providers involves the limits of tolerance—where to draw the line between accepting patterns of decision making between couples or within families that contrast markedly with the prevailing cultural norm of shared parental responsibility for decision making.

A third challenge arises because not only are parents and physicians products of their own respective cultures but also their interactions occur within a further "culture"—that of medicine and intensive care itself—with its own values, assumptions, and understanding of what should be done.

Although the health care team should recognize how families' interests are shaped by social, cultural, and other contexts, it is important *not to stereotype* the members of specific social, cultural, ethnic, or religious groups. Individuals' affiliations may not be predictive of their beliefs and values in the care of their infant, and the health care team should regard each patient and family as *unique* and attend carefully to their specific views and values.

When attentiveness to the views and values of families is difficult because of language barriers, professional interpreters should be used. Use of an interpreter is advisable for three reasons: (1) it ensures that parents' views are available to the health care team, (2) it removes the burden on family members or friends for the transfer of information, and (3) it limits the potential for miscommunication. In certain situations, a *cultural interpreter* not only can facilitate language comprehension but can also provide useful information about cultural norms and traditions that are unfamiliar to the health care team. Access to high-quality

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interpretation services is an essential component of ethically and culturally sensitive care that also satisfies a regulatory requirement and decreases medicolegal risk.

Religion and the more general concept of *spirituality* as a major determinant of culture, tradition, and family values often needs to be addressed with parents, particularly when end-of-life decision making is undertaken. A qualitative questionnaire study completed by parents after their child's death revealed the emergence of four explicitly spiritual/religious themes: prayer, faith, access to and care from clergy, and belief in the transcendent quality of the parent-child relationship that endures beyond death.[121] Other significant themes with a religious/spiritual dynamic include finding meaning, hope, trust, and love. In another study focused on the delivery room consultation, mothers stated that religion, spirituality, and hope were the major factors that guided their decision making.[14] The implication of these studies is that health care teams need to consider whether they have or need to create an environment that is hospitable to, and supportive of, religious or spiritual practice; that clinical staff recognize parents' spiritual needs and provide access to hospital chaplains and community clergy; and, on a deeper level, appreciate parents' religious and spiritual perspectives in prenatal consultations and end-of-life discussions.

Consensual Decision Making

Consensual decision making implies that the parents and the physician/health care team are involved in the decision-making process—that they share relevant information with each other, they express their treatment preferences, and when a final decision is made, all parties are in agreement. The ideal consensual decision is one in which neither party feels individually responsible for that decision. Parents often feel *burdened* by what they perceive as their responsibility for the decision.[24] When the process of consensual decision making is handled well by the physician/health care team, the burden of the consequences of the decision is shared.

Team Consensus in Ethical Issues

How teams that normally function synergistically in terms of purely medical matters operate when dealing with ethical issues may be very challenging, not only because of the difficulty in defining roles and responsibilities in matters of ethical deliberation but also from a more fundamental aspect in that the two major professions, medicine and nursing, have differed over time in their preparation for this practice.[131] Medical professionals tend to view their role as one in which the patient's best interest is served by being given the medical care best supported by scientific evidence, with less attention to deeper questions such as the goals and limits of medicine and the moral core of the profession. The seemingly less objective goals, such as emotional support and values exploration, are relegated to other health professionals, such as nurses and social workers.[10] In interactions concerning the end of life of a neonate, physicians see the focus of their moral obligations on decision making with parents, whereas neonatal nurses see their moral obligations focused on the process and moment immediately surrounding death.[36] What is needed, according to Storch and Kenny,[131] is "shared moral work": Interprofessional practice implies that individual health care practitioners are aware of their own professional values and the need to work collaboratively, build understanding, and work toward resolution with other professionals, particularly when different perspectives threaten team function. The beneficial effects of multidisciplinary participation and perspectives have been well shown in teams developing guidelines for decision making, such as those at the limits of viability.[11,63]

Clinical Applications in Specific Moral Problems

Refusal of Treatment During Pregnancy

When a pregnant woman acts in such a way as potentially to create a serious risk of harm for her developing fetus, either by declining a recommended intervention or by actively engaging in a behavior that is harmful to the fetus, some authorities argue that state intervention is morally justified in an effort to promote fetal health and well-being. Other authorities maintain that such intervention not only violates the pregnant woman's autonomy, integrity, and privacy, but also undermines the principle of reproductive freedom.[40]

Authorities who advocate state intervention place some limits on the principle of reproductive freedom: Whatever rights a pregnant woman may have to direct the course of her pregnancy, they do not include an unlimited right to harm the fetus. In practice, which maternal behaviors lead to state intervention is generally determined by the legality rather than the inherent harmfulness of the intervention, leading, for example, to paradoxically harsher repercussions for occasional tetrahydrocannabinol use than for heavy alcohol consumption, even though the harms to the fetus from the former are not nearly as well described as those from the latter.

Arguments in favor of limiting the autonomy of the pregnant woman are based, at least in part, on the argument that, in choosing to continue her pregnancy, the woman has incurred an obligation to do what is necessary to ensure that the fetus is born healthy.[94] If she violates this obligation, the state has the authority, and perhaps even the obligation, to intervene to protect the fetus. However, this argument mischaracterizes the relationship between the pregnant woman and fetus as adversarial—the woman is cast in the role of aggressor with the fetus in the role of innocent victim, failing to account for numerous psychosocial and socioeconomic complexities that play a role in reproductive health decisions and outcomes, on substance use disorders and their treatment, and on priorities in law enforcement.

Significantly, professional bodies have commonly resolved the moral dilemma between the pregnant woman's

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autonomy and the fetus's well-being in favor of respecting the *principle of autonomy*. The American College of Obstetricians and Gynecologists has stipulated, "Every reasonable effort should be made to protect the fetus, but the pregnant woman's autonomy should be respected. … The use of courts to resolve these conflicts is almost never warranted."[6] Similarly, the Society of Obstetricians and Gynecologists of Canada Ethics Committee "opposes involuntary intervention in the lives of pregnant women. … The primary objective of physicians who work with pregnant women should be to promote women's health and well-being while respecting their autonomy."[129]

This emphasis on the autonomous rights of the pregnant woman is informed not only by a principled commitment to individual autonomy but also by another set of other claims. First, punitive state intervention rarely provides direct fetal benefit (the injury has already occurred). Second, a policy of state intervention may discourage women whose fetuses are most at risk from seeking appropriate care, for fear of being prosecuted.[90] Third, state interventions disproportionately impact poor and minority women and more generally enforce societal gender biases and inequities, ignoring paternal actions that are hazardous to the fetus.[86] Fourth, state intervention in pregnancy is an intrusion into the lives of pregnant women in excess of anything that would be tolerated to protect nonfetal lives.[40] The moral obligations of health professionals caring for pregnant women who decline recommended interventions or engage in medically ill-advised behaviors are to offer information, resources, and support, with clear and direct recommendations. Anticipatory guidance about possible postnatal repercussions of maternal behaviors, such as investigation by child protection agencies or the need for additional medical observation or treatment for the infant, is essential. Coercive behaviors by physicians in pursuit of perceived good for the fetus are not ethically permissible.

Prenatal Consultation at the Limits of Viability

With advances in medical technology, neonatology teams have developed the capacity to maintain physiologic signs of life at extremely low gestational ages, with survival possible after a gestation of 22 weeks. Use of a physiologic definition of viability, such as the point at which life can be maintained outside of the uterus, might suggest that every neonate born at such gestational ages should be given an opportunity for extrauterine life and be actively supported. Other definitions of viability do not focus exclusively on the likelihood of survival but rather include quality-of-life considerations in which there is an explicit value judgment regarding the degree of morbidity that is acceptable if such a life were to be maintained.

In clinical practice, there is no universally accepted definition of a *viable* fetus; however, guidelines from professional societies in several countries have defined gestational age ranges at which the benefit-to-burden ratio of aggressive obstetric or neonatal care becomes questionable.[85,114,126] Recent exploration of the outcomes of infants born at 22 weeks' gestation identify some survivors, and some neurologically intact survivors, resulting in a recent shift to move the lower border of marginal gestational viability from 23 to 22 weeks.[28,124] Similarly, examination of the outcomes of infants born at or after 25 weeks suggests that the majority of these infants survive, and the majority of NICU graduates survive without moderate or severe neurodevelopmental impairment. Although some intensive care units continue to allow parents to forego resuscitation until 26 weeks, resuscitation of infants born at or after 25 weeks should be considered to be the default plan in the absence of major comorbidities, such as extreme intrauterine growth restriction or major congenital anomalies.

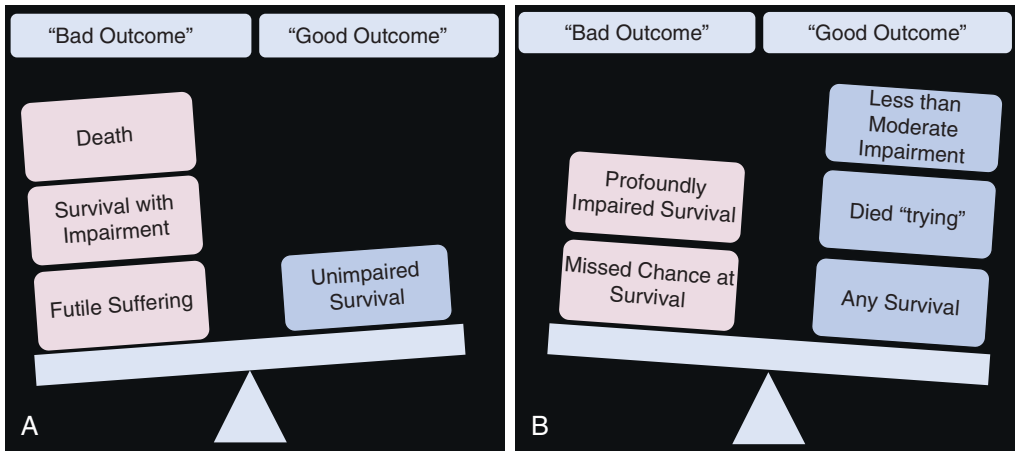
The challenge facing the life-defining "resuscitate or not" issue for parents and the neonatal team in the "gray zone" is compounded by the "moral strangeness" between the participants, the vulnerability and unfamiliar physical and emotional context for parents, constraints of time, and the great degree of medical uncertainty in prognosticating outcome for individual infants. Nevertheless, the urgent context exerts its own demands, and the opportunity for prenatal consultation must be optimized, because it is considered more conducive to an exploration of parental and physician/team views than if this conversation occurs in the delivery room or in the NICU in the first few hours of the infant's life. In all situations, descriptions of gestational viability in prenatal consultation should be sensitive to the parents' identification of personhood of the fetus. Reduction of a future child, whose sex might be known, whose name is picked out, and whose bedroom is already decorated, to the status of a "nonviable fetus" has the potential to be antagonizing to parents and present an obstacle to productive prenatal decision making.

A discussion with the pregnant patient about the limits of viability, even earlier in pregnancy, free of the threat of imminent delivery and with enough time for absorption of information and ability to participate objectively in such difficult decisions, has been proposed.[22,125] Generating an *advance directive* for managing early delivery would obviate much uncertainty for the medical team; this approach may gain momentum, despite the potential of producing anxiety in most pregnancies that would continue to term. A limitation to this approach is the question of whether a parent's response to *hypothetical* preterm delivery differs considerably from her response when faced with the *actual* circumstance.[78]

The prenatal consultation at the limits of gestational viability has two primary aims: (1) to provide information on which decisions can be based and (2) to support parental decision making about whether a trial of therapy will be undertaken in the delivery room. These activities should be viewed as inextricably linked rather than sequential components of the consultation encounter.

It is important to have the best data available[84]—data that are current, based on a number of pertinent factors rather than simply gestational age, and germane to the unit

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• **Fig. 3.1** Values-based shared decision making in the antenatal period. **A,** A neonatologist may perceive a high likelihood of nonsurvival paired with a high chance of moderate-to-severe impairment among survivors as dismal, with a very low chance of the "desired" outcome of intact survival. Due to the statistical probabilities, the burdens of infant suffering and societal cost may appear to outweigh benefit of therapy, and comfort care may logically be recommended. **B,** A parent, however, may view these outcomes very differently. If any survival, even with significant impairment, is seen as a desirable outcome, the probability of a "good" outcome rises. If having a surviving, very impaired, child is considered the most undesirable outcome, the risk of this is quite low, as many of the sickest infants die. Finally, if dying following intensive care is perceived as more favorable than possibly missing an opportunity to have an intact survivor, the risk of the unfavorable outcome falls to zero if an attempt at resuscitation is made. (From Kukora SK, Boss RD. Values-based shared decision-making in the antenatal period. *Semin Fetal Neonatal Med*. 2017;23:17-24.)

in which the patient is being cared for (or the geographic region, where appropriate). The data should include survival statistics *and* information about the long-term outcomes—including quantitative and qualitative measures when available (functional abilities, learning, behavior, impact on family)—with recognition that parents may differ in their previous experiences with disability and chronic disease and the value they place on these outcomes; this emphasizes the importance of thorough medical record review and history taking as part of the counseling endeavor. Kukora and Boss have offered a conceptual model parental characterization of a "good" or "bad" outcome (Fig. 3.1), which offers explanation for why some parents pursue interventions in the face of a poor prognosis. Even in the setting of a value-exploration approach, a standardized form (Fig. 3.2) may provide a reminder to the clinician of topics that should be covered.[46] Access to reasonably up-to-date outcome data has been facilitated by the development of population-based outcome tools. Tyson and coworkers, for example, developed an "outcomes estimator" that takes into account five factors (gestational age, estimated birth weight, singleton status, antenatal steroids, and gender) and provides the likelihood of death or adverse neurodevelopmental outcome. The estimator is available without charge on the Internet (http://www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/pages/epbo_case.aspx), and although not perfect, it does seem to "promote treatment decisions that are less arbitrary, more individualized, more transparent, and better justified than decisions based solely on gestational age thresholds."[136] Use of this predictive model, in particular, has been instrumental in highlighting the limitations of gestational age alone in decision making. However, although this instrument is widely used, not all neonatologists find that it and similar instruments are helpful to expectant parents.[104] This may be explained, at least in part, by the tendency for parents to "use hope and denial to interpret the limits imposed by statistics."[26] The counselor should be cognizant of important differences in the way seemingly objective information can be shared with expectant parents. An evolving body of science explores how best to support patients and parents in preference-sensitive decision making and have largely focused on use of decision support tools and enhanced information to improve this process.[47–49]

In one qualitative study of counseling at the margin of gestational viability, two models were used by neonatologists regarding resuscitation decisions at this threshold.[111] In a *neutral information model*, parents ultimately made their decision after comprehensive information, which they were to interpret independently, was given. In an *assent model*, the neonatologist's preferences were clearly expressed, and a decision was sought during the consultation. Prognostic statistics were used as information to justify and reflect on the suggested course of action.

Neither the neutral information model nor the assent model fully addressed parental expectations. In the neutral information model, parents expressed the need for a more individualized and humane relationship, which could not be addressed by a clinical focus on "objective/neutral facts." In the assent model, when decisions between parents and neonatologists were in accord, parents felt included, but when the neonatologist's recommendation did not fit with the parents' expectations, parents tended to feel abandoned and left on their own to confront the event. This study advocated that between the "liberal autonomous decision"

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Prenatal Consultation

University Hospitals Case Medical Center
Division of Neonatology
(216) 844-3387

Obstetrician:	Date	Time
Neonatologist (print):	❑ Attending ❑ Fellow	**LMP**
Reason for Consult:		GA

Mom:____ yo G ___ P _____ Bld type ____ Ab ___ PMH: _____

_____

SCREENS

	Pos	Neg	Unk
GBS	❑	❑	❑
VDRL	R ❑	NR ❑	❑
HepB SAg	❑	❑	❑
GC	❑	❑	❑
Chl	❑	❑	❑
HIV	❑	❑	❑
Rubella	NI-❑	I-❑	❑

PREGNANCY COMPLICATIONS / MEDICATIONS

- ❑ Preterm labor
- ❑ Maternal Fever - _____
- ❑ PROM – Time _____
- ❑ Preeclampsia – ❑ Magnesium Sulfate
- ❑ Diabetes – Class _____ ❑ Insulin
- ❑ Multiple Gestation - ❑ twins ❑ triplets
- ❑ Tobacco ❑ Alcohol ❑ Other Drugs
- ❑ Abruption
- ❑ IUGR
- ❑ Oligo / Polyhydramnios
- ❑ Abnormal Fetal HR
- ❑ Chromosome abnormality
- ❑ Malformations_____
- ❑ **Antibiotics** _____
- ❑ **Steroids**_____
- ❑ _____

Other Info: _____

_____

Discussed with _____

Overview

- ❑ Listened to parents' understanding of situation
- ❑ Discussed survival odds / Morbidity & mortality
- ❑ Discussed uncertainty of dates / Prognosis
- ❑ Explained NICU team presence / Role at delivery

Immediate morbidities/treatments

- ❑ Risk of RDS / Intubation / Surfactant
- ❑ Risk factors for infection / Need for antibiotics
- ❑ Access / Verbal consent obtained for UAC / UVC
- ❑ Blood conservation / Anemia / Possible transfusion

Long-term morbidities

- ❑ Risk of chronic lung disease
- ❑ Risk of intraventricular hemorrhage
- ❑ Risk of mental disability / Cerebral palsy
- ❑ Risk of blindness and deafness

Other

- ❑ Benefits of Breast Milk / Nutrition
- ❑ Location of NICU / Visiting policy
- ❑ Approximate length of stay
- ❑ Parental questions and concerns addressed

Discussion / Plan: _____

_____

_____

_____

❑ Parents told plan may need to be modified after the baby has been born and examined

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❑ I spent ____ minutes on this consult

_____
Signature

• **Fig. 3.2** Standardized form for the prenatal consultation.

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and a "paternalistic decision-making process,"[107] there is the need for an intermediate "shared relational space"—for a more caring relationship between the decision makers and more time to allow exploration of the facts, expectations, and values that are inherent in this interaction.

It is crucial to explore with prospective parents their preferences in relation to the data provided. Some parents may regard 20% as a fair chance of a "good enough" outcome, whereas others may regard 80% as not enough of a guarantee.[45] Elucidating parents' views raises the question of how much *moral weight* should be given to these views for delivery room decisions. Leuthner described different weightings ascribed to parental views in terms of models of best interests[82]: in a *medical expertise model*, outcome data are used in more directive counseling in pursuit of the physician's judgment of the best possible outcome, with less parental input. In the *negotiated model*, parental input is maximized and the decision attends to the moral values of the physician and the parents.

It is worth reflecting on the reasons for the lack of congruency in decisions between physicians and parents, where differences seem to arise from three sources:[111]

1. *Different starting points*. Physician's intent is to give the facts, whereas the family's reaction is to the premature interruption and fracture of the family narrative and a threat to their anticipated parenthood.
2. *How information is used*. Physicians attempt to be as objective as possible with facts and figures, whereas parents reformulate those chances.
3. *What constitutes the "right" decision*. For physicians, a good decision follows full parental comprehension of provided information. For parents, it is after they have had their own experience taken into account, and their decision is supported by a scientifically competent and humane medical team.

By focusing first on the *parents*, sharing two-way information, recognizing the importance of "relational space," and overcoming differences in starting points, physicians may achieve greater consensus and more acceptable decisions for all. The challenge in moving forward from a purely information-sharing interaction cannot be overemphasized; in a survey study, neonatologists viewed their primary role as providing factual information almost exclusively, with few considering their role as assisting in weighing risks and benefits and only 2% regarding their primary role as discussing potential differences in views between parents and the medical team.[10]

Numerous guidelines and frameworks for decision making at the limits of viability have been developed and are helpful in setting out parameters of practice.[13,63,114,126,145] They are generally not intended to be prescriptive, however, and decisions still need to be made specific for the individual patient, parent, physician, and team. Treatment considerations for extremely premature infants must be viewed in context against other areas of medicine in which difficult decisions must be made. There is evidence that, without clear justification, premature infants are considered "morally different" from older children and adults.[58,59,79] Despite repeated recommendations that "decisions should be made on a case-by-case basis,"[19,38,87] individualization requires that in each interaction, relevant information is methodically and thoroughly collected but applied consistently and fairly; all families are different, but decisions for that family should not depend on which doctor is on call. A model of "controlled improvisation" seeks to employ the benefits of scripted information gathering and sharing while recognizing the need for interpersonal connection and individualization.[52] In addition, the individuals undertaking these decisions need to make their reasoning behind their approach explicit. "Message framing," for example, whether the reported outcome is mortality or survival, and a priori "default options" have a major impact on decision making.[53]

Although populations of infants born with congenital anomalies and genetic disorders have not been as extensively studied, either in terms of short- and long-term outcomes or in terms of approaches to counseling and decision making, many of the principles that apply to antenatal consultation at the margin of gestational viability are also applicable to these other maternal and fetal complications. Particularly for rare diseases or constellations of congenital anomalies without a well-described natural history, recognizing and grappling with prognostic uncertainty remains a challenge for both providers and expectant parents. "Perinatal palliative care" has gained momentum as an approach to advance care planning for the delivery of infants born with life-limiting diseases.[92]

Withholding and Withdrawing Life-Sustaining Medical Treatment in the Neonatal Intensive Care Unit

Withholding life-sustaining medical treatment involves a choice not to provide a form of treatment that is not considered beneficial, whereas *withdrawal* involves a choice to remove treatment that has not achieved its beneficial intent.[140] From a moral perspective, there is no difference between these two acts: If it is morally right (or wrong) to withhold treatment deemed to be ineffective, it is equally right (or wrong) to withdraw this same treatment after it is started, should it later become clear that the treatment is ineffective. However, this concept is emotionally difficult to accept for many parents *and* for many health care providers. Supporting stakeholders struggling with the moral weight of withdrawing an ongoing therapy with reinforcement of the ethical equivalence of withdrawing and withholding is crucial to provision of end-of-life care, particularly as many neonates die with stable physiology after decisions to discontinue life-prolonging care rather than with unstable physiology after a code.[139] It is also important to avoid using phrases such as "withdraw support" or "withdraw care," as these may reinforce fears that families may have of being abandoned by their medical providers once a decision has been made to prioritize palliative goals, or that they

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themselves have made a decision to abandon or "give up on" their baby. *Withdrawal of life-sustaining medical treatment* and *redirection of care* are more appropriate terms for these activities.

Criteria for decisions to withhold or withdraw life-sustaining medical treatment are usually based on one of three general criteria:

1. *Inevitability of death*. When infants are very likely to die in the NICU, regardless of whether life-sustaining treatment is continued, life-sustaining treatments that serve only to delay the moment of death need not be continued. However, clinicians must recognize the difficulty in predicting outcomes with certainty, as studies suggest that in many circumstances neither clinical intuition nor objective scoring systems are reliably able to predict mortality in critically ill neonates.[99] In addition, while additional hours or days of survival might not ultimately change the outcome for the infant, this time might be highly valued by the family, either as a good unto itself or as an opportunity to gather friends and loved ones in anticipation of the death of the infant.
2. *Ineffective treatment*. Treatment that has not or is not expected to meet the intended goals, particularly when the treatment that imparts pain and suffering to the infant without appreciable benefit is considered ineffective.
3. *Poor quality of life*. As described previously in this chapter, despite the difficulty in determining the quality of a life with limited cognitive or relational capacity, mobility, or self-awareness, or a life of continued pain and suffering, poor quality of life is a valid consideration and ethically permissible reason to withdraw or withhold life-sustaining interventions.

Some authors cite *futility* of medical treatment as a criterion for withholding or withdrawing medical treatment. It is difficult to know what follows from such claims, however, because there is considerable debate and diversity of opinion as to the meaning of futility.[57] True futility, in which death is inevitable or exceedingly likely, should not be conflated with risk of a poor neurologic outcome. In addition to the debate about the meaning of the term *futility*, arguments have emerged about the authority of the physician to determine when an intervention is futile. Some authors contend that futility is a medical decision to be made by the physician alone, whereas others believe that the decision is value-laden and that parents should be involved in this determination. When futility is determined solely on the basis of medical or physiologic factors (a rare occurrence unless death is imminent), unilateral decision making by the physician based on sound medical knowledge and expertise may be appropriate. When subjective elements form part of the determination, however, the physician has no unique claim to moral expertise. In consideration of these more value-laden and subjective determinations of futility, the term "potentially inappropriate" has been put forth as more encompassing of the complexities of these situations.[72] The Society for Critical Care Medicine has published a seven-step process for an organizational approach to conflict resolution in consideration of potentially inappropriate treatments.[71] These guidelines, which are not specific to neonates, do take into account the value of neurologic recovery to the point of being able to "perceive the benefits of treatment" and emphasize the role of individualization, time-limited trials of interventions, and careful attention to pain and suffering. The American Academy of Pediatrics offers specific guidance on forgoing life-sustaining medical treatment for children, which recognizes the role of parents in decision making, communication, iterative examination of the child's condition and prognosis, and reliance on other supportive hospital services, such as ethics committees, pastoral care, palliative care, and others.[142]

Collaborative, Procedural Framework for End-of-Life Decision Making

Following a structured decision-making process helps to ensure that appropriate views and preferences are made explicit. Harmonious decision making is promoted, as all of the participants in the process may come to understand the reasons and values underlying a particular choice. The following procedural framework is suggested.

1. Create an optimal environment for discussion. It is important to create a quiet and uninterrupted environment in which ethical issues and values can be thoroughly explored, despite the demands on the time and energy of parents and staff. In the setting of a teaching hospital, the value of educational opportunities for students and trainees should be balanced with parent-centered goals of creating a comfortable and nonintimidating environment.
2. Establish that the presenting issue is an ethical problem, one in which moral values conflict or moral uncertainty exists. Ethical deliberation is often complicated by communication problems and psychological issues. These need to be disentangled from the ethical issues. Consultation with hospital ethics committees, or in some cases palliative care or clinical mediation services, can be helpful in supporting constructive, nonconfrontational dialogue and use of a common, respectful vocabulary. In most hospitals, ethics committees will offer nonbinding recommendations or delineate whether the proposed course of action is ethically permissible. Generally, clinical ethics consultants will not interpret medical facts or supplant the responsible physician as the arbiter of medical decisions.
3. Identify the rightful decision makers. Many individuals may legitimately be involved in the decision-making process, including, at least, the parents, the physician with primary responsibility, and other members of the health care team directly involved in the care of the patient. More generally, individuals who bear the greatest burden of care and conscience; individuals with special knowledge; and nurses and other health care professionals with the most continuous, committed, and trusting relationship with

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the patient or parents should be involved in decision making.[101] Thorough documentation of family meetings, medical decision making, and ethical rationale can be helpful to unify the team and minimize miscommunication, particularly when shift work and irregular schedules preclude participation of important medical provider stakeholders. Disagreements about the rightful surrogate decision makers for neonates are rare, as in most cases, parents assume this role by default. Rare scenarios, in which parents disagree with each other, are incapacitated and unable to participate in decision-making, or in which biological or legal parenthood is in dispute, may call for consultation with the hospital ethics committee, along with other ancillary hospital services.

4. Establish the relevant facts. "Good ethics begins with good facts." Medical facts include the diagnosis, the prognosis (and the estimated certainty of outcomes), past experience on the unit, relevant institutional policies, and relevant professional guidelines. Nonmedical facts include information about family relationships, language barriers, cultural and religious beliefs, and past experiences with the health care system. It is also important to explore parents' understanding of the medical facts, parents' expectations of the technology involved, the quality of communication between the parents themselves, and the degree of trust in physicians and the medical system. The willingness of the physician to discuss personal views and beliefs may enhance gathering of such information.
5. Explore the options. Explicit discussion of treatment options and their known potential short-term and long-term consequences should occur. The principle of informed consent requires parents to be presented with the risks, benefits, and alternatives of each option. How the information is presented can strongly influence parents, and clinicians must be careful to avoid coercion.[54]
6. Develop consensus. All decision makers should be in agreement with the plan of action proposed at the time, even though, occasionally, agreement may be a temporizing measure. Open, honest discussion of the goals and consequences of treatment allows parents, physicians, and other legitimate decision makers to consider carefully a range of professional and personal beliefs, values, and preferences, and to explore reasoned arguments for and against various options meaningfully. This process holds the promise of harmonious, consensual decision making. Although care must be taken to ensure that parents do not feel abandoned or overburdened by these high-stakes decisions, a decision to withdraw or withhold life-sustaining treatment unilaterally against parental wishes should occur only after all avenues of reconciliation, including transfer of care to another institution for a second opinion, have been exhausted.
7. Implement the decision. When a consensual decision has been reached, additional issues may need to be addressed with parents to ensure effective implementation. When the decision is made to withhold or withdraw life-sustaining treatment, there should be an open discussion about the manner of death, the option for parents to be present, the performance of religious rituals, the anticipated grieving process, and the supports available for bereaved parents.[147] Clinicians always have a duty to care for their patients, even when the goals have shifted from aggressive measures to comfort and palliation.

Specific Issues in End-of-Life Care

Brain Death, Donation After Cardiac Death, and Organ Donation

Brain Death

Brain death is well-defined for older age groups and has been accepted in most jurisdictions for decades as the threshold criterion for the removal of organs from heart-beating donors (without violating the dead donor rule). Guidelines for determining brain death in children were first published in 1987. Numerous clinical issues initially limited the usefulness of the concept in this patient population, including the difficulty of establishing the exact cause of the coma, the clinical assessment of brain death (particularly the determination and reliability of the absence of brainstem reflexes), and the uncertainty regarding the validity of adjunctive laboratory tests. Revised guidelines were published in 2011 and reaffirmed in 2015. These guidelines retain the definition of brain death as "irreversible cessation of all functions of the entire brain, including the brainstem."[105] The updated guidelines contain detailed algorithms, tables, and examination checklists to aid the clinician. Determination of brain death in a term neonate generally requires two examinations performed at least 24 hours apart. Because of insufficient data, there are no criteria to diagnose brain death in premature infants.

While brain death has been well accepted, it is not without controversy. As noted in a *New England Journal of Medicine* editorial from 2001, "one subject [that] can be said to be at once well settled and persistently unresolved…[is]…how to determine that death has occurred."[20] This was demonstrated in a recent highly publicized pediatric case. Thirteen-year-old Jahi McMath was declared brain dead following a postoperative hemorrhage after a tonsillectomy on December 9, 2013. The parents are "Christians with firm and sincerely held religious beliefs that as long as a person's heart is beating, that person is alive."[30] While a death certificate was issued for Jahi, a judge granted the McMath family's request to transfer Jahi to a Catholic hospital in New Jersey where a tracheostomy was performed. Nearly five years later, on June 22, 2018, Jahi was declared dead by cardiac criteria following complications of an intestinal surgery.[33a,93]

Donation After Cardiac Death

The traditional definition of death occurs when an individual has sustained "irreversible cessation of circulatory and

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respiratory function."[105] This is generally known as cardiac death, and often under these circumstances the warm ischemia time renders many organs unsuitable for transplant. In an effort to improve the ability to obtain viable organs from non-heart-beating donors, there have been recent efforts to better control the circumstances of withdrawal of life support, thereby allowing "donation after cardiac death" (DCD). The DCD protocols are considerably different from traditional end-of-life situations. The patients are brought to the operating room before withdrawal of life support, and once there has been circulatory arrest for a period of time; organ recovery efforts are immediately begun.

Although the goal of DCD is laudable and there is a major shortage of organs for the neonatal and pediatric population, there are a number of ethical concerns that have yet to be satisfactorily addressed. First, there is no consensus on the length of time between the onset of circulatory arrest and pronunciation of death. Indeed, there is considerable variability, from less than 2 minutes to more than 5 minutes.[7] Second, there must be clear management of the potential conflict of interest between the donor's interests and the preparations that must be made before death that are meant to benefit the recipient rather than the donor. This can be accomplished with a clear separation of roles of the care team and the transplant team.[4]

Finally, there must be a unified approach that continues to focus on humane and compassionate care of the patient and family. Many NICUs have well-established bereavement and end-of-life care protocols that encourage families to gather, participate in religious and cultural traditions, and spend hours to days with their baby after death has occurred. Donation after cardiac death policies may disrupt the flow of this care and families need to be informed about the changes. It is also essential that DCD protocols provide families "a clear understanding of the DCD donation process and a realistic understanding of all possible outcomes of donation, including successful transplant or an inability to recover or transplant for medical reasons."[148]

Use of Analgesic Agents at the Time of Withdrawing Life-Sustaining Medical Treatment

Both physicians and nurses have an ethical obligation to relieve pain and suffering, and this applies to infants at the end of life.[102] Partridge and Wall showed that in most cases of withholding or withdrawing life support from critically ill infants, neonatologists provided opioid analgesia to these infants, despite the potential respiratory depression of these agents, the so-called double effect.[109] The *intent* of the action—to alleviate pain and promote comfort—distinguishes the use of analgesics from the use of other agents, such as paralyzing agents, whose intent is to *ensure* death. The introduction of neuromuscular blocking agents at the time of withdrawal of life-sustaining medical treatment is considered ethically inappropriate, as is any form of active euthanasia.[134]

Although the expressed intention of alleviating suffering and discomfort is usually cited as justification for the "double effect" of analgesics and sedatives, the distinction from hastening death is sometimes difficult. To some authors, such as April and Parker,[8] the ban on active euthanasia (i.e., the use of drugs with the specific intent to end life) exists largely because professional guidelines in most jurisdictions call for the distinction and as such is a reflection of current consensus. They contend that relief of symptoms and concern for a newborn's suffering should be the primary goal, and the ban on physicians' role in active euthanasia is in their view not a moral argument but an appeal to public opinion and the moral primacy of the status quo.

This issue has been stirred by the Groningen protocol in the Netherlands where, in rare cases, in a newborn with an extremely poor prognosis and intractable suffering, and after all measures to alleviate the suffering have been unsuccessful, the deliberate ending of life may be considered legal.[62,138] Many, but not all, authorities consider such active neonatal euthanasia to be unsupportable and believe that the Groningen protocol should be abandoned.[70,132] Most authorities believe, similar to Costeloe,[27] that despite the conceptual difficulty in defining the difference between drugs used to alleviate pain and drugs given with the intention of ending life, in practice, "experienced neonatologists and neonatal nurses feel comfortable with this distinction." They can discuss it openly with families and help them understand the acceptability of infusing opiates at a dose that controls pain and distress but the unacceptability of increasing the dose further with the primary intention of hastening death.[27]

Palliative Care in the Neonatal Intensive Care Unit

Until recently, withdrawal or withholding of life-sustaining treatment in the NICU tended to be considered only when life-prolonging treatments were determined to be ineffectual and burdensome and death seemed imminent. Many factors may account for the slow adoption of palliative care in the NICU, such as the uncertainty in determining an infant's terminal prognosis, the difficulty in moving away from an interventionist approach when therapeutic options still seem possible, the divergent caregiver perceptions of the "right" action, a degree of moral and legal ambiguity in pursuing such a course, the fear of a "lingering death,"[95] a tendency for the compartmentalization of medical care into specialist teams with differing agendas, and a lack of formal training and experience in this aspect of care.

The dilemma of continuing the intensive care of a critically ill newborn when it is likely to result in a prolonged dying process or survival with profoundly limited capabilities and long-term suffering for the infant and his or her family has highlighted the need for a change in this approach. This has led to the incorporation of palliative care practices into the NICU environment, where a cure-oriented approach is replaced by an entire spectrum of

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management to prevent and relieve suffering and improve the transition to dying. This approach has been supported in three general clinical situations: (1) congenital anomalies incompatible with survival, (2) newborns born at the limits of gestational viability, and (3) infants who have overwhelming illness not responding to life-sustaining intervention.[103] This approach is also being increasingly considered when a diagnosis is made prenatally in conditions of certain lethality. Palliative care principles can be used to guide supportive conversations during the pregnancy and enable the preparation for a perinatal death in facilities supportive of such an approach.[92] Greater adoption of palliative care at the time of birth for antenatally diagnosed lethal anomalies has had an impact on decisions of pregnant women regarding termination during the pregnancy.[17]

Palliative care involves a team approach to the prevention and relief of physical, psychological, social, and spiritual suffering for the dying infant and the family.[23] Protocols aim to ensure continuity of care; symptom management and comfort care for the infant; family-centered decision making; practical, emotional, and spiritual support for the parents; and organizational, emotional, and spiritual support for the intensive care clinicians.[25] The ultimate goal is personalized decision making that empowers the parents in developing a care plan, which can also incorporate input from appropriate hospital and community resources, and occasionally the district coroner, in situations when there is the strong likelihood of the infant dying at home.[34a]

Within the spectrum of palliative care, after other, more obviously invasive forms of life-sustaining medical treatment have been withheld or withdrawn, the *withdrawal of artificial hydration and nutrition* may become a focus of consideration. Justification for this practice (after clearly showing the inability of an infant to tolerate oral feeds safely) revolves around the question of whether providing hydration and nutrition via other routes is a medical treatment or an obligatory part of basic humane care. All forms of maintaining artificial hydration and nutrition (the passage of nasogastric tubes, the insertion of intravenous needles, or more invasive interventions such as the surgical placement of a gastrostomy tube) are invasive to some extent and carry medical risks of dislodgment, migration, error, infiltration, and infection.[60] There has been general agreement, at least over the past two decades, that artificial nutrition and hydration is a *medical treatment*, on par with mechanical ventilation and other life-sustaining technologies,[60,135] and that it should not be held to a higher standard than other forms of life-sustaining treatment.[21]

In terms of the best interests standard of judgment in which the benefits and burdens of withdrawing or withholding hydration and nutrition are considered, studies in adult patients have shown that death is caused by dehydration, not starvation, and that dehydration leads to a decrease in nausea, vomiting, diarrhea, and urine output, with little, if any, discomfort, perhaps because of the release of endogenous opioids with fasting and ketosis.[149] In addition, patients experience little, if any, hunger or thirst if appropriate mouth care is provided.[34] One qualitative study that explored parents' experiences found that all of the parents were satisfied with their decisions to withdraw artificial nutrition and hydration and perceived their children's deaths as peaceful and comfortable.[118] Withdrawal of artificial hydration and nutrition in newborns is considered an ethically legitimate option by organizations such as the American Academy of Pediatrics when it is clear that cure is no longer possible and that an interventionist approach does not serve the child's (or family's) best interests.[5,83]

Despite the acceptance by many authors of withdrawal of hydration and nutrition as a moral way of responding to severe terminal suffering,[117] the literature has highlighted difficulties, particularly for nurses with "ethical proximity" to the patient, when this has been implemented.[113] These types of issues require significant attention if this practice is to become more clinically accepted. When withdrawal of medically provided fluids and nutrition occurs in the hospital setting, it is advisable to have a plan in place to support care providers who find this practice to be morally unacceptable, in some case by use of institutional conscience-based refusal policies.

Conflict Resolution When Consensus Cannot Be Reached

In most instances, participants in a decision-making process can arrive at a morally sound decision regarding the best course of action in a particular situation. Attempts at consensual decision making are sometimes unsuccessful, however, and may result in conflict and intractability. Occasionally, this conflict is between parents who disagree with each other regarding what is in the best interests of their newborn. More frequently, the conflict is between the parents of a newborn and the health care providers who have different perceptions of the child's best interests.[119]

The following guidelines are proposed to promote continuing negotiation and resolution of conflict in the NICU:

1. *Allow time for further clinical observation*. In the specific case of parental objections to forgoing treatment that the physician believes is not beneficial, it may be unrealistic to expect agreement from the parents the first time this option is raised. Prudence suggests moving as fast as the slowest member of the decision-making group, provided that the infant is not compromised further.
2. *Ensure full parental comprehension of the medical information*. Early expressions of treatment preference by parents, such as "do everything possible," need to be examined carefully. There is a tendency for busy medical teams to reduce parental expressions into simple one-line statements and not to explore their meaning. Such statements may be an expression of parental love or an expression of frustration with the medical team and not really an informed choice about what is in the best interests of the newborn. In addition, in view of parents' potential denial of the severity of their infant's condition, it is

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important to check parents' understanding repeatedly. If it seems that inconsistent information has been provided by different individuals or teams, it may be advisable to convene a formal interdisciplinary case conference to explicate these differing viewpoints.

3. *Continue to discuss, explore, and challenge the underlying reasons for the differences in choice*. It is important for health care providers to try to understand the parents' views, beliefs, and preferences. Physicians must recognize that the parents' beliefs and values are informed by ethnic and cultural traditions, customs, and institutions, and that these influences may be significantly divergent from their own.
4. *Continue to negotiate toward consensus*. Parents may have great difficulty in making an unassisted decision. The burden and potential guilt of decision making experienced by parents is often immense and may be underappreciated by the medical team. The consensual nature of a joint decision-making process and the shared burden of the decision must be reinforced. In addition, there may be medically imposed obstacles to achieving consensus, such as frequent changes in the responsible physician from one neonatologist to the next, the failure of a physician to establish a therapeutic alliance with the parents, the persistence of communication barriers between the physician and the parents, or the development of a "contest of wills" between the physician and parents as to who will sway the other. All these factors need to be overcome when negotiating with parents toward consensus.
5. *Broaden the parents' moral community*. Identifying the locus of decision-making authority within each family's moral community may involve the inclusion of additional family members, grandparents, significant others, and religious or spiritual advisors in meetings with parents and the physician/team or in less structured communication opportunities.
6. *Share the attending physician's moral load by actively seeking opinions from colleagues*. Although the attending physician responsible for the infant bears the final responsibility for the approach taken with the parents, for personal and legal reasons, it is often helpful to obtain a second opinion from a colleague.
7. *Involve a bioethicist or ethics consultation team, as appropriate*. It may be beneficial to involve an institutional ethics committee with experience in case consultation and review, a clinical ethics consultation team, or a clinical ethicist, depending on available resources. Many hospital ethics committees are multidisciplinary in nature and include experts in medicine, nursing, philosophy, law, religion, and social services. The function of these committees varies widely. In some institutions, the ethics committee as a whole reviews cases; more commonly, a smaller subcommittee, an infant care review team, or an individual ethics consultant undertakes this responsibility. Ethics consultants can be very helpful in working to clarify values and build consensus (i.e., a process to ensure that facts are confirmed, relevant parties are involved, and decision makers are empowered, but not to be the decision-making group per se). In a multidisciplinary ethics committee, team members may disagree among themselves, some members may dominate others, the committee or consultation team may not be qualified to deal with the subject matter, or the team may be overly concerned with the institutional impact of a decision rather than with the specifics of the case. Experience suggests that consultation with individual bioethicists and smaller ethics consultation teams may be of greater benefit to decision makers than the practice of "ethics by committee."
8. *Consider transferring responsibility of care for the infant to another accepting service or institution*. In some situations, the therapeutic alliance between a particular physician and an infant's parents can be fractured beyond repair, and transfer to another unit or another hospital becomes a reasonable option. Although this can be procedurally difficult and require an adjustment for the parents as well as the infant, realities of NICU staffing schemes "firing" of specific neonatologists (or other care providers) is difficult to carry out and is not generally advisable, as it is potentially harmful to the functioning of the medical team. However, when differences of opinion remain and the degree of physician moral compromise is significant, it may be advisable to involve another staff member with whom the parents have formed a therapeutic alliance to help mediate the conflict.

Despite these efforts, the moral problem may not be amenable to consensual resolution. Rational people of good will may hold views that are irreconcilable. Individuals involved in a failed attempt at deriving consensus may experience what Webster and Baylis[141] term *moral residue*—"that which each of us carries with us from those times in our lives when in the face of moral distress we have seriously compromised ourselves or allowed ourselves to be compromised."

Until consensus can be achieved, withdrawal of life-sustaining medical treatment should generally not be undertaken. Rarely, physicians seek authority to make *unilateral decisions* via institutional or legal redress. When ethical conflict seems intractable, an institutional decision may be made to seek *legal recourse*. This course of action, although sometimes necessary, is generally unsatisfactory: It increases the anguish for patients and families, it destroys the parent-physician relationship, it creates (or increases) conflict between members of the health care team, and it invariably results in a significant drain on staff time and morale. It can also be extremely costly and time consuming for all parties involved. Ideally institutional policies developed by the hospital ethics committee and staff should be in place to minimize the need for judicial intervention.

Ethics of Research in the Neonatal Intensive Care Unit

Clinical research on sick newborn infants is required to advance clinical care; improvements in the practice of clinical

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neonatology would not occur without such research. Research in children, let alone newborn infants, has historically been difficult to justify. Until more recently, a very protectionist view prevailed, such that studies in children were justified only if they were unsuitable in adults. This perspective has changed, reflecting the move from the dominance of beneficence or protectionism toward vulnerable groups, such as infants, to a stance based more on the principle of justice as the important consideration whereby individuals who are the subject of a treatment should have an equal opportunity to share the benefits of human research. This move is also a reflection of the fact that newborns have been harmed by the adaptation of results of treatment in other groups being applied to them without adequate research.

Despite the imperative for research, there are many challenges to neonatal research.[77] It is difficult to obtain "authentic," morally valid, informed consent from parents, because this requires surrogate decision making by anxious and stressed decision makers, often following an unanticipated, acute emergency. In addition, parents are often young, healthy members of society with little prior medical exposure and familiarity with the concept of medical research. Language and cultural and religious diversity add further complexity, and the act of soliciting consent itself often further exacerbates parental stress. Parents or guardians feel beholden to the caregivers of their vulnerable infants, and in cases in which the relationship between caregiver and researcher is unclear, there is the potential for "therapeutic misconception" (i.e., attributing therapeutic intent to research).

It may also be disturbing for parents to learn that there is much uncertainty about neonatal practice, such that their confidence in NICU caregivers may be diminished. Before discussing informed consent in neonatal research, other more general issues facing the ethical conduct of research need to be ensured, including the scientific value and validity of the study proposal, the existence of clinical equipoise in randomized trials, the distinction between therapeutic and nontherapeutic research (where the study would not lead to direct benefit for that infant), the existence of any potential conflicts of interest or financial incentives, and the overall risk/benefit analysis of the research proposal.

Informed consent is enshrined as a foundational cornerstone of the ethical practice of protecting human subjects from research risk.[69] The four domains within informed consent are (1) disclosure of information, (2) understanding, (3) competence or capacity, and (4) voluntariness or freedom to choose. Decisions that adults make on their own are morally robust, but decisions made for others cannot have the same degree of authenticity and are necessarily less valid in children.[69] Despite these challenges, it is widely accepted that neonatal research investigators have the obligation to obtain truly informed parental consent. Golec and colleagues described various models of consent in neonatal research[44]; this includes the standard model in which parents are solicited when their infant becomes eligible for a study, given written and verbal information, encouraged to ask questions, and required to sign a consent form. Other means of obtaining consent have included a steplike process of consent[3]; advanced consent, in which parents are approached in anticipation that their infant may meet inclusion criteria at a later date; emergency consent; and randomization without consent, in which randomization occurs before potential participants are approached, and only participants allocated to experimental therapies are informed of the trial and invited to give or withhold consent (Zelen randomization).[128] The individuals allocated to continue with standard therapies are not informed that they are trial participants at that stage.

Significant controversy involving consent and neonatal research issues surrounded the National Institute of Health–funded Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). The study was designed to determine the appropriate range of oxygen saturation in extremely premature infants by using two target saturation ranges, one low and one high. Consumer advocacy group Public Citizen accused the investigators of deceiving parents with "egregious" deficiencies in the informed consent process.[39] While the consent documents varied by institution, they were approved by 23 institutional review boards, and while there were certainly ethicists criticizing the study, most leading pediatric ethicists vigorously defended the ethics of the study.[88,144] Ultimately, the most positive outcome of the controversy has been a renewed focus to optimize the consent process in neonatal research, including "deliberative democratic discussions with a broad array of societal representatives (parents, clinicians, researchers, and ethicists)."[67]

The optimal model for consent for neonatal research is one that protects and promotes parental authority, is sensitive to the vulnerability and stress of the parents, and is beneficent to the infants. Golec and colleagues[44] suggested that a "morally optimizing approach to research recruitment" is one in which:

1. Parents are approached one study at a time.
2. Studies have relevance to the current clinical status of the neonate.
3. Researchers minimize information overload.
4. Researchers promote respect for parental autonomy.
5. Researchers inform parents about research in a continuing process, not as an event.
6. Adequate time is allowed to make decisions.
7. There are limits on subsequent solicitation approaches.

No model of soliciting parental permission is perfect, and the concept of informed consent cannot be the sole safeguard protecting the welfare of the neonate in research studies. The integrity of the researcher, the role of the institutional review board, and safety and monitoring by all individuals involved help to ensure the safety and protection of neonates. Another important resource to ensure ethical conduct of neonatal research is the role of the NICU nurse. Not only are nurses in a strategic position to promote parental understanding and improve the likelihood that the conditions of informed consent are met, but nurses also can

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• BOX 3.3 Ethical Responsibilities of Neonatal Physicians

- To neonatal patients—"right and good" action in their best interests
- To parents—constructive, respectful relationship
- To NICU team—leadership, direction with open, questioning culture
- To trainees—educational experience and model of professionalism
- To institution—in accord with mission, maintenance of data, review of practice
- To society—trust in profession, technical competence, and moral discretion in resource use
- To self—moral conscience

NICU, Neonatal intensive care unit.

help set priorities in neonatal research by playing an active role in the formulation of research policy and being "at the table" where priorities are set.[42]

Ethical Responsibilities of Neonatal Physicians

How neonatal medicine is practiced will certainly change, but the fundamental ethical obligations of neonatal physicians and health care practitioners will remain unchanged (Box 3.3). The physician's responsibility to the competent pregnant patient is defined and well established—to respect the patient's wishes regarding treatment even when this may be contrary to fetal best interests. So too, the physician's responsibility to the neonatal patient is well defined and established—right and good action within the best interests standard of judgment. In the broadest terms, these responsibilities are best discharged in the context of a constructive and mutually respectful parent-physician relationship that recognizes that patient and family values and beliefs are integral to the decision-making process. Physicians' responsibilities include the necessity of challenging parental views that they consider contrary to the patient's best interests.

In the context of team medicine, the attending physician is responsible for developing and maintaining positive relationships with all members of the health care team to promote better, open discussion of moral problems and to work toward consensus among the individuals directly involved in the patient's care. The physician also has an obligation to foster the ethical experience and education of the interdisciplinary team and that of junior staff and trainees. The perinatal high-risk unit or NICU team should be more than a group of physicians, nurses, and many other professionals working in an isolated area of the hospital trying to master new technology and break new ground. Ideally it should be an open, analytic, self-critical, and responsive group providing ethically responsible care to pregnant women, newborn infants, and their families.

By setting a standard of ethical responsibility for the care of newborns and families, physicians working in neonatal care send a message to society that promotes public confidence and trust in their professional practice and responsible use of expensive resources. Finally, all health care practitioners in neonatal care need to consider their own moral conscience and agency. Ethical deliberation is essentially a reflective task that requires participants to be explicit about what they believe and why, as well as what they value and on what grounds.

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Key Points

- Ethical issues in the NICU occur as physicians attempt to determine what is right and good for the patient, taking into consideration the values parents place on different outcomes.
- The standard of best interests of the newborn acts as a threshold for judgment, yet the subjective nature of this assessment and the fact that the assessment is being done by surrogate decision makers must always be recognized.
- Prenatal consultation at the limits of viability should provide parents with data on which decisions can be based and support parental decision making.

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4

Legal Issues in Neonatal-Perinatal Medicine

JONATHAN M. FANAROFF AND ROBERT TURBOW

Clinicians, especially clinicians working in the intensive care unit environment, are accustomed to a modicum of predictability. Treatment plans are generally based on years of clinical experience coupled with robust dialogue with one's colleagues. How should physicians react to the $21 million "wrongful birth" verdict against a geneticist who missed the diagnosis of Smith-Lemli-Opitz syndrome? How does one prepare for the resuscitation of a 23-week-gestation infant knowing that some physicians have been sued for resuscitating such infants and others have been sued for failing to resuscitate them? Does the Born-Alive Infants Protection Act require that 22-week fetuses be given a trial of an endotracheal tube?

The medical profession tends to view the legal system with mistrust. The unfamiliar concepts and vocabulary coupled with the seemingly unpredictable nature of legal decision making can create an environment of confusion and apprehension. For various reasons, these concerns are particularly acute for neonatal-perinatal practitioners. Tremendous clinical and ethical uncertainty can surround the decision to resuscitate an extremely premature infant. Neonatologists are often asked to attend deliveries for premature infants at the limits of viability. Must the physician honor the parents' requests? What if the parents request that their extremely premature infant not be resuscitated? What are the roles and duties of the perinatologist, the neonatologist, and the hospital administration? These questions are not obscure or theoretical. A $60 million verdict by one jury, subsequently overturned, accentuates the importance of a clinician's familiarity with the laws that affect clinical practice. In these cases, the legal system can seem capricious and arbitrary. When the stakes are so high, and there is a lack of applicable case law, it is understandable that clinicians are left in a quandary.

During residency and fellowship training and after training is completed, clinicians interact with the legal system. This interaction may be in the form of a contract with a new employer, a lease for office space, or as a defendant in a medical malpractice suit. This chapter focuses on more recent legal developments in neonatal-perinatal medicine that can affect the daily professional lives of individuals who work in high-risk maternal units, delivery rooms, and neonatal intensive care units (NICUs). Several complex issues are addressed: What are the legal ramifications of a neonatologist disregarding a parent's request to forgo delivery room resuscitation? What are a physician's liabilities when providing phone supervision of an ambulance transfer of a critically ill patient? What are the elements of a medical malpractice case?

Practicing clinicians must understand their rights, duties, and liabilities as physicians. They must understand the legal relationship that they have with their employers, the hospital, referring physicians, consultants, and neonatal nurse practitioners (NNPs), and physician assistants (PAs) they supervise.

This chapter also assists the clinician in understanding basic terms and concepts of medical law. A certain baseline vocabulary is necessary to discuss the relevant issues adequately. Terms and definitions are introduced throughout the chapter. Additionally, certain landmark cases are discussed. This chapter provides legal background so that the clinician has a more complete understanding of the legal principles, cases, and statutes that affect the daily practice of neonatal-perinatal medicine.

Although the focus of this chapter is on the US legal system, the rate of medical malpractice litigation has been increasing internationally at a dramatic rate. Many European countries have seen double-digit (Great Britain >50%) and triple-digit (Germany and Italy >200%-500%) percentage increases in the number of cases presumed "malpractice or bad health care."[28] Clinicians across the globe must be aware of the legal environment particular to the country in which they practice.

Disclaimer

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Abstract

This chapter focuses on legal developments in neonatal-perinatal medicine that can affect the daily professional lives of individuals who work in high-risk maternal units, delivery rooms, and neonatal intensive care units (NICUs). Several complex issues are addressed: What are the legal ramifications of a neonatologist disregarding a parent's request to forgo delivery room resuscitation? What are a physician's liabilities when providing phone supervision of an ambulance transfer of a critically ill patient? What are the elements of a medical malpractice case?

Keywords

law
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educating clinicians. Nothing contained in this chapter should be viewed as substantive legal advice. This chapter does not create an attorney-client relationship between the authors and any readers.

Laws generally vary from state to state in the United States. Federal laws may represent a separate body of rules that can affect a given practitioner.

Legal cases often hinge on very specific facts. Courts and juries make determinations based on the facts of a given case. A slight variation in circumstances, or the same facts argued by a different lawyer or in front of a different jury, can result in a completely different legal outcome. A practitioner should never assume that his or her situation is identical to the parties in another situation. Seasoned practitioners recognize that not all 27-week-gestation infants with respiratory distress syndrome have identical courses. Likewise, each legal situation has its own nuances that can determine a distinct outcome. Courts expend considerable effort to distinguish the facts when comparing one case with another.

The authors neither advocate for nor reject the judicial decisions and legislative actions described in this chapter. Readers should become familiar with the current laws that affect practice in their states. If readers have specific questions, they should consult with a qualified attorney.

General Legal Principles

Legislative Law and Case Law

Individuals unfamiliar with the US legal system may have difficulty understanding the distinction between case law and statutes. Generally, a significant portion of US law is based on the common law. These laws have roots in English law from the last few hundred years. In many ways, the common law provides the foundation for the US perspective on contracts, property, torts, criminal law, evidence, and many other legal disciplines.

The common law was created by judges who were generally evaluating disputes between parties. More recently, well-known cases such as *Brown v Board of Education* or *Roe v Wade* are examples of judicial decisions that became US law. These were cases that involved defined parties. The US Supreme Court made a determination, and the law was established.

In addition, many laws are created by elected legislative bodies, such as the US Congress or a state legislature. Often court opinions state that it is not the role of the judiciary to redefine or change the definition of laws that were created by a legislative body; rather, the legislature is generally responsible for changing a law.

The case of *Vo v Superior Court* is illustrative.[83] This Arizona case involved a woman who was shot in the head during a drive-by shooting on the freeway. The woman and her 23-week fetus died as a result of the shooting. The prosecutor subsequently charged Nghia Hugh Vo with two counts of murder. The Arizona Court of Appeals considered the propriety and legality of charging Vo with two counts of murder. The court stated that when the legislature created the murder statutes, it did not intend to include a fetus in the definition of a person or human being. The court concluded that the unlawful killing of a fetus could not be murder. Then the court stated that if the legislature intended to include a fetus in the definition of a person, it was the responsibility of the legislature to change the homicide statute. Shortly after the *Vo* opinion, the Arizona legislature amended the manslaughter statute to include "knowingly or recklessly causing the death of an unborn child by any physical injury to the mother."[13]

The *Vo* case serves as an example of the dynamic balance between the two branches of government that create law. In this case, the judges stated that it was the responsibility of the legislature to change the definition of manslaughter. The legislature responded to this case by expanding the definition of manslaughter to include unlawful killing of a fetus. Although the *Vo* case has also been included in the acrimonious debate of fetal rights, it is presented here to elucidate the concept of legislative law as opposed to judicial law.

State Law and Federal Law

Another area of potential confusion is the differences between state laws and federal laws. Medicine is generally regulated at the state level, and consequently most clinicians find themselves in state court subjected to state laws. Significant restrictions exist that keep most cases out of federal court. A civil rights case, a dispute involving the Americans with Disabilities Act (ADA), or a malpractice case that occurred at a military hospital are three examples of cases that could be adjudicated in federal court. Unless a case meets narrow criteria to qualify for federal adjudication, most legal disputes involving perinatal or neonatal practitioners are tried in state court.

How do laws in one state affect clinical practice in another state? Practitioners may wonder how a Michigan court decision would affect a practitioner in Ohio or Nevada. Generally state court decisions are binding only in that state. If the Texas Supreme Court has ruled on an issue, the court's findings are viewed as state law in Texas, and the legislatures and courts of California, North Carolina, or Wyoming are not bound by the Texas court ruling. A state court's ruling could be persuasive in other states, but the conclusions of one state court are not generally viewed as binding on courts in other states.

This concept of one state's laws affecting another state also holds true for laws passed by state legislatures. If the California legislature passes a law concerning access to prenatal care, the law would have essentially no effect on citizens of Connecticut or Virginia. Issues such as the definition of "live birth" are treated differently by different state governments. Clinicians should be familiar with their applicable state laws before relying on case law or statutes cited in this chapter.

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General Structure of the Federal and State Court Systems

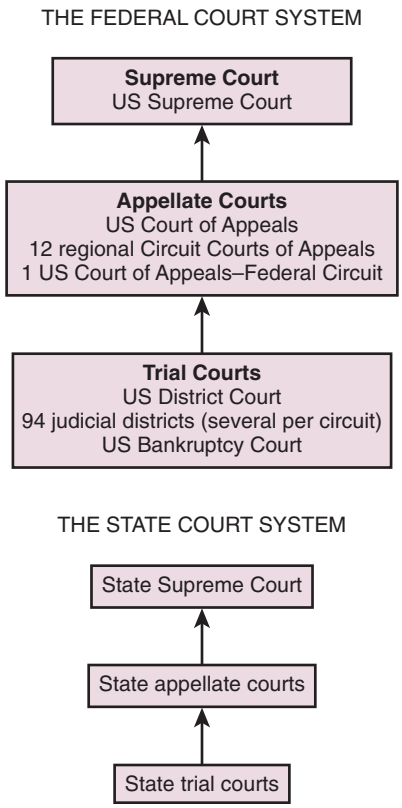
Several of the cases cited in this chapter mention the holdings of various state and federal appellate courts, and several US Supreme Court decisions are also discussed. How does a case get to an appellate court or to the US Supreme Court? Various rules determine which court hears a dispute and which appellate court has the jurisdiction to review the decisions of the lower courts. Most of the cases discussed in this chapter would be adjudicated in the state court system. The general hierarchies of the federal and state court systems are depicted in Fig. 4.1.

Supervision of Others

Theories of Liability for Attending Physicians

Attending neonatologists carry substantial responsibility. Generally, they bear ultimate medical responsibility for the neonates under their care. Practically speaking, it is impossible for one physician to provide all of the care for a sick newborn. Depending on the clinical setting, nurses, NNPs, PAs, respiratory therapists, social workers, residents, fellows, consultants, and many others all contribute greatly to patient care. The exact demarcation of responsibility and liability borne by attending physicians for these alternate providers is often difficult to determine.

In holding attending physicians liable for the acts of others, courts tend to rely on three different theories of liability. An early theory of attending liability was known as the "captain of the ship doctrine." Physicians, particularly surgeons, were assumed to be similar to naval captains and to have complete control over the operating room (the "ship") and all the medical personnel (the "crew") within. With this control came responsibility for all negligent actions performed by anyone under the surgeon's "command."[63] Most courts now recognize the increasing complexity of health care provision and have rejected the captain of the ship doctrine as "an antiquated doctrine that fails to reflect the emergence of hospitals as modern health care facilities."[49]



• **Fig. 4.1** Hierarchy of the federal and state court systems in the United States.

Respondeat superior is a more accepted doctrine of physician liability for negligence of others under his or her control. *Respondeat superior* literally means "let the master answer." Because an attending physician has a right of control over an NNP or resident, the negligence of that provider is imputed to the attending physician in certain circumstances. Under *respondeat superior*, the attending physician would be responsible if a resident negligently places umbilical lines or an endotracheal tube. The attending physician would not be liable, however, under *respondeat superior* if a bedside nurse was negligent in the observation or reporting of a significant intravenous infiltrate. Under the earlier "captain of the ship" doctrine, the attending physician may have been deemed to be responsible for the intravenous infiltrate.

The attending physician can also be held liable for providing "negligent supervision." For supervisees under his or her charge, the attending physician is responsible for providing adequate training and supervision. The attending physician must be readily available and promptly respond to requests for assistance. This responsibility was underscored in a 2004 obstetric malpractice case in which the attending anesthesiologist was not immediately available for an emergency cesarean section, and the fetus allegedly suffered as a result. The case was settled for $35 million.[14]

Finally, in many cases, an attending physician becomes liable for the actions of supervisees by the creation of a physician-patient relationship that flows from the patient through the supervisee to the attending physician. In a case in New York, a patient was seen by a nurse practitioner in an emergency department, and the nurse practitioner misdiagnosed the condition. The attending physician discussed the patient with the nurse practitioner and signed the chart but did not personally examine or speak with the patient. The court, interpreting New York's law regarding nurse practitioners, held that "the ultimate responsibility for diagnosis and treatment rests with the physician."[66]

Residents and Fellows

During their postgraduate training, residents and fellows gain increasing experience and clinical skills under the supervision of attending physicians. Under the doctrine of *respondeat superior*, the educational institution and the attending physician are generally responsible for the medical care provided by residents and fellows.

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Residents who have completed their first year of training are eligible to be licensed to practice medicine without supervision. Because of this fact and the expectation of appropriate supervision, most states treat residents as physicians rather than students and hold them to "the same standard of care as physicians who have completed their residency in the same field of medicine."[15] Nevertheless, because trainees are thought to be agents of the hospitals in which they work, often have limited financial resources from which to pay a judgment against them, and always have an attending physician assigned to the patients for which they are caring, the institution and the attending physician are almost always named in the lawsuit as well.

Neonatologists must be very careful about appropriately supervising residents and fellows. In some cases, inexperienced trainees are responsible for caring for some of the sicker patients in the NICU. From a legal standpoint, the supervising neonatologist must remain involved in the care of these patients and provide an appropriate level of oversight. The level of supervision would vary based on a variety of factors, including the condition of the patient, the likelihood of major changes in that condition, and the experience and skill of the resident providing the care. Failure to provide appropriate supervision can result in liability for negligent supervision.[45]

Physician Assistants

Many NICUs now employ physician assistants (PAs). A PA is a health care professional who may practice medicine only with physician supervision. A certified PA is a health care professional who has completed training and passed a national certification examination. The scope of practice of PAs is governed by state law and varies from state to state. In many states, PAs are authorized to prescribe medications. Physician assistants can contribute greatly to the care of neonates, and some centers that have found it difficult to recruit an adequate number of NNPs have found PAs to be an "untapped resource for the NICU."[67] It is important, however, for physicians to determine the scope of practice for PAs in their individual state for two reasons. First, there is increased potential malpractice liability for the supervising physician when PAs exceed their scope of practice. Second, physicians may risk loss of their licenses if they are "found to have condoned the unauthorized practice of medicine by a nurse or other health care professional for whose conduct [they are] responsible."[17]

Advanced Practice Neonatal Nurses

There has been a rapid increase in recent years in the number of advanced practice neonatal nurses (APNNs) in the United States. An APNN is a registered nurse who has completed a master's degree in advanced nursing practice and, in most cases, has passed a national certifying examination. Advanced practice nurses are regulated at the state level, and educational requirements can vary. Most states require a graduate degree, generally a master's, for authorization to practice at the advanced practice level, and 45 states require national certification.[56] Additionally, the National Association of Neonatal Nurses supports a "future goal" of having all APNNs be prepared through a Doctor of Nursing Practice.[57] APNNs have played an invaluable role in improving health care for neonates in various settings ranging from urban academic centers to small rural hospitals. Under certain circumstances, there can also be additional liability for the physician.

In neonatology, there are generally two recognized types of APNNs: clinical nurse specialist and neonatal nurse practitioners. The clinical nurse specialist is a registered nurse with a master's degree who has expertise in neonatal nursing. The NNP is a registered nurse with experience in neonatal nursing (many have completed a master's degree) and additional clinical training in the management of newborns. Neonatal nurse practitioners are allowed to assess, diagnose, and treat newborns independently or under the supervision of a physician.

The licensure and scope of practice of APNNs vary considerably from state to state. Each institution must have policies and procedures for granting privileges for APNNs. The American Academy of Pediatrics Policy Statement on Advanced Practice in Neonatal Nursing released in June 2003 recommends the following:

- A neonatologist should supervise an APNN in the NICU.
- The APNN should collaborate and consult with other health care professionals.
- The APNN should be certified by a nationally recognized organization and should maintain that certification.
- The APNN should participate in continuing education.
- The APNN should comply with hospital policy regarding credentialing and recredentialing.[10]

One critical issue concerning APNNs is the liability of the supervising physician. In some states, NNPs are licensed to practice independently and require no supervision under the law. If an NNP is hired by a hospital as an independent contractor with his or her own privileges, the physician does not employ the NNP. In these situations, when the NNP and physician are interacting in the management of an infant, the physician is acting the same as when consulting with any other provider, with similar liability.

In most instances, however, and in almost all NICU environments, APNNs are not hired as independent contractors but rather as employees of the physician or hospital. In these cases, the employer is vicariously liable for the acts of the employee. The NNP is often supervised by an attending neonatologist who bears ultimate responsibility for the patient, as discussed earlier.

Malpractice

Medical malpractice litigation can be contentious and acrimonious. It is a pervasive issue that appears with great regularity in the popular press. Many books have been dedicated to the subject of medical malpractice. In his 2011 State of the Union Address, President Obama voiced support for

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• BOX 4.1 Common Malpractice Suits in Neonatology

Delivery Room Management or Resuscitation

- Poor neurologic outcome
- Cerebral palsy: neonatologist named as codefendant with obstetrician-perinatologist
- Neonatal encephalopathy: plaintiff alleges some component of injury occurred postnatally

Line Complications

- Vascular accidents related to central venous lines
- Loss of fingers or toes associated with central lines
- Thrombus and complications from thrombus

Delay in Diagnosis or Treatment

- Poor blood gases, prolonged hypotension
- Delay in antibiotic administration
- Congenital hip dislocation
- Congenital heart disease

Transport Team

- Medications or care provided by transport team (e.g., excessive heparin given)

Failure to Monitor Adequately

- Blood glucose
- Blood oxygen: either hypoxia (brain damage) or hyperoxia (retinopathy of prematurity)
- Seizure

"medical malpractice reform to rein in frivolous lawsuits."[77] This section is largely limited to a discussion of malpractice in neonatal-perinatal medicine (Box 4.1).

Malpractice is part of a broader area of law known as *torts*. Tort law largely deals with the duties and responsibilities that individuals have toward one another. Torts are generally divided into two groups: intentional torts and unintentional torts. Defamation, invasion of privacy, civil battery, and professional malpractice are all torts, but malpractice is a type of unintentional tort.

Negligence means that an individual's behavior has deviated from a standard of "due care." Malpractice is considered a specific type of negligence. By some interpretations, malpractice is also considered a type of breach of contract with the patient, so the defendant is technically being accused of committing a tort and violating contract law.

Lawyers, accountants, physicians, and other professionals are held to a certain level of conduct. If one's professional conduct is substandard and a client, customer, or patient is harmed by this substandard conduct, a plaintiff may attempt to show that the practitioner has committed malpractice. To win a malpractice case, the plaintiff must show four critical elements: duty, breach, causation, and damages.

Duty

"The duty of care owed to an individual, for purposes of a claim of medical malpractice, is based primarily on the existence of the physician-patient relationship."[73] To proceed with a negligence case, the plaintiff must show that the defendant had a duty to the plaintiff. This has been described as a "threshold issue." Does the defendant owe a duty to the injured party? If there is no duty, no claim of negligence can be sustained.

If a neonatologist has privileges only at hospital A, and the physician is called and refuses to attend a high-risk delivery at hospital B, the physician likely would have no professional relationship with the pregnant woman or her infant at hospital B. The neonatologist cannot breach his or her duty if no duty to the defendant exists. This concept of duty is separate from the moral or ethical obligation to provide care. A physician cannot be liable to a patient if there is no legal duty. Likewise, if NNP Smith is on call for the evening, and NNP Jones has left town with his family for a scheduled vacation, it would be difficult for an injured plaintiff to show that NNP Jones had a duty to attend a high-risk delivery while he was out of town.

Does a physician caring for a pregnant woman have a duty to the newborn even after the infant is born and being cared for by another physician? In *Nold v Binyon*,[59] a woman tested positive for hepatitis B. Her newborn did not receive hepatitis B immunoglobulin or the hepatitis B vaccine, and the infant subsequently became a chronic carrier for hepatitis B. The trial court ruled, and the Kansas Supreme Court agreed, that the delivering physician had a duty to inform the woman of her hepatitis B status. The Supreme Court stated, "A physician who has a doctor-patient relationship with a pregnant woman who intends to carry her fetus to term and deliver a healthy baby also has a doctor-patient relationship with the fetus."

Supervising Others

As discussed earlier, neonatologists are often asked to supervise the care provided by others. This supervisory role generally establishes a physician-patient relationship with any patient who is cared for by the supervised NNP or PA. In these cases, the physician has a duty to the patient even if the supervised NNP is providing all of the bedside care.

Telephone Advice

Is "duty" established when one physician consults with another over the phone? Telephone advice and transport present an interesting legal challenge. On many transports, the responsible physician at the receiving facility is not physically present with the transport team. The receiving physician often begins to offer clinical advice, however, when first contact is initiated by the referring facility. Generally, this can be a situation of shared duty. The referring physician and the receiving physician may have a duty to the patient. The receiving physician may have no duty to the patient, however, if the receiving physician is acting more in the role of a consultant.

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In *Sterling v Johns Hopkins*,[73] a woman was admitted at approximately 32 to 33 weeks' gestation to a hospital, and she developed severe preeclampsia and suspected HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. The treating physician called the emergency transport service to arrange transport to Johns Hopkins, because the receiving hospital had a NICU that could potentially care for a premature infant. The receiving physician spoke with the referring physician on the telephone. The woman became unresponsive during the transport. She experienced an intracranial bleed and later died.

The husband sued the receiving hospital, alleging negligent advice given over the phone. The court determined that there was no physician-patient relationship between the receiving physician and the pregnant woman. Because the receiving physician was acting more in the role of a consultant and the referring physician was free to make his or her own management decisions, the court ruled that the receiving physician did not have a duty to the pregnant woman. "Where the treating physician exercises his or her own independent judgment in determining whether to accept or reject [a consultant's] advice, … the consultative physician should not be regarded as a joint provider of medical services with respect to the patient." In this case, the court determined that the treating physician maintained decision-making power and that the physician at the receiving facility was acting more as a consultant than co-managing the patient. The court determined that no duty existed between the receiving facility and the patient.

Telemedicine

With changes in technology, there has been a rapid increase in the use of telemedicine, which is defined by the American Telemedicine Association as "the remote delivery of health care services and clinical information using telecommunications technology. This includes a wide array of clinical services using internet, wireless, satellite, and telephone media."[12] A number of legal issues have arisen with respect to telemedicine, and the law has not been able to keep pace with the technology. Many of these issues have to do with licensure, credentialing, and reimbursement as well as liability. For example, a physician based in state A who cares for a patient via telemedicine located in state B may be found to be practicing without a license and subject to disciplinary action in state A as well as medically liable in state B. Some states have created special laws or offer limited telemedicine licenses. Other states have specific regulations about the care provided. Colorado, for example, requires that "Any health benefits provided through telemedicine shall meet the same standard of care as for in-person care."[23] Additionally, many malpractice insurance policies specifically exclude telemedicine coverage. There is little question that telemedicine has significant potential to improve quality and access to care for patients, especially in underserved areas. Given the legal risks, however, it is important to seek legal counsel and be aware of relevant laws and regulations.

Prenatal Consultation

Prenatal consultations might or might not give rise to a duty between the neonatologist and the pregnant woman and her child. Among the determining factors, courts seem to evaluate the formality of the consultation and the presence or absence of contact between the parties. In *Hill v Kokosky*,[37] an obstetrician informally consulted with a neonatologist. The plaintiff had been admitted to the hospital at 22 weeks' gestation with a diagnosis of incompetent cervix. The two physicians informally discussed the case over the telephone. The obstetrician discussed the case in the abstract, and the neonatologist tended to agree with the obstetrician's management. There was no referral or formal consultation. From the record, it seemed that the neonatologist did not review the chart, speak with the mother, or even know the mother's name. The infant was born 2 weeks later and developed severe cerebral palsy.

In her malpractice action against the neonatologist, the mother maintained that the neonatologist gave substandard advice concerning birthing options and that this substandard advice contributed to her infant's injuries. Given the facts, the court concluded that no physician-patient relationship existed between the neonatologist and the family. It is important to understand why the court ruled for the defendant in this case. Casual telephone advice was given to a colleague. The neonatologist did not know the name of the patient and never spoke with her. The court concluded that the neonatologist did not prescribe a course of treatment but rather gave recommendations that could be accepted or rejected by the obstetrician.

In contrast to this case, if a neonatologist is formally consulted and speaks with a family and makes recommendations concerning management, there may be a duty to the mother and her infant. Judicial decisions also seem to hinge on whether or not a consulting physician is recommending a specific course of therapy or merely making suggestions that the original physician either can follow or can ignore.

Generally, it is not difficult for a plaintiff to establish that a clinician had a duty to the patient. Usually, the physician has provided care to the patient, and the plaintiff easily establishes that the duty requirement has been met. Especially in the case of hospital-based physicians, such as neonatologists, the element of "duty" is generally established.

Breach

Standard of Care

What is the duty that is owed? The duty is to provide reasonable care under the circumstances. Although generalists are held to a standard of "same or similar community," specialists and subspecialists, such as neonatologists, NNPs, and perinatologists, are generally held to the higher national standard of care.[60] An expert witness from a different state can testify about the national standard of care for a neonatologist. In these cases, the neonatologist's care

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is not being compared with the care provided in a similar community; the care is evaluated in light of national standards.

In many malpractice suits involving obstetricians, perinatologists, and neonatologists, considerable emphasis is placed on this element. Often the defense vigorously maintains that "the doctor did nothing wrong." The defense often takes the position that there has been an unfortunate outcome, but the defendant practiced within the standard of care. If the defense can prove that the physician acted within the standard of care, the plaintiff cannot successfully maintain a malpractice action.

A typical case is a brachial plexus injury after birth. In *Knapp v Northeastern Ohio Obstetricians*,[46] a mother alleged that her infant's brachial plexus injury was the result of excessive traction applied by the obstetrician. The trial court found, and the appellate court affirmed, that the evidence did not support the mother's allegations. The court concluded that the obstetrician had not breached the standard of care.

Retinopathy of prematurity (ROP) is another common source of negligence cases involving newborns. In *Brownsville Pediatric Associates v Reyes*,[20] a pediatrician was found liable for substandard ventilator management. The expert witness testified that the child's resulting brain damage and ROP were related to hyperventilation and hyperoxia. The plaintiff was awarded $8 million, and the defendant's appeal was denied.

Another ROP case dealt with the responsibility of the neonatologist, the pediatricians, the pediatric ophthalmologist, and the parents when 29-week-gestation twins missed their follow-up appointments for ROP evaluation.[34] The twins became legally blind. In this case, the neonatologist apparently provided all necessary referrals and documentation, and she was not named in the resulting suit.

Role of the Expert Witness

In tort proceedings other than medical malpractice, a person with common knowledge generally knows and understands "due care." If someone is walking down the street with closed eyes and bumps into someone else and injures the other person, a lay juror does not need an expert witness. The lay juror understands that one should not walk down the street with closed eyes, because someone else could be injured as a result. In medical malpractice cases, however, the lay juror generally does not have a grasp of "reasonable care under the circumstances." This is one of the roles of the expert witness. To serve as an expert witness, an individual must have specific knowledge and training that qualifies him or her to serve in this capacity. The Rhode Island statute,[68] for example, states "only those persons who by knowledge, skill, experience, training, or education qualify as experts in the field of the alleged malpractice."

If a fetal monitoring strip shows severe, repetitive, late decelerations, should the obstetrician perform a cesarean section? It is the role of the expert witnesses to educate the jury so that the jurors have a grasp of what is (and is not) reasonable care under the circumstances. Both sides (plaintiff and defendant) usually hire their own expert witnesses. The plaintiff's expert generally maintains that the physician practiced outside of the standard of care. The defense expert maintains just the opposite. After the expert witnesses are examined and cross-examined, it is up to the jury (or arbitrators) to decide whether the clinician committed a breach in the standard of care.

Expert witness testimony is often required in neonatal-perinatal malpractice cases. Expert witnesses were used in the 2000 Pennsylvania case *Sonlin v Abington Memorial Hospital*.[71] In this case, a premature infant girl who was born at approximately 34 weeks' gestation had an umbilical line. The infant developed vascular compromise in her left leg, which resulted in a thrombus that required amputation of the extremity. The plaintiff maintained that the neonatologist did not recognize the thrombus and that he did not institute corrective action in a timely fashion.

Expert witnesses would have to explain to a jury why umbilical lines are placed, how long they are left in place, and the potential complications from indwelling arterial catheters. In this case, an expert would have to explain the effect of prematurity on lung development and the subsequent necessity for monitoring blood oxygen levels. Basically, the expert must explain the standard of care, the indications for the procedures, and the potential complications.

In the Louisiana case *Hubbard v State*,[39] a full-term newborn was admitted with meconium aspiration and hypoglycemia. A peripheral intravenous infusion of 10% dextrose in water was ordered. After a change was made in the intravenous fluid, it was noted that the infant's hand became red and swollen, and the infant became lethargic. His blood glucose was 450 mg/dL. Because of an error, the infant had received 50% dextrose in water instead of the 10% dextrose in water that was ordered. The infant sustained third-degree burns that left permanent disfigurement of the hand, and a computed tomography scan showed a "possible venous thrombosis of the transverse and sagittal sinus." By the time this case reached the Louisiana Appellate Court, the child was almost 8 years old. In the interim, the child had been found to have Russell-Silver syndrome, a condition known to be associated with developmental impairment. The expert witnesses were extensively questioned about whether the dehydration and possible venous thrombosis contributed to the child's observed mental delays.

These cases represent a potential breach in the standard of care. Mistakes were made, infants were harmed, and the families attempted to hold the caregivers responsible for the damages that occurred. In both of these cases, expert witnesses were needed to assist in delineating the standard of care for the legal decision makers.

Unbiased and truthful expert witnesses are an important component of the American tort system. An American Academy of Pediatrics policy statement describes professional

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expectations for expert witnesses, including "thorough, fair, objective, and impartial" testimony provided for reasonable compensation.[11] Additionally, the experts must base their opinions on "sound scientific principles."

Res Ipsa Loquitur

Res ipsa loquitur is a legal doctrine that means "the thing speaks for itself." Common medical examples of this doctrine include a retained surgical sponge, removal of the wrong kidney, or operation on the wrong patient. These three examples are factually simple. A juror's common knowledge would guide him or her to a reasonable conclusion. In practical terms, *res ipsa loquitur* generally means that the plaintiff does not need an expert to show that there was a deviation in the standard of care.

The doctrine means that certain things do not just happen. Historically, the *res ipsa loquitur* doctrine can be traced to an English case from 1863 in which a passerby was injured when a barrel fell from a window.[21] The doctrine was developed to explain that barrels do not fall out of windows unless someone has acted negligently.

A 2003 case from New York relied on the *res ipsa loquitur* doctrine. In *Rosales-Rosario v Brookdale,* a woman was hospitalized to give birth.[69] An epidural line was placed, and she was partially anesthetized. It was subsequently noted that she had sustained a burn to her leg. She had no idea how she sustained the injury. Her leg possibly was burned by an examination light, but because of her anesthetized state, she did not recall how the injury occurred. She relied on the doctrine of *res ipsa loquitur*. The trial court dismissed the case, but the appellate court reversed the lower court's decision. The appellate court stated the rule of *res ipsa loquitur*: "To rely on the doctrine of *res ipsa loquitur*, a plaintiff must submit sufficient proof that: (1) the injury is of a kind that does not occur in the absence of someone's negligence; (2) the injury is caused by an agency or instrumentality within the exclusive control of the defendants; and (3) the injury is not due to any voluntary action on the part of the injured plaintiff."[69]

In the *Rosales-Rosario* case, the court concluded that leg burns do not just occur, so the first element of *res ipsa loquitur* was satisfied. In addition, the physicians and hospital personnel were in exclusive control of all equipment in the delivery room, including the examination light. Finally, the patient did not engage in a voluntary act that resulted in her injuries.

Showing *res ipsa loquitur* means that the plaintiff has overcome the burden for breach. The plaintiff still has the burden of showing the other elements of the tort suit, but the deviation in standard of care has been proved if the court accepts the doctrine of *res ipsa loquitur*.

Causation

Of the four essential elements of a tort suit, causation is perhaps the most challenging to understand. Regardless of whether the dispute is malpractice or another civil complaint, causation is not always intuitive. In brief, the defendant's breach must be the cause of the plaintiff's injury; mere correlation is insufficient. The plaintiff must show a reasonable inference that the deviation in care resulted in the injury. Stated differently, assuming the plaintiff has suffered an injury, did the deviation in standard of care cause this injury? Expert testimony is often required to answer these questions. Did the obstetrician's decision to allow a vaginal birth in the face of severe decelerations result in the newborn's neurologic damage? Did the neonatologist's "delay" in the decision to perform a double-volume exchange transfusion result in kernicterus that would have otherwise been avoided?

In many malpractice cases, the issue of causation can be complex. Causation can be particularly perplexing, however, in the context of a neonatal-perinatal medical malpractice case. In the *Hubbard* case described earlier,[39] multiple expert witnesses disputed whether the severe dehydration contributed to the child's mental delay. What is the impact of the diagnosis of Russell-Silver syndrome? Was this the cause of the mental delay? The child had also had at least two documented falls during early development. Did the head injuries, which led to evaluation in an emergency department, cause the findings?

This case elucidates the particular challenge of causation. Board-certified neonatologists and pediatric neurologists could have well-substantiated, yet differing, opinions on the etiology of this child's mental deficits. How is a jury to rule on this complex issue? As in essentially all medical malpractice cases, expert witnesses must testify on the issue of causation. The concepts are usually too specialized for a nonexpert juror. Absent the testimony of an expert witness, a juror's common knowledge is often inadequate to decide the issue of causation.

Damages

The final element that a plaintiff must show is *damages*. For plaintiffs to recover any type of award, they must show that they were harmed. They experienced either pain and suffering or a loss of some kind, such as loss of wages or loss of consortium. In some cases, damages are presumed. If a surgeon leaves a surgical sponge in the patient, the patient requires an additional surgery to remove the sponge. In this case, the patient would be able to show that the second surgery led to discomfort, time away from home, time away from work, and lost wages.

To understand the concept of damages, one should be familiar with the common distinction between economic and noneconomic damages. Economic damages include medical expenses, costs of burial, lost earnings, and loss of employment. These damages are often less complicated to calculate. Alternatively, some plaintiffs claim noneconomic damages, which are more subjective. Among other claims, noneconomic damages can include pain and suffering, emotional distress, mental anguish, or destruction of parent-child relationship.

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Many state legislatures have attempted to cap awards for pain and suffering or for wrongful death. The California legislature has placed a $250,000 cap on noneconomic damages.[22] This generally means that any litigation involving the death of a newborn has a maximum pain and suffering award of $250,000. If older patients die, their estate can seek damages for lost wages, lost consortium, or other losses. The award for wrongful death of a newborn is essentially capped in California, however. In addition, several state legislatures have placed caps on other noneconomic damages such as pain and suffering. In Louisiana, the Malpractice Liability for State Services Act has capped state hospitals' liability at $500,000 for "pain and suffering."[47]

A great deal of tort reform litigation deals with the issue of damages. There continues to be a national debate concerning caps on noneconomic damages as well as multiple legal challenges to state caps on noneconomic damages. These challenges have had mixed success, with state courts recently upholding limits in some states (Louisiana, California, Indiana), whereas other states have ruled the limits unconstitutional and thus invalid (Oklahoma, Georgia, Illinois).[30]

If a negligent act is committed and someone is harmed, damages are usually limited to compensatory awards. Punitive damages are awarded if the defendant is found to have committed a particularly egregious act. These damages are rarely awarded in medical malpractice cases. If a physician were to alter a chart or make another attempt to change the medical record, however, a jury may award punitive, or punishment, damages. "Spoliation of evidence" can lead to punitive damages.

Burden of Proof

How does a plaintiff win a case? Generally, each element must be proved by a preponderance of the data. This is also called the "51% test." The attorneys often frame their questions in terms of "is it more likely than not." Whether the attorneys are questioning expert witnesses or making statements to the jury, they often refer to the burden of proof. Generally, this burden is on the plaintiff. The plaintiff must show that the defendant had a duty, that the duty was breached, that the plaintiff sustained damages, and that the breach was the legal cause of the damages. The plaintiff must prove each of these elements by a preponderance of the data.

Burden of proof can be contrasted with the common criminal standard of proof known as "beyond a reasonable doubt." In criminal cases, the state must show the defendant's guilt beyond a reasonable doubt. Another standard that may be familiar to readers is the "clear and convincing" standard. This standard is sometimes used in cases involving the withdrawal of care when the patient cannot communicate his or her wishes.[41] In civil cases, and particularly in malpractice cases, the standard is generally a preponderance of the evidence.

Protected (Nondiscoverable) Proceedings

Many hospitals have committees that review the care provided at that institution. Although the precise operations of these committees might differ, committees generally review cases that have had an untoward or unexpected result. In some institutions, all deaths are reviewed. Many state legislatures have provided protection for the proceedings from these committee meetings. The Georgia statute specifically shields the specified proceedings from being used by a plaintiff in a medical malpractice case.[31] This is an issue of public policy. It is believed that care would be improved if caregivers could discuss challenging cases openly in a protected environment.

Clinicians must recognize that these proceedings do not limit the plaintiff's ability to bring suit against the physicians or the institution. A meritorious plaintiff can still subpoena hospital records and successfully bring suit against the caregiver. The protected proceedings would be unavailable as evidence in the case, however. From a legal standpoint, the proceedings are "nondiscoverable." Before a physician discusses a case with an untoward outcome at a medical staff proceeding, the physician might wish to confirm that the proceedings of that meeting are nondiscoverable.

Other Tort Actions

In the context of neonatal-perinatal medicine, there are two unique causes of action. These actions are *wrongful life* and *wrongful birth*. There are distinctions between the two, and these causes of actions are not allowed in some states.

Wrongful Birth

Wrongful birth cases are brought by parents who have given birth. The cause of action is maintained on behalf of the parents. The parents contend that the child should never have been born, and they seek recovery based on the birth. These cases are often seen after the failure of a sterilization procedure or after a physician has assured a patient that he or she is not fertile. The parents generally seek economic damages related to the cost incurred in raising the child.

In 2007, a Florida family was successful in suing a geneticist on a wrongful birth cause of action. The case involved the alleged misdiagnosis of a child with Smith-Lemli-Opitz syndrome.[24] The family had one child with multiple anomalies, including microcephaly, micrognathia, cleft palate, syndactyly, hypospadias, and cryptorchidism. This child also had severe developmental delays. The family alleged that they brought the child to a geneticist who failed to make the diagnosis. The family was allegedly told that their chances of having a normal child were the same as anyone else's. Based on this information, the family conceived and did not seek genetic diagnosis of the fetus. Within hours of birth, this child was diagnosed with Smith-Lemli-Opitz syndrome. Subsequently, the first child was also diagnosed with Smith-Lemli-Opitz syndrome.

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The family contended that they would have terminated the pregnancy if they had been aware of the diagnosis of the second fetus. Expert witnesses testified that failure to diagnose the older child with Smith-Lemli-Opitz syndrome was below the standard of care. A plaintiff's expert also testified that the conduct of the original geneticist was egregious. The plaintiff expert testified that the family should never have been told that they had no increased risk of having a child with birth defects. The family sued, and a jury awarded more than $21 million.[76]

Wrongful Life

Wrongful life cases are maintained on behalf of a newborn. The plaintiff usually maintains that there was negligence in the diagnosis or treatment of the mother and that the infant should not have been born. In essence, the parent is claiming that the infant would be better off if the infant had not been born. Historically, these cases tended to be brought on behalf of newborns with severe congenital anomalies. A family maintains that an obstetrician or ultrasonographer missed certain important findings. The family claims that they would have terminated the pregnancy if they had known the child's diagnosis.

Ethically and philosophically, this tort raises many more questions. What is the value of human life? Can a person actually sustain a cause of action simply because that life exists? Would any person actually be better off if he or she had not been born?[33] As ill-equipped as many clinicians are to deal with these questions, the courts are at an even greater disadvantage. Courts tend to rely on facts and evidence. How does one compare a damaged existence with no existence at all?

Courts have grappled with this issue. Some courts have stated that there is sanctity in an impaired existence but that this sanctity does not preclude a child's recovery for wrongful birth.[81] Courts have said that there is an almost insurmountable challenge in attempting to compare what judicial opinions characterize as the "utter void of nonexistence" with an impaired existence; however, some states do allow recovery.

The *Estrada* case addresses some of the issues associated with genetic testing.[32] If genetic testing is indicated and is not offered to a family, certain states allow a wrongful life cause of action. Most states do not allow this cause of action.

Wrongful Death

A wrongful death action is seen in other civil suits as well as in medical malpractice cases. If a person dies as the result of another's negligence, the estate may pursue a wrongful death claim. If a pregnant woman is involved in a car crash and she miscarries as a result, the woman may be able to sue for wrongful death of her fetus.

Although wrongful death claims can be part of other negligence suits, the claim is common in malpractice actions. Although some states allow for the wrongful death of a fetus, other states recognize this claim only after a live birth.[18] A case in Connecticut seems to allow for a wrongful death if the fetus is viable.[29] Other states, such as West Virginia, allow recovery for the wrongful death of a fetus of any gestation.[27]

Strategies for Avoiding Tort Litigation

Physicians maintain a vested interest in avoiding malpractice litigation. When untoward medical complications arise, physicians may experience deep empathy for the patient and personal feelings of doubt or inadequacy. The allegation of medical malpractice may lead the physician to experience numerous physical and emotional symptoms, collectively referred to as the *medical malpractice stress syndrome*.[70] Besides the mental anguish that one can experience as a result of being named as a defendant in a malpractice case, these proceedings are often time consuming and expensive. Physicians can adopt certain personal guidelines to minimize their chances of being named in a malpractice suit (Box 4.2).

Clinicians should make all necessary efforts to stay current in their discipline. Attending conferences and reading journals and textbooks assist physicians in their clinical practice. In the 1990s, dexamethasone was widely used to wean premature infants with chronic lung disease from ventilators. Because of long-term neurologic concerns, this therapy is now normally reserved for only the sickest infants. A neonatologist who does not keep up with current practices could be administering a medication or offering a form of therapy well after its use has been widely abandoned or curtailed.

Neonatal intensive care units are often part of a regional system of neonatal-perinatal services. Small and large community NICUs can maintain professional ties with one another and with larger medical centers. These ties allow professional interchange of ideas and recent developments. Clinicians would be wise to view their professional development as an ongoing process.

A clinician who is faced with a rare or particularly challenging case can consider calling a colleague. Attending physicians often maintain contact with their former trainees. These contacts with former mentors can provide great benefit for one's patients. Perhaps a former attending

• BOX 4.2 Strategies to Avoid Tort Litigation

- Stay current by reading journals and textbooks and by attending continuing medical education conferences.
- Maintain professional ties with a tertiary care medical center.
- When facing a difficult situation, consider consulting with a colleague.
- Maintain open communication with parents and families.
- Practice timely documentation of procedures, communication, complications, and persons present.
- Document telephone advice.
- Be aware of state laws that affect your practice.

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physician can shed some light on a difficult situation. At large academic centers, attending physicians generally make it a point to discuss regularly the most difficult clinical cases at fetal boards, morning report, grand rounds, or other venues. By phoning a colleague, a community-based neonatologist can maintain a similar professional network.

In addition to maintaining good communication with colleagues, few issues are more vital than optimal communication with parents. It is not always easy to maintain good communication with parents, but the implications of poor communication are generally unacceptable. If parents believe a clinician is hiding something from them, they often become frustrated and angry. Parents are already dealing with having a sick infant in the NICU. If they feel mistrust, the physician's relationship with a family can quickly deteriorate. A suboptimal relationship with the family of a sick newborn can be a harbinger of a pending malpractice suit.

Besides optimal communication, the clinician's other major defense to a tort suit is documentation. Entries in the chart should be punctual, legible, and accurate. If circumstances necessitate that a late entry be made, this should be clearly documented as such. If a particularly important event has occurred, whether a complication with the infant or a comprehensive family conference, it should be documented in the chart. With respect to family conferences, it is important to document who was present and what was discussed.

One area clinicians often fail to document is the advice that they give over the phone. Because this can be time consuming and logistically difficult, some physicians open themselves to liability by giving advice and failing to document that advice. Referring physicians or parents may ignore a physician's advice. In these situations, documentation of the phone discussion can save a tremendous amount of money, time, and frustration at a later date.

Many neonatologists are now using electronic medical records (EMR) to document patient care. The medicolegal impact of the EMR is unclear. With widespread access to the full patient record, no legibility issues, and the ability to provide support for decisions, there is hope to improve safety and quality and to decrease liability. Experience so far, however, has shown that in addition to benefits there are a number of drawbacks, including system failures (rendering the chart completely inaccessible), inefficiency (poorly designed, slow systems), and inappropriate shortcuts (use of cut-and-paste that transfers incorrect information into the patient note). As a result, liability may potentially increase with improper use of the EMR.[74]

Finally, clinicians should be aware of state laws that affect their practices. This chapter presents cases and statutes from several states. Which ones affect a particular physician's practice? Many issues, such as resuscitation of extremely premature infants or accreditation of NICUs, are largely controlled by state law.

Trends in Malpractice Legislation

For the last several decades, insurance companies, large corporations, and attorneys have actively participated in the tort reform debate. Tort reforms may include limits on noneconomic damages, limits on attorney fees, expert witness standards, and inadmissibility of apology statements by health care providers.[58] In the context of malpractice law, consumer advocates argue that meritorious plaintiffs are entitled to compensation when they are injured by medical negligence. Insurance companies and providers counterargue that juries should be restricted from awarding massive monetary verdicts, because the costs of these verdicts are reflected in increasing health care bills, physicians' unwillingness to practice in certain locales, and the increase of "defensive medicine."

California enacted the Medical Injury Compensation Reform Act of 1975 (MICRA) in an effort to address increasing malpractice premiums. The MICRA addressed various issues, including caps on noneconomic damages (e.g., pain and suffering, loss of consortium) and mandated that attorneys' contingency fees be based on a sliding scale. The American Medical Association has expressed its support for MICRA-type reforms.[51]

Tort reform is often considered by state legislatures to address a medical malpractice system that is considered "costly and inefficient." Estimates of the national overall medical liability system costs, including "defensive medicine," run from $55 billion annually to $200 billion.[58] Generally, state legislatures have evaluated the merits of the medical malpractice system and passed bills designed to curb certain monetary awards.

In a move that alarmed many physicians and hospitals, Florida voters passed a constitutional amendment that has come to be known as the "three strikes malpractice law."[78] Article X, Section 26 of the Florida Constitution automatically revokes the license of any physician with three malpractice judgments against him or her. To avoid a "strike" from losing a malpractice case, there is strong incentive for physicians to settle all malpractice claims.

In contrast, legislation placing limits on damages in Texas, authorized by a constitutional amendment, resulted in a 50% increase in physicians applying to practice in that state. An environment in Texas that provides some protection for physicians has helped to relieve specialty shortages in rural areas. Challenges to the Texas legislation are illustrative of national efforts to overturn tort reform. In 2008, a class action lawsuit was filed alleging that limits on damages violate constitutionally guaranteed rights, including equal protection and due process. The plaintiffs in this class action suit claimed that the state-mandated limits on medical malpractice awards do not provide adequate compensation for their injuries. Among the plaintiffs were at least two children who allege injuries they sustained as newborns. One plaintiff in this suit allegedly sustained permanent brain damage because fetal distress was not diagnosed quickly enough. Another infant plaintiff allegedly sustained injury

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because of inappropriate respiratory management and because hypoglycemia was not promptly diagnosed and treated.[79] In 2012, a Texas court of appeals ruled that the cap on damages was in fact constitutional.[52]

Conclusions

Generally, a plaintiff must show that all four elements (duty, breach, causation, and damages) are present. Showing only that the physician made a decision outside an acceptable standard of care is insufficient. Likewise, a patient cannot sustain a cause of action simply because of a poor outcome. The physician may have no duty to the patient, or the damages sustained may have no relation to the alleged breach in the standard of care. Of the four elements, breach and causation are the main elements that are commonly disputed in a malpractice case. The plaintiffs argue that the physician's care deviated from an acceptable standard and that this deviation harmed the patient. The defendant maintains that the care was acceptable and that any damages were not the result of faulty care (or decision making) by the defendant.

Live Birth

As the fetus descends through the birth canal and emerges as a living infant, many critical transitions occur. Readers of this textbook are familiar with the physiologic adaptations that accompany a live birth. In a legal sense, the fetus generally acquires full personhood when there has been a declaration of a live birth. Before birth, the cases cited earlier determine the fetus's legal status. Although the rules differ from state to state, there is consistent interpretation that at the moment of live birth, the infant has all of the associated rights, privileges, and consequences of personhood in civil and criminal matters.[80]

It would seem intuitive how to define "live birth." Each state has a definition for "live birth," and there is considerable overlap in these definitions, but some states have placed additional clarification in the statutory language.

The Utah statute states that live birth "means the birth of a child who shows evidence of life after the child is entirely outside of the mother."[82] This statute can be contrasted with the Alabama statute, which states, "When used with regard to a human being, [live birth] means that the human being was completely expelled or extracted from his or her mother and after such separation, breathed or showed evidence of any of the following: beating of the heart, pulsation of the umbilical cord, definite movement of voluntary muscles, or any brain-wave activity."[8]

A common thread in the states' statutes is to include some physiologic sign of life, whether it is a beating heart, pulsation of the umbilical cord, spontaneous respiratory activity, or spontaneous movement. Beyond these findings, some states clarify further that an infant is considered to be alive whether or not the placenta is still attached and that an infant of any gestation can be a live birth.[53] Some statutes specifically differentiate between heartbeats and "transient cardiac contractions."[26] There is also an effort to distinguish breathing from "fleeting respiratory efforts or gasps."

The Alaska statute seems to contemplate all of these variables.[9] It states that "live birth means the complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy, that, after the expulsion or extraction, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached." Additional language is added to the Maine statute, which specifically states that "[e]ach product of such a birth is considered live born and fully recognized as a human person under Maine law."[50]

In the context of criminal law, the *American Law Reporter* proposes a different test for "life." This is known as a showing of a "separate and independent existence."[6] For purposes of homicide, a newborn is considered to have been born alive if it ever showed a separate and independent existence from its mother.

Born-Alive Infants Protection Act

In 2002, Congress passed by an overwhelming majority the Born-Alive Infants Protection Act (BAIPA).[65] The act states that when the terms *individual*, *person*, *human being*, and *child* are used in any law, it should be interpreted to include every infant who is born alive at any stage of development. The law defines *born alive* to mean "the complete expulsion or extraction from his or her mother of that member, at any stage of development, who after such expulsion or extraction breathes or has a beating heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, regardless of whether the umbilical cord has been cut, and regardless of whether the expulsion or extraction occurs as a result of natural or induced labor, cesarean section, or induced abortion."[65]

The BAIPA was passed with the notion that legal protections should be provided to infants born alive after failed abortions. According to the US Congress, it was not relevant if the parents intended to have a live infant. If the infant was born alive, the infant must receive a "medical screening," and appropriate care must be provided.

There has been some concern that the impact of the BAIPA would be to require neonatologists to resuscitate all extremely premature infants at every gestation.[16] The American Academy of Pediatrics Neonatal Resuscitation Program Steering Committee has maintained a different position, stating that the BAIPA "should not in any way affect the approach that physicians currently follow with respect to the extremely premature infant."[61]

In the first decade the Act has seemed to have little impact. At a minimum, however, the federal law requires that all live-born infants require the same level of medical screening regardless of the reasons for the birth.

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Handicapped Newborns

Federal and state governments have created protections for the most vulnerable members of society. This section deals largely with federal issues, but the states have also adopted guidelines to protect handicapped individuals. Individuals with disabilities are protected by the Americans with Disabilities Act (ADA).[4] All children are protected by child abuse and child neglect statutes. The government generally places a high emphasis on protecting the lives of fragile children. Parents can lose custody of their children if they violate laws related to abuse or neglect, and they can be incarcerated for criminal endangerment if their behavior is particularly egregious.[54]

With the growing expertise in prenatal diagnosis, it is increasingly rare that the family and the health care team are surprised by the birth of an infant with congenital anomalies. Maternal serum markers, prenatal ultrasound, amniocentesis, prenatal percutaneous umbilical blood sampling, and other procedures provide the practitioner with a considerable armamentarium to diagnose anomalies. In the case of "lethal" anomalies, this advance notice gives the family time to consider how they wish to proceed. There is often ample opportunity for the practitioners and the family to discuss the diagnosis, the implications of the diagnosis, and the care options. In the case of lethal anomalies, care options selected by the parents may include comfort care only, aggressive resuscitation, or any level of care in between.

Federal law prohibits discrimination on the basis of handicap. Under this law, nourishment and medically beneficial treatment (as determined with respect for reasonable medical judgments) should not be withheld from handicapped infants solely on the basis of their present or anticipated mental or physical impairments.[4]

Baby Doe

Handicapped newborns and the care that they receive became a mainstream issue in the 1980s. The controversy created by the Baby Doe case still governs many decisions made by neonatologists. Baby Doe lived for less than 1 week, but his legacy remains more than a quarter century later.

Many neonatal-perinatal practitioners are familiar with the basic facts of Baby Doe.[42] The infant was born with Down syndrome in Bloomington, Indiana, on April 9, 1982. As is the case with many infants with this disorder, he had a gastrointestinal tract atresia. Practitioners recognize that gastrointestinal atresias are usually surgically correctable. Duodenal atresia is more common in Down syndrome, but Baby Doe had esophageal atresia. Because of the atresia, the infant could not be fed. Baby Doe's parents, on the advice of their obstetrician, elected to forgo surgery. After discussions with the family, food and water were not provided, and the infant died at 6 days of age.

Down syndrome is not considered a lethal anomaly. Had Baby Doe not had Down syndrome, deferring surgery would not have been considered an acceptable option. Because Baby Doe did not have lethal anomalies, it was assumed that medical and surgical care were withheld because of the mental deficits associated with Down syndrome. The hospital went to court trying to override the parents' decision and force surgery for Baby Doe. Because the obstetrician agreed surgery should not be done, the judge sided with the parents, stating that the parents should "have the right to choose a medically recommended course of treatment." Because Baby Doe had already died by the time of appeal, higher courts[72] refused to hear the case.[40]

The case received national attention, and the decision to forgo care was largely viewed as unacceptable. Advocates for the handicapped were particularly concerned about this case. They proposed that Baby Doe had been discriminated against on the basis of the infant's handicap and that there had been a violation of Section 504 of the Rehabilitation Act of 1973.[1]

For various reasons, the Baby Doe case was a landmark decision. In the 3 years following Baby Doe's death, the executive, legislative, and judicial branches of the federal government became involved. The American Medical Association, the American Academy of Pediatrics, the American College of Obstetrics and Gynecology, and other professional organizations also became involved. The Reagan administration's position was that all handicapped newborns must be treated aggressively unless the care is obviously futile. The Reagan administration believed that physicians should be liable for neglect and discrimination if they did not comply with these rules.

The Reagan administration attempted to force hospitals to treat all severely handicapped newborns, regardless of the parents' wishes. The Department of Health and Human Services (HHS) promulgated "Baby Doe regulations" that required federally funded hospitals to post certain rules in the hospital.[5] Notices were to be prominently posted in delivery wards, maternity wards, pediatric wards, and each nursery. These signs encouraged concerned parties to call the HHS toll-free number to report suspected cases of discriminatory withholding of care from handicapped newborns. The rules also encouraged the creation of infant care review committees to assist in decision making for difficult cases. Many of these regulations were ultimately disallowed by the courts. The current incarnation of the Baby Doe regulations is found in the Child Abuse Protection and Treatments Act (CAPTA), which prevents the "withholding of medically indicated treatment," which is defined as "failure to respond to the infant's life-threatening conditions by providing treatment … which, in the treating physician's … reasonable medical judgment, will be … effective in … correcting all such conditions."[2]

Although infant care review committees are encouraged, the courts have ruled that parents, in conjunction with their physicians, should have the right to make health care decisions for their handicapped children. When the US Supreme Court decided against hearing the Baby Doe case,

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the matter was deferred only for a few years, until the Baby Jane Doe case.

Baby Jane Doe

In 1983, the year after Baby Doe died, a child was born in New York with meningomyelocele, hydrocephalus, microcephaly, bilateral upper extremity spasticity, a prolapsed rectum, and a malformed brainstem. She has been immortalized in the neonatal literature as "Baby Jane Doe." Her parents were presented with two options to treat the meningomyelocele: primary skin healing or surgical repair. The parents refused consent for surgical repair of the defect and for the placement of a shunt for hydrocephalus. Instead, the parents requested that the infant be treated with antibiotics and nutritional support.

An attorney who was not related to the family thought that the parents' request was an inappropriate medical decision. This attorney requested that the trial court appoint an independent guardian for the infant so that consent could be given to perform the surgeries. The trial court granted the attorney's request, but the appellate court overturned that decision the following day. The appellate court found that the parents had chosen an acceptable medical option and had acted in the best interest of their child.

While this issue was being dealt with in the state court system, HHS received a complaint from a "private citizen." This complaint stated that Baby Jane Doe was being discriminated against because of her handicap. The Department of Health and Human Services referred the case to Child Protective Services, which concluded that there was no cause for state intervention. During this time, HHS also made repeated requests of the hospital to produce the infant's medical records. The hospital refused on the grounds that the parents had not consented to release the records. The federal government sought to compel access to the medical chart and filed a suit in federal district court under section 504 of the 1973 Rehabilitation Act.[3] The courts found that the hospital had not violated any of the pertinent statutes, because it was willing to perform the surgery if the parents would consent.

As the case proceeded through the federal court system, various judges asserted that the infant was not being discriminated against on the basis of her handicap. Ultimately, the case reached the US Supreme Court.[19] The US Supreme Court took the opportunity to review the Baby Doe case, the Baby Doe regulations, the care of handicapped newborns, the role of the federal and state government in these cases, the rights of parents, and the rights and duties of caregivers.

The court found that there was no violation of Section 504, because the withholding of treatment was secondary to lack of parental consent, not secondary to discriminatory withholding based on the infant's handicap. Among other conclusions, the US Supreme Court found that the parents had made reasonable decisions that were consistent with the best interests of their child. The court found no discrimination. The court also stated, "A hospital's withholding of treatment when no parental consent has been given cannot violate Section 504, for without the consent of the parents or a surrogate decision maker the infant is neither 'otherwise qualified' for treatment nor has he been denied care 'solely by reason of his handicap.' Indeed, it would almost certainly be a tort as a matter of state law to operate on an infant without parental consent." The final sentence of this quotation raises interesting questions in light of the Miller case, which is discussed later.

Baby K

Baby K was found prenatally to have anencephaly.[43] Her mother declined termination of the pregnancy, and the infant was delivered by cesarean section on October 13, 1992. The infant was initially placed on mechanical ventilation so that the diagnosis could be confirmed. After confirmation of the diagnosis, the caregivers approached the infant's mother to request permission to withdraw the ventilator. Based on the mother's religious beliefs that all life is sacred and must be protected, she insisted that the ventilator support be continued.

When the infant was 9 days old, the hospital ethics committee met with the physicians and concluded that the care was futile. Attempts to transfer the infant to another facility were not successful, and eventually Baby K no longer required the ventilator and was transferred to an extended care facility. Baby K required three subsequent hospitalizations secondary to respiratory distress. Each time, the mother insisted that the infant be reintubated. The caregivers and the infant's father believed that the treatment was futile and inappropriate.

The hospital sought a federal court ruling that would allow them to withhold the ventilator from Baby K in the future. The hospital sought a declaratory judgment that by withholding the ventilator that they would not violate the Emergency Medical Treatment and Active Labor Act (EMTALA), the state Child Abuse Amendments, the state Malpractice Act, or ADA. The court ruled (and the 4th Circuit of the US Court of Appeals[44] upheld) that the hospital was not entitled to such a declaration. The court reasoned that the infant's anencephaly qualified her as "handicapped" and "disabled" for the purposes of ADA. Because of procedural concerns and federal and state issues, the court did not rule on the topics of malpractice or child abuse.

In the court's interpretation of EMTALA, it reasoned that because "stabilization" included establishing and securing an airway, the refusal to intubate Baby K would be a violation of EMTALA. Because Baby K was handicapped and disabled, and the hospital received federal funds (e.g., Medicare payments), the hospital could not deny the requests of Baby K's mother.

The EMTALA legislation was initially intended to prevent hospitals from "dumping" nonpaying patients to

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other facilities. In this case, the hospital was not contending that the issue was payment for the treatment. The court found that EMTALA applied, however, and Baby K must be intubated and ventilated as long as that was the mother's wish. The court stated that "absent finding of neglect or abuse, parents retain plenary authority to seek medical care for their children, even when the decision might impinge on a liberty interest of the child."

The 4th Circuit of the US Court of Appeals stated that it was beyond its judicial limits to address the moral and ethical implications of providing emergency care to anencephalic infants. It stated that Congress did not want a case-by-case analysis but rather desired that hospitals and physicians provide stabilizing care to all patients who present with an emergency condition.

Many ethicists and clinicians view anencephaly as "a paradigm case of medical futility."[48] For them, the Baby K decision was considered inappropriate, mandating treatment that would not be considered in the best interests of the patient. Four years after the original decision, the 4th Circuit placed some limits on the reach of the Baby K decision. In *Bryan v Rectors of the University of Virginia*,[7] the court limited the scope of EMTALA to emergency stabilizing treatment and declined to apply EMTALA to a hospital that entered a "do not resuscitate" order against the wishes of the family 12 days after the patient had been admitted.

Sun Hudson

Sun Hudson was born in Houston, Texas, in September 2004 to his mother, Wanda, and an unknown father. He was intubated shortly after birth and subsequently diagnosed with thanatophoric dysplasia, a typically fatal short-limbed skeletal dysplasia. The neonatologists and bioethicists at Texas Children's Hospital believed that "it would be unethical to continue with care that is futile and prolongs Sun's suffering."[38] His mother disputed the hospital's diagnosis, however, and fought to keep Sun on the ventilator. Under the Advance Directives Act,[75] signed into Texas state law by then-governor Bush, physicians and hospitals can unilaterally withdraw life support against the family's wishes as long as the hospital's ethics committee agrees with the decision. The hospital is also required to allow at least 10 days so that the family can find another facility to accept the patient. In Sun's case, Texas Children's contacted more than 40 hospitals but was unable to find another facility to accept him. In addition, although court approval is not required by the statute, the hospital offered to pay Ms. Hudson's attorney fees, and the case was heard in court.

After several months, a judge supported the position of the hospital. Sun was extubated and died in February 2005. The case is significant because it represents a rare case in which a judge has allowed withdrawal of life-sustaining treatment against a parent's wishes.

Conclusions

The preceding cases present the challenges faced when damaged newborns receive a level of care that is viewed to be inappropriate by some observers. If a child has "lethal" anomalies or a "terminal" condition, the courts generally find that parents are the primary decision makers concerning the level of care.

In the Baby Doe case, the infant did not have a lethal underlying condition. Treatment would not have been "futile," and, in retrospect, many observers believed that the decision to forgo surgery was not "reasonable." The resulting national outcry was a measure of people's dissatisfaction with the decision made by the physicians and the parents.

In contrast, Baby Jane Doe had a course of therapy that was selected by her parents. Although it was not the most aggressive course of treatment, some experts believed that allowing the skin to grow over the meningomyelocele was an acceptable option. Other experts take issue with this course of therapy. The court ruled, however, that the parents selected an acceptable treatment option for their daughter.

In the Baby K case, the child had what is largely viewed as a "lethal" anomaly. Despite the heartfelt objections of the physicians and staff, the courts ruled that care could not be withheld simply because the caregivers considered it to be morally and ethically inappropriate.

The case of Sun Hudson shows that parents' rights are not completely unlimited. In this case, however, the medical community and bioethicists agreed that Sun was suffering, and Texas had a law in place specifically allowing unilateral withdrawal of support.

Can these four cases be reconciled? In the Baby Doe case, the parents made decisions that could be viewed as neglect. Baby Doe did not receive life-saving surgery because he was handicapped. It would seem that such withholding of treatment would not be accepted if Baby Doe were born today. Baby Jane Doe's parents made a choice that the court ruled was a reasonable one. There was no discriminatory withholding of care. In Baby K's case, the courts supported a parental decision to ventilate a child with no cerebral cortex, a decision that many clinicians find untenable. Sun Hudson's condition, thanatophoric dysplasia, was believed to lead to his prolonged suffering, and this may have contributed to the judge's decision to override the mother's wishes. If conclusions can be drawn, they would seem to indicate that the courts support parents' interests as long as decisions are not being made solely on the basis of handicap and as long as the infant is not believed to be suffering. The personal morals and ethics of the caregivers are fundamentally irrelevant in the legal context of parental decision making. If the parents' decisions are reasonable and if there is no evidence of neglect or suffering, parents seem to have substantial decision-making power.

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Providing Care Against Parents' Wishes

One of the most challenging aspects of neonatology is caring for extremely premature infants. A substantial portion of this textbook addresses the medical issues involved in caring for these infants. Although the care of extremely premature neonates largely defines the parameters of the specialty, it also creates many of the legal and ethical quandaries for caregivers and families. These tiny individuals existing on the cusp of viability have the same legal rights as all citizens. They are entitled to equal protection, due process, and all other constitutionally guaranteed rights and privileges of the citizens of the United States. By virtue of a heartbeat or spontaneous respiratory effort, an extremely premature infant is transformed into a "person." As mentioned in the earlier discussion of live birth, in many states, the gestational age and whether the placenta is attached are legally irrelevant.

The pending delivery of a 23-week-gestation fetus generally carries a wide variety of concerns. What are the family's wishes? Will the resuscitation go smoothly? Will all the equipment function properly? How will the infant respond to the resuscitation? Will stabilization be difficult? Will the infant require significant ventilator support, volume boluses, or an infusion of catecholamines?

More recently, the overriding concern is whether the infant must be resuscitated if considered to be previable. What if the parents request no resuscitation? Are the caregivers liable if they overrule the parents and proceed with resuscitation of a 23-week-gestation infant? What if the parents request no resuscitation for a 25-week or 26-week infant?

This extraordinarily difficult situation is exacerbated by a relative lack of statutory and case law. The existing case law seems to conflict with itself. This section addresses the unique challenge associated with the delivery of extremely premature infants. To gain insight into this convoluted area of law, the reader should review the material on perinatal issues (maternal-fetal conflict), live birth, informed consent, and limiting care. The reader should have a grasp of the *Cruzan* decision[25] and the associated liberty interest in keeping one's body free from unwanted medical intervention. Likewise, one must appreciate that courts have found that parents generally have the right to refuse certain unwanted medical interventions for their children as long as this refusal is not neglect or abuse. Without a familiarity with the rules governing informed consent, the reader lacks the necessary foundation to appreciate the following discussion.

Miller Case

In 1990, Karla Miller went into preterm labor at approximately 23 weeks' gestation. After the neonatologist explained the grim prognosis for infants born at this gestation, Mark and Karla Miller requested that the infant not receive heroic measures. Initially, the obstetrician and neonatologist agreed to honor the parents' wishes. A hospital administrator claimed, however, that the hospital had a policy requiring that the infant be resuscitated if she weighed more than 500 g. This policy was explained to the parents, who again requested that the infant not be resuscitated.

Sidney Miller was born later that night, several hours after Mrs. Miller was admitted to the hospital. The infant was resuscitated, and she survived with severe impairment. The parents sued the hospital, asserting claims in battery and negligence. They did not sue the physicians, although they were involved in the trial, because they believed that the physicians were following orders from the administration. The main allegation was that the hospital was liable for mandating Sidney's resuscitation without parental consent. The hospital maintained that the parents had no right to refuse lifesaving intervention.

The jury awarded the family approximately $60 million. The appellate court overturned this verdict.[35] In its analysis, the appellate court stated that this was a situation of the emergency exception to the informed consent rule. The court also relied on the Advance Directives Act. This act protects caregivers and hospitals who withhold care from terminally ill patients. The court reasoned that because Sidney Miller's condition did not fit the definition of terminal, the parents had no right to refuse lifesaving therapy. The court stated that although parents have a right to determine health care decisions for their children, this is not an absolute right, and the state also has an interest in the health of children. "Having recognized, as a general rule, that parents have no right to refuse urgently needed life-sustaining medical treatment to their non-terminally ill children, a compelling argument can be made to carve out an exception for infants born so prematurely and in such poor condition that sustaining their life, even if medically possible, cannot be justified." The appellate court concluded that perhaps the legislature should address the issue of defining "terminal" with respect to some premature infants who are born so small and so sick.

A dissenting judge on the appellate court believed that the parents' course of action was lawful. This judge supported his opinion by quoting the US Supreme Court's decision in the Baby Jane Doe case. This dissenting judge stated that no emergency existed. The emergency exception to the informed consent rule was not available to the caregivers. According to the dissent, it was the caregivers' delay and indecision that led to the urgency.

Thirteen years after Sidney Miller was born, the Texas Supreme Court ruled on the case.[36] This court found that the hospital was not liable for resuscitating the infant. Although the Texas Supreme Court analyzed the case differently than the appellate court had, the decision was the same: The hospital had no liability. The high court reasoned that because it was impossible to predict how sick the infant would be at birth, the emergency did not exist until after Sidney was born. The physician could not evaluate the situation until after the infant was born.

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Messenger Case

Gregory Messenger and Traci Messenger were faced with a situation similar to that of the Miller family. Traci Messenger went into labor at 26 weeks. Gregory Messenger was a physician (dermatologist). After discussing their options with their caregivers, the Messengers requested that the infant not be resuscitated. The request was not honored. The infant was resuscitated and brought to the NICU. Dr. Messenger went into the NICU, extubated his son, and placed him in Traci Messenger's arms. The baby died shortly thereafter. The neonatologist listed the cause of death as "homicide." Approximately 1 year later, Dr. Messenger was acquitted of manslaughter.[62] Among other conclusions, the jury believed that Dr. Messenger was acting in the "best interest"[84] of his son.

The Messenger case was a criminal trial with a higher standard of proof. Dr. Messenger was acquitted of a crime. He removed his own extremely premature son from a ventilator, and he was found to be not guilty of intentional killing.

Montalvo Case

Baby Emanuel (Montalvo) Vila was born in Wisconsin in November 1996 at 23 weeks' gestation weighing approximately 679 g. His mother had presented earlier with preterm labor, and after attempts to delay his birth were unsuccessful, a cesarean section was performed after informed consent was obtained. Three years after his birth, the family sued the obstetrician, the neonatologist, and the hospital, alleging that they had resuscitated Emanuel without advising the parents of the risks or potential consequences of an extremely premature infant. The trial court found for the physicians and the hospital, and the family appealed.

The Wisconsin State Court of Appeals agreed with the trial court for two reasons. First, the court noted that under Wisconsin law, in the absence of a persistent vegetative state, a parent does not have the right to withhold life-sustaining medical treatment. Second, the court looked at the current incarnation of the Baby Doe regulations, known as CAPTA regulations (discussed earlier). The court believed that the parents did not have a choice to refuse resuscitation because "[t]he implied choice of withholding treatment … is exactly what CAPTA prohibits."[55] The trial court and the appellate court addressed the public policy issues associated with resuscitation of extremely premature infants, and both courts pointed out that the decision-making authority in these cases cannot be placed "wholly" in the hands of the parents. This portion of the opinion would seem to imply that parents and caregivers have decision-making responsibility in these cases.

The potential implications of the Montalvo case are considerable. Because neonates are rarely in a persistent vegetative state, the ruling does not seem to give the option to withhold or withdraw treatment for most critically ill neonates. The decision applies only in Milwaukee, which is the area covered by District 1. Also, the court stated that parents were not "wholly" responsible for these decisions. This language would imply some role for parental decision making in concert with the attending physicians. To date, the *Montalvo* decision has not been widely upheld in other courts.

Conclusions

The *Miller* case was one decision made in one state. The decision was made by the Texas Supreme Court, so the decision is the current law only in Texas. The court's decision in the *Miller* case may or may not have any effect in any other state. Currently, if one practices in Texas, *Miller v HCA* controls one's practice. Clinicians should be familiar with the facts and the judicial conclusions in this case. It seems that clinicians and hospitals in Texas would not be liable for resuscitating 23-week-gestation infants against the parents' wishes. Despite the parents' clear request to forgo resuscitation, a lapse of several hours between the time of the request and the time of birth, and no effort on the part of the clinicians or the hospital to transfer care to another provider, the court found no liability. It is also important to recognize that the physicians would not be liable for respecting and adhering to the parents' wishes under the *Miller* opinion.

In Wisconsin, the Montalvo case seems go a step further and suggests that neonatologists may be required to resuscitate all extremely premature infants. In stark contrast to the American Academy of Pediatrics' emphasis on shared decision making, the court claims that parents have no rights to decline treatment under the current Baby Doe regulations. Yet this interpretation is controversial. The Institute of Medicine report on preterm birth notes that the Baby Doe regulations "were not originally intended to apply to premature infants; rather, they were intended to apply to disabled full-term infants."[64] As a state appellate court ruling, however, this interpretation applies only in the Milwaukee area.

In the Baby Jane Doe case, the US Supreme Court did comment on decision making being taken away from parents. In defending the hospital's decision to honor the request of Baby Jane Doe's parents, the US Supreme Court stated, "It would almost certainly be a tort as a matter of state law to operate on an infant without parental consent."

What of the remainder of the United States? Perhaps some courts in other states would follow the trial court or the appellate court dissent in Miller. The trial court in Miller allowed a $60 million verdict. The dissent in the appellate court quoted the US Supreme Court decision in Baby Jane Doe, to question the propriety of imposing on parents the consequences of resuscitation of 23-week-gestation infants.

The Texas Supreme Court and the Wisconsin Appellate Court decided, using different rationales, that parents have no right to refuse resuscitation of their extremely premature infants. The Texas court relied heavily on its interpretation that the emergency did not exist until Sidney Miller was

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born. The hospital and caregivers would basically always be protected by the emergency exception to the informed consent rule. The *Montalvo* court relied on a State (Wisconsin) Supreme Court ruling and the federal Baby Doe regulations. The court believes that CAPTA prohibits withholding of resuscitation no matter how small or immature the infant. This is a drastic change from the manner in which many clinicians currently practice and removes physician judgment and the parents' view of what is best for their child from the equation.

How does one reconcile Miller, Montalvo, and Messenger? It is intellectually dissatisfying to conclude that the major difference among these cases is that they were adjudicated in different states. The inherent conflict between the cases must have more substantial legal underpinnings than a simple difference in jurisdiction. The fact that the Messenger case was a criminal trial with a higher burden of proof on the prosecution has some effect on the legal comparisons, but the inherent inconsistencies exist.

In the Miller case, an extremely premature infant is resuscitated against the parent's wishes, and the hospital has no liability. In the Montalvo case, an extremely premature infant is resuscitated, and when the parents state that they were not adequately informed, the court states that informed consent is irrelevant because the Baby Doe regulations do not allow parents to refuse resuscitation for even the smallest and most immature patients. In the Messenger case, an extremely premature infant was resuscitated against the parents' wishes, and the father had no criminal liability for disconnecting the ventilator with the intent to hasten the infant's death. If the infant was lawfully being cared for, how could the father be acquitted of manslaughter? If caring for the infant against the parents' wishes was not lawful, why did the Miller and Montalvo courts find for the hospital?

These cases leave in question the exact legal status of extremely premature infants. The infant is "alive" by statute. In some jurisdictions, the infant can recover for wrongful life. In some jurisdictions, a wrongful life claim would be denied because the parents have no right to refuse the care. In some jurisdictions, there is no criminal liability for a parent who overrules the physicians and takes matters into his or her own hands.

So what should a clinician do when called to the birth of a previable or periviable newborn? One should understand the issues, understand the rights of the newborn, understand the rights and the duties of the parents, and understand one's own rights and duties. Box 4.3 provides some general lessons from existing case law concerning situations in which parents and caregivers disagree on the care of critically ill newborns.

What would happen if Sidney Miller had been born in a state other than Texas? Did state politics play a role in this case? Is it a coincidence that Gregory Messenger was acquitted in Michigan? These are not trivial questions, but they are unanswerable given the current case law on this issue. To the family of Sidney Miller, the Supreme Court of Texas determined that the child and the family should recover nothing.

• BOX 4.3 When Parents and Caregivers Disagree on the Care of Critically Ill Newborns: Lessons From Existing Case Law

Parents Request Full Supportive Care and Caregivers Disagree

- General rule: provide full supportive care.
- Anencephaly: Baby K case likely controls (federal case).

Parents Want No Resuscitation and Caregivers Disagree

- Miller (Texas): no liability for caregivers.
- Montalvo (opinion covers Milwaukee, Wisconsin): no liability for caregivers.
- Messenger (Michigan): no criminal liability for father who disconnects the ventilator.

Parents and Caregivers Agree to Forgo Aggressive Treatment

- Possibly covered by Baby Jane Doe case: parents have right to make reasonable choice.
- Baby Doe case: cannot make decision solely based on present or future handicap.
- Montalvo (opinion covers Milwaukee, Wisconsin): parents may not have right to make reasonable choice.

Summary

A physician facing a legal issue can experience various difficulties. Physicians are often unfamiliar with the legal process, and the new terminology can be daunting. Compared with science, legal results can seem to be unpredictable. In law, there are no double-blind, randomized, controlled trials. Additionally, legal events often elicit strong emotions. With respect to malpractice, families may have suffered tremendous losses, and juries in some states can award tens of millions of dollars.

Generally, practicing strong clinical medicine requires the clinician to stay current in the specialty, to maintain excellent communication with families and the hospital staff, to strive consistently to make ethical decisions, and never to violate the law knowingly. Veteran neonatologists know the value of good documentation and effective communication with colleagues, staff, and families. Many other nuances exist, however. Practitioners benefit from understanding the elements of a tort suit; recognizing the importance of informed consent; and knowing the law concerning the care of handicapped newborns, anencephalic infants, and extremely premature infants. With respect to extremely premature newborns, it is particularly difficult to discern clear legal principles from the various court decisions in this arena. This issue speaks to the importance of knowing the law in the state in which one practices. In Wisconsin,

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clinicians must know the appellate court district in which they are practicing.

Although the law may seem to be arbitrary, there are substantial underlying principles that courts and legislatures have honored for hundreds of years. Fundamentally, the legal system is not unpredictable. It can be daunting to a physician, but the process can be demystified. If one is experiencing a significant health problem, one seeks out medical advice. Likewise, the legal profession can provide meaningful insight to a physician who is in need of counsel.

Key Points

1. Physicians and other health care professionals should understand their rights, duties, and liabilities while practicing health care.
2. While both federal and state laws affect the practice of medicine, medicine is primarily regulated by the states.
3. Strategies to minimize the risk of a malpractice lawsuit include staying up to date, communicating well with parents as well as other members of the health care team, and documenting in a factual and professional manner.

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5

Evaluating and Improving the Quality and Safety of Neonatal Intensive Care

JOCHEN PROFIT, HENRY C. LEE, JEFFREY B. GOULD, AND JEFFREY D. HORBAR

Making improvements happen also requires … unshakeable belief in the idea that everyone in healthcare really has two jobs when they come to work every day: to do their work and to improve it.[6]

More people die in a given year as a result of medical errors than from motor vehicle accidents, breast cancer, or AIDS.[152]

Systematic evaluation of the quality, safety, and efficiency of clinical care has become an integral part of medical practice. Physicians, hospitals, and large health care organizations are under increasing pressure to monitor, report on, and continuously improve their services. Public release of hospital performance data is becoming increasingly common. In this new era, health professionals in neonatology must learn how to evaluate themselves and learn how they will be evaluated by others, including policy makers, hospital administrators, regulators, payers, and the families and public they serve.

Evaluation is not an end in itself. Health professionals must learn how to use available information to improve the quality and safety of medical care continuously. This is not just an option. It is a responsibility. Since 2010, the American Board of Pediatrics' maintenance of certification requirement that neonatologists be actively engaged in quality improvement emphasizes this professional responsibility (www.ABP.org).

In this chapter, we review the ways data can be collected, evaluated, and applied to improve the quality and safety of medical care for newborn infants and their families. We discuss the available sources of such data for neonatology and describe how these data can be used to evaluate and improve the processes and outcomes of medical care for newborn infants, as well as the organizational context in which care is delivered.

The Case for Improvement

Public health and health care delivery systems in high-income nations have a great deal of which to be proud. Over the last century, they have combined to reduce infant and maternal mortality, as well as to prolong life expectancy to unsurpassed levels. During the twentieth century, infant mortality dropped from more than 100 per 1000 live births to about 5 per 1000 live births; maternal deaths dropped by 99% to about 10 per 100,000 live births.[45,52]

During the first half of the twentieth century, these improvements were driven largely by advances in public health, especially access to clean water, which dramatically reduced infection-related morbidity and mortality. However, although health care delivery conferred little benefit to population-based health during the first half of the century, there have since been demonstrable contributions to added life expectancy. Neonatal intensive care is a case in point. Although relatively few interventions (i.e., heated incubator care, intravenous nutrition, oxygen) were available to support sick newborns until the 1960s, technical and scientific advances in nutrition, physiologic monitoring, mechanical ventilation, and pharmaceuticals have made it possible for infants to survive previously fatal degrees of prematurity, genetic disease, or other (or acquired?) newborn disease.[49,51]

On the other hand, new medical treatments in combination with greater access and demand for care, a rise in the prevalence of chronic disease conditions, and inefficient market conditions have resulted in rising health expenditures, which have outpaced national incomes.[171] As a consequence, in the United States, health care consumes an ever-greater proportion of gross domestic product (GDP). In 2015, national health expenditures accounted for 17.8% of GDP, which severely strains the budgets of those paying for health care: consumers, through taxes, co-pays, deductibles, insurance, and reduced wage growth; companies,

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Abstract

The concern for quality and safety in health care has increasingly become an integral aspect of medical practice, both for individual practitioners and health care systems. The continued presence of variations in care and health outcomes signifies that strategies to improve and provide equitable care are necessary for perinatal medicine. Health care has benefitted from pioneers in quality improvement science both within and outside of the medical profession, and innovators working today continue to advance the field. This chapter gives a broad overview of the history and current state of quality improvement science, issues concerning data for improvement, and sustainment of initiatives, and also provides an example of a local quality improvement project.

Keywords

quality improvement
collaboratives
infant
newborn
organizational context

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through insurance; and state and federal governments, through obligations under Medicaid and Medicare.

In light of these resource constraints, a commitment to population health requires optimization of the value of each dollar expended for health care. However, research summarized in the sentinel Institute of Medicine of the National Academy of Sciences report *To Err Is Human* has consistently highlighted that health care delivery, including neonatal intensive care, falls short of its potential.[152] This report as well as its successor, *Crossing the Quality Chasm: A New Health System for the 21st Century*, present a clear and compelling challenge to all health care professionals to improve the quality and safety of the medical care for the patients and families they serve.[53]

Despite overwhelming evidence that deficiencies in quality and safety are widespread throughout the American health care system, many health care professionals in neonatology may feel that these problems do not apply to our clinical specialty. This is not the case. In neonatology, as in other clinical fields, opportunities for improving the quality and safety of medical care are substantial.

First, there is a large body of literature documenting tremendous variation in how medical resources are distributed, care is delivered, and outcomes are achieved. One of the best-known examples is the work by Wennberg and Fisher, who developed the *Dartmouth Atlas of Healthcare*.[160,161] For more than 25 years they have documented large variations in the efficiency of local delivery systems that are not explained by patients' health or preferences for care or by malpractice pressure and that do not seem to be associated with systematically better quality of care, patient outcomes, or satisfaction. In fact, this kind of variation has been shown across many settings (states, regions, cities, hospitals), many different types of patients (newborn, elderly), and many different types of care (medical, surgical, hospital, outpatient). Differences in care delivery and cost are almost entirely explained by differences in the volume of health care services received by similar patients, that is, "supply-sensitive care."[27,28] Higher-spending regions have more hospital beds, doctors, and specialists. Neonatology is no exception. The presence of this variation means that the goal of lowering costs while preserving quality is attainable and already achieved by many providers.

In the neonatal intensive care unit (NICU) setting, in addition to supply-sensitive care, dramatic variation in the processes and outcomes of care has been documented that cannot be explained by differences in case mix, suggesting differences in the quality of care delivery.[46,74,126,156] In a study of over 400,000 infants with birth weights of 401 to 1500 grams born from 2005 to 2014 and cared for at 756 Vermont Oxford Network–member NICUs in the United States, the ratio of the risk-adjusted rates for mortality and major morbidities at hospitals with the highest 10% of the rates to the risk-adjusted rates for hospitals. The lowest 10% of rates in 2014 were 1.2 for mortality and severe intraventricular hemorrhage, 1.7 for chronic lung disease, 1.9 for late onset infection and necrotizing enterocolitis, and 2.0 for severe retinopathy of prematurity. This means that for several major morbidities of very low birth weight infants, NICUs in the worst decile have rates nearly twice as high as those in the best decile. For comparison, an analysis including 22 million all-payer inpatient adult admissions demonstrated a 2.1-fold difference in risk-adjusted mortality rates and an 18.3-fold difference in central venous catheter bloodstream infection rates between top and bottom decile hospitals.[123]

Despite the variation among NICUs, there has been dramatic improvement in mortality and morbidities for very low birth weight infants in the last decade.[46] Health care–associated infection rates provide a striking example.[145] At the 756 US NICUs in the study described above, the rate of late bacterial (including coagulase-negative staphylococcus) or fungal infection significantly decreased from 2005, when 21.9% of infants had infections, to 2014 when 10.1% of the infants had infections. Dramatically, by 2014, 98% of NICUs had achieved rates for late onset infection as low or lower than the rates achieved by the best 25% of units only a decade earlier, and 91% of NICUs had achieved rates as low or lower than the best 10% of units.[155] Over the last decade, reduction of health care–associated infections has been at the center of national health policy efforts to improve the value of health care delivery, including aligning hospital payments with quality-of-care delivery. Widespread efforts in the neonatal community have proved successful in facilitating broad-based and sustained reductions in health care–associated infection rates and represent an encouraging blueprint for improvements in care in other areas.[51] However, the continued wide variation indicates that opportunities for improvement in many NICUs still remain.

Another indicator for quality deficits in the neonatal intensive care setting is the widespread delivery of inappropriate care—defined as underuse, overuse, and misuse of interventions.[15] Examples include the underuse of hand hygiene by NICU personnel,[100] the overuse of antibiotics, and the misuse of medications because of medical errors.

We have provided an example of underuse above. A good example of an effort to address overuse and misuse is the Choosing Wisely (www.choosingwisely.org) effort.[44] Medical interventions are frequently overused or misused and contribute to health care waste. Choosing Wisely, an initiative of the American Board of Internal Medicine, has challenged national medical specialty societies to identify Top Five lists of tests or procedures commonly used in their field whose necessity should be questioned and discussed with patients. The American Academy of Pediatrics Section of Neonatal Perinatal Medicine (SONPM) developed a Top Five list for newborn medicine using a process that began with a survey of neonatologists in SONPM and physicians, nurses, other NICU health professionals, and families of NICU patients at the Vermont Oxford Network Annual Quality Congress. The survey asked participants to provide from one to ten examples of tests and treatments that, in their opinion, met one or more of the following criteria:

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• BOX 5.1 Choosing Wisely Top Five List for Newborn Medicine

- Avoid routine use of antireflux medications for treatment of symptomatic gastroesophageal reflux disease or for treatment of apnea and desaturation in preterm infants.
- Avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection.
- Avoid routine use of pneumograms for predischarge assessment of ongoing and/or prolonged apnea of prematurity.
- Avoid routine daily chest radiographs without an indication for intubated infants.
- Avoid routine screening term-equivalent or discharge brain MRIs in preterm infants.

(1) evidence of lack of efficacy, (2) insufficient evidence of efficacy, or (3) unnecessary utilization of staffing or material resources. Next, a multidisciplinary expert panel of fifty-one individuals used a modified Delphi Process in which they scored each item. After the first two rounds, the items with the highest scores were subjected to a literature review and the strength and quality of the evidence were summarized using Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria.[40] The panel reviewed the GRADE summaries in the final round, and the five items with the highest total points in that round were included in the newborn medicine Top Five list. The final Top Five items are shown in Box 5.1.

Another important example of misuse are medical errors, which will be briefly discussed here. Current health care operations produce unacceptable rates of medical errors that result in patient injury or death. In *To Err Is Human,* the Institute of Medicine concluded that between 44,000 and 98,000 Americans die annually from hospital errors, killing more Americans than breast cancer, traffic accidents, or AIDS.[152]

Preterm infants in the NICU are particularly vulnerable to medical errors owing to their small size, physiologic immaturity, and limited compensatory abilities.[113,142] These circumstances make preterm infants particularly vulnerable to lapses in patient safety.[36,117] A study at two Boston hospitals has documented that errors in the process of ordering, dispensing, or monitoring medications occurred for more than 90% of the infants cared for in the NICU. Another study, using a trigger tool in the electronic health record, identified 0.74 adverse events per patient.[138] Fifty-six percent of these were deemed preventable. These estimates are likely only the tip of the iceberg.

Using a voluntary, anonymous, Internet-based error-reporting system established by the Vermont Oxford Network, Suresh and colleagues have documented a broad range of errors and near errors at 54 neonatal intensive care units.[147] Only about half of the reported events involved medications; the remainder involved a wide variety of errors in multiple domains of care. A study from eight Dutch NICUs found that incidents concerning mechanical ventilation, blood products, intravascular lines, parenteral nutrition, and medication dosing errors pose the highest risk to patients in the NICU.[143] Medication errors are a common problem in sick newborns owing to breakdowns in patient identification,[35] rapid changes in physiologic maturity, body weight, and volume of distribution requiring frequent dose adjustments. Although establishing the frequency of medication errors in the NICU is difficult, published studies indicate that medication errors in the NICU are common, ranging from 13 to 91 medication errors per 100 NICU admissions.[141] One study found that medication errors occurred in 57% of infants less than 27 weeks' gestation age, compared with 3% reported in the care of full-term infants.[63] In addition, NICU patients are more likely to experience a medication error than other hospital patients[138] and to experience more harm when a medication error occurs.

Finally, our health care delivery system has not reliably delivered many interventions that are deemed to be effective. McGlynn,[85] first in adults and later with Mangione-Smith in children,[82] demonstrated that Americans receive guideline-recommended care only about half the time. In the newborn setting, although antenatal steroids have been demonstrated to prevent respiratory distress syndrome and intraventricular hemorrhage after preterm birth, there remains wide variation in its administration to eligible mothers.[70,105,158]

The inability of the health care system to consistently deliver the highest quality of care results in enormous waste in human lives and valuable resources. Berwick and Hackbarth showed that "in just six categories of waste—overtreatment, failures of care coordination, failures in execution of care processes, administrative complexity, pricing failures, and fraud and abuse—the sum of the lowest available estimates exceeds 20% of total health care expenditures. The actual total may be far greater."[11]

In the United States, the care of preterm infants consumes about $35 billion annually (adjusted for inflation).[171] These health expenditures directly affect families and patients. About one half of the 1.45 million American families that filed for bankruptcy in 2001 cited medical causes, even though three-fourths of them had insurance at the onset of illness. About 10% of families cited childbirth-related and congenital disorders as the principal cause.[43]

With the recognition of the extent of the opportunities for improvement have come efforts by providers, provider networks, payers, nongovernmental organizations, and governmental agencies to improve the value of health care expenditures. At the provider network and health system level, efforts have focused on quality assurance and alignment of financial incentives. For example, quality assurance has been pursued through benchmarking of performance by provider networks such as the California Perinatal Quality Care Collaborative (CPQCC)[32] or the Vermont Oxford Network[48]; other statewide neonatal collaborative organizations, including those in Massachusetts, Ohio, Tennessee,

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North Carolina, Florida, Wisconsin, and Michigan; or by Medicare through its Hospital Compare Program. (http://www.medicare.gov/hospitalcompare/search.html). Significant efforts have been made to develop, evaluate, and harmonize quality measures through organizations such as the National Quality Forum. Public reporting[41,77,89] of quality measures and realignment of financial incentives away from a fee-for-service system toward a pay-for-quality system are becoming more widespread. More detail on these issues is provided later in this chapter.

At the hospital level, providers have engaged in quality improvement efforts to meet the expectations of this changing marketplace. Several institutions have undergone fundamental re-engineering of their health care delivery systems. Intermountain Healthcare, under the leadership of Brent James, has been a pioneer in this transformation and an example for many other health care systems.[54]

Intermountain's transformation has been the consequence of a growing recognition that the current model of health care delivery is in many ways outmoded and has failed to incorporate many of the lessons that propelled other sectors of the economy to large gains in quality and productivity. Even today in many health care organizations, the norms for care delivery are founded on a cottage industry–based delivery model wherein the physician artisan, through training, personal competence, and professionalism, devises individualized diagnostic and treatment regimens.[148] Although this approach may offer ideal care for some, it has limited ability to promote continual learning and improvement, because each physician may have a differing approach to a similar patient while firmly considering his or her own approach to be optimal. However, even the expert mind is fallible: (1) there is often a lack of knowledge regarding best therapy, resulting in variability of approaches and outcomes that are often not systematically tracked; (2) expert opinion has been shown to yield widely disparate results,[21] undermining its validity and reliability; (3) humans have inherent biases that are hardwired into our brains and lead to biased judgments[56,165]; (4) the expert mind is limited to processing information on 7 ± 2 variables simultaneously, often less than what is required in complex critically ill newborns; and finally (5) the exponential expansion of medical knowledge, with a doubling time reduced to 8 years, makes it very difficult to stay up to date on the latest science.[15,*] For all these reasons, a continuation of a craft-based approach to health care delivery has become untenable, and a new approach based on standardization and systematic use of clinical data and evidence rather than opinion must be pursued. Other industries have grappled with similar transitions and have provided a blueprint for improvement that is now actively pursued by many high-performing health systems. We briefly examine some of the historical foundations of these developments.

*The line of reasoning presented here reflects teachings by Dr. Brent James at Intermountain Healthcare's Advanced Training Program.

Brief History of Industrial Quality Improvement

A thorough description of the history of quality improvement is beyond the scope of this chapter. Instead, we provide a brief overview of stages of progress that are particularly salient for medicine.

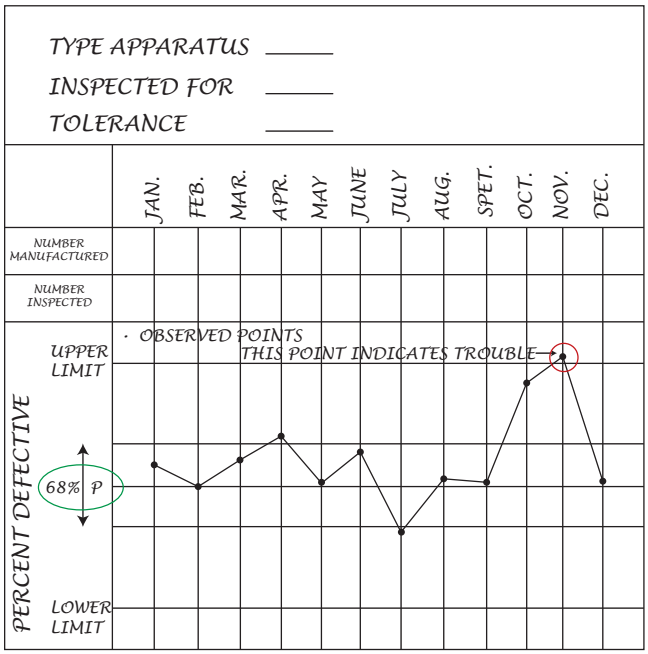
Before the late nineteenth and early twentieth centuries, quality was largely conceived of as quality assurance (oversight) and the result of personal excellence and training. For example, craftsmen organized in guilds chose their trainees selectively, often based on heritage, and provided formal apprenticeships. Mastery of the craft was achieved through training, supervision, and ongoing practice. The guilds secured a livelihood for their members through a combination of trade secrecy, price collusion, and monopolistic behaviors. The quality of labor and goods was the result of limited competition, quality controls by the authorities, and peer review. This approach is still prevalent in medicine today.

With the advent of industrialization and mass production of goods, a new field called scientific management emerged, a field that combined lessons from statistics, management, and economics. The goal of this movement was to increase productivity, reduce scrap, and reduce cost. Frederick Taylor (1856–1915) was one of the main innovators during this era. A mechanic and pattern maker by training, Taylor used time and motion studies and statistical production sheets to increase efficiency and workflow. Famous for his principles, Taylor held seminars on scientific management and worked as a consultant. One of his contractors was the Ford Motor Corporation, where Taylor played an important role in the success of the famous Model T. Gains in factory efficiency substantially lowered the overall cost of each car and enabled Ford to undercut the price of other cars on the market.

Taylor's methods transferred the control of production away from frontline workers to management and engineers, but his methods proved controversial. He was quoted as saying: "Hardly a workman can be found who doesn't devote his time to studying just how slowly he can work." This negative view of frontline workers and the drive to maximize their efficiency not infrequently resulted in social unrest. The large power differential between management and workers also tended to exclude those with the most detailed knowledge of production processes from participating in quality improvement.

The next leap in industrial management was achieved through the work of Walter Shewhart (1891–1967). An engineer, physicist, and statistician, Shewhart is known as the "father of statistical quality control." Before Shewhart, industrial quality mostly involved inspection and removal of defective products. Working at Bell Telephone Laboratories, he investigated variation in production systems and pointed out the importance of reducing variation in manufacturing processes, a concept that also offers an important lesson

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• **Fig. 5.1** Control chart by Walter Shewhart. (From http://www.firstmetre.co.uk/methods/tutorials/412/; accessed October 31, 2017.)

for medicine. Shewhart highlighted that continual process adjustment in reaction to process nonconformance actually increases variation and degrades quality. This behavior is called "tampering" and is common in patient care. Shewhart framed the problem of process variation in terms of assignable and chance variation (Deming later called these special and common cause variation) and developed the "control chart" (Fig. 5.1) to operationalize these concepts. A control chart or the related run chart, described later in the chapter, allows for simple tracking of process variation. It allows one to estimate the extent to which a process varies over time; the idea being that excessive common cause variation indicates a poorly controlled process that is not being addressed in a standardized way. It also identifies special cause variation according to a variety of patterns, including, for example, performance outside of statistical control limits. Both excessive common cause and special cause variation are indications of opportunities for quality improvement and should be further investigated and remedied. Shewhart emphasized the importance of bringing and keeping a production process in statistical control so as to predict and manage future output.[166]

William Edwards Deming (1900–1993) is perhaps the most influential thinker on quality during the last century. Inspired by Shewhart's teachings on statistical process control, Deming realized that these principles could be applied not only to manufacturing processes but also to the management of companies.

Deming is most famous not for his work in the United States but for his contributions to Japan's economic revival after World War II. While working under General Douglas MacArthur as a census consultant to the Japanese government, he famously taught statistical process control methods to Japanese business leaders. Difficult to imagine today, Japan once had a reputation for poor-quality products. Quality control relied largely on inspection, rework, or scrapping of finished products (control of the output). This production system produced lots of waste and became a major impediment to postwar reconstruction. Japanese industrial leaders and the American Engineering Corps recognized the need to change the quality of industrial output through process control rather than output control to rebuild Japanese infrastructure and industry. In 1950, on invitation from the Japanese Union of Scientists and Engineers, Deming gave a legendary lecture series to engineers, managers, scientists, and leaders of Japanese industry. His teachings sparked an industrial revolution and are widely credited with jump-starting the Japanese postwar revival. In the United States, Deming's teachings remained largely unknown until American industry was rapidly losing market share to the Japanese competition. In 1980, he explained his ideas in an NBC broadcast "If Japan can … why can't we?"

Deming's philosophy taught that by adopting appropriate principles of management, organizations can increase quality and simultaneously reduce costs (by reducing waste, rework, staff attrition, and litigation while increasing customer loyalty). When organizations focus on quality by improving their work processes, costs will fall. Oppositely, when organizations focus on costs, then quality will fall and costs will rise. Deming developed the Plan-Do-Study-Act (PDSA) cycle, which he called the Shewhart cycle, a strategic staple in modern quality improvement. He also developed 14 Key Points in Management and 7 Deadly Diseases (Box 5.2).

Deming was a strong opponent of performance appraisals, incentives, short-term thinking, and punitive benchmarking, all strategies currently proposed as "solutions" to increase the value of health care delivery. For Deming, the key to success was to practice continual improvement in the quality of products, uniformity of processes, and qualification of employees. He taught that all processes yield three parallel outcomes that must be measured: a work product (medical outcome), cost outcome, and service outcome (patient satisfaction). All processes contain built-in variation (common cause), but they are also affected by external factors (special cause). Management, not frontline workers, controls common cause variation through systems design. In opposition to Taylor's view of frontline workers, Deming cherished their contributions and felt that involving them in improving care processes would instill meaning and pride in their work.

Kiichiro Toyota, the founder of Toyota Motor Company, was among Deming's audience in 1950. Based on his lectures, Toyota developed the Toyota Production System (TPS), an integrated sociotechnical system that comprises its management philosophy and practices. The system is a precursor of the more generic "Lean Manufacturing." At the core of TPS is elimination of waste (muda) and total focus on reliable high quality through continuous improvement

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• BOX 5.2 Deming's Management Principles and Deadly Diseases

14 Management Principles

1. Create constancy of purpose toward improvement of product and service, with the aim to become competitive, stay in business, and provide jobs.
2. Adopt the new philosophy. We are in a new economic age. Western management must awaken to the challenge, learn their responsibilities, and take on leadership for change.
3. Cease dependence on inspection to achieve quality. Eliminate the need for massive inspection by building quality into the product in the first place.
4. End the practice of awarding business on the basis of a price tag. Instead, minimize total cost. Move toward a single supplier for any one item, on a long-term relationship of loyalty and trust.
5. Improve constantly and forever the system of production and service, to improve quality and productivity, and thus constantly decrease costs.
6. Institute training on the job.
7. Institute leadership. The aim of supervision should be to help people and machines and gadgets do a better job. Supervision of management is in need of overhaul, as well as supervision of production workers.
8. Drive out fear so that everyone may work effectively for the company.
9. Break down barriers between departments. People in research, design, sales, and production must work as a team, so as to foresee problems of production and usage that may be encountered with the product or service.
10. Eliminate slogans, exhortations, and targets for the work force, asking for zero defects and new levels of productivity. Such exhortations only create adversarial relationships, because the bulk of the causes of low quality and low productivity belong to the system and thus lie beyond the power of the work force.
11. a. Eliminate work standards (quotas) on the factory floor. Substitute with leadership.
    b. Eliminate management by objective. Eliminate management by numbers and numerical goals. Instead substitute with leadership.
12. a. Remove barriers that rob the hourly worker of his right to pride of workmanship. The responsibility of supervisors must be changed from sheer numbers to quality.
    b. Remove barriers that rob people in management and engineering of their right to pride of workmanship. This means, *inter alia*, abolishment of the annual or merit rating and management by objectives.
13. Institute a vigorous program of education and self-improvement.
14. Put everybody in the company to work to accomplish the transformation. The transformation is everybody's job.

7 Deadly Diseases

1. Lack of constancy of purpose
2. Emphasis on short-term profits
3. Evaluation by performance, merit rating, or annual review of performance
4. Mobility of management
5. Running a company on visible figures alone
6. Excessive medical costs
7. Excessive costs of warranty, fueled by lawyers who work for contingency fees

(kaizen). Lean production focuses on just-in-time use of materials and optimization of production flow (mura) in response to customer demand. Toyota's success derived from its innovative production engineering, which puts quality control in the hands of the frontline workers who can stop the production line and call for help when something goes wrong. However, production engineering is only part of Toyota's success. An equally important contributor to Toyota's success has been coined the Toyota Way, which embodies a relentless focus on the needs and desires of customers.

Another variant of statistical process control originally developed by Motorola in 1985 is called Six Sigma. Six Sigma comprises a set of tools and strategies for process improvement and seeks to improve quality by minimizing defects and variability. In Six Sigma, a defect is defined as any process output that does not meet customer specifications or that could lead to creating an output that does not meet customer specifications. The term "Six Sigma process" means that if one has six standard deviations between the process mean and the nearest specification limit, only 3.4 out of 1 million outputs will fail to meet specifications. To illustrate, if a hospital achieved Six Sigma in the administration of antenatal steroids, only about three in a million preterm infants would fail to receive them. Although technically this equates to only a 4.5 sigma process, the remainder is meant to account for the fact that over the long term, processes tend to become more error prone (entropy). A one sigma process produces 69%, a two sigma process produces 31%, and a Six Sigma process produces 0.00034% defective outputs. Current evidence suggests that much of health care operates at the one to two sigma level.[82,85] Six Sigma includes methodologies that lean on Deming's PDSA cycle, such as DMAIC for reengineering existing processes. DMAIC stands for define the problem; measure key aspects; analyze data for key relationships; improve the current process (using a set of specific techniques); and control the future process.

Industry has undergone fundamental changes over the last century. Scientific approaches to process improvement and management have resulted in dramatic increases in quality and productivity. Health care systems that have implemented change based on Deming's principles have seen similar benefits.

Industrial quality improvement methods have been applied to health care for more than 30 years. In *Curing Health Care: New Strategies for Quality Improvement*, Berwick and co-workers provided the initial evidence that the tools of modern quality improvement, with which other industries have achieved breakthroughs in performance, can help in health care as well.[10] Since then, the core ideas of quality improvement have been adapted to the particular

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needs of health care and implemented by health care organizations around the world. In neonatology, multidisciplinary teams from NICUs across the United States have applied quality improvement tools and methods to address the quality and safety of medical care for newborn infants and their families.[25,32,58,97]

An additional challenge for effective QI is that many health care providers have not been actively engaged in quality improvement efforts or exposed to the lessons from industrial engineering. Successful adaptation of these methods to the NICU setting requires recognition that health care is a process and that quality improvement requires process management. Albeit, a focus on care delivery processes, although necessary, is not sufficient. Rather, similar to the way that Deming expanded Shewhart's focus on process control to include organizational management, medical process management needs to be accompanied by efforts to optimize the organizational environment in ways that promote continual learning, teamwork, and adherence to the mission of serving patients and families.

Several theoretical frameworks exist to further our understanding of the complex interplay between organizational environment, process, and outcomes.

Definition and Conceptual Frameworks for Quality

Definition

The Institute of Medicine defines quality of care delivery as the extent to which health services provided to individuals and patient populations improve desired health outcomes. In *Crossing the Quality Chasm*, it developed the following six domains of quality of delivery of care.

Safety: Avoiding preventable injuries, reducing medical errors
Effectiveness: Providing services based on scientific knowledge (clinical guidelines)
Patient-centeredness: Care that is respectful and responsive to individuals
Efficiency: Avoiding the wasting of time and other resources
Timeliness: Reducing wait times, improving the practice flow
Equity: Consistent care regardless of patient characteristics and demographics

These domains are useful guideposts for practitioners in developing comprehensive quality programs and measurement systems.[47]

Conceptual Framework for Quality

Various authors have developed conceptual or explanatory models that provide users with a systematic understanding of the components and facilitators of high-quality health care delivery. These frameworks are often adapted from other sciences, including manufacturing, engineering, organizational theory, and psychology. The key to these frameworks and their application is an understanding that high quality of care delivery is the result of efforts to create a work environment in which people work together to reliably execute processes that are known to work or thought to work and to avoid care that is known to be unhelpful.

Donabedian: Structure, Process, Outcomes

Maybe the best-known framework for quality improvement was developed by Avedis Donabedian, MD (1919–2000). Donabedian was the first to collate evidence on the quality of health care delivery; he derived a simple structure, process, and outcome model of quality that has been the mainstay of quality research.[20]

Structure traditionally has been interpreted as the physical facilities and the training and education of staff. This notion has been expanded to include executive leadership, organizational culture, organizational design, incentive structure, and information systems and technology.[30] Processes comprise the activities clinicians and support staff undertake as part of or in support of care delivery. Outcomes are the results of these activities.

Pawson and Tilley: Realistic Evaluation

Similar but distinct frameworks have been described by others. Social scientists Ray Pawson and Nick Tilley highlight the importance of local context in their book, *Realistic Evaluation*.[95b] Realistic evaluation goes beyond the traditional cause-and-effect paradigm and poses that program effectiveness also depends on many interrelated contextual variables. This is formalized by the following formula: Context + Mechanism = Outcome (C + M = O). A given intervention does not necessarily work for the group as a whole but may be quite useful to some individuals, depending of their specific circumstances.

Batalden: Five Knowledge Systems

Batalden applies a similar formula to quality improvement and describes how knowledge systems combine to produce improvement: Generalizable Scientific Evidence + Particular Context → Measured Performance Improvement.[6] Each of the five components in this formula is driven by knowledge. Knowledge of scientific evidence stabilizes context as a variable and reduces its effect on what is being studied. Knowledge of context is gathered through inquiry of local care processes and culture. Knowledge on the benefits and side effects of the intervention is developed through appropriate measurement over time. The plus symbol represents knowledge about the locally available modalities (forcing functions, academic detailing, standardization, etc.) for implementing the scientific evidence. The right arrow represents knowledge required for execution of the intervention. Acquiring all five kinds of knowledge requires both scientific and experiential learning and is critical to optimizing quality improvement.

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Complexity Theory

Complexity theory is another framework that has seen increasing prominence in health care. Complexity theory recognizes that health care delivery is nonstatic, fluid, and interconnected. This makes improving health care delivery quite different from improving a machine. Providers must give consideration to how changes in a care delivery process affect other actors in the system. Driving out variation through rigid care guidelines may not improve overall care delivery because perceived improvements in one area may have detrimental effects in others. In addition, even when evidence-based, guideline-driven care needs to account for individual patient complexity. Quality improvement according to principles of complexity uses global guideposts and promotes interdisciplinary, small-scale experimentation to test the effect of change on the health care delivery system.[101,102]

Translation of Frameworks into Action

Frontline application of quality improvement efforts draws from the various theoretical frameworks presented in the preceding section. In the following, a few approaches are highlighted that are commonly applied in neonatology. For practitioners, the practical application of quality improvement work may be more effective if supported by a formal approach, as provided by Dr. Deming (integration and standardization as practiced by Intermountain Healthcare), Lean, Six Sigma, or the Model for Improvement, advocated by the Institute for Healthcare Improvement. Each of these frameworks makes use of various management tools to assist with project planning and execution, including team organization, process mapping, problem identification, problem resolution, task prioritization, and execution. We briefly mention several of these in the section titled Quality and Safety Applied. However, a full description of these tools is beyond the scope of this chapter. For more detail on these, refer to the extant literature.

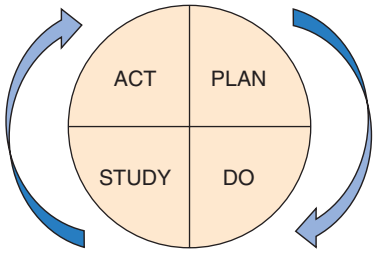
Model for Improvement

The Model for Improvement has been widely adopted as a strategy for collaborative quality improvement in the neonatal community.[150] It is based on *The Improvement Guide*, by Langley and Nolan, and identifies four strategic elements of successful process improvement[65]: (1) specific and measurable aims, (2) measures of improvement that are tracked over time, (3) strategic changes that will result in the desired improvement, and (4) a series of PDSA cycles during which teams learn how to apply crucial change ideas.[150] These principles correspond to three questions asked of collaborative teams (Fig. 5.2).

The first question, which refers to the aim(s) of the project, is "What are we trying to accomplish?"[150] In other words, what are the main outcomes that the team is trying to change or improve? There are several concerns when considering the aim of a prospective project. Are there historical and/or peer benchmark data to suggest that there is a problem in the local NICU? Is there a variation in the outcome among NICUs to suggest that variations in practices can lead to differences in outcomes? Are there evidence-based practices that have been shown to improve the outcome of interest? The aim should be well defined and realistic. It should also be quantifiable and encompass a defined time period.[22]

One helpful framework in crafting a well-designed aim statement is the "SMART Aim" approach (Box 5.3). An example of a suboptimal aim statement may be, "Reduce

- What are we trying to accomplish?
- How will we know that a change is an improvement?
- What change can we make that will result in improvement?



• **Fig. 5.2** The Model for Improvement.

• BOX 5.3 SMART Aim Statement

Specific
- *What exactly are we going to do for whom?*
  - Should specify target population, setting, and actions.
  - Uses verbs such as train, increase, decrease.

Measurable
- *Is it quantifiable and can we measure it?*
  - Source and mechanism for collecting data are identified, and collection of data is feasible.
  - Baseline data are available to document change.

Achievable
- *Can it be done (time frame and resources)?*
  - Project is feasible with available resources and appropriate in scope.
  - A more time-limited aim may make it easier to collect relevant clinical and cost data.

Relevant
- *Will this objective have an effect on the desired mission/broader goal?*
  - May be informed by literature review, best practices, or your theory of change.

Time Bound
- *What is the time frame for change? When will this be accomplished?*
  - Indicate a specified and reasonable time frame in the aim statement.
  - Take into consideration the environment, scope of change, and how it fits into the overall work plan.

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infection rates in our NICU." Although a worthy goal, that statement is vague, and it will be difficult to assess if it has been accomplished. In contrast, the following aim statement is more specific and follows the SMART Aim approach: "Reduce by 50% the number of central line–associated bloodstream infections as defined by the Centers for Disease Control in infants born at 24 to 30 weeks' gestational age in the NICU by using an insertion and maintenance bundle over a 12-month time period."

The second question, corresponding to the measures of the project, is "How will we know that a change is an improvement?" As a team embarks on a quality improvement project, one can consider three main groups of measurements: outcomes, processes, and balancing measures. The outcome measure is typically a clinical outcome, such as nosocomial infection or bronchopulmonary dysplasia. A process measure related to reduction of nosocomial infection could be the use of an insertion checklist. In some instances, a process measure can serve as the main outcome of a quality improvement project, when that process measure has been clearly linked to a benefit in clinical outcomes. Examples are a focus on improving the rate of antenatal steroid administration for premature birth or on increasing breast milk provision for premature infants. A balancing measure for increased breast milk provision for premature infants may be growth velocity, which may have a negative correlation.[114] The idea behind a balancing measure is to ensure that the quality improvement intervention does not generate unwanted secondary effects.

The third question, which corresponds to the strategic changes that will lead to improvement, is "What changes can we make that will result in improvement?" These changes should be evidence based, but must also take into account local cultural and organizational characteristics. Plsek has coined the term "potentially better practices" rather than "better" or "best" practices to stress that no change idea is truly better or best until it has been adapted, implemented, and tested in the local context in which it will be applied. This is consistent with the ideas surrounding "context" described by Pawson and Batalden, as noted in the previous section on frameworks for quality. The PDSA cycles in the Model for Improvement can be conceptualized as an application of the scientific method (see Fig. 5.2). Each PDSA cycle is a test of a hypothesis of how a specific change will affect the system.

Integrated Quality Management

Another method for quality improvement in health care focuses on the elimination of process variation. This approach derives from Deming's work and has been adapted with success for health care by several organizations. For example, Dr. Brent James, former Chief Quality Officer and Executive Director, Institute for Health Care Delivery Research, Intermountain Healthcare, helped refocus the health systems quality improvement efforts on process standardization, active management, and ongoing organizational learning. Work units identify high-value clinical processes and set up multidisciplinary provider teams to develop evidence-based detailed care pathways (shared baselines) to execute these processes in a consistent, reliable manner. The name *shared baseline*, rather than protocol or guideline, highlights its development and ongoing refinement by the local work unit. Control rests with frontline care providers, not managers. The purpose of these shared baselines is to minimize the variation that is driven by providers and not accounted for by patient need. Providers are encouraged to deviate from the shared baseline as warranted by the needs of individual patients. This approach allows providers to bring their expertise to bear on the clinical situations that truly warrant an alternative treatment approach. It also effectively ameliorates concerns regarding "cookbook" medicine, given an explicit expectation that no guideline perfectly fits any patient. On the contrary, providers are asked to assess situations where they have deviated from the shared baseline. This information is then used to modify the shared baseline when appropriate. Overall, the use of shared baselines makes the workflow more predictable, efficient, safer for patients, and less stressful for nursing staff.[18,54,94]

Similar to the Model for Improvement, the modified Deming approach uses key measures to track cornerstones of the process, clinical outcomes, service outcomes (such as patient satisfaction), and cost. The shared baseline is eventually integrated into the electronic medical record and managed according to results. The key to promote organizational learning and standardization is tracking of process deviations and systems to modify the shared baselines according to ongoing provider input. To facilitate the success of local projects, strategic staff from clinical work units receive training and technical support for their improvement work from a centralized quality improvement institute.[54] Institutional commitment is foundational to achieving excellence in care delivery in the NICU. Neonatal providers often embark on grass root QI efforts that may not align with hospital leadership priorities. Close communication and support is necessary to assure that efforts are properly prioritized, aligned with frontline and leadership needs, and executed. Sufficient resources for QI management are critical for their staff to carry out "two jobs," their primary work duties, as well as efforts to do their jobs better.

Lean

Lean methodology has become increasingly popular with health care administrators and providers. Lean focuses on reducing process waste and improving process flow.[169] The seven wastes on focus with Lean are overproduction, inventory, waiting, transportation, defects, staff movement, and unnecessary processing. Lean has an intense focus on customer, patients, and families, and encourages users to examine their process steps and eliminate those that do not provide value to customers. A focus on flow attempts to optimize the use of time and resources.

These approaches and others are guiding practical and theoretical improvement work. Although meaningful in

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their differences, their common thread lies in the centrality of managing work processes while optimizing the care delivery environment. Organizational goals for high-quality care delivery and patient safety are undergirded by strategies that encourage continuous monitoring of processes and outcomes, facilitate continuous learning, and minimize unwarranted waste and process variation.

Data and Methods for Quality Improvement

Not everything that can be counted counts.
Not everything that counts can be counted.

—ATTRIBUTED TO ALBERT EINSTEIN

It is essential that quality improvement be data driven. First, to identify opportunities for quality improvement, data are necessary to determine performance relative to historical performance or peer-derived benchmarks. Second, once quality improvement is undertaken, data are used to track the effect of changes and interventions, both to assess the impact of quality improvement and also as an essential component of the improvement process to determine next steps. Third, data are essential to further the knowledge of how specific processes and factors may influence quality measures. In addition to traditional concepts of data in the context of quality improvement, there is also an increasing need to be aware of the environment in which quality improvement occurs.

Data Elements for Assessment

A strategic component of quality improvement is a standardized data collection system to create benchmarks for performance, both historically and across centers. In following Donabedian's framework, the main data types in such collections can be categorized as structural or contextual measures, process measures, and outcome measures (including medical outcomes, cost, and service outcomes such as family satisfaction with care). Characteristics of infants and their families may have important influences on clinical outcomes and are discussed in conjunction with these measures.

Structure and Institutional Context

Although the focus of quality improvement has largely been on changing processes of care, often narrowed down to a list of things "to do," there is an increasing awareness of the importance of the context in which improvement activities occur. A focus on care context features prominently in several of the frameworks discussed in the preceding. Because quality improvement in our field often relies on changing systems of care as well as the behavior of many individuals who are part of the health care team, including leaders, frontline staff, and administrators, the organizational environment may be an important aspect of performance. The goal of ascertaining measures of the structure and context of care delivery is an attempt to identify elements that if modified lead to better outcomes of care. Such data are typically obtained through surveys of either essential informants or frontline care providers.

Maybe the best-examined aspect of structure is the patient-to-nurse ratio. In adult and pediatric intensive care unit settings,[3] rising patient-to-nurse ratios have been linked to worse clinical outcomes and higher mortality. In neonatology, this link is less well understood.[64] Although most studies imply a benefit of greater staffing ratios, this finding is not uniform.[140] Nurse staffing ratios may be suboptimal in general and associated with nosocomial infection rates.[122] Other examples of structural measures include academic teaching status, 24-hour coverage by an in-house intensivist, patient volume, and level of care.

Contextual measures are different from traditional measures in that they attempt to assess the links between how care delivery is organized and supported by the institution and quality of care. Kaplan and colleagues developed a framework for examining these linkages and coined it Model for Understanding Success in Quality (MUSIQ).[57] This article highlights different components that support improvements in the processes and outcomes of care delivery at various levels of the institution, including characteristics of the improvement team (diversity, physician involvement, leadership) and the NICU, as well as higher-level organizational functions (quality improvement leadership and administrative support).[59] Validation studies in support of this model are currently underway.[37]

One well-researched aspect of care context is safety culture. NICU safety culture describes the shared norms of leadership, staff, and the organization with regard to patient safety, or simply, the "way we do things around here." Culture influences quality of care in important ways. Whether a process is failure-proof depends on how reliably it is implemented. Non-adherence to care standards may reflect a clinical need but also lack of a standard or willful disregard. Safety culture assessments attempt to capture safety context through surveys that ask about health worker perceptions. The measured domains are called climates (i.e., teamwork climate or safety climate). The term "climate" reflects that perceptions are shared among health workers (i.e., they cluster more strongly within a work unit, e.g., the NICU) than between work units.

Ongoing assessment of safety culture is a requirement for hospital accreditation by the Joint Commission, an accreditation agency that assesses safety and quality of care. There are several validated survey tools to measure safety culture.[24,113,144] The Safety Attitudes Questionnaire (SAQ) reflects caregiver attitudes on safety culture, is psychometrically sound, and has demonstrated wide interinstitutional variation across NICUs.[112,113] Safety culture, as measured by the SAQ, has been linked to a variety of clinical and organizational outcomes. Most famously, this instrument was used by Pronovost and co-workers in their implementation of the Comprehensive Unit-based Safety Program

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(CUSP) in 103 adult ICUs in Michigan, where through implementation of a checklist and a focus on teamwork and safety, median catheter-related bloodstream infection rates were reduced to zero.[115] This program has been endorsed for implementation in all ICUs by the US government. In a study of 44 NICUs and over 2000 respondents, teamwork was associated with health care–associated infections among very low birth weight infants, such that the odds of an infant contracting an HAI decreased by 18% with each 10% rise in NICU respondents reporting good teamwork.[109] Of note, physicians tend to rate safety culture significantly higher than nurses and other personnel, highlighting an apparent disconnect in perceptions, which should prompt some reflection on behalf of physicians.

Various approaches to improving safety culture have been described. Among them are leadership engagement via Leadership WalkRounds[131] and a teamwork training curriculum developed by the Agency for Healthcare Research and Quality called "Team Strategies and Tools to Enhance Performance and Patient Safety" (TeamSTEPPS). The intervention includes assessment, training, and sustainment phases focused on four core competencies: (1) team leadership, (2) situation monitoring, (3) mutual support, and (4) communication.[17] This approach has been used in multiple health care settings,[84,124] including one reported intervention, which included NICU providers and demonstrated an improvement in perceptions of teamwork.[7]

Safety culture, its improvement, and associations to outcomes of care for sick newborns are topics of active research. Instructions on how to use the Safety Attitudes Questionnaire for the promotion of safety and teamwork goals have been published.[132]

Another emerging aspect of care context is caregiver resilience, operationally often defined as the absence of burnout. Burnout describes a condition of fatigue, detachment, and cynicism resulting from prolonged high levels of stress.[108] In the critical care setting, burnout rates may be consequent to high workload and frequent changes in technology and guidelines, as well as emotional challenges of dealing with critically ill patients and their families.[13,103,120,154] Burnout affects between 27% and 86% of health care workers,[87,137,151] with over half of physicians reporting burnout and around one-third of nurses and physicians meeting criteria for severe burnout.[8,134,136,137] Burnout has negative consequences for health care providers, organizations, and patient care (Box 5.4).

Burnout is usually measured through validated survey tools, such as the Maslach Burnout Inventory[83] or abbreviated versions thereof.[108] A recent systematic review identified that both organizational as well as individually focused interventions are effective in reducing physician burnout.[162] Additional research is being conducted to further test and refine measurement and interventions, and health care systems are increasingly recognizing the need and benefits of supporting staff resilience (for an example, see http://wellmd.stanford.edu).

• BOX 5.4 Impact of Burnout in Health Care

Health Care Professionals

Higher mortality rates[1]
More arteriosclerotic disease[61]
Worse work-life balance[14,29,38]
More depression[26]
More post-traumatic stress[87]
Worse sleep quality[19]

Organizational Functioning

Lower job satisfaction[135,139,170]
Lower safety and teamwork[108,130,131]
More turnover[86,88,139]
Lower sense of control at work[86,139]

Patients

Higher rates of medical errors[104,133,135,159,163]
Higher rates of suboptimal care[120,135]
More medical lawsuits[38]
Higher infection rates[16,135,149]
Less family support[120]
Higher mortality[2]

Overall, context provides the soil on which efforts for high quality of care either thrive or wither. Leadership recognition of these factors is critical; to provide high quality of care of our patients, we must also care for ourselves and our colleagues.

Processes

Process measures are an important element of quality assessment as certain processes of care may be linked to the quality of outcomes. As noted, reducing process variation has been a strategic component of quality improvement, going back to Shewart and control charts to detect deviations. The study of how certain process measures relate to outcomes can also contribute to the broader evidence basis for best clinical practices. An example of processes and practices that could relate to the reduction of line infection in the NICU is shown in Box 5.5.

In those cases in which there is a clear evidence base for the link between a process and a desirable or undesirable clinical outcome, the process measure itself can serve as a quality measure. Antenatal steroids have been demonstrated in clinical trials to prevent respiratory distress and reduce morbidity, and their use in eligible populations is considered an important measure of the quality of perinatal health care delivery.[70] Thus, a goal of using process analysis for quality improvement is to detect the underuse of processes that have been shown to improve outcomes, such as the use of antenatal steroids. Process analyses can also detect the overuse of processes that have been demonstrated to be detrimental, such as the provision of postnatal steroids for chronic lung disease.

In addition to therapeutic processes, preventive measures and screening tests can also be a component of measuring

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• BOX 5.5 Processes to Reduce Central Line Infections in Neonates

Checklists	• Cognitive tool to ensure best practices in insertion and maintenance
Dedicated Line Cart	• To have supplies readily available for line insertion
Insertion Practices	• Assessment of need for catheter • Maximal sterile barriers—patient sterile covering and clinician sterile precautions (gown, gloves, mask, hat) • Hand hygiene • Appropriate site preparation and dressing
Maintenance Practices	• Daily assessment of line necessity • Daily assessment of line site to check for signs of infection or infection risks • Dressing change practices • Appropriate catheter access practices, including hub scrub and hygiene • Appropriate tubing change practices

quality of care. Because impaired vision or blindness from retinopathy of prematurity is a potentially preventable condition, timely screening exams are an important measure of the quality of care delivery.[5]

The study of the relationship of processes to outcomes can be an ongoing aspect of quality assessment. The clinical impact of various processes may help to prioritize resources and quality improvement activities when it can be demonstrated that improving processes leads to improved outcomes. Breast milk for premature infants has been shown to have a protective effect for necrotizing enterocolitis. When a quality improvement activity to increase breast milk expression and provision for premature infants leads to decreased rates of necrotizing enterocolitis, the process measure of breast milk provision can be considered a crucial quality measure.[73]

Another use of process measure collection may be for compliance tracking. This can be particularly useful when certain clinical outcomes are rare but are known to be associated with certain practices. For example, vertical infection of a newborn with hepatitis B may be quite rare, but rates of appropriate maternal and newborn testing and prophylactic treatment and immunization can be tracked and may serve as a risk signal.

In addition, compliance measurement is critical to institutional learning. Providers that do not comply with care guidelines may either do so unintentionally, a signal that the default pathway has not been instituted effectively, or intentionally. Intentional noncompliance may lead to eventual improvement of the care guideline as the provider group learns about an aspect of patient care not previously so considered, or in the case of a provider's willful refusal to adhere to the group standard, may have implications for personnel management.

Outcomes

Outcomes are the end results of the clinical care delivery process and represent what patients, families, and providers truly care about. Pragmatically, outcomes are negative events such as death and morbidity, and quality is inferred on the basis of a lower-than-expected negative event rate. It is important to record a wide spectrum of outcomes, but for an outcome to serve as an effective quality indicator, evidence must be strong that variations in process or structure can change its occurrence. A widely used outcome measure is health care–associated infections or their more specific cousin, central line–associated bloodstream infections. These infections are important quality indicators because they cause significant morbidity, and incorporating certain processes of patient care (e.g., hand hygiene and intravenous line care) has been shown to reduce their occurrence.

The effort to reduce such infections, although still a work in progress, has served as a success story and model for other quality improvement activities. Studies of health care–associated infections in the NICU have shown wide variation by hospital, signifying opportunities for improvement, leading to successful efforts to reduce infections at collaborative levels, and contributing to identification of high performers who can serve as role models for other NICUs.[72,96,128,168]

Balancing Measures

In addition to the main outcome measures that are the targets of quality improvement, it is also important to consider which balancing measures to track. In the midst of improving quality for one aspect of clinical care, it is possible that a related outcome may be adversely affected. For example, a decrease in growth velocity may be observed with a focus on improving breast milk feeding rates. Balancing measures may be clinical outcomes such as growth or morbidities but can also include other aspects of quality such as cost or patient satisfaction. These balancing measures should be collected in or close to real time to detect any unintended consequences of quality improvement projects. Although traditionally balancing measures were developed to assess the possibility of negative effects, they are also emerging as important motivational indicators that the new way of doing things is safe. This is an important facilitator of change in that a major roadblock to adopting a new way of practice is the concern that the new approach will fall short, leading to missed or ineffectively treated cases.

Assessing the Total Impact of a Quality Improvement Initiative

In the preceding discussion, the essential role of data in conducting a quality improvement initiative has been stressed. Although a successful initiative typically presents data on the extent to which processes ("hand washing has increased 50%") and outcomes ("catheter-related infections decreased by 50%") have been improved, these statistics fail to capture

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the initiative's total impact and economic consequences. Successful initiatives have significant impact across many domains. For example, a decrease in catheter-related infections might reduce the need for high-intensity nursing, equipment (infusion pumps), materials (catheter setups), laboratory and radiographic studies, blood products, antibiotics, and parenteral nutrition solutions. It might also decrease the mortality, pain, and discomfort experienced by the infant and the stress experienced by the family, and may improve responses to satisfaction surveys. By working in collaboration, many of these impacts can be objectively measured, with quantitative data obtained from routine administrative sources used by nursing, central supply, pharmacy, laboratory, and radiology. Presenting the total impact of a quality improvement initiative is an effective way to demonstrate its value to hospital administration as well as to the many individuals and departments whose support is essential to the NICU. The impact on resource utilization can also be translated to dollar savings.[121]

Risk Adjustment/Fair Comparisons

For performance assessment *within* an organization, tracking a process or outcome measure over time may be sufficient to spur quality improvement activities and assess their impact. However, for comparative performance assessments *between* organizations, as currently applied for purposes such as setting benchmarks, pay-for-performance, or public reporting, further statistical and methodologic considerations are required to ensure fair comparisons.

The use of risk adjustment levels the playing field regarding the reporting of patient outcomes by accounting for expected rates of positive or negative outcomes. Expectation is pivotal to the notion of quality, because quality may be inferred from the relation between an observed and an expected outcome. In the context of clinical medicine, expected outcome includes the extent of risk features and co-morbidities that are not under the control of the clinician. Does hospital A with an observed neonatal mortality rate (NMR) of 5 provide better care than hospital B with an observed NMR of 10? Without knowing the expected rate of mortality at these two hospitals, it is impossible to assess their relative quality of care. For example, hospital B might be a tertiary care center, in which an observed NMR of 10 is much lower than its expected NMR. Hospital A could be a primary care hospital, in which an observed NMR of 5 is much higher than its expected NMR.

Mathematically, risk-adjustment methods level the playing field regarding comparisons through the use of one of the variants of multivariate regression. A model is generated in which not only the outcome of interest among the sample (NICUs) is assessed, but also statistically or clinically important characteristics of the NICU and its patient population are taken into account simultaneously.

To illustrate, patient characteristics used in risk adjustment for neonatal quality assessment will encompass both maternal sociodemographic and clinical factors as well as infant factors. In considering what variables to use in risk adjustment, there are two essential requirements. First, the variable should be a risk factor for the outcome of interest. Second, the variable should not be under the control of the entity being evaluated. Birth weight, gestational age, plurality, intrauterine growth, birth defects, and gender are risk factors that are commonly used as risk adjusters to control for institutional differences in case mix so as to make fair comparisons across NICUs.[118] They are highly predictive of morbidity and mortality and are not under the control of clinicians in the NICU. Mode of delivery and antenatal steroid use are also important predictors of mortality. Although not under the control of the neonatologist, they may be under some control of the obstetrician. If neonatal mortality is used to compare the quality of care across NICUs, one can include these two factors in the risk adjustment. However, if the goal is to use neonatal mortality to compare the quality of care across perinatal services, these factors should probably not be included, because they are at least partially under the control of the obstetrician and perinatal system.

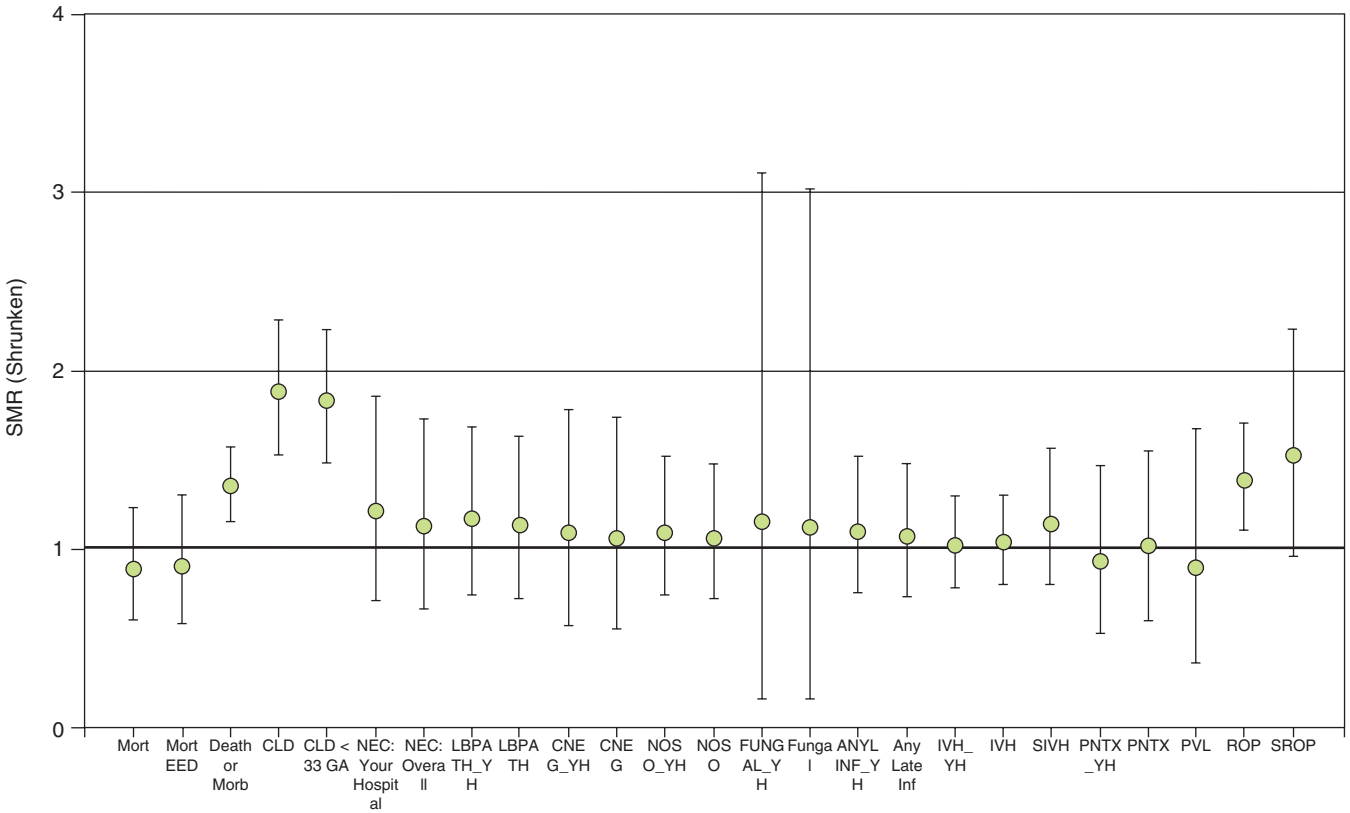
Using this approach, the expected number of deaths (or adverse outcomes) at each NICU can be determined based on the characteristics (risk-adjustment variables) of infants treated at that NICU. The ratio of the observed number of deaths (or adverse outcomes) to the expected number of deaths (or adverse outcomes), called the standardized mortality (or morbidity) ratio (SMR), can then be calculated.

Rather than reporting the SMR as a measure of performance, an alternative approach is to calculate the difference between the observed and expected number of cases (O-E), where the expected number can be determined using the same regression approach described earlier. The Vermont Oxford Network routinely reports the O-E for mortality and major morbidities to its members using a method that accounts for risk using regression models and accounts for chance variation using an empirical Bayesian shrinkage method. These data are reported with 95% confidence intervals in table and graphic form to give an individual center an estimate of its performance in relationship to the overall group (Fig. 5.3). It is important to recognize that all estimates of risk-adjusted performance must be interpreted carefully and that these estimates are only the first step in assessing the quality of care.[127]

Because the statistical power to detect quality of care outliers using multivariate risk-adjustment methods based on a single year may be low, it may be useful to consider performing analysis on data combined from several years. Even employing very accurate predictive models and combining several years of data might not be able to overcome the problem of a small sample size in some NICUs. In this case, multivariate risk models may be useful for identifying individual infants who died despite having a low predicted probability of death. The medical records of such infants can then be chosen for detailed review and audit.

Recognizing that risk adjustment based on infant characteristics is imperfect, there is value in reporting comparative

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• **Fig. 5.3** Data report from the Vermont Oxford Network. This sample screenshot from the Vermont Oxford Network Nightingale Internet Reporting System for a fictitious center displays risk-adjusted estimates for key performance measures for infants 501 to 1500 grams. The figure displays standardized ratios (SMR = Observed/Expected) and 95% confidence intervals. Estimates are calculated using an empirical Bayesian method.[98,99] Authorized users at network member centers have secure access to confidential reports for their own center. SMR, Standardized mortality (or morbidity) ratio. (Courtesy of the Vermont Oxford Network, Burlington, VT.)

performance data stratified by the type of NICU. The Vermont Oxford Network provides such stratified comparisons to its members. The Committee on the Fetus and Newborn of the American Academy of Pediatrics has proposed a NICU classification system that may be useful for this purpose.[4] In addition to reporting standardized ratios of observed-to-predicted rates for mortality, the Vermont Oxford Network and the CPQCC provide their members with the opportunity to compare important morbidities with similar centers, with the goal of using these data to identify opportunities for improvement. However, there is a caveat to this approach. In certain situations it may be quite appropriate to compare outcomes based on only patient characteristics and not on NICU characteristics. This is especially true in investigations that focus on whether infants are born and receive care at appropriate-level NICUs. Studies have shown that lower level of care and patient volume is associated with neonatal mortality for preterm infants.[60,99] In this situation, it would be critical to directly compare NICU performance based on patient characteristics and not adjust for level of care at the hospital of birth. Otherwise, a NICU that inappropriately retains patients beyond its capacity would get an unwarranted "free ride." In situations in which lower-level NICUs are always only compared with each other, there may be no poor performers identified in that group, even if they are all performing worse than higher-level NICUs. Therefore, if entire strata of NICUs are performing poorly, it may be worth questioning the stratification of quality comparisons. For example, the CPQCC provides both level of care adjusted and level of care unadjusted estimates. It also allows comparison with hospitals within one's perinatal region.

Although multivariate prediction models that are based on admission variables perform well for infants with very low birth weights for whom gestational age or birth weight is highly predictive of mortality, physiologic measures of disease severity have been felt to be necessary to achieve similar predictive performance for larger, more mature infants. In addition to stratification and multivariate modeling based on patient characteristics that are present before therapy is initiated, it is also possible to perform case mix adjustment based on comparable severity of illness.

Several physiology-based severity scores have been developed for use in neonatal intensive care, including the Clinical Risk Index for Babies (CRIB),[148a] which uses infant characteristics within the first hour after birth; the CRIB

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II[95a] score (a five-item version of the CRIB score); the Score for Neonatal Acute Physiology (SNAP), a physiology-based illness severity score based on measurements of 26 routine clinical tests and vital signs; the SNAP-PE, an additive score based on birth weight, 5-minute Apgar score, size for gestational age, and SNAP; and SNAP II (a six-item score based on variables collected during the first 12 hours after admission).[119]

Zupancic and co-workers compared the SNAP and SNAP-PE scores, which include physiologic measures with the Vermont Oxford Network risk adjustment based on basic patient descriptors. Unexpectedly, the authors found that models based on perinatal descriptors perform similarly to those based on physiologic measures.[172]

These illness severity scores are potentially useful for comparing mortality rates and other outcomes at different NICUs. One drawback of such scores is their use of variables that are measured up to 12 hours or more after NICU admission. This raises two potential problems. The first problem, as stated by Richardson and associates, is that the longer the period of observation, "the more contaminated it becomes with the effects of successful (or unsuccessful) treatment and thus no longer reflects admission severity."[118] The second problem is that the observed severity of illness in the first hours of life may differ from the observed severity of illness in the very same infant in the first 6 hours following transfer and admission to another unit.

The Transport Risk Index of Physiologic Stability (TRIPS) is a scoring system that was developed to assess infant transport care. Based on the collection of only four variables (temperature, respiratory status, systolic blood pressure, and response to noxious stimuli), this approach predicted 7-day survival (area under the receiver operating curve [AROC] of 0.83) and severe intraventricular hemorrhage (AROC of 0.74).[75] This scoring system has also been used to evaluate the effectiveness of different Canadian transport systems. An advantage of this score is that it assesses infant condition in a time frame that is not limited to the first 24 hours of life with very high prediction characteristics. CPQCC modified TRIPS to take into account the use of cardiac pressor medications and the level of oxygen in intubated infants and obtained an AROC for prediction of 7-day survival of 0.88 in all infants and 0.86 in infants transported after day 7 (calculator available at http://www.health-info-solutions.com/CPQCC-CPeTS/tripsmobile/tripsmobile.html). CPQCC also developed a quality of transport estimate, the Quality Change Point 10th Percentile (QCP 10), a benchmark of the greatest deterioration in TRIPS score seen in 10% of the transports by top performing teams. The risk of death increased 2.4-fold in infants whose deterioration exceeded the QCP 10.[34]

Tyson and colleagues have used the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network database to develop a multivariable model to predict survival and neurodevelopmental outcome for preterm infants of 22 to 25 weeks' gestation based on birth weight, gestational age, gender, multiplicity, and antenatal steroid status.[153] This estimation has been validated in a population-based cohort that includes a diverse group of community and academic NICUs.[69] An online calculator is available to estimate survival and survival free of disability for specific values of the five variables in the model (http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/epbo_case.cfm). While the data used for the calculator are dated, an updated version is under construction.

Another group of variables that may be included in datasets are identifiers. Because of the requirements of Health Insurance Portability and Accountability Act (HIPAA), it may be safer to remove personal identifiers such as name and medical record numbers when using data for quality improvement. However, at stages of development when identifiers are available, the opportunity exists for linkage to other datasets so as to increase the breadth of data for quality assessment and risk adjustment. However, even when identifiers are not available, strategies for data linkage in perinatal care exist by using combinations of variables such as birth weight, gender, hospital of birth, and maternal data, as described in the next section.

Although the importance of risk adjustment for fair comparison of quality among providers has been discussed, there are two other important aspects regarding patient characteristics. Intrinsic to the risk-adjustment process is estimation of the contribution of risk factors to the outcome of interest. First, by identifying certain characteristics that are associated with an adverse outcome, we may learn about the physiology of a disease process, as well as identify high-risk groups for study or intervention. Second, in some instances, it may be beneficial to use observed rates in assessment without considering patient characteristics for risk adjustment. This may be true for processes in which health care systems and clinicians would play a larger role than biologic factors. For example, regardless of patient characteristics, it may be argued that processes such as antenatal steroid administration or retinopathy of prematurity screening may be a reasonable goal for all eligible infants, regardless of sociodemographic factors. For example, risk adjustment for race/ethnicity for these measures could have the potential to perpetuate disparities in care.

Data Sources

Considering the data elements that are required for quality improvement, we can consider the concept of "green data" or recycling of existing datasets for several purposes. Although quality improvement in health care may have started as an "extra" component of clinical care or a hobby for interested doctors, nurses, and administrators, it has now become an integral component of daily workflow. Because of this increasing emphasis on quality improvement, there has also been a demand for data collection for this purpose. Although some data may be collected specifically for the purpose of quality improvement, currently available data such as hospital administrative data and vital statistics may allow for increased efficiency.

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Administrative Data

Examples of secondary datasets that have been used to evaluate quality of care are the hospital discharge database, billing data, and files that link birth certificates and death certificates. Although these secondary databases were not primarily designed for evaluating perinatal care, they contain data elements that have made it possible to examine risk-adjusted perinatal complication rates, maternal morbidities,[80] cesarean delivery, and neonatal readmission rates. Although secondary datasets can provide useful information, the accuracy and completeness of reporting poses a potentially important limitation.

A major advantage of using secondary data is the potential for increased efficiency. However, there are also several potential disadvantages. Because the original design may not have considered its use for quality improvement, secondary data sources may not have all of the desired data items. Data definitions might not be appropriate or the same as those used in other NICUs. In some instances, there may be inadequate standards for accuracy. For example, demographic information, prenatal care, mode of delivery, and birth weight tend to be fairly reliable on birth certificates.[31] However, the presence of congenital anomalies, an important item because of the high degree of complexity and mortality in this group, is markedly underreported on both birth and death certificates.

Linked birth and death certificate files are an important source of population-based studies of factors that affect perinatal outcomes. These studies span a wide range of areas (e.g., the effect of the increase in multiple births on infant mortality, labor outcomes at advanced maternal age,[95] factors associated with the birth of infants with very low birth weight at non-NICU hospitals,[33] trends in cesarean delivery for various conditions,[68,71] and quality assessment of perinatal regionalization). There are both advantages and disadvantages of using vital records for quality improvement purposes.[31] However, to maximize the potential usefulness of vital records, clinicians must become actively involved in ensuring their uniformity of definition, accuracy, and completeness.

The hospital discharge abstract can be a useful data source for evaluating neonatal care. The US Department of Health and Human Services mandates that a uniform hospital discharge dataset, which includes 14 core data items, be submitted for each acute patient whose care is paid for by Medicare or Medicaid. Introduced in 1992, the most widely used format for these submissions is the Uniform Bill. UB-04 contains data items for patient identification, insurance coverage, total charges, and entries for up to five diagnostic and three procedural codes. These codes are assigned based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). UB-04 is required for hospitals submitting claims to Medicare, Medicaid, Blue Cross, and other commercial insurers. Although hospitals are not required to submit UB-04 for all neonates, most hospitals do complete this form. The Uniform Bill can provide useful information on procedures, diagnoses, and charges. The major advantage of this data source is its widespread use at a large number of institutions and its ready availability as a computer dataset at many hospitals.

Several weaknesses of this source of data must be considered, however. The Uniform Bill was designed for reimbursement, not for monitoring institutional performance or for clinical research. As a result, distortions in the data may result from attempts by hospitals to code diagnostic and procedural data with the goal of maximizing reimbursement. Significant errors in diagnostic coding may occur. For example, although some perinatal conditions such as third- and fourth-degree lacerations appeared to be coded fairly completely, the validity of a variety of perinatal conditions and procedures was quite variable, ranging from quite good to very poor. The accuracy of coding for neonatal conditions has not been studied in detail. Another problem with hospital discharge abstract data is the absence of birth weight as a data item.

One solution to the limitation of important missing variables is linkage to other data sources. Highly successful links can be established without using personal data such as names, hospital numbers, or social security numbers; instead, links can employ virtual identifiers such as postal code of residence, clinical factors, and demographic factors. California's Office of State Health Planning and Development sponsored a project to link the state-linked infant birth and death file with a modification of the UB-92 file (predecessor to the UB-04). This database allowed one to select outcomes from the ICD-9-CM and procedure codes available on the discharge billing file and adjust these outcomes based on the birth weight and clinical, demographic, and socioeconomic information from the birth certificate. Further links to this database have included the mother's discharge file for the current pregnancy as well as all infant readmission discharge files during the first year of life.

Examples of population-based studies using this linked database include the relationship between discharge timing after birth and infant readmission, shoulder dystocia, risk factors and neonatal outcomes, and neonatal outcomes in childbearing beyond the age of 40.

Preliminary analyses suggest that the ICD-10 codes contained within the UB-04 will have similar analytic functionality to their ICD-9 counterparts (personal communication, Elliot Main M.D., medical director, CMQCC).

Diagnosis-related groups or DRGs are another example of secondary data used to evaluate perinatal care. Defining case mix to be able to compare outcomes and resource use across institutions is of great importance to payers. Diagnosis-related group systems are classification schemes that use data that are routinely available in hospital discharge abstracts to group patients into relatively homogeneous categories. Outcomes and resource use are compared for similar DRGs across institutions. Because of the widespread use of DRGs, it is important for neonatologists to

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be familiar with these systems. However, there are several serious limitations in using DRGs to assess quality. First, even with numerous DRG groups to choose from, the heterogeneity of patients within a single DRG can still be quite broad. Second, the DRG is not assessed before the clinical course of the infant and therefore can actually be influenced by the quality of care received.

Strategies to improve the collection and recording of quality indicators on secondary datasets may be an important approach to building a primary data collection system.

The California Maternal Quality Care Collaborative (www.cmqcc.org) is applying this approach by giving hospitals close to real-time (within 45 days from discharge) data based on linking the infant's birth certificate to the mother's and infant's discharge ICD-10 codes.

In addition to perinatal quality metrics, CMQCC also provides a near real-time assessment of data quality as part of an ongoing initiative to improve its administrative data sources. The confidential reports include Joint Commission perinatal metrics, which can display data on an adjustable time frame with a resolution that allows the creation of run charts to track quality improvement initiatives. The reports also contain confidential drill down analyses to identify ways to improve performance. For example, if there was an increase in early term elective delivery for a hospital (Fig. 5.4), one could examine cases over a period of time to check if there are certain diagnoses that may be contributing to an increase in the elective delivery rate. The rate of elective delivery can also be calculated by provider to see if there are opportunities to work with individuals who may be contributing most to an increased rate. A demonstration site with artificial data is available at https://demo.datacenter.cmqcc.org.

Clinical Data

Primary clinical data collection is necessary for assessing quality of care when existing data are not sufficient. However, because primary data collection is labor intensive, it is important to minimize the collection of data elements to essential components that are critical for the assessment and work of quality improvement. These data elements will consist of outcome and process measures, as well as patient characteristics for risk adjustment as described in the preceding.

ELECTIVE DELIVERY UNDER 39 WEEKS (PC-01) | Decrypt Case Numbers | Provider: Blinded

Discharge Dates: 10/01/2011–12/31/2011 (N=16) | Print

Displaying all 16 numerator cases

Case Number	Delivery Date	Gest. Age	Diagnoses	CS or Induction	Provider ID	Opportunities for Improvement	C
e6461b8cc1	10/03/2011	38+5	654.21, V27.0	CS	Provider #868	D C P OK	
ff9a22b18c	10/04/2011	38	654.21, 560.1, 674.82, 292.89, 654.11, 218.9	CS	Provider #868	D C P OK	More v figu h
82aa41ff13	10/13/2011	38	659.61, 648.91, 654.21, V02.51, 663.11	CS	Provider #420	D C P OK	
22854b7b08	10/20/2011	38+4	654.21, V27.0	CS	Provider #991	D C P OK	
853db23a64	11/04/2011	38	648.91, V02.51	Induction	Provider #637	D C P OK	
18d30c5d27	11/03/2011	37	654.21, 659.61, 671.11	CS	Provider #868	D C P OK	
83fb5dabae	11/11/2011	38+1	659.61, 654.21, V27.0	CS	Provider #637	D C P OK	
dc7bcee69c	11/10/2011	38+5	654.21, V27.0	CS	Provider #637	D C P OK	
4dae23cf35	11/20/2011	37+0	654.21, 644.21, V27.0	CS	Provider #113	D C P OK	

• **Fig. 5.4** Screenshot from the California Maternal Quality Care Collaborative. In this sample screenshot from the data center of the California Maternal Quality Care Collaborative is an assessment of one hospital (fabricated data) in the measure of elective delivery under 39 weeks. This is a Joint Commission measure that aims to reduce cesarean section (CS) or induction before 39 weeks' gestational age. This is a "drill down" menu in which a quality officer could search for opportunities for improvement. Depending on the role of the person studying the report, the provider (physician) ID may be masked or revealed. (The ability to test a demo center is available at https://demo.datacenter.cmqcc.org/hospitals/1; accessed November 3, 2017.)

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Data elements should be clearly and systematically defined for both data abstractors and users of data in a manual of operations to facilitate both coding and interpretation of the data. Fair and useful benchmarking of quality measures and the study of variation in care are dependent on uniform definitions across institutions.

There are several methods for transferring these items to a database. The most efficient technique is to download information that has already been collected via an electronic medical record. In addition to its potential to provide data to inform quality improvement, the electronic medical record can also be used to facilitate standardized practice. Examples include prompts and/or requirements to perform and report ROP eye examination in preterm infants and notification that an infant with a central line has reached an enteral intake of 120 mL/kg and requires justification for continued use. Such systems will allow for the close alignment of clinical care and quality assessment.

Although this will doubtless be a major component of the standard method in the future, it is still in the early stages of development. This approach will need to be informed and iteratively improved by studies on accuracy and consistency for algorithms across centers. For example, the diagnosis of patent ductus arteriosus may be different at individual NICUs, and an objective and consistent assessment of such a variable may or may not be possible from electronic medical records.

When data are collected primarily for the purpose of quality assessment, computer-based data entry systems using local or Web-based data entry interfaces allow for efficiency in checking for errors such as missing fields or out-of-range entries. Examples include the Vermont Oxford Network, which provides members with dedicated software, eNICQ, to collect, manage, and submit standardized data, and CPQCC, which supports data submission and management with a dedicated online tool. An advantage of these systems is that they detect errors in completeness, range, and consistency as the data are being abstracted and entered. When the data entry program detects an error, it requests a valid value and does not allow data entry to proceed until it receives the correct value. The result is a clean record at the point of data entry that avoids costly off-site error detection and correction cycles. However, even with this system, it is important to use methods to minimize data entry errors, such as visual verification.

Qualitative Data

Because not everything that counts can be counted, qualitative techniques are an important set of tools that can provide practitioners with valuable insights regarding the design, execution, and outcome of quality improvement interventions. These techniques may include strategic informant interviews, focus groups, written evaluations, and observations directly or by video. So-called "mixed methods" approaches may use a variety of research tools to explore underlying themes that impact quality of care and help to discover strategies for improvement. Research in this area can address aspects of care that may not be readily collected in the medical record, such as a parent's ability to speak up to promote safety for their child in the NICU.[79]

• BOX 5.6 Lessons Learned in Quality Improvement Through Qualitative Research

Facilitators

- Organizational structure and culture
- Previous experience with quality improvement
- Adequate resources
- Clinician engagement
- Comparative process measurement and data tracking
- Active communication among stakeholders

Barriers

- Shifting priorities
- Interruption of usual workflow
- Challenges to debriefing
- Lack of physician buy-in
- Disparities

During a quality improvement initiative or in the evaluation phase, qualitative research can help to discern which aspects of a project were the key drivers of change and what steps might be taken for similar subsequent projects. While the subject matter and aim of the project may differ, there may be common barriers and facilitators for implementation in quality improvement projects. A summary of such findings undertaken in three different projects (maternal hemorrhage, breast milk nutrition for preterm infants, delivery room management) is shown in Box 5.6.[66,73,78]

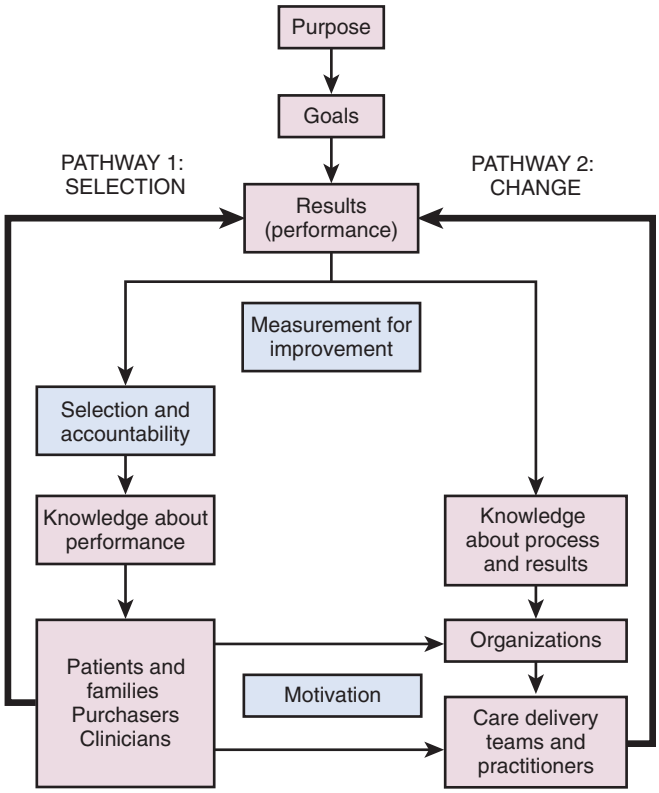
Evaluation of these data can be labor intensive in a research environment, but quality improvement teams can often rapidly extract meaningful and usable information. When there is a deficiency in care or perhaps when things are going well from a quality perspective, these approaches may help to better understand the reasons underlying the results.

Quality Measurement and Improvement

Now that the different types of data that may be available to improve quality of care delivery have been reviewed, it is necessary to consider what data are needed for what purpose and how best to present the data for each of those purposes. Quality measurement is necessary for improvement but not sufficient. Although all stakeholders, such as providers, consumers, payers, or policymakers, have an interest in improving quality of care delivery, they have different information needs and different levers to motivate or effect improvement. Berwick, James, and Coye developed a framework that divides quality measurement according to purpose into two pathways (Fig. 5.5).[12]

Pathway 1 highlights the purpose of selection. One of the main interests of stakeholders in this pathway is to gain knowledge about provider performance and to either

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• **Fig. 5.5** Pathways to Quality Improvement. (Adapted from Berwick, James, and Coye[12] to the NICU setting.)

seek out care for themselves or their constituents accordingly. Stakeholders have the ability to "motivate" providers by either forgoing care or paying less to low-performance providers.

Pathway 2 highlights the pathway of change. The stakeholders here are the organization and the frontline care providers themselves. Motivation for measurement is derived from an internal desire to optimize care delivery for organizational improvement. In the following sections, practical and theoretical considerations regarding quality measurement in these different pathways are provided, including what types of measures may be appropriate for each, recognizing the substantial overlap between them.

In general, the information need regarding the *process* of care delivery is highest for frontline providers (pathway 2), whereas stakeholders who are further removed from the organization are more interested in *outcomes* of care (pathway 1). This is not to say that frontline providers do not care about outcomes of care, rather that the process of care executed in the local care context is what delivers the outcome. Because local contexts differ, a focus on outcomes by external stakeholders and consumers sets guideposts for quality expectations and provides NICUs space for experimentation and innovation to meet them. External stakeholders should avoid a proscriptive focus on process measurement, unless the supporting scientific evidence is strong (e.g., antenatal steroid administration for preterm infants <34 weeks' gestational age).

It is important to recognize that data collection costs of individual institutions are significant, potentially diverting resources from other care priorities. Possibly with the advent of functional electronic health records, these collection costs will drop. However, until then, it is necessary for external stakeholders and quality improvement practitioners to be parsimonious in their choice of quality measures.

Data for Selection

There is an increasing demand for transparency and public reporting of quality in health care to spur consumer choice, allow for performance-based reimbursement, and ultimately improve processes and outcomes of care. Further research is required to identify the best models for predicting neonatal risk and to determine their precision in identifying individual cases or institutions with poor quality of care. However, even without a firm foundation in research, risk-adjusted comparisons of NICUs will become more common. The public release of risk-adjusted comparisons of a variety of safety and quality measures using administrative and claims data for US hospitals by the Centers for Medicare and Medicaid Services is an example of this phenomenon (http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/OutcomeMeasures.html).

The Leapfrog Group, a consortium of Fortune 500 companies, provides hospital-specific performance data to the public. Although measurement of perinatal care is limited, the group does provide a rating of quality of care for high-risk deliveries, defined as the care provided for VLBW infants (http://www.leapfroggroup.org/). Neonatologists must understand the strengths and weaknesses of different methods for making risk-adjusted comparisons of neonatal outcomes as they attempt to assist the public in understanding these data and to use the data themselves to monitor, evaluate, and improve the quality of care that they provide.

One of the rationales for public reporting of health care quality is the concept that the existence of such reports motivates and influences providers and organizations to improve their quality of care. The Agency for Healthcare Research and Quality has promoted the use of public reporting and guided its implementation for many organizations (http://www.talkingquality.ahrq.gov/about.htm). Although there needs to be continued research on the impact of public reporting on health care quality, thus far results are mixed. Public reports do not appear to inform consumer choice significantly, and improvements in quality measures are moderate at best.[116]

Another source of ratings of health care quality is lay press sources such as *US News & World Report,* which has produced a popular series of "Best Hospitals" and "Best Children's Hospitals." Consumer Reports (www.consumerreports.org) is another consumer-oriented organization that presents hospital quality assessments. These sources have not been well validated and have shown conflicting results with other measurement tools.[93] These publications generally use league tables (rank ordering of institutions) and can

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provide an idea of how one center might compare with other similar centers for specific measures. However, the interpretation of league tables must be informed by the context of reliability of measurements, adequate risk adjustment, and consistency of results as what may appear to be an orderly ranking may not ultimately denote significant differences between NICUs. For example, in a league table the difference between a top and middle performer may not be clinically or statistically significant. Nevertheless, hospitals feature such ratings prominently in marketing their services, and substantial intramural efforts are devoted to maximizing ratings.

The use of public reporting for perinatal care is relatively underdeveloped. However, it may be an untapped strategy for improving quality. Women of childbearing age are among the most frequent users of the Internet, and pregnancy is the featured topic of many websites geared toward this group. Studies have shown that women in general, and specifically expectant and current mothers, view the Internet as a way to connect to other women having similar experiences and to share information with one another so that each woman who finds a public reporting website useful may communicate that experience to others. Although providers may be wary of the validity of publicly reported quality information on neonatal and maternal care and outcomes, websites are increasingly making such information available. For example, Yelp is now showing several perinatal indicators as a standard feature (Fig. 5.6).

National Quality Measures

Interest in quality assessment continues to increase for perinatal medicine. An important development in ensuring that proposed measures can actually reflect the quality of care has been the work of the National Quality Forum (NQF) (www.qualityforum.org), a multi-stakeholder group that evaluates proposed quality measures. In considering measures, several important areas are assessed, including the importance of the measure to making significant gains in health care quality, the measure's reliability and validity, the extent to which the results can be understood and be useful for decision making, and the feasibility of collection. The Joint Commission published a list of core perinatal measures in 2007. A list of current measures from the NQF is noted in Table 5.1. When considering a potential measure for widespread use, it is important to have evidence that the aspect of care that the measure reflects has been shown to be malleable, that is, shown to be improvable, in at least one multi-institutional quality improvement initiative.

Although the list of quality measures continues to grow, it may become overwhelming for stakeholders, including clinicians, payers, and consumers, to extract a meaningful global picture of quality of care delivery at a given NICU. In addition, Profit and colleagues demonstrated that correlations between quality measures of the care provided to VLBW infants are generally weak, meaning that it is difficult to infer overall quality of care delivery based on a small subset of clinical measures. Strategies for global assessments of quality may provide a more comprehensive assessment.[90] Two of these are explored in the next section.

Data for Improvement

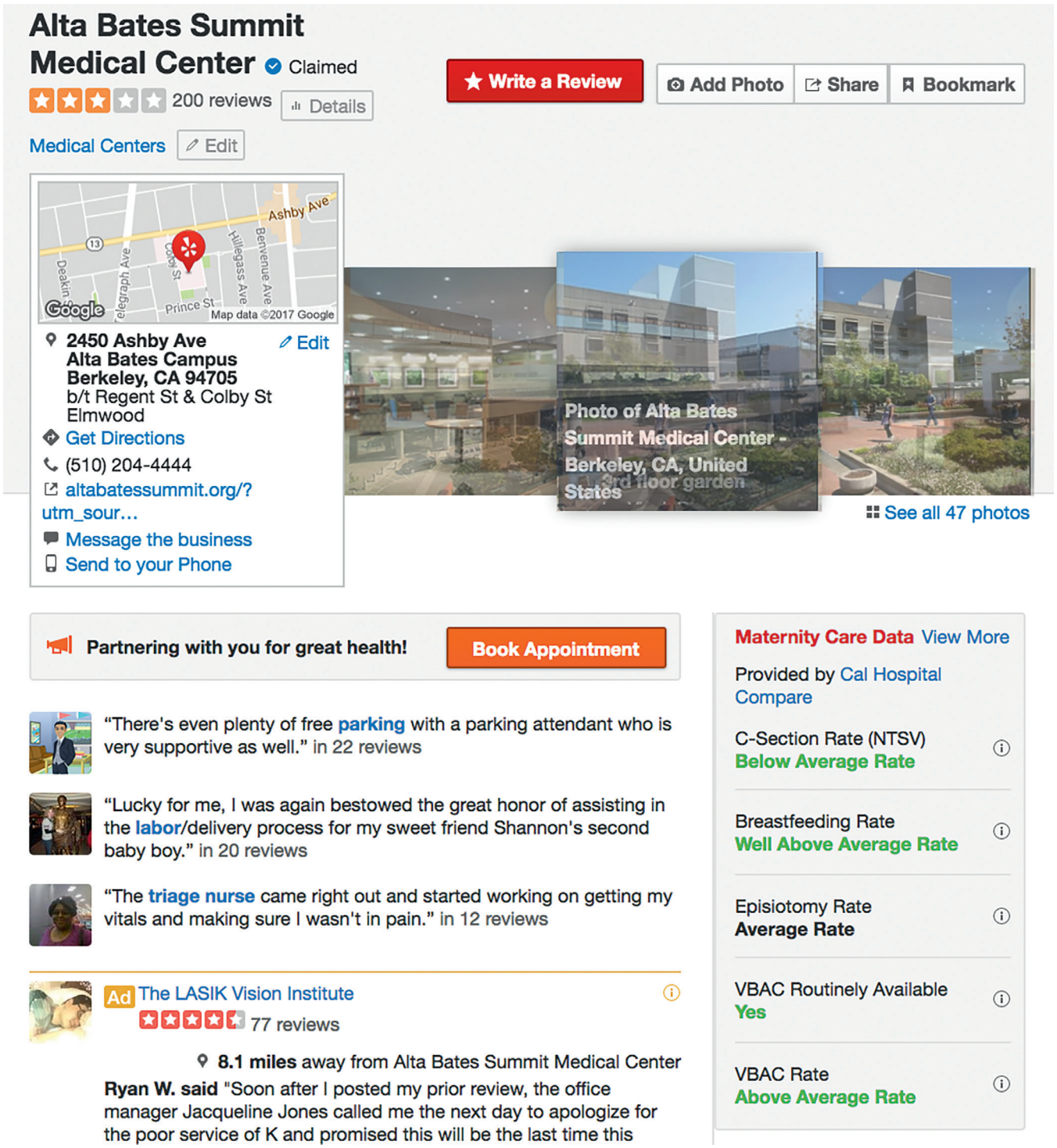
Although so far the collection and presentation of data for provider selection has been discussed, the active work of quality improvement requires different considerations. First, as the purpose of data collection for quality improvement is geared toward identifying potential areas of need and tracking change as soon as possible, there may be a lower threshold for identifying what might be considered an outlying value. In other words, data that are "good enough" to expose areas sorely in need of improvement may be better than waiting for "perfect" data. Second, there may be additional demands for data collection. Although some of the data sources noted in the preceding may allow for facilitation of quality improvement activities to some extent, there are several other aspects of data necessary for active quality improvement, or data collections that may allow a specific question in quality improvement to be answered.

When data are analyzed for the purposes of benchmarking and comparisons, historical data that are collected over a stable period of time may be optimal. However, in the midst of an effort to improve quality for specific processes or outcomes, data will need to be collected and presented in or close to real time.

A strategic aspect of data collection for quality improvement may be the need for additional process measures to be collected. For example, in an effort to increase temperature of very preterm infants at delivery, there may be several important variables that could contribute to this effort, including delivery room temperature, use of devices such as plastic wrap or chemical warming mattress, and use of checklist or noting of adequate team communication before delivery. Another example could be a project to reduce central line infections, in which the team may want to collect data on whether a line insertion or maintenance checklist is being followed, number of line days, and whether the line necessity is being assessed regularly. Although temperature and the presence of an infection may already be part of real-time data collection, the other data elements may not be typically collected or even noted in the medical record in a systematic fashion but may be crucial in the quality improvement process. During the quality improvement project, this data may be collected to facilitate the quality improvement cycle and identify areas for improvement. These data can be tracked and assessed on a regular basis by the quality improvement team.

When several groups participate together in a collaborative to improve quality, an extranet may serve as a common data repository and serve several useful purposes. First, it allows for the systematic collection of data as described in the preceding in real time and for the specific purpose of the quality improvement project. Second, it allows each center to assess how it is doing compared with other groups and therefore to identify areas for improvement. Third, it

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• **Fig. 5.6** Yelp ratings of maternity care in California.

can give insight into what processes may be most important to the main outcome of interest for the quality improvement project. The Institute for Healthcare Improvement (IHI) provides the opportunity for multicenter collaborative groups to enter and track data in real time (www.ihi.org).

An essential purpose of data assessment of provider performance is to serve as an agent for change. To fulfill this purpose, data must be available in a timely manner. Data that are too old cannot inform decision making reliably. Because of the lengthy hospitalization of the very premature infant, it may be useful to review data at the end of the first 28 days as well as at discharge. This strategy facilitates the timely analysis of neonatal outcomes.

The format in which data reports are produced and distributed is evolving from fixed, periodic (i.e., annual) reports to more flexible reporting that also allows for user

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TABLE 5.1 Perinatal and Reproductive Health Measures Endorsed by the National Quality Forum (2016)

Quality Measures	Brief Description	Source
Reproductive Health		
Chlamydia screening in women	The percentage of women 16-24 years of age who were identified as sexually active and who had at least one test for chlamydia during the measurement year.	National Committee for Quality Assurance
Contraceptive care	Three measures (for women aged 15-44 years): a) Most & moderately effective methods b) Postpartum c) Access to long acting reversible contraception	US Office of Population Affairs
Labor and Delivery		
Elective delivery	Patients with elective vaginal deliveries or elective cesarean sections at ≥37 and <39 weeks of gestation completed.	Joint Commission
Incidence of episiotomy	Rate of episiotomy.	Christiana Care Health System
Cesarean section	Nulliparous women with a term, singleton baby in a vertex position delivered by cesarean section.	Joint Commission
Labor and Delivery – High Risk Pregnancy		
Antenatal steroids	Patients at risk of preterm delivery at ≥24 and <32 weeks' gestation receiving antenatal steroids before delivering preterm newborns.	Joint Commission
Newborn		
Unexpected complications in term newborns	Hospital level performance score reported as the percent of infants with unexpected newborn complications among full-term newborns with no preexisting conditions.	California Maternal Quality Care Collaborative
Hepatitis B vaccine coverage	Hepatitis B vaccination coverage among all live newborn infants before hospital or birthing facility discharge.	Centers for Disease Control and Prevention
Newborn Premature/Low Birth Weight		
Percentage of low birth weight births	The percentage of births with birth weight <2,500 grams.	Centers for Disease Control and Prevention
Late sepsis or meningitis in VLBW infants	Risk-adjusted rate of late-onset sepsis or meningitis in very low birth weight neonates.	Vermont Oxford Network
Neonatal blood stream infection rate	Infection rate for VLBW infants.	Agency for Healthcare Research and Quality
Health care–associated bloodstream infections in newborns	Staphylococcal and gram-negative septicemia or bacteremia in high-risk newborns.	Joint Commission
Retinopathy screening	Proportion of infants 22 to 29 weeks' gestational age screened for retinopathy of prematurity.	Vermont Oxford Network
Postpartum		
Exclusive breast milk feeding	Exclusive breast milk feeding during the newborn's entire hospitalization.	Joint Commission

VLBW, very low birth weight.

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choice in measures presented, time period, comparison groups, and type of presentation. The Vermont Oxford Network Nightingale Internet Reporting System provides users with secure real-time access to all data submitted since 1990, allows users to track trends over time, and enables them to compare their unit's performance with the Network as a whole and with predefined subgroups of units similar to their own. Annual center-specific reports provide additional information on rates of key performance measures compared with the Network, trends over time, and estimates of the Observed minus Expected (O-E) number of cases (see Fig. 5.7*A*). The CPQCC also provides its members with Web-based reports (www.cpqccreport.org). The CPQCC Web-based system has an integrated data entry and report structure that generates confidential individual member reports and network-wide benchmark metrics in real time. Advantages of electronic media reports are the ease of performing local secondary data analysis as well as the ability to easily incorporate the report's tables and figures into local customized presentations. The presentation of a hospital's data in comparison with that from other NICUs in a network plays an important role in motivating quality improvement activities.[167] Although the user can take advantage of the multiple features for selection of data presentation, there is also the option of a simpler "NICU dashboard" that presents crucial quality measures for recent years (Fig. 5.7*B*). This dashboard shows case mix–adjusted individual NICU's performance in comparison to its peers. Other features of CPQCC's online reports are shown in Fig. 5.7*C-F*.

Run charts (Fig. 5.7*C*) and standardized process control (SPC) charts (Fig. 5.7*D*) are powerful tools for quality improvement.[98] A run chart displays a series of data according to a criterion, usually time. Time is recorded on the x-axis, and the quality indicator is shown on the y-axis. This simple run chart can provide important insights regarding trends and variation in the process that results in the quality indicator. A Shewhart chart or SPC chart similarly tracks a quality indicator over time. This chart utilizes the mean or median and statistical control limits (two [95%] or three standard deviations [99%]). Run charts and SPC charts may differ in identifying a significant change in the process[98]; the following rules are used at the CPQCC to identify trends and special cause variation: observed point is outside the control limit (external disturbance); nine points in a row above or below the central line (process shift); six points in a row steadily increasing or decreasing (process shift); fourteen points in a row alternating up and down (source of variability).

To further aid with the interpretation of a control chart, the method of change point analysis was adopted.[164] Change point analysis looks at the trend observed over a period of time and attempts to find likely points of change. For the CPQCC change point analysis, CUSUMs (cumulative sum control charts) are calculated, which use cumulative derivations from the mean over time to identify changes in underlying trends. A segment of a CUSUM chart with an upward slope indicates a period where the values tend to be above the overall average; a segment of a CUSUM chart with a downward slope indicates a period where the values tend to be below the overall average. A change in direction of the CUSUM might indicate a sudden shift or change in the average. Whether such a change point represents a significant new trend is extracted using statistical methods.

In addition to these charts, which are not case mix adjusted, users are able to query risk adjusted trend charts (Fig. 5.7*E*) and comparison charts (Fig. 5.7*F*). Various subgroup analyses can be conducted to provide further specificity.

Global Assessments of Perinatal Quality: The Value Compass

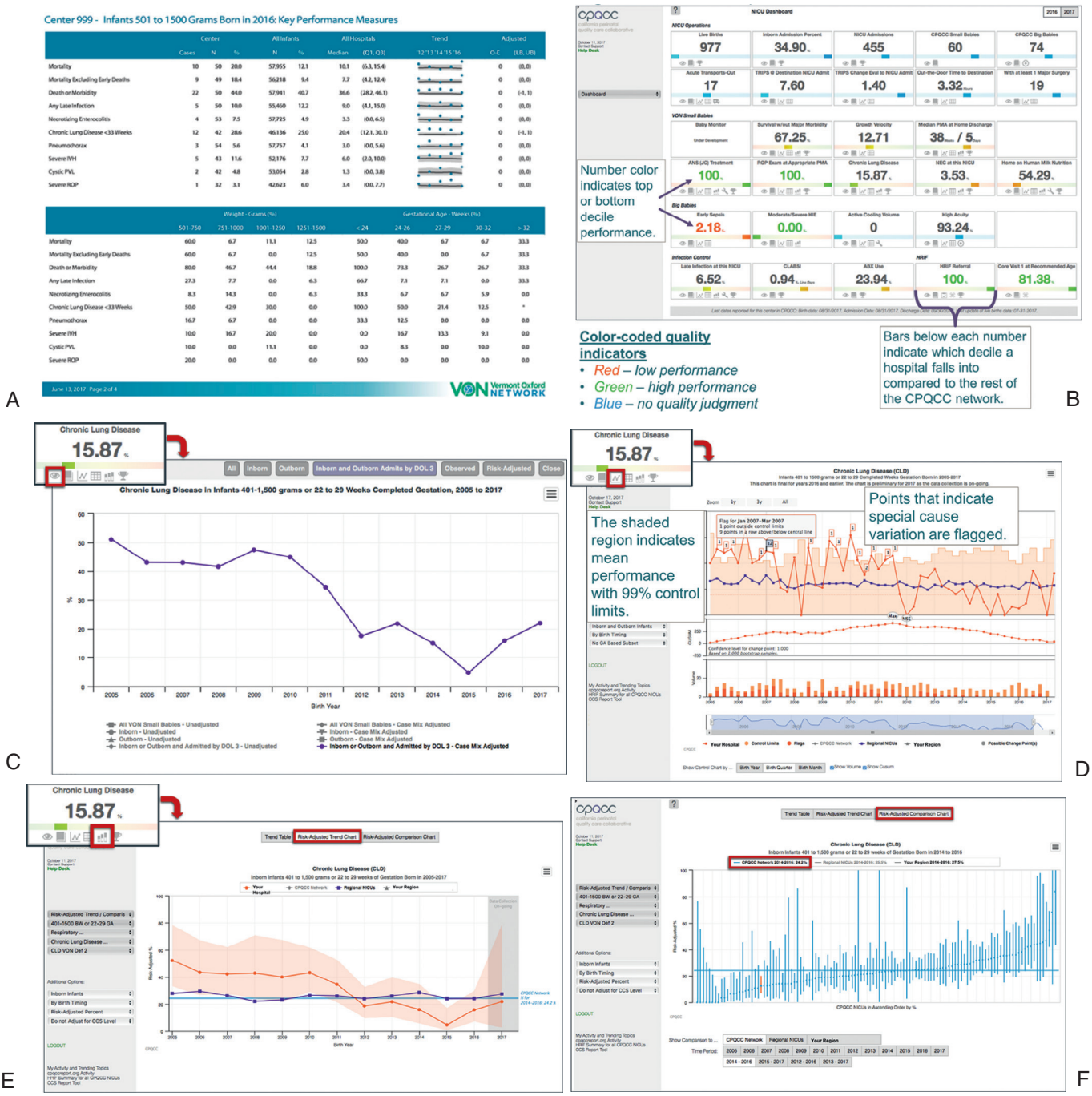
One approach to comprehensively monitor quality of care delivery is via a balanced scorecard. In a scorecard, measures are generally displayed in various separate care domains. A particularly refined and comprehensive adaptation of this approach is the Value Compass by Nelson and colleagues.[91] The four value compass directions are: clinical status, functional capacity, satisfaction, and costs. Through the inclusion of patient satisfaction and cost, the value compass pays deliberate tribute to the informational needs of nonclinical stakeholders, including families and administrators. The aim of the Value Compass is to provide stakeholders with a balanced set of variables that enables them to design, implement, and sustain meaningful improvements that all stakeholders recognize as important. The ability to assess performance on individual measures and potential tradeoffs in performance is a strength of the balanced scorecard. However, the scorecard's granularity may also limit the user's ability to assess overall quality progress. Such a global assessment requires a further level of aggregation.

Global Assessments of Perinatal Quality: The Baby-MONITOR

Another method to cut through the thicket of individual quality measures is to combine them meaningfully into a composite indicator. To simplify the presentation of quality assessment, a composite quality rating may ultimately serve as a simple way to quickly assess quality. The Baby-MONITOR, developed by Profit and colleagues, is an attempt at providing such a simplified global assessment tool.

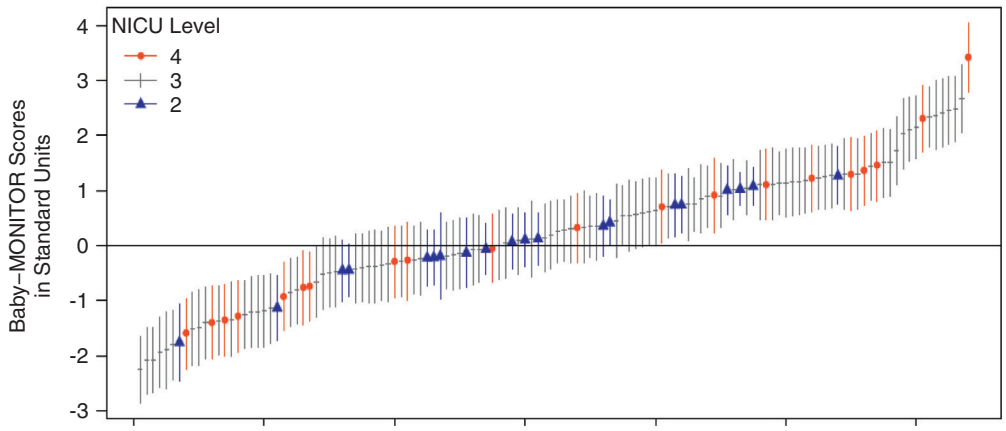
Composite indicators of quality are aggregates of individual measures of quality. During the aggregation process, developers have to make certain editorial choices with regard to the quality measures combination. For example, measures have to be normalized to a common unit. Each measure in the composite needs to assume a weight relative to the others. Most commonly, an equal weighting scheme is applied by developers, but this need not be so. Users may have differential preferences for individual measures. Finally, during the aggregation phase developers might consider to

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• **Fig. 5.7** **A,** Vermont Oxford Network Annual Report of infants 501 to 1500 grams. A sample page from a Vermont Oxford Network Annual Report of infants 501 to 1500 grams for a fictitious center displays data in the upper table on strategic performance measures at the center (*N*, percent, adjusted O-E, and confidence interval) and for the Network as a whole (overall percent, values for the first and third quartiles, Q1 and Q3). The 5-year trend for the Network (*gray area*) and for the center (*green dots*) is displayed as a sparkline. In the lower table, the center data are displayed within birth weight and gestational age categories. Confidential annual reports are available to authorized users at Network centers in printed form and as PDF files. (Courtesy of the Vermont Oxford Network, Burlington, VT.) **B,** The CPQCC Report Interactive Dashboard. The dashboard is divided into several subsections, including NICU Operations, VON Small Babies, Big Babies, Infection Control, and High Risk Infant Follow Up. Icons under measure headings allow for drill down ability. Color coding indicates relative performance compared to peer NICUs. **C,** The Quick Look feature. Run Chart displays rates over time, with options to adjust for case mix or refine by location of birth. **D,** Statistical Process Control (SPC) and Cumulative Sum Control (CUSUM) Charts. These charts identify special cause variation and changes in trends of quality efforts. Unadjusted data is used for this longitudinal tracking of an individual's NICU over time. Types of special cause variation are flagged. **E,** Risk-adjusted Trend Charts. These charts facilitate longitudinal tracking of performance in relation to CPQCC network, the region, or other units of the same level of care. **F,** Risk-adjusted Comparison Charts. These charts facilitate cross-sectional comparison to CPQCC network, the region, or other units of the same level of care. Various time intervals can be selected.

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• **Fig. 5.8** Distribution of composite scores in 22 California NICUs.

what degree they might allow NICUs to compensate for poor performance in one area with good performance in another. Addition of measures would allow full compensation; multiplication of measures allows only partial compensation, giving preference to NICUs that perform average to those with positive and negative outliers. There are also noncompensatory techniques. These choices require that the development of composite indicators proceed in an explicit, systematic, and transparent manner, and that the impact of the developers' choices on NICU performance ratings is subjected to sensitivity analysis.

The Baby-MONITOR is an aggregate of nine measures of quality routinely collected by members of the VON and the CPQCC. The nine measures were selected by an expert panel and validated by a sample of clinicians.[62,111] Quality measures are risk-adjusted, standardized by calculating an observed-expected event ratio, and equally weighted and averaged. Fig. 5.8 shows an example of a distribution of composite scores among 22 California NICUs. Sensitivity analysis invoking different aggregation and weighting schemes showed the Baby-MONITOR to be robust. Subsequent use has shown large variation across California NICUs by level of care[106] and by race/ethnicity.[107]

Another composite measure of NICU outcomes developed by Kaempf aggregates eight measures in a "benefit" measure and divides these by length of stay in a "value" measure.[55] These first formal iterations of composite indicators need to be validated against neurodevelopmental outcomes but provide a yardstick for the future development of multidimensional quality measures.

Although composite measurement is still in its early days, such a tool may prove useful in a variety of ways. It may allow users to monitor overall progress on key quality measures as well as to summarily assess the effect of quality interventions on performance. Through a more holistic focus, composite measurement may provide an incentive for NICUs to engage in systems-based quality improvement efforts that have the potential to affect multiple aspects of quality simultaneously. In addition, it may facilitate discussions with other stakeholder groups on quality of care. Without a comprehensive assessment tool of quality of care delivery, external stakeholders may increasingly subject NICUs to piecemeal appraisals that may not do justice to their overall performance.

Quality and Safety Applied

The previous sections have focused on the history, theoretical frameworks, and data necessities that underpin quality improvement work either at the individual unit or the health system level. Neonatology has been at the vanguard of the quality improvement field. Experimentation and refinement of applied methods occur in a large variety of formats. Neonatal providers undertake improvement work at the individual unit level and in collaboration with vast networks. Formats include in-person or Web-based collaboration, and methods for improvement use quantitative as well as qualitative techniques. Neonatology has also been a leader in engaging families in improvement work (Box 5.7).[39] Over time, there has been a transition from efforts of individuals to NICU-wide efforts to network-based efforts. Increasingly, these efforts engage multiple stakeholders, including families, providers, payers, purchasers, and regulators. In this section is an example of a practical real-world quality improvement project that highlights some of the successes and failures that beset many similar projects. This example also makes use of a small subset of management tools used in such projects.

Local Quality Improvement Applied: An Example

The example NICU experienced an unexpected string of inadvertent extubations after introduction of a new

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• BOX 5.7 Family Engagement in Quality Improvement

There is an increasing recognition that involving family members in health care decisions and processes can improve safety and quality. This is particularly evident in the NICU, where the families, however they are defined, are essential to an infant's health and well-being and are allies for quality and safety within the health care system. The importance of the parental perspective in quality and safety in the NICU makes it imperative to include parents in multiple roles in quality improvement activities. Strategies for promoting family engagement in hospital safety and quality are to:

- Engage parents to participate as advisors, working team members, leaders, and faculty in all quality improvement activities.
- Promote effective communication among families and health care professionals so that family knowledge, values, beliefs, and cultural backgrounds are incorporated into the planning and delivery of care.
- Provide timely, complete, and accurate information to families to enhance their participation in care and decision making.
- Involve families in discharge planning throughout the hospital stay.

Adapted from Agency for Healthcare Research and Quality: Guide to patient and family engagement in hospital quality and safety. https://www.ahrq.gov/professionals/systems/hospital/engagingfamilies/index.html; Conway JB, Celenza J, Abraham MR. Advancing patient- and family-centered newborn intensive care. In: Horbar JD, Leahy K, Handyside J, eds. *NICQ 2007: Improvement in Action*. Burlington, VT: Vermont Oxford Network; 2010. http://www.vtoxford.org/quality/ebook/NICQ_2007_Chapter_1.pdf. Accessed November 3, 2017.

endotracheal tube securement device, prompting an effort to reduce such events. A multidisciplinary team, composed of a physician champion, a neonatal nurse practitioner, a nurse, a respiratory therapist, and a parent advisor was formed. The team developed the following aim statement: "To reduce the inadvertent extubation rate in infants in the Newborn Center by 50% within 12 months." Inadvertent extubations were defined as those not ordered by a physician or nurse practitioner.

The team began with a brainstorming session, in which members considered factors that contributed to inadvertent extubations. All ideas were collected and grouped in themes, such as baby, device, method, caregiver, and procedure. These themes were then graphed in a fishbone diagram (Fig. 5.9) for clarity. Factors were then assessed with regard to whether they were amenable to intervention and with regard to their likely importance as contributors to inadvertent extubations. A resulting small set of factors was extracted, and over the course of the next several weeks, the team followed up each inadvertent extubation with a key informant interview (usually the bedside nurse present during the extubation). Results were tallied and graphed in a Pareto chart (Fig. 5.10). Based on this information, the team developed a driver diagram (Fig. 5.11), a version of a cause-and-effect diagram, which clarified the team's perceived linkages between the overall aim and key change strategies for achieving the aim as well as change hypotheses. The change strategies were introduced in successive PDSA cycles.

The primary outcome measure was the number of inadvertent extubations per 100 ventilator days. The team recognized several barriers to change, including staff resistance to the new securement method and concern regarding increased mobility of the endotracheal tube with this device, as well as its cost. Because of the recognition of potential risks of fewer inadvertent extubations, such as prolonged intubation, several balancing measures, including the number of days on nasal continuous positive airway pressure and the rate of chronic lung disease, were followed. These measures were already being collected as part of the NICU's membership in the Vermont Oxford Network.

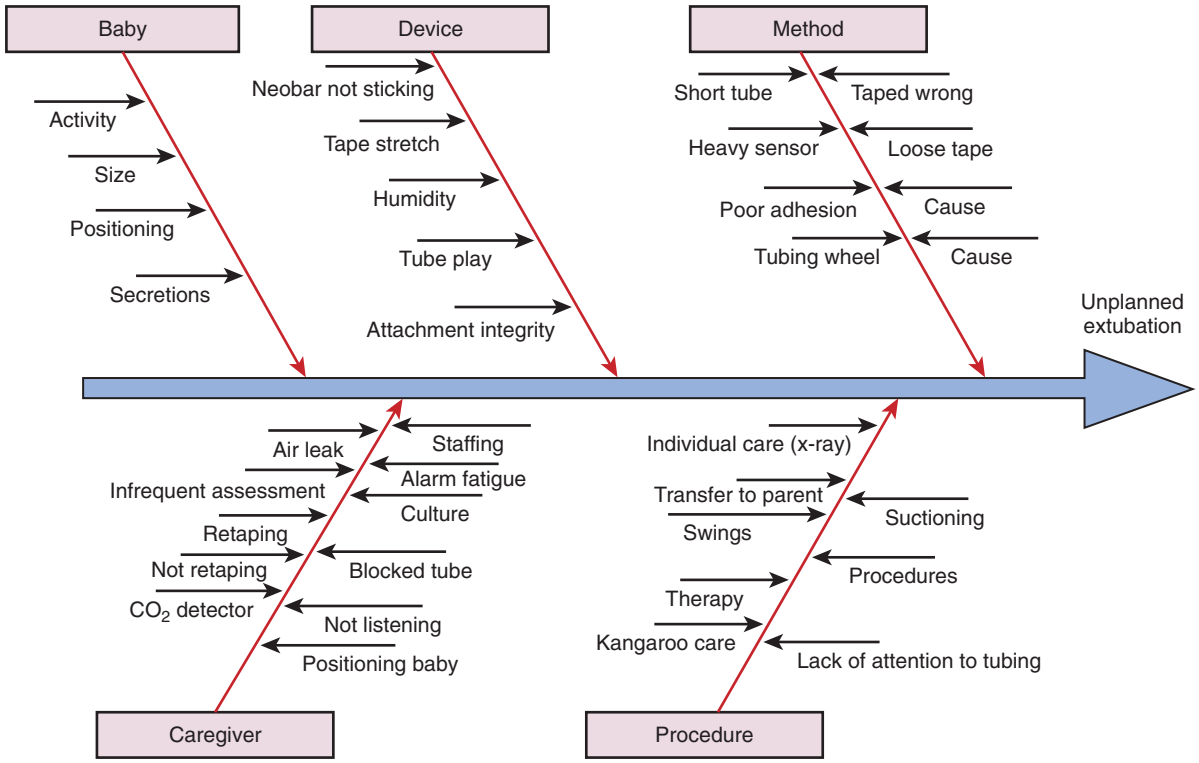
The planned interventions were presented to the service, revised as needed, and approved for implementation. A staff education plan was devised and implemented. Small cycles of change were used to further refine process details. A process control chart was set up (Fig. 5.12), and caregivers received intermittent project updates. As can be gleaned from Fig. 5.12, introduction of the securement device led to a further spike in extubation rates beyond the control limit, indicating special cause variation. The new baseline is displayed. After successive implementation of the change ideas, extubation rates dropped substantially (again special cause variation), prompting another resetting of the baseline. After these initial successes, a renewed deterioration in inadvertent extubation rates occurred when caregiver attention was diverted by the introduction of a new electronic health record. This period spotlights a common concern for quality improvement practitioners, the difficulty of holding the gains, bringing us to our next section.

Sustainability

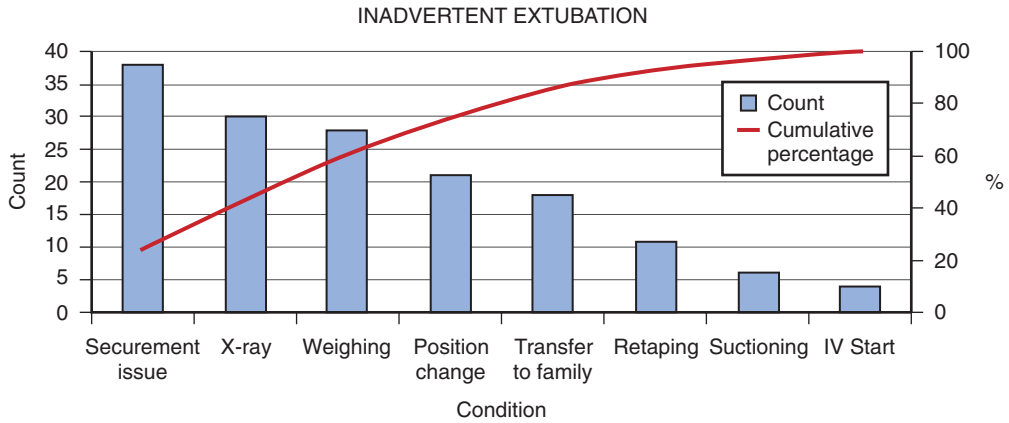
While there are now many examples of successful quality improvement projects, less is known about sustainability, particularly after resource-intensive projects. The goal to sustain improvement may rely on two potential strategies. One is to design an intervention such that new processes are seamlessly integrated into unit workflows and do not rely on extra effort by staff. Another approach may be to create a culture of improvement rather than just focusing on the intervention itself, where improvement becomes "the way we do things around here." Quality improvement, as with many other skills, may benefit from practice and experience. Indeed, hospitals participating in a California Maternal Quality Care Collaborative project had greater improvement if they had experience participating in a previous quality improvement project.[81]

In a qualitative study of CPQCC NICUs, factors perceived to give the best chance for sustained improvement included the following themes: incorporation into daily work flow, advanced approach to staff education, multidisciplinary team involvement with emphasis on physician buy-in, and a data-driven feedback system.[146] As quality

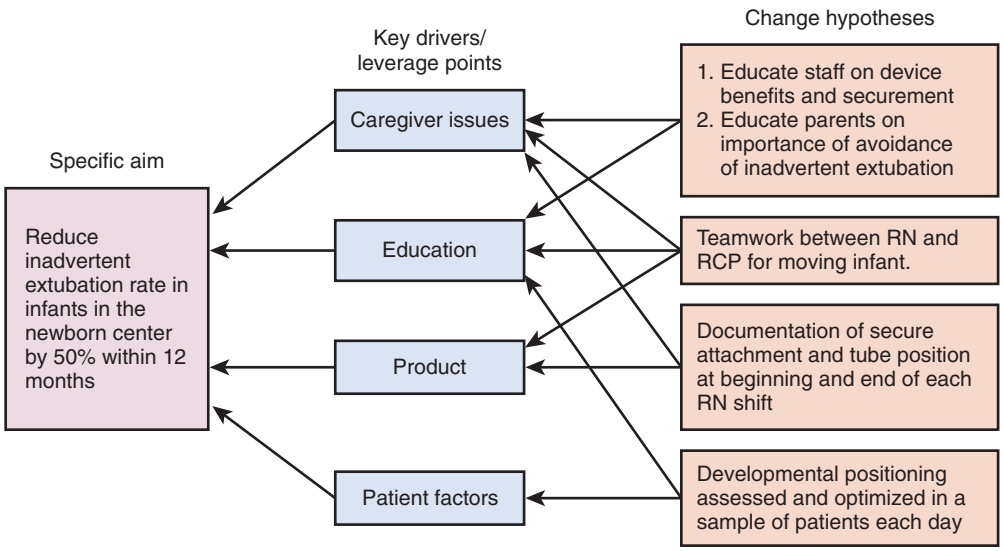
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• **Fig. 5.9** Sample fishbone diagram.

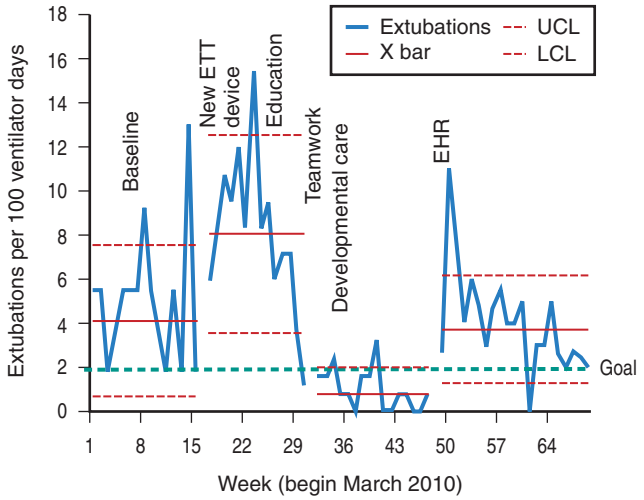


• **Fig. 5.10** Sample Pareto diagram.



• **Fig. 5.11** Sample driver diagram. RCP, Respiratory care practitioner.

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• **Fig. 5.12** Sample process control chart. U-chart demonstrating the weekly extubation rate per 100 ventilator days. The type of chart used depends on the type of data collected. Breaks in the baseline are shown based on the introduction of new interventions or with signs of "special cause variation," that is, weekly extubation rates exceeding the upper or lower control limits. (To maintain clarity, we elected to reset the baseline at each special cause event.) EHR, Electronic health record; ETT, endotracheal tube; LCL, lower control limit; UCL, upper control limit; X bar indicates the mean.

leaders consider how to advance overall quality in their institutions, attention to both the project at hand and the culture of a unit may be beneficial. Focusing too intensely on just the main aim of the project may lead to team members concluding that their quality work is complete after achieving that aim.

The Institute for Healthcare Improvement has published a White Paper on "Sustaining Improvement," which provides further theoretical frameworks for sustainability and some practical suggestions.[129] This resource focuses primarily on organizational structure and management and how that context can provide optimal opportunities for sustained improvement.

As quality improvement science advances, sustainability will increasingly be considered as part of the goal. A few potential strategies could be tested. One may be to "wean down" from a complete intervention to a lighter version, such as reducing the set of measurements to a minimal set needed to track progress. Another strategy could be to keep motivation going by periodic "reunions" of staff to celebrate accomplishments. Another could be training the whole staff in a specific quality improvement methodology, with forums for staff to implement their own projects. Sustainability is an active topic of quality improvement research.

Quality Improvement Research

The evidence-based movement in medicine has been a hallmark of our time, and the randomized controlled trial has emerged as the gold standard by which research studies are judged and whereby clinicians adopt certain practices. However, the dissemination and implementation of evidence-based practices is not always an easy task. It has been noted that the time for new knowledge generated by clinical trials to be incorporated into general practice may be 17 years. Therefore, one could argue that the study of the translation of evidence into practice is a crucial subsequent step in maximizing and expediting the impact of the discoveries made in clinical trials.[67] The study of quality improvement activities may sometimes not be amenable to a traditional trial, and such a trial may not be the optimal approach. Nevertheless, rigorous research is needed to avoid the adoption of inferior or ineffective practices in the name of quality improvement.

The importance of publishing and, therefore, disseminating the results of quality improvement projects has been recognized by the pediatric community, with the journal *Pediatrics* establishing a "Quality Reports" section since 2011. Another recognition by the broader medical community of the importance of quality improvement research has been the formation of the Standards for Quality Improvement Reporting Excellence (SQUIRE) guidelines (Table 5.2). These guidelines and their 2.0 iteration were established to promote rigor in designing and reporting quality improvement research.[92] Although the usual conventions for publishing scientific papers largely apply, the SQUIRE guidelines recognize several relatively unique aspects of quality improvement research. First, although a rigorous clinical trial requires prespecification of patient groups and interventions, the course of a quality improvement study may be somewhat dynamic. Improvement strategies may be modified in response to feedbacks from the ongoing project. The results of a clinical trial are "hidden" until the end of the study to avoid bias and change of behavior from the investigators. On the other hand, the clinicians involved in a quality improvement project may continuously try to learn from the contextual environment and ongoing results and subsequently modify their behavior to increase the impact of the intervention.

For the mentioned reasons, Berwick has referred to randomized controlled trials as being "an impoverished way to learn" in the context of quality improvement, suggesting that learning from experience "while doing" can be an important part of improving the quality of care.[9] In a simulation study comparing "learning" and putting into practice findings from significant randomized trials only versus quality improvement collaborative projects, the quality improvement model was found to be a potentially superior approach.[23]

In addition to the aspect of learning while doing, a patient-level randomization study for quality improvement may not be feasible as improvement activities on intervention subjects in a single NICU, whether patients or clinicians are likely to contaminate the control group. Approaches such as cluster randomization or step wedge

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TABLE 5.2 SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence) Guidelines

Title and Abstract	
1. Title	Indicate that the manuscript concerns an initiative to improve health care (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of health care).
2. Abstract	a. Provide adequate information to aid in searching and indexing. b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions.
Introduction	***Why Did You Start?***
3. Problem description	Nature and significance of the local problem
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies
5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work
6. Specific aims	Purpose of the project and of this report
Methods	***What Did You Do?***
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable
12. Ethical considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest
Results	***What Did You Find?***
13. Results	a. Initial steps of the intervention(s) and their evolution over time (*e.g.*, timeline diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s) f. Details about missing data
Discussion	***What Does It Mean?***
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project
15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs
16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps
Other Information	
18. Funding	Sources of funding that supported this work; role, if any, of the funding organization in the design, implementation, interpretation, and reporting

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designs may be better suited for experimental studies of quality improvement.[50,157] The Canadian Neonatal Network conducted a cluster randomized trial of 12 NICUs in which half of the units focused on nosocomial infections, whereas the other half focused on reducing bronchopulmonary dysplasia rates.[76] Although bronchopulmonary dysplasia was reduced only in the corresponding group, nosocomial infections decreased in both groups. Their findings may suggest that quality improvement activities in one area may also influence quality in other areas, making the interpretation of such trials challenging. Walsh and colleagues conducted a cluster randomized controlled trial on the effect of benchmarking and multimodal quality improvement at 17 member NICUs of the National Institute of Child Health and Human Development on bronchopulmonary dysplasia rates. Three NICUs were selected as best performers, and the remaining 14 NICUs were randomized to intervention or control. Changes in rates of survival free of bronchopulmonary dysplasia were compared between study year 1 and year 3. Intervention NICUs did change practices related to bronchopulmonary dysplasia, but no statistically significant difference in the primary outcome was found.[157] Horbar and colleagues conducted a cluster randomized controlled trial in 114 NICUs (57 intervention units and 57 control units) alongside a quality improvement collaborative of surfactant timing at delivery. Eligible infants at 23 to 29 weeks' gestational age cared for in the intervention NICUs received surfactant in a more timely manner (median of 21 minutes versus 78 minutes, $p < .001$).[50]

The literature surrounding the effectiveness of quality improvement collaborative activities is still in its infancy. However, relative to other specialties, neonatal-perinatal medicine is at a relatively advanced stage. In a systematic review of the impact of quality improvement collaborative studies by Schouten and co-workers, four of the nine studies considered in the main analysis concerned neonatal outcomes.[125] There are still many opportunities for studying many aspects of quality improvement: its effectiveness as well as optimal designs for broader implementation. Furthermore, although infection reduction has been a success story for health care quality improvement in the NICU, it is perhaps time to focus further on other areas for advancing the science and improving care.

Quality and Safety in the International Context

Although this chapter has focused on some of the quality work done in the United States, similarly sophisticated regional and national collaborative networks as well as quality efforts by individual NICUs are underway throughout the developed world, including, among others, some in Canada, Europe, Australia, and New Zealand.

In addition, there has been increasing appreciation of the high value for money provided by NICU care in low- and middle-income nations. For example, one cost-effectiveness analysis found NICU care in Mexico to be effective in saving healthy life years and to be providing excellent value for the money for infants greater than 23 weeks' gestational age.[110] In many middle-income countries, mothers and newborns have access to medical care, but substantial opportunities for improvements in the quality and safety of care delivery remain. Although in low-income nations access to health care delivery is often a predominant problem, for those who do gain access, high quality of care delivery has been achieved using quality improvement methodologies (http://www.hciproject.org/node/1397). This is because many effective quality improvement interventions such as checklists are low technology and low cost, and patients in middle- and low-income countries have much to gain from applying these techniques.[42]

The World Health Organization and numerous countries have recognized these opportunities and have initiated efforts to train providers in patient safety and quality improvement skills, as well as in ways to conduct basic monitoring of clinical outcomes. These approaches should be complemented by a better understanding of the sources of quality gaps in the care delivery for sick newborns in resource-constrained settings, including potential lack of materials and equipment, workforce training, and availability, as well as institutional context for quality. In addition, a systematic accounting of improvement efforts that work and that do not is necessary to leverage and spread existing knowledge.

Conclusion

The miracles of modern medicine are maybe nowhere as apparent as in the progress of the fields of neonatology and perinatology. However, the impact of these advances can be limited by the performance of providers at the systems and clinician levels. The recognition that there is widespread variation among physicians and hospitals in clinical practice and patient outcomes and the growing pressure to increase the quality, safety, and cost effectiveness of medical care have resulted in unprecedented interest in assessing, evaluating, and improving medical practice. If health professionals are to function successfully in this environment, they must understand how to evaluate their own performance and how their performance will be evaluated by others. These evaluations require accurate and reliable information.

Most important, neonatologists and other health care professionals must learn how to use the information to improve the quality and safety of the medical care they provide. Although neonatologists should not be expected to become experts in industrial quality improvement theory, database management, and evaluation methods, they do need to develop a basic understanding that will allow them to work effectively with other professionals in the changing health care environment.

In this "era of assessment and accountability," we must all develop the knowledge, skills, and motivation necessary

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to assume leadership roles in multidisciplinary collaborative quality improvement within our institutions, in larger health care organizations, and across regions. Only then can the potential benefits of modern databases and information systems be translated into better medical care for newborn infants and their families.

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Key Points

- There continue to be many opportunities for addressing gaps in quality and safety in neonatal care, whether in underuse, overuse, or misuse of various therapies.
- Collaborative networks, including at the state level, have allowed for benchmarking of quality to promote better outcomes.
- Accurately and efficiently derived data that is available in a timely manner provides the framework for assessing and tracking measurements in quality and safety.

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6

Simulation and Debriefing in Neonatal-Perinatal Medicine

LOUIS P. HALAMEK

Introduction

Whereas teaching is something that is (passively) done to trainees, learning is something that trainees must (actively) do themselves.[39] Because not everything that is *taught* is necessarily *learned*, programs that best facilitate skill acquisition in trainees are those that focus on learning rather than on teaching. Traditional didactic programs are passive by nature, and the settings in which they are held are typically isolated from realistic cues, distractors, and time pressure; thus, such programs are unable to prepare learners adequately for all of the challenges inherent when working in the real environment. Learning is best facilitated when the learning opportunities are tailored to meet the needs of the learners. Training models that offer the same content in the same fashion to all learners (thus implying that competency can be attained and maintained simply by spending a particular, often arbitrary, amount of time at a task) fail to recognize that adults have different strengths, weaknesses, and life experiences and acquire and maintain different skills at different rates. Some characteristics of effective adult learning strategies include the following:

- Focus on active rather than passive learning activities.
- Integration of skill sets while performing under realistic conditions.
- Emphasis on competency/proficiency (the ability to perform successfully) rather than compliance (adherence to rules, such as participation in an activity for a predetermined period of time).

Although learning in a real environment may appear ideal at first glance, a deeper analysis reveals otherwise. The most obvious problem with using the real environment as the primary source of skill acquisition and maintenance is that any mistake could negatively affect (even prove lethal) to the human beings in that environment. The pace of actual work in the real environment is often too fast to allow trainees to take full advantage of the learning opportunities therein. Moreover, typically there is no way to ensure that all important learning opportunities will present themselves in the real environment during the time that the trainee is present. Finally the real environment is also typically a very expensive environment and is populated with a number of professionals whose job description may not include providing learning opportunities for trainees.

Simulation may be defined broadly as any exercise that allows an individual to experience a situation that, although not real, nevertheless generates authentic responses on his or her part.[38] The best simulations realistically recreate the key visual, auditory, and tactile cues of actual situations to provide experiences that closely mimic the conditions encountered when working in the real environment. Provision of these key cues creates a high level of fidelity to the real environment. As a result of this degree of realism, those participating in the simulation respond as they would to a real-life situation; thus, their performance during a simulated situation can be hypothesized to resemble what it would be in the real world. In general, the term *simulation* is typically reserved to describe more comprehensive learning, assessment, and research activities that occur in realistic physical and virtual environments; activities conducted in less comprehensive environments (case studies, role-playing, and practice of one particular skill in isolation from other elements associated with that skill) may be better labeled as task training. By suspending their knowledge that they are working in a contrived situation, participants display knowledge, skills, and behaviors similar or identical to those manifest when working in the real environment. The closer a participant in a simulation mimics real-life performance, the more likely he or she will be able to identify and address any weaknesses that become apparent. Identification and remediation of weaknesses is the raison d'être of simulation.

What are the features of the best simulation-based learning programs that make them effective in facilitating the acquisition and maintenance of cognitive, technical, and behavioral skills? Each element of a successful program, including the scenarios, is built around specific learning objectives that are tailored to meet the needs of the participants. Every effort is made to ensure that the scenarios to which they are exposed are realistic in detail, challenging in

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Abstract

The delivery of safe, effective, and efficient care to ill neonates is the goal of every neonatologist. Preparation for delivery of neonatal care can be facilitated by the application of simulation-based training coupled with objective debriefing. Simulation-based training is, at its core, practicing doing the right thing under realistic conditions to elicit true-to-life responses from those undergoing this training. When such responses are evoked, trainees have the opportunity to discover their strengths and weaknesses during a debriefing. Debriefings should focus on the actions of the individual team members, how those actions contributed to the performance of the team, and how team performance influenced the care of the patient. In addition, strategies for replicating actions that facilitate successful human and system performance and avoiding those that are ineffective or harmful should be developed during debriefings. The combination of realistic simulated clinical scenarios with objective debriefings provides many advantages over more traditional training methodologies and is ideal for the acquisition and maintenance of the cognitive, technical, and behavioral skills necessary for modern neonatal care.

In addition to its use for training, simulation can be used to create highly standardized clinical environments that allow the investigation of issues that are difficult to study in the real health care environment. It is also likely that, over time, simulation will play a steadily increasing role in the delivery of care to actual patients.

Keywords

simulation
debriefing
training
learning
skills
Neonatal Resuscitation Program (NRP)

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scope, and relevant to their daily work. Finally, expert feedback and facilitated debriefings assist the participants in their critical self-reflection on performance. Effective simulation is not dependent on the purchase and use of highly complex and expensive technology; more important are carefully designed scenarios that align with the needs of the participants, provision of *important* (not necessarily *all*) cues, and conduct of skillfully led debriefings.

Simulation-Based Training in High-Risk Industries

Simulation-based learning opportunities are the standard for skill acquisition in industries such as commercial aviation, aerospace, nuclear power, and the military, in which the risk of death or severe injury to human beings is very real. The use of simulation in these domains is characterized by an emphasis on probing human beings and the systems they design (both technological and social) for weaknesses and then designing and testing solutions to address those weaknesses. This type of learning is the result of a culture that not only fosters but also demands a willingness to learn from mistakes made during simulated events, thus decreasing the chances of repeating such mistakes when working in the real environment.

The National Aeronautics and Space Administration (NASA) was established in 1958 to conduct aeronautical research and administer the human and robotic exploration of space. Space travel is an inherently risky business; how else can one describe a process that places human beings in a rocket filled with tons of liquid fuel and then ignites that fuel in the hope that it will propel those humans into the vacuum of space? The value of simulation was made clear during the Apollo 13 mission, launched on April 11, 1970, as the third mission to land humans on the moon. To prepare for this mission, the three members of the prime crew, Jim Lovell (captain), Tom Mattingly (command module pilot), and Fred Haise (lunar module pilot) trained in NASA's flight simulators for months. One week before launch, Mattingly was exposed to the measles; because he was not immune to the disease, his backup, Jack Swigert, was given simulator time with Lovell and Haise in the week preceding launch to "ensure that Lovell, Swigert, and Haise could function with unquestioned teamwork through even the most arduous and time-critical simulated emergency conditions."[31] A decision by the flight surgeon only one day before launch scrubbed Mattingly from the prime crew and placed Swigert in the left-hand seat as command module pilot for the mission. Fifty-six hours into the flight, as Apollo 13 was approximately 200,000 miles away from the earth en route to the moon, an explosion in the service module's cryogenic oxygen system resulted in the uncontrolled venting of oxygen into space, creating a situation that threatened not only the success of the mission, but also the lives of the crew (oxygen was the source of the crew's breathing air and substrate for the fuel cells that generate electrical power). As has been thoroughly documented, the crew did return safely to earth. What is less well known is that, years before Apollo 13 launched, the procedures that allowed the crew to survive and recover from this devastating event were devised by engineers charged with envisioning every possible failure and then designing procedures to address these failures.[27] These procedures were tested under current mission parameters in the flight simulators almost continuously during the crisis and when deemed reliable were relayed to the crew.[10] In the formal postmission debriefing, the crew referred to their experiences in flight simulation in excess of 40 times.[3] The successful track record of simulation, established over decades in other domains, serves as a model for its use in health care.[35]

Simulation-Based Training in Health Care

Any discussion of training in health care must start with what it is that can be learned. There are three sets of skills that may be acquired and refined by health care professionals:

- What we know in our brains (cognitive skills—content knowledge and decision making)
- What we do with our hands (technical skills)
- How we employ the first two skill sets while caring for patients and working under realistic time pressure with our colleagues (behavioral skills)

Content knowledge is the skill set most familiar to trainees and is typically the major (or only) skill set that is formally evaluated, usually through written or online tests. Decision making may also be evaluated in this manner through the use of clinical vignettes followed by questions as to appropriate next steps to be taken. Technical skills such as intubation are critical to many aspects of health care delivery. Despite their importance, such skills are most commonly practiced at skills stations using models that poorly represent human anatomy and physiology; in addition, they are typically evaluated by subjective rather than objective criteria. Behavioral skills (including but not limited to leadership, teamwork, and effective communication) are also important to successful patient outcomes (Box 6.1). Unfortunately, these skills are rarely, if ever, specifically addressed in learning programs directed at health care professionals. Many patient care tasks actually incorporate elements of all

• BOX 6.1 Key Behavioral Skills

- Know your environment.
- Anticipate and plan.
- Assume the leadership role.
- Communicate effectively.
- Delegate workload optimally.
- Allocate attention wisely.
- Use all available information.
- Use all available resources.
- Call for help when needed.
- Maintain professionalism.

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• BOX 6.2 Skills Necessary for Successful Intubation

Cognitive Skills

- Know the indications for intubation.
- Know how to recognize these indications when present.
- Know what equipment (e.g., size of endotracheal tube, laryngoscope blade) to use to accomplish intubation.
- Know the indications of a successful intubation.

Technical Skills

- Assemble the laryngoscope.
- Hold the laryngoscope in the left hand.
- Expose the airway to view.
- Insert the endotracheal tube into the airway.
- Assess for proper placement of the endotracheal tube in the airway.
- Secure the endotracheal tube in the airway.

Behavioral Skills

- Communicate effectively with team members regarding the need for intubation, specific pieces of equipment, and other needs.
- Distribute the workload so that specific tasks are assigned to the team members most likely to carry them out successfully.
- Delegate responsibility and supervise appropriately.
- Call for help when necessary.

three of these skill sets. Intubation is one such example. Far from being simply a technical skill, effective and safe intubation requires coordination and integration of multiple cognitive skills (knowing the indications for intubation and the signs of successful and unsuccessful intubations), sequential discrete technical skills (assembling, testing, and inserting the laryngoscope), and a number of behavioral skills (effectively communicating observations and needs, evenly distributing the workload, and delegating responsibilities), all of which must also be accomplished in a time-efficient manner (Box 6.2).

Much has been made of the importance of the concept of *fidelity* in simulation-based training in health care. Simulation fidelity is typically thought of in terms of its physical, biologic, and psychological elements. Physical fidelity refers to the realism of the physical space in which training occurs; this space is made to look real by including appropriate working medical equipment, fluids, pharmacologic agents, beds, and the other elements necessary for patient care. Biologic fidelity includes the patient simulators and standardized patients as well as the human beings acting as confederates during the simulation, playing roles designed to assist the evolution of the scenario. Patient simulators have been described as high, medium, and low fidelity; unfortunately, there is no standardized definition of simulator fidelity in health care. In reality, no physical patient simulator currently in use bears close resemblance to a human being, either in terms of anatomy or physiology. The use of the term *high fidelity* when describing the current generation of patient simulators more likely refers to high complexity or high cost rather than any intrinsic similarity to a living human being. Finally, all of the previously mentioned elements interact with the mindset brought into the scenario by the trainees to create a sense of realism or psychological fidelity. The overall goal of simulation-based training is to provide experiences that closely mimic the conditions encountered when working in the real clinical environment. The major difference between the simulated environment and the real environment is the absence of real human patients. Although debate continues in the health care simulation community as to how much fidelity is necessary, and although some may argue that the higher the fidelity of the scenario to real life, the better the learning opportunity, it should be understood that as long as sufficient attention is paid to providing the key (not all) visual, auditory, and tactile cues for trainees, allowing them to form a shared mental model of the nature of the situation that they are facing, they will have the opportunity to work effectively to resolve the clinical problems that become manifest during the scenario and, therefore, achieve the learning objectives.

In health care simulations, the patient may be represented by a human being (actor or standardized patient), physical model that can be touched and handled (mannequin or patient simulator), virtual models that are created via software and exist only in the memory of a computer, or hybrid models that require participants to interface with both physical and virtual elements. Simulation in health care encompasses a wide spectrum of activities ranging from computer-based interactive *virtual* environments populated by virtual patients and computer-generated representations (avatars) of oneself and one's human colleagues to highly realistic *physical* environments in which real human health care professionals work as a team providing care for sophisticated patient simulators while using real working medical equipment.

Simulation-based training provides many obvious advantages over more traditional training methodologies. Because patient simulators replace human beings, there is no risk to patients; invasive procedures can be practiced without the fear of patient harm or medical liability. Unlike what happens in the real environment, learning opportunities using simulation can be scheduled at convenient times and structured so that specific learning objectives are consistently achieved. Simulation-based training is an ideal methodology for allowing participants to practice integration of multiple skill sets while working under highly realistic and often stressful conditions. Rather than being directed solely at the individual, simulation accommodates the learning needs of multidisciplinary teams. Simulation-based training activities can be scaled in intensity to meet the needs of participants at all levels of experience, and they can be used to foster both the acquisition and maintenance of particular skills. It can also be hypothesized that those who participate in simulation-based exercises likely will be better prepared and will need less supervision when entering or re-entering the real environment (Box 6.3).

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• BOX 6.3 Advantages of Simulation

- Presents no risk to human patients
- Permits training in environments usually inaccessible to less experienced trainees
- Can be tailored easily to the needs of individual trainees regardless of level of experience
- Allows practice without interruption or interference
- Fosters integration of cognitive, technical, and behavioral skills
- Facilitates multidisciplinary team training
- Creates training opportunities for rarely encountered but highly challenging or risky situations
- Provides structured training opportunities with defined learning objectives
- Can be scheduled at times convenient to trainees and instructors
- Permits formal objective performance assessment
- Facilitates use of debriefings as a source of detailed constructive feedback
- Provides a very rich training experience in a relatively short period of time
- Optimizes use of time, money, and other resources

Simulation-based training in its broadest sense has been used for decades in domains outside of health care in which the risk to human life is high, and it is a core component of maintenance of certification programs in those domains. Historically in health care, the emphasis has been on evidence-based practice, and the gold standard of evidence has consisted of the prospective, randomized, controlled, sufficiently powered clinical trial in which the results focus on patient outcomes. However, the debate about the type and extent of evidence required to adopt quality assurance/improvement efforts in health care continues. At one end of the spectrum are clinicians and investigators who insist that quality initiatives must be subject to the same rigorous testing that precedes the introduction of new pharmacologic therapies and medical instrumentation to prove that they actually improve quality and enhance patient safety. Alternatively, others note that requiring randomized controlled trials to assess the safety of innovations with high face validity may place humans at undue risk and, therefore, prove impossible to conduct. In fact, some authors are of the opinion that to not use simulation-based training methodologies, relying instead solely on practice on real patients, is ethically indefensible.[69] Thus, we are left with a situation in which the need for more definitive evidence, although desirable, is felt by at least some members of the health care education and training community not to be necessary or practical. Although numerous studies across multiple health care domains have shown that simulation is capable of producing short-term improvement in skills, and the body of objective data supporting the use of simulation in health care continues to expand, little evidence has been published that definitively documents its effect on patient outcome or its return on investment. That said, it should be emphasized that no one working in other high-risk domains would consider conducting a prospective, randomized, controlled trial with subjects who are randomized to the "no simulation" group; indeed, simulation-based training remains standard operating procedure for these professionals.[53]

Simulation-Based Training in Neonatal-Perinatal Medicine

Approximately 4 million babies are born in the United States every year; of these, around 10% require some degree of resuscitation, with 1% needing extensive resuscitative efforts such as chest compressions, intubation, and delivery of medication.[65] Many different types of health care professionals are responsible for caring for newborns at the time of birth and in the days and weeks that follow. These professionals include, but are not limited to, neonatologists, pediatricians, family practitioners, obstetricians, midwives, neonatal nurse practitioners, nurses, and trainees at all levels in these disciplines. Given the large number of births, the frequency of resuscitation, and the diversity of professionals bearing responsibility for caring for patients in the neonatal period (the first 28 days of life), the need for effective means of acquisition and maintenance of the skill sets necessary to deliver safe and competent care is of tremendous importance. Traditionally the apprenticeship model of assuming graduated responsibility for the care of real patients has been used to address this need. Unfortunately, the assumption underlying this model—that placing a trainee in a supervised clinical environment for a set period of time will allow him or her to experience a sufficient number and breadth of clinical cases to ensure the ability to practice independently and safely in the community—does not always prove to be true. Similarly, maintenance of skill cannot be guaranteed by the routine, nonmentored delivery of patient care.

In 1999, the Institute of Medicine (IOM) published *To Err Is Human: Building a Safer Health System*, a report on human error and patient safety in the United States.[46] In this report, the authors estimated that between 44,000 and 98,000 Americans die each year as a result of medical errors. Although this figure has been highly debated, it is based on extrapolation of the data contained in studies out of Colorado, Utah, and New York published in peer-reviewed literature. The 1999 report was followed in 2001 by another from the IOM, *Crossing the Quality Chasm: A New Health System for the 21st Century*, in which the types of interventions (including training methodologies) necessary to improve patient safety were discussed.[17] Subsequently in 2004, the Joint Commission (JC) published a *Sentinel Event Alert* describing ineffective communication as a major cause in almost 75% of the 47 cases of neonatal mortality or severe neonatal morbidity (lifelong serious neurologic compromise) reported to that agency; since that time, an additional 62 cases have been added.[44] In response to these root cause analyses, the JC recommended that all health care organizations responsible for delivering newborns "conduct team training in perinatal areas to teach staff to work

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together and communicate more effectively" and "for high-risk events, such as shoulder dystocia, emergency cesarean delivery, maternal hemorrhage, and neonatal resuscitation, conduct clinical drills to help staff prepare for when such events actually occur, and conduct debriefings to evaluate team performance and identify areas for improvement."

The ever-expanding body of knowledge of the basic processes underlying normal and abnormal neonatal physiology has allowed those clinicians responsible for caring for newborns to generate evidence-based clinical practice guidelines under the auspices of the International Liaison Committee on Resuscitation (ILCOR) and its member organizations (Neonatal Resuscitation Program of the American Academy of Pediatrics, the American Heart Association, the Heart and Stroke Foundation of Canada, the Inter-American Heart Foundation, the European Resuscitation Council, the Australian and New Zealand Committee on Resuscitation, and the Resuscitation Councils of Southern Africa). ILCOR was founded in 1992 to facilitate international collaboration on issues involving neonatal, pediatric, and adult cardiopulmonary resuscitation and emergency cardiovascular care.[11] As knowledge about the physiologic processes underlying neonatal cardiorespiratory decompensation and the list of therapeutic interventions grow, so too do the expectations for mastery of this knowledge and associated skill sets that are placed on those responsible for caring for the neonate in distress. In 2010, ILCOR noted that a number of studies have demonstrated that the use of simulation-based learning methodologies enhances performance during simulated resuscitations. Although acknowledging that the interpretation of data generated by these studies is often complicated by their inherent heterogeneity and limitations, ILCOR nevertheless recommended that simulation, briefing, and debriefing techniques should be used during training when caring for simulated patients and in the course of clinical activities involving real patients to facilitate the acquisition and maintenance of the skills necessary for effective neonatal resuscitation.[45,50] This recommendation continues to remain in effect with the publication of the 2015 ILCOR guidelines.[5]

Neonatal care occurs in environments that are extremely dynamic and complex, and the nature of the work performed in those environments requires that correct decisions be made and appropriate interventions be carried out, often while working as a member of a multidisciplinary team in the context of intense time pressure. Simulation is an ideal learning methodology to allow teams of learners to practice working in these types of environments.[2] The first simulation-based learning program in neonatal-perinatal medicine (and one of the first in all of health care) is the NeoSim program developed at the Center for Advanced Pediatric and Perinatal Education (CAPE) located at Packard Children's Hospital on the campus of Stanford University in Palo Alto, California. Launched in 1997, NeoSim has been a very successful innovation in training in the cognitive, technical, and behavioral skills necessary for optimal care of the newborn in distress.[40] Subsequently, the NeoSim program was adopted as the model for extensive ongoing revision of the Neonatal Resuscitation Program (NRP) of the American Academy of Pediatrics (AAP).[37] Since 1987, the NRP of the AAP has set a national standard and an international example for training in the resuscitation of the newborn and has enjoyed tremendous success by claiming more than 3.9 million trainees and more than 23,000 instructors in the United States alone. The NRP's *Textbook of Neonatal Resuscitation* has been translated into 24 languages, and the NRP has been taught in 130 different countries around the world. In the past decade the NRP has undergone a major shift in learning methodology. Instructors are now required to shift their role from that of a teacher responsible for imparting knowledge to learners to that of a facilitator who fosters acquisition of skills by trainees as these trainees accept primary responsibility for their own learning. The NRP Steering Committee also developed a list of the characteristics desired in a cost-effective human neonatal patient simulator and published this online in 2005 as a request for proposals to industry. This marked the first time in the history of health care simulation that a professional body, rather than industry, drove development of a realistic patient simulator based on established learning objectives. Since that time, a number of full-term and preterm neonatal patient simulators have been developed by several commercial companies, indicative of the growth of the simulator industry at large and the field of neonatal simulation in particular. Development of a career-long learning program in neonatal resuscitation that is relevant to professionals from multiple disciplines at all levels of experience and is embedded with robust learning opportunities and valid performance metrics is the ongoing focus of the NRP as it continually adapts to stay relevant and provide optimal simulation-based training experiences.[1]

In addition to resuscitation, simulation has been used to facilitate the acquisition and maintenance of the skills necessary for successful delivery of multiple aspects of neonatal care. Simulation-based training programs have been developed in areas of neonatal care as diverse as reducing central line-associated infections, extracorporeal membrane oxygenation (ECMO), transport medicine, conducting difficult discussions, and outreach.[6,7,8,23,32,43,60,61,67]

The subspecialty of neonatal-perinatal medicine is unique in that one patient (the fetus) exists inside of another patient (the pregnant woman); in the case of multiple gestations, two or more fetal patients await birth inside of the pregnant female patient. The possibility of a sick woman delivering a sick newborn creates a situation in which optimal preparation occurs only when the neonatology and obstetric teams train together.[4] The multitude of events that can complicate human birth and the neonatal period make this an especially appealing target for simulation-based learning. Thus it makes sense that the neonatologists, obstetricians, and nurses from labor and delivery units and newborn nurseries who work closely together in the delivery room caring for patients also conduct joint simulation-based training exercises.[48]

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Some of the most convincing work published to date regarding the value of simulation-based training involves the reduction in the incidence of serious sequelae of shoulder dystocia after implementation of comprehensive simulation-based training. In the Obstetrics Emergency Training Programme at Southmead Hospital, Bristol, United Kingdom, Draycott and colleagues used a variety of patient simulators in several simulated environments to show that simulation-based learning resulted in enhanced content knowledge and improved technical management of shoulder dystocia.[19,20,21,22,24] In addition, the same group found in a retrospective multicenter cohort observational study of 19,460 infants that (1) the incidence of infants born with 5-minute Apgar scores of 6 or lower decreased from 86.6 to 44.6 per 10,000 births ($p < .001$), and (2) encephalopathy decreased from 27.3 to 13.6 per 10,000 births ($p < .032$) over a 5-year period following the introduction of a training program consisting of a review of fetal heart rate tracings and hands-on drills in the management of shoulder dystocia, postpartum hemorrhage, eclampsia, twin delivery, breech presentation, and maternal and neonatal resuscitation.[25] This work has been replicated and shown to produce similar improvements in clinically relevant outcomes, serving to document the value of rigorous immersive training.[9,18,58,62,64] The rationale for employing simulation-based training in neonatal-perinatal medicine is clear. The management of serious neonatal pathology is one example of the classic low-frequency, high-risk event that lends itself well to simulation-based training. Many health care professionals who care for newborns have the opportunity to manage serious or rare disease processes on an infrequent basis. Even for those for whom a sufficient number of opportunities do exist, one must question whether it is acceptable to essentially practice on real living patients who are not capable of providing informed consent on their own. Although parents do act as surrogate decision makers for children below the age of consent, few want to contemplate that their child will be the first one on whom someone will perform their first spinal tap, first intubation, or first thoracostomy tube placement. Therefore, it may be argued that the ethical imperative for simulation is stronger in pediatrics in general, and in neonatal-perinatal medicine in particular, than in any other field of health care.

Debriefing Simulated Events

A debriefing is defined as a discussion of events that have already occurred and may be led by an individual or a group; this is in contrast to a briefing which is held to discuss planned or future events. In a debriefing of a health care team the flow of information is both between the leader(s) and the members of the team, as well as among the members of the team. Feedback is the provision of information (from a person or a device) to a person where the flow of that information is one way. While not as interactive as a debriefing, it is important to note that not all learning requires the type of interaction typically ascribed to debriefing. For example, the acquisition and maintenance of a technical skill such as intubation does not require debriefing; rather, the provision of feedback as to appropriate finger and hand position on the laryngoscope and other aspects of intubation technique can be provided by an instructor experienced in intubation without the extensive interaction with trainees ascribed to debriefing.

Much of the health care literature has been devoted to the theoretical underpinnings of debriefing, rather than actual practical strategies and techniques, and focused on relatively inexperienced trainees rather than experienced health care professionals. Most of the models described in that literature use a very similar approach consisting of three primary phases:

1) An individual trained in debriefing who is not a member of the team leads the discussion;
2) the discussion typically includes reaction, description, analysis, and summary phases; and
3) patient outcome is not routinely emphasized (and may actually be avoided if felt to potentially produce negative reactions in team members).

This stands in contrast to how debriefing is conducted in other industries in which the risk to human life is high. In these industries the emphasis of debriefing is on facts, not feelings, and objective outcomes, not subjective interpretations.[13,26,28,29,30,42,47,68]

The debriefing model that has been adopted by the NRP for use after simulated neonatal resuscitation originated at CAPE. The CAPE debriefing model focuses on the actions of the individual, how those actions contribute to the performance of the team, and ultimately how team performance influences the care of the patient, therefore aligning closely with debriefing methods used by aerospace, commercial aviation, and the military. In this model, the person(s) leading the debriefing draws the assessment of individual and team performance from the team members themselves as they evaluate patient outcome in response to their actions and objectively critique those actions. Upon the conclusion of the debriefing, team members must understand how actions beneficial to the patient can be replicated and how any actions that were nonproductive or harmful can be avoided. The guiding principles and specific strategies that facilitate delivery of this model of debriefing are listed in Box 6.4 and Box 6.5, respectively.

It is very important to understand the difference between a technical performance debriefing (used to assess human and system performance) and a critical incident stress debriefing (conducted to provide emotional/psychological support). A critical incident is defined as "an event that has the potential for people to experience significant physical, cognitive, emotional, and behavioral reactions immediately after the incident or days, weeks, months, and even sometimes years later."[63] If simulated clinical scenarios are well-designed and the associated debriefings are conducted in an appropriate manner, a critical incident stress debriefing

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• BOX 6.4 Guiding Principles for Technical Performance Debriefing

- Debriefers should set a professional, business-like, matter-of-fact tone for the debriefing and maintain that tone whether the performance of the team members was exemplary or highly flawed.
- The role of the debriefer in a debriefing is to facilitate, rather than dominate, discussion among team members.
- Debriefings should be focused on the actions of the individual, how those actions contributed to the performance of the team, how team performance influenced patient outcome, and developing strategies for replicating actions that facilitate successful human and system performance and avoiding those that are ineffective or harmful.

should very rarely be required; if it is, appropriate professional counseling should be arranged.

While the few studies conducted to date have not consistently shown clear benefits to the use of video during debriefing, it must be acknowledged that in order for the cognitive, technical, and behavioral skills of the team members to be effectively debriefed, an accurate record of the display of those skills must be available.[14,41,56,59] Reliance on memory alone to provide such an accurate record is dubious at best. The ability to display a video stream illustrating key viewing angles coupled with an audio stream that picks up communication among team members provides an objective record of events that is capable of effectively bridging any gap between team members' memories and the actual facts of the scenario.

Debriefing Actual Clinical Events

While the guiding principles and specific strategies remain the same, there are several important differences between debriefing simulated clinical events and real clinical events.[54] Actual patient care events are spontaneous, unlike scripted simulated events, and thus those debriefing real events must do so without the benefit of written checklists of debriefing points. Those debriefing actual clinical events are often members of the team who were intimately involved in delivering care to the patient; this can make it more difficult to create a mental log of issues to be debriefed and offer objective input during the debriefing. Effective time management is critical when debriefing real clinical scenarios because the health care professionals involved in the debriefing must return to patient care as soon as the debriefing is concluded. Because the time that can realistically be devoted to debriefing actual clinical events is limited, it may be necessary to concisely debrief the single most important issue and defer others for review at a later time. Finally, the legal issues inherent in clinical medicine mandate absolute confidentiality when discussing the care of real patients, and consultation with professionals in risk management should be undertaken prior to developing a formal process for debriefing real clinical events.

• BOX 6.5 Specific Strategies for Technical Performance Debriefing

- Preparation of learners: Clearly communicate expectations.
- Initiating debriefings: "What happened in 10 words or less?"
- Sequencing debriefings: Chronological order is easiest to follow.
- Pacing debriefings: Maintain awareness of time remaining for debriefing.
- Facilitating discussion: Target a question-to-statement ratio of 3:1.
- Formulating pertinent questions: Create lists of debriefing points.
- De-emphasizing the instructor's viewpoint: Limit use of first person pronouns.
- Avoiding qualitative statements: Draw performance assessment from learners.
- Minimizing personal anecdotes: Focus on learner (not instructor) experiences.
- Eschewing hindsight bias: Debrief as if experiencing the event for the first time.
- Using silence: Wait approximately 10-15 seconds for a response.
- Deconstructing defensiveness: Limit use of second person pronouns.
- Dealing with emotion: It is not necessary to assume all learners need to ventilate.
- Listening for "red flags": Listen for phrases that indicate a need to drill down.
- Drilling down: Use a series of four questions—
  a. What happened/what did you notice (at that point in the scenario)?
  b. What circumstances led to that?
  c. What happened to the patient as a result?
  d. What can be done to:
     i. facilitate the recurrence of that positive event?
     ii. prevent that negative event from happening again?
- Debriefing with video: Scroll to segments of interest and pause playback for discussion.
- Deciding when to intervene:
  e. inability to recognize performance gaps
  f. talking over one another
  g. lack of gravitas
  h. inappropriate laughter
  i. harsh criticism
- Debriefing novices and experts: Employ the same strategies regardless of experience.
- Debriefing simulated and real clinical events: Formal process is required for real events.
- Terminating debriefings: "Any final questions/comments?"

Simulation-Based Assessment

Simulation is most frequently used in health care as a learning tool to facilitate the initial acquisition of cognitive, technical, and behavioral skills by relatively inexperienced trainees. Although not a frequent occurrence as of yet, it can also be used by experienced professionals to maintain (or reacquire) skills.[55] Regardless of experience level, simulation may in addition be used to objectively assess and document whether a physician or other health care professional can competently deliver care to patients. Appropriate metrics

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capable of objectively assessing all three skill sets (cognitive, technical, behavioral) must be developed and validated if simulation is to be used for formal evaluation of human performance in the health care domain.[34] Although the objective assessment of content knowledge has long been achieved through written and oral responses to multiple-choice and open-ended questions, the evaluation of technical and behavioral skills remains poorly defined. For example, although the technical skill of intubation can be broken down into a number of discrete steps and each step evaluated in great detail, in the end what is most clinically relevant is whether the patient is intubated successfully and safely, not the summary of the scores on each individual step of the procedure. This implies that there may be steps in the procedure that are so critical that failure in any one of them produces a "fatal error"; such errors result in overall failure in the task, even if all of the other steps are completed successfully. The assessment of behavioral skills presents similar issues. How does one define and score skills such as leadership and communication? Another challenge is the evaluation of performance over time. Providing a single comprehensive score of performance is difficult if that performance varies from minute-to-minute; dividing the event into discrete epochs of time may not completely resolve difficulties with scoring. Before working with a patient simulator can be used for high-stakes assessment, it must be shown to accurately predict performance with real human patients. An evidence-based approach to skill assessment will require collaboration with professionals in fields such as psychometrics, human factors, psychology, and others. If undertaken in a rigorous manner, it will be possible in the future to use simulation for high-stakes assessments such as hospital privileges, state licensure, and board certification in much the same way as flight simulators are used today to determine whether a pilot is capable of safely flying a particular type of aircraft.

Simulation-Based Research

Because all of the elements of the simulated environment (e.g., structure of the physical space, location and function of equipment, amount of various supplies, level of the ambient noise, appearance and reactions of the patient simulator, actions of human confederates in the environment) can be standardized, simulation provides an extremely powerful research methodology for studying clinically relevant issues in a highly controlled manner. The advantages of simulation as a research methodology are illustrated in a study conducted by Chitkara and co-workers.[15] In this study of the ability of human health care professionals to accurately detect heart rate via auscultation and palpation, the following elements were standardized:

- Heart beat: rate, volume, tone, location
- Umbilical cord pulsations: frequency, amplitude, location
- Stethoscope: quality
- Reaction of the simulated neonate to interventions
- Responses of the bedside nurse
- Responses of the bedside respiratory therapist
- Environmental noise
- Other distractors

Unlike the actual clinical environment in which all of these elements would be variables, in the simulated environment they were controlled with great precision; thus, differences in the performance of the subjects could be ascribed to intrinsic human factors rather than extrinsic aspects associated with their environment.

Simulation is especially well-suited to conduct research that is difficult to accomplish in the real clinical environment. Many aspects of neonatal-perinatal medicine are characterized by decisions that carry life-or-death outcomes, procedures that must be successfully completed under intense time pressure, and highly charged emotional situations that challenge both family members and health care professionals alike. Obtaining informed written consent in these situations, even if technically possible, is nevertheless made extremely difficult in that parents who are in a time of crisis must be asked for their willingness to allow their newborn to participate in a research protocol. Even when those involved conduct themselves in a competent and compassionate manner, this remains a challenging situation for all. A number of studies involving comparisons of various procedures during resuscitation and design of devices such as code carts have been published in recent years, illustrating the utility of conducting research in simulated, rather than real, environments.[12,16,49,51,52,57,66]

Simulation as the Basis of Clinical Care

Simulation will be playing a steadily increasing role in the delivery of care to actual patients. Radiologic data are currently being used by surgeons and interventional radiologists to create simulated anatomic models for use in planning and practicing invasive procedures such as tumor removal, catheter placement, and pinpoint delivery of therapeutic agents. Similarly, mathematical models of human physiology allow testing of experimental devices and pharmaceuticals in vitro/in silico rather than in vivo. Although a sophisticated comprehensive virtual model of human physiology, complete with all of its nuances and interdependencies, does not currently exist, virtual models of single organs and organ systems have been developed and are currently being used to assess the potential effects of various technologies and drugs in research and development settings around the world today. Continued work in this area will lead to the accurate simulation of human physiologic responses at the tissue, organ, cellular, and molecular levels and holds tremendous promise for revolutionizing health care on many fronts. The foreseeable future will bring the ability to integrate fetal imaging and biomarkers obtained from maternal blood or amniotic fluid with sophisticated anatomic and physiologic models to produce true high-fidelity simulations capable of accurately predicting the type and severity of eventual neonatal pathophysiology and thereby allow for patient-specific, evidence-based choices of pharmacologic

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agents, ventilator strategies, and other clinical interventions during postnatal life.[36]

The Future of Simulation in Neonatal-Perinatal Medicine

Human birth is characterized by nearly continuous changes in the physiology, anatomy, and spatial relationships among various physical structures in both the pregnant woman and fetus, and simulation of the process of labor and delivery is, therefore, a technically complex endeavor. Purely mechanical devices are not able to simulate vaginal birth in a manner akin to real life in a cost-effective manner or to allow practice of highly invasive procedures such as cesarean section. Development of hybrid technologies that combine materials similar to the plastics used for physical patient simulators with visual displays and haptic interfaces capable of generating the images and tactile sensations associated with patient care will create training opportunities that are currently impossible to achieve in the absence of a real patient. Thus, combinations of physical whole body simulators with virtual reality interfaces designed to compensate for the physical simulators' limitations will play a major role as neonatal and obstetric simulation evolves. In addition to physical and hybrid patient simulators, highly interactive web-based virtual environments will allow multiple professionals located in geographically distinct regions to participate in simulated clinical scenarios tailored to meet their specific learning needs. Following the example of the NRP, close collaboration among physicians, computer scientists, biomedical engineers, medical artists, and others will allow the technical challenges that currently exist to be overcome in a timely and cost-efficient manner.

Simulation in neonatal-perinatal medicine has made great strides in the past decade; however, the temptation to become content should be avoided, as much remains to be accomplished to reach the levels of safety, effectiveness, and efficiency that have been achieved in other industries where simulation and debriefing are integral components of daily work.[33] Although a number of technical, financial, and cultural challenges must be met to realize the full potential of this powerful methodology, none of these challenges is insurmountable. Failure to embrace simulation and debriefing will impede the practice of safe and effective health care and lead to harm of the smallest and most vulnerable patients.

Key Points

- Simulation-based training is practicing doing the right thing under realistic conditions.
- Simulation-based training is integral to safety programs in many high-risk industries.
- The key to effective simulation is the display of true-to-life responses by those experiencing it, allowing them to understand both their strengths and weaknesses.
- Debriefings should be focused on the actions of the individual team members, how those actions contributed to the performance of the team, and how team performance influenced the care of the patient.
- Debriefings should also facilitate the development of strategies for replicating actions that make possible successful human and system performance and avoiding those that are ineffective or harmful.
- Standardized simulated clinical environments allow the investigation of issues that are difficult to study in the real health care environment.

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7

Practicing Evidence-Based Neonatal-Perinatal Medicine

SUZANNE M. LOPEZ AND JON E. TYSON

This chapter focuses on five strategic processes in practicing evidence-based, neonatal-perinatal medicine: (1) asking a focused clinical question; (2) searching MEDLINE, the Cochrane Library, and other sources for high-quality evidence (primary reports and systematic reviews); (3) critically appraising the retrieved evidence for its validity; (4) extracting the data; and (5) applying the results to patient care. The role of the Cochrane Collaboration in the preparation, dissemination, and timely updating of systematic reviews of evidence from randomized clinical trials is highlighted. Strategies for promoting evidence-based clinical practice are presented.

Evidence-based medicine (EBM) has been described as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[34] The practice of EBM requires efficient access to the best available evidence that is applicable to the clinical problem.

It is essential, however, to make two disclaimers. First, not every clinical decision can be based on strong evidence, because such evidence might not exist. In a study at McMaster University Medical Centre, the primary intervention for the primary diagnosis of admissions to the neonatal intensive care unit (NICU) was evaluated for category of supporting evidence as a treatment. Only 34% of cases were prescribed treatment based upon good randomized controlled trial (RCT) evidence. The majority of patients' primary (96%) and secondary (86%) diagnoses were managed with interventions based upon sound evidence.[6] Similar findings were found by Ellis and co-workers in the care provided on a general medicine inpatient service in England.[13] The estimated principal treatments prescribed for patients' primary diagnoses were based on strong evidence from RCTs in about 50% of cases, convincing non-RCT evidence in about 30% of cases, and no substantial evidence in about 20% of cases. These findings were based on evaluations of institutions emphasizing the practice of EBM. The proportion would undoubtedly be substantially lower than 50% in other institutions. Many widely used therapies have not been well evaluated with respect to either effectiveness or safety.[1]

Second, evidence provides a necessary but insufficient ground for clinical decisions. Clinical expertise is no less important under the evidence-based approach; an accurate history, physical examination, and clinical diagnosis are crucial to a properly directed search for evidence that is directly applicable to the patient's problem. In addition, for some treatment decisions, it is essential to consider the values and preferences of parents with respect to the probable clinical outcomes of the treatments being considered for their infant.

Asking a Focused Clinical Question

A focused clinical question should contain the following elements:

- Patients of interest
- Treatment or exposure of interest
- Nature of any comparisons to be made
- Primary outcome of interest and other important outcomes

The exact form of a focused clinical question depends on whether the question concerns treatment or prevention, etiology, diagnosis, or prognosis.[17,46] For questions concerning treatment or prevention, a focused question has the following form: In (patient, problem, or risk factor) does (treatment of interest) compared with (control or alternative treatment) reduce (adverse outcome[s])?

Two examples follow: (1) In women carrying fetuses of 24 to 34 weeks' gestation who are at risk of delivering, does corticosteroid (dexamethasone or betamethasone) compared with no treatment reduce the incidence of respiratory distress syndrome (RDS) in their infants? (2) In infants ≥36 weeks with hypoxic ischemic encephalopathy, does hypothermia treatment using either whole body hypothermia or selective head cooling, compared with no hypothermia treatment, reduce the frequency of moderate to severe neurodevelopmental impairment or death at 18 to 24 months of age?

Armed with a focused clinical question based on an accurate delineation of the clinical problem, the treatment

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Abstract

This chapter focuses on five strategic processes in practicing evidence-based neonatal-perinatal medicine: (1) asking a focused clinical question; (2) searching MEDLINE, the Cochrane Library, and other sources for high-quality evidence (primary reports and systematic reviews); (3) critically appraising the retrieved evidence for its validity; (4) extracting the data; and (5) applying the results to patient care. Some strategies for promoting evidence-based clinical practice are presented.

Keywords

evidence based medicine
neonatal clinical practice
critical appraisal

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alternatives being considered, and the important clinical outcomes, a targeted search can be conducted for valid evidence that is applicable to the problem.

Finding Evidence

Sources of Evidence

Clinical evidence that is relevant to problems in neonatal-perinatal medicine is appearing at an accelerating rate and can be found in journals, conference proceedings, online databases, and other sources. Many published reports provide only weak evidence because strong research designs were not used. Evidence-based recommendations are constantly changing as new evidence becomes available. The challenge for a busy clinician is to be able to identify evidence that is valid, up-to-date, and applicable to the clinical problem using strategies that are comprehensive and yet efficient. These strategies are usually directed at retrieving primary reports and systematic reviews.

Recent review articles might seem like an efficient source of best available evidence. Because most review articles do not use explicit review methods, however, systematic reviews (discussed later) are a better source of summarized evidence. Although textbooks can provide valid evidence that is based on systematic methods of review, very few textbooks (except books that focus on evidence-based practice[8,14,30,38]) require contributors to use explicit and systematic methods when reviewing evidence and making treatment recommendations. There tends to be a long time gap between the appearance of new evidence and its impact on therapeutic recommendations found in textbooks.[2] In neonatal-perinatal medicine and other fields in which new evidence is rapidly accumulating, it is especially important to be able to access systematic reviews that are frequently updated.

Efficient Strategies for Searching for Evidence

Primary Reports

Primary reports that are relevant to neonatal-perinatal medicine are published in numerous journals. Most of these journals are indexed in MEDLINE, but additional reports may appear in journals indexed in other computerized databases, including CINAHL and EMBASE. With access to the Internet, one can now search MEDLINE for clinical evidence using PubMed; other databases maintained by the National Library of Medicine also can be accessed. PubMed can be accessed at www.ncbi.nlm.nih.gov/pubmed. An increasing number of full-text articles are available through PubMed Central (accessible through PubMed).

To define the topic of a search, one uses medical subject headings (MeSH terms), text words, or a combination, combining them appropriately in a Boolean search with *AND* or *OR* (a medical librarian can quickly teach the logic of this). Help is also available online in the PubMed tutorial. Search terms for the patient population, the intervention, the comparison, the outcome of interest, or all of these may be included.

Often the clinician finds that a MEDLINE search based only on topic descriptors yields a long list of reports that he or she does not have time to scan or read. Busy clinicians need to prune potentially cumbersome lists by incorporating into the search a strategy for limiting the retrieval to reports that are likely to be of high methodologic quality and more likely to provide valid evidence. This strategy includes using methodologic filters that have been validated against hand-searching[20,21,50] to identify articles that, depending on the type of focused question posed, have the methodologic quality attributes shown in Table 7.1. These methodologic filters are used together with topic descriptors (with the use of *AND*) so that only articles that are clinically relevant and satisfy the methodologic criteria are retrieved.

By choosing different methodologic filters, the clinician can maximize either the sensitivity (for comprehensiveness) or the specificity (for fewest methodologic false-positive results) of his or her search. To do this, one uses PubMed's Clinical Queries page (click on Clinical Queries on the PubMed page or access directly at https://www.ncbi.nlm.nih.gov/pubmed/clinical). After entering the clinical search terms, one is asked to click on the category of the question one is asking (therapy, diagnosis, etiology, prognosis, or clinical prediction guide) and on whether the scope of the search should be broad or narrow. If a clinician is reviewing a topic and wants to be comprehensive in retrieval of sound clinical studies, he or she would select a broad filter. If the clinician has limited time and wants

TABLE 7.1 Searching MEDLINE for Sound Clinical Studies Using Methodologic Filters

Type of Question	Criterion Standard for Methodologic Quality
Treatment	Random or quasi-random allocation of participants to treatment and control groups
Etiology	Formal control group using random or quasi-random allocation; nonrandomized concurrent controls; cohort analytic study with matching or statistical adjustment; or case-control study
Diagnosis	Provision of sufficient data to calculate sensitivity and specificity of the test, or likelihood ratios
Prognosis	Cohort of subjects who, at baseline, have the disease of interest but not the outcome of interest

Modified from Haynes RB, et al. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *J Am Med Inform Assoc*. 1994;1(6):447-458.

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urgent access to perhaps only one or two reports that are likely to be methodologically sound, he or she would select a narrow filter.

Reviews

Systematic reviews[7,40] are distinguished from other types of reviews by the rigor of the review methods. The objectives and methods are explicitly planned a priori, and they are documented in the review. A review without a methods section is unlikely to be a systematic review.

Systematic reviews of RCTs attempt to identify all trials that have compared a defined therapy against an alternative in a defined population. Trials are included or excluded from the review on the basis of methodologic rigor (without consideration of the trial results). If the populations and the contrasting interventions are similar, the results may be summarized quantitatively by calculating a typical effect based on the results of all eligible trials. This latter step, called a *meta-analysis,* increases the precision of the estimates of treatment effect. A meta-analysis is not a necessary part of a systematic review, however; if there is clinical or statistical heterogeneity across trials, it may be inappropriate to calculate a typical effect. Systematic reviews can be found in MEDLINE by limiting the publication type to "Meta-Analysis" or by using PubMed's Clinical Queries (Systematic Reviews column).

An example follows: The clinician wishes to find a systematic review, with meta-analysis, of studies of women at risk for preterm delivery that assesses the effect of antenatal corticosteroids on the incidence of RDS in their infants. Using PubMed, the search terms are entered: corticosteroid *AND* respiratory distress syndrome. The search is limited by publication type to meta-analysis. Alternatively, topic descriptors could be entered into the Clinical Queries page, and the output would be viewed under "Systematic Reviews."

Cochrane Systematic Reviews

The Cochrane Collaboration is an international organization that prepares, maintains, and disseminates up-to-date systematic reviews of health care interventions. The reviews are prepared by members of collaborative review groups, including the Pregnancy and Childbirth Review Group and the Neonatal Review Group. The reviews are published electronically in the *Cochrane Library,*[9] which is published every 3 months and allows the reviews to be updated as new evidence appears. The reviews prepared by the Neonatal Review Group formally maintained by the National Institute of Child Health and Human Development can now be found at www.neonatal.cochrane.org/our-reviews. Cochrane reviews are indexed in MEDLINE, so they can also be identified using PubMed searches (using the topic descriptor alone or limiting the search by using the topic descriptor *AND* Cochrane). A description of these reviews has also been published.[41]

Critically Appraising Evidence for Its Validity

The fundamental goal of clinical research is to obtain an unbiased answer to the question posed. Bias leads to an answer that is systematically different from the truth. Guides to assessing the validity of clinical research in the realms of therapy, etiology, diagnosis, prognosis, and reviews are available.[18,19,22,24,25,32] Box 7.1 provides a simple distillation of the major methodologic issues to be considered. More comprehensive guides, with specific applicability to therapeutic studies in neonatal-perinatal medicine, have been published.[33,48]

Most studies on treatment or prevention use designs that can be classified into one of four categories, listed in order of increasing methodologic rigor:

1. Case series without controls
2. Nonrandomized studies using historical controls

• BOX 7.1 Readers' Guides for Appraising the Validity of Clinical Studies

Therapy

- Was the assignment of patients to treatments randomized?
- Was randomization concealed (so that the decision to enroll a patient could not be influenced by knowledge of planned group assignment)?
- Were all patients who entered the trial accounted for and attributed at its conclusion?
- Were outcomes assessed "blindly," without knowledge of treatment group?
- When possible, were patients and caretakers blind to treatment?

Etiology or Harm

- Were there clearly defined comparison groups, similar with respect to important determinants of outcome, other than the one of interest?
- Were the outcomes and exposures measured in the same way in the groups being compared?
- Was follow-up sufficiently long and complete?
- Is the temporal relationship correct?

Diagnosis

- Was there an independent, blind comparison with a criterion standard?
- Did the patient sample include the kinds of patients to whom the diagnostic test would be applied in practice?
- Were the test results prevented from influencing the decision to perform the criterion standard (workup bias avoided)?
- Can the test be replicated on the basis of the method reported?

Prognosis

- Was there a representative, well-defined sample of patients at a uniform point in the course of the disease (inception cohort)?
- Was follow-up sufficiently long and complete?
- Were objective and unbiased outcome criteria used?
- Was there adjustment for important prognostic factors?

Criteria from references 17, 18, 22, 24, and 25.

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3. Nonrandomized studies using concurrent controls
4. RCTs

The randomized trial is the strongest design for evaluating the effect of treatment. It offers maximum protection against selection bias that can invalidate comparisons between groups of patients. The allocation process should be truly random (not quasi-random, e.g., alternate) and masked so that the person(s) making enrollment decisions cannot discern the next group assignment. In addition, follow-up should be complete, with all randomized patients being accounted for in the primary analysis, and outcome measurements should be made by observers who are masked to the treatment allocation. When feasible, masking of the caretakers, the patient, and the patient's family to the treatment allocation should be accomplished. When reading reports of therapeutic studies, the clinician should scan the "Methods" section to assess validity using these criteria.

Extracting the Data and Expressing the Effect of Treatment

Table 7.2 displays the structure of a typical study that assesses the effectiveness of a treatment. There are two exposure groups (labeled *treated* or *control*) and two possible outcome categories (labeled *event* or *no event*). An event is a categorical adverse outcome, such as occurrence of disease, adverse neurodevelopmental outcome, treatment side effect, or death. The effect of treatment is given by comparing the event rate in the treated and control groups, which can be accomplished using either relative or absolute treatment effect estimators.

The relative risk (RR) is the ratio of risk in the treated group to the risk in the control group, [a/(a + b)] / [c/(c + d)]. This is a relative, but not absolute, measure of risk in the event rate. The complement of the relative risk is the relative risk reduction (RRR). Relative risk reduction (1-RR) is the percent reduction in risk in the treated group compared with the controls. Relative risk of 0.75 represents 25% RRR. The risk difference (RD) or absolute risk difference (ARD), [c/(c + d)] − [a/(a + b)], indicates the absolute magnitude of reduction or increase in risk between the control group and treatment group. A risk difference of 0.05 represents an absolute 5 percentage point reduction of the event rate in the treated group.

The ARD can be termed absolute risk reduction (ARR) when the risk is decreased with treatment or absolute risk increase (ARI) when the risk is increased with treatment. The reciprocal of the absolute risk reduction (1/ARR) indicates the number of patients who must be treated to expect to prevent the event in one patient. For an ARR of 5% or 0.05, 20 patients (1/0.05) need to be treated to prevent the event in one patient. The number needed to treat (NNT) is particularly relevant when deciding whether to use a treatment that is effective but causes important clinical side effects or is very expensive. The patient's expected event rate in the absence of treatment may be a crucial determinant of this decision. When outcome data are reported on a continuous scale (e.g., blood pressure measured in mm Hg), a different measure of effect, the mean difference, is computed.

TABLE 7.2 Structure of a Study to Assess the Effect of a Treatment and Measures of Treatment Effect

	Outcome	
Exposure	**Event**	**No Event**
Treated	a	b
Control	c	d
Treatment Effect Measures		
Relative risk (RR)	a/(a + b) / c/(c + d)	
Relative risk reduction (RRR)	1 – RR	
Odds ratio	ad/bc	
Risk difference (RD) or absolute risk difference (ARD)	c/(c + d) – a/(a + b)	
Number needed to treat (NNT) or number needed to harm (NNH)	1/RD = 1/ARD	

Applying the Results to Patient Care

The results of randomized trials of therapy indicate the likely effects of the therapy—beneficial and adverse—on important clinical outcomes. These effects are average effects in the patients who are entered in the trials, however, and they may or may not accurately predict the net benefit to be expected in specific subgroups or individual patients.[12,15] This problem becomes especially important when a treatment produces benefits and harm. Often, patients at high risk of the primary outcome are more likely than patients at low risk to benefit from an effective therapy. Because patients at high risk and patients at low risk are exposed to the adverse side effects of that treatment, the balance between likely benefits and harm can shift. This problem is compounded because individual patients may place different values on the relative importance of benefits and harm caused by treatment.

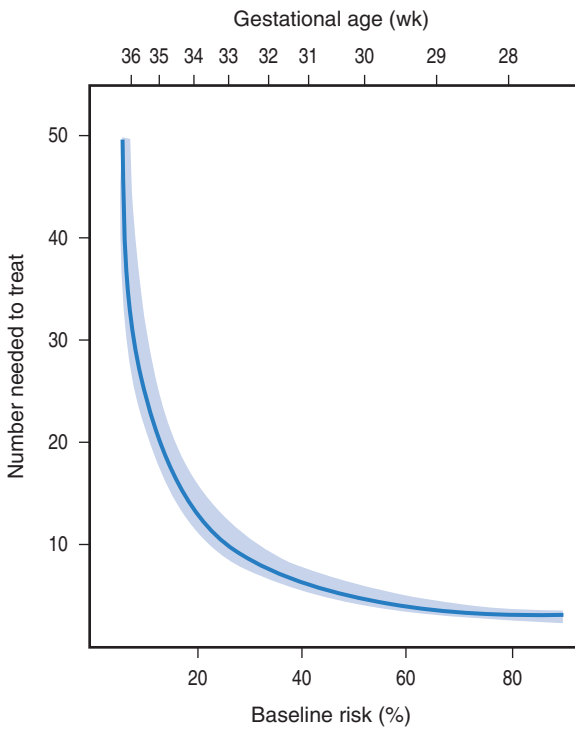
In deciding whether to use an effective therapy in an individual patient, particularly when the therapy results in important clinical side effects, one must consider the relative likelihood that the therapy would actually prevent the adverse target event, or cause adverse side effects, in that individual patient. One way of approaching this decision is to determine whether the report of the relevant trial or systematic review of trials described the size of risk reduction for the primary outcome, and risk increases for any side effects caused, according to patient subgroups defined by patient characteristics at entry. If outcomes are reported for sufficient numbers of patients in these subgroups, it may be possible to derive a relative likelihood of being helped or harmed from the subgroup most similar to the individual

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patient. More often, however, either RRR across subgroups is not clearly different, or the clinician cannot judge this because data by subgroups are not presented, or the groups are too small for meaningful comparisons.

Assuming that RRR is constant across the range of baseline risk, one can calculate a patient-specific ARR using the formula ARR = RRR × PEER, where *PEER* is the patient's expected event rate in the absence of treatment. In neonatal-perinatal medicine, such information may often be available from cohort studies reporting risk based on gestational age, birth weight, and postnatal age. Using this approach, ARR (and its inverse, NNT) would be shown to vary with PEER. In patients at high risk, ARR would be high and NNT would be low, whereas in patients at low risk, the reverse would be true.[16,19,39,44]

An example of this form of analysis is shown in Fig. 7.1. A systematic review of randomized trials of antenatal corticosteroid for the prevention of RDS in infants of mothers at risk of delivering prematurely showed that this therapy was effective in reducing the incidence of RDS, with RRR of 41%.[11] Relative risk reduction was fairly constant across subgroups based on gestational age. Because the expected risk for RDS is high at short gestation, but decreases markedly with increasing gestation, NNT to prevent one case of RDS is low when gestation is less than 30 weeks, but it increases sharply after 34 weeks. Although the trials did not show short-term harmful effects, few of them undertook the assessment of long-term effects. Given the uncertain balance at gestation periods beyond 34 weeks between the small likelihood of short-term benefits and the undocumented but not well-studied possibility of long-term risks, the National Institutes of Health (NIH) Consensus Conference on prenatal corticosteroids recommended that women carrying fetuses of 34 weeks' gestation or less who threaten to deliver prematurely be considered candidates for steroid treatment (see Chapter 19).[31] Subsequently, administration of betamethasone to women at risk for late preterm delivery (34 wks 0 days-36 wks 4 days) was shown to significantly reduce the rate of neonatal respiratory complications.[19a] Other examples and a more detailed discussion of how to balance the risks and benefits in prescribing therapies for individual patients have been published.[44]



• **Fig. 7.1** Number of fetuses who must be treated (number needed to treat [NNT]) with antenatal corticosteroid to prevent one case of respiratory distress syndrome (RDS) as a function of baseline risk. The NNT is derived from the typical relative risk reduction of 41% calculated from the data of the trials included in the systematic review of Crowley. The *shaded zone* indicates the 95% confidence interval. As the gestational age increases, baseline risk for RDS decreases and NNT increases. (From Crowley P. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials. *Am J Obstet Gynecol*. 1995;173(1):322-335.)

Promoting Evidence-Based Clinical Practice

The evidence-based practice paradigm places responsibility on the physician to develop and maintain the skills needed to find relevant evidence efficiently, appraise it critically for its validity, and apply it to the clinical problem. The development of these skills should begin in undergraduate medical education, and there is evidence that teaching critical appraisal skills can be incorporated successfully into clinical clerkships.[3] A useful tool for acquiring these skills and enabling evidence-based care is the critically appraised topic,[37] which comprises asking a focused question about a patient, finding and appraising relevant articles quickly, and synthesizing the evidence into a one- or two-page summary.

Attainment of the required skills by individual practitioners poses a challenge. A survey of English general practitioners[28] revealed that although they were favorably disposed to the concept of evidence-based clinical practice, they believed they lacked the necessary knowledge and skills to carry it forward. Only 16% had formal training in searching for evidence, and only about 33% believed they had sufficient understanding of key terms, such as *relative risk* and *number needed to treat,* that they could explain them to others. Most believed that the best way to promote evidence-based practice was the introduction of evidence-based practice guidelines or protocols.[28] Experts in Europe have developed a formal electronic-based curriculum (www.ebm-unity.medmonash.edu/index.html) designed to improve the skills of busy clinicians to integrate EBM at the bedside and other clinical settings.[10,47] Once fully implemented, the project will lead to a specialist qualification in teaching EBM. Utilizing a self-directed electronic-based curriculum alone has demonstrated only similar effectiveness in teaching evidence-based medicine skills as formal teaching methods.[5,49]

The preparation and dissemination of practice guidelines or consensus recommendations does not ensure their use in

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practice.[4,29] Several strategies aimed at promoting behavioral change among clinicians have been tested, and some have been found successful. Two of these strategies—introducing guidelines through opinion leaders and providing audit and feedback—were included in an intervention package designed to encourage the use of antenatal corticosteroids in eligible women, in accordance with the NIH Consensus recommendations.[31] In a randomized trial in which this package was compared with a control intervention consisting of the usual dissemination of recommendations, the evidence-based use of antenatal corticosteroids was increased in the experimental group.[26,27] Cluster randomized trials are being increasingly used to evaluate competing strategies for promoting the use of evidence in clinical practice.[27,42] More of these studies are needed.

There is also a need for the further development of practical methods for measuring the importance or value that patients, caregivers, and the lay public attach to clinical outcomes.[44,45] In neonatal-perinatal decision making, these values are usually sought from the parents by using informal and unsystematic approaches. Formal systematic methods for measuring preferences,[23] including rating scales and the standard gamble, have been developed. These were used to measure quality of life as perceived by adolescent survivors of extremely low birth weight and their parents.[35] Such methods for rating health outcomes could be used increasingly in the future to assess the importance that parents attach to the probable outcomes of neonatal-perinatal treatment alternatives and to help guide evidence-based decision making for individual patients or patients in specific risk categories.[36,43] For assistance in applying the evolving standards for evaluating and applying evidence to perinatal care, obstetricians, neonatologists, and pediatricians are encouraged to consult the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[16a,17a]

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Key Points

- The practice of evidence-based medicine requires efficient access to the best available evidence that is applicable to the clinical problem.
- There are limitations to EBM in that evidence may not exist about the specific clinical problem in question.
- Evidence is necessary but not sufficient to provide clinical care. Clinical judgment must be linked with the evidence to provide optimal treatment.

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8

Perinatal and Neonatal Care in Developing Countries

WALDEMAR A. CARLO

The science and practice of modern neonatology evolved as a medical specialty in the United States and the Western world over the last 70 years. Neonatology as a specialty in developing countries is still evolving. The increased attention to improving newborn care at a global level can be traced to the recognition by the World Health Organization (WHO) of unacceptably high infant mortality in low- and middle-income countries (LMICs).[96,97] The Alma Ata Declaration was the first serious effort by WHO to address the problem of high infant mortality rate (IMR) among developing countries.[27] Since then, several policies have been proposed and implemented to decrease the IMR and neonatal mortality rate (NMR) across the globe. Since the latter part of the twentieth century, there has been steady improvement in overall global newborn care resulting in the reduction of NMR and IMR in LMICs. These developments can be attributed to rapid globalization of health-related information and technology from developed high-income countries (HICs) to LMICs. Also, increased awareness of health and change in health care–seeking behavior among women during the past decade has improved maternal and child health. The major factors responsible for overall improvements in maternal and child care in LMICs probably include: (1) improved access to medical and technical information, (2) rapid transfer of technology, and (3) international campaigns such as the advocacy of the Millennium Development Goals (MDGs)[95] and the Sustainable Development Goals (SDGs).[94] Several large controlled trials have demonstrated the benefits of selected interventions, including packages of care such as the Mother-Baby Package[61] and the Essential Newborn Care program.[15,16,55,96,97] Considerable progress is being made in reducing maternal and child mortality in developing countries; however, many challenges remain. This chapter provides an overview of global neonatal and perinatal problems, presents data on the changing trends in IMR and NMR, and discusses strategies to decrease the IMR and NMR in developing countries.

Global Initiatives to Reduce Infant Mortality Rate and Neonatal Mortality Rate

Historical Perspective

Because of concerns of high global IMR, numerous interventions have been proposed and implemented by world organizations over the past four decades (Table 8.1). The Alma-Ata Declaration of 1978 by the WHO and the United Nations Children's Fund (UNICEF) set a goal to achieve "Health for all by the year 2000."[54] The declaration included a goal for the reduction of maternal and infant mortality through primary care. In 1987, the International Conference on Safe Motherhood drew attention to high maternal mortality rates (MMRs) in developing countries and encouraged policymakers to develop new strategies to reduce maternal mortality.[104] This action led to the worldwide program of Safe Motherhood, placing an emphasis on antenatal care. A similar resolution, the Bamako Initiative, was instituted at the annual meeting of the African Ministries of Health in 1987.[32] The objective was the achievement of universal maternal-child health coverage at the periphery by 2000. In 1988, the Task Force for Child Survival set objectives for a reduction in MMR and IMR.[90] One of these objectives was a worldwide reduction in mortality by at least half, or by 50 to 70 per 1000 live births, whichever can be achieved first, for children 5 years old and younger. Another objective was the reduction of MMR worldwide by at least half.

In 1994, WHO developed the Mother-Baby Package to help reduce MMR and NMR further.[61] Recognizing that MMR remained high, in 1999 WHO re-emphasized the need for an acceleration of national and international efforts to decrease MMR and perinatal mortality rate through the Safe Motherhood program. At the 48th World Assembly of WHO, the concept of integrated management of childhood illness was adopted to improve the well-being of the whole

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Abstract

Developing countries continue to share the major burden of neonatal and infant mortality including about 98% of the deaths worldwide. The most frequent causes of neonatal mortality in low- and middle-income countries are preterm birth complications, birth asphyxia, and sepsis/meningitis. The major causes responsible for such disparity between countries are a lack of health facilities, lack of skilled personnel, and lack of access to health care. Considerable progress is being made in reducing maternal and child mortality in developing countries; however, many challenges remain. By the end of the twentieth century, a significant decrease in maternal and infant mortality was reported to be one of the top health achievements of the century. The Sustainable Development Goals program declared in 2015 is the single most influential program bringing the world community, governments, scientists, and policymakers together to address the issues of high neonatal and infant mortality in low- and middle-income countries. There is evidence-based data that show which antenatal, intrapartum, and neonatal interventions are most effective. Several large controlled trials have demonstrated the benefits of selected interventions, including packages of care such as the Mother-Baby Package, Helping Babies Breathe (resuscitation), and the Essential Newborn Care programs. Neonatology is a work in progress in low- and middle-income countries.

Keywords

mortality, infant
mortality, neonatal
developing countries
perinatal death
global/health

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TABLE 8.1 Global Initiatives to Decrease Neonatal, Child, and Maternal Mortality

Initiative	Organization	Year and Occasion	Goals
Declaration of Alma-Ata	WHO, UNICEF	Sept 1978, USSR, International Conference on Primary Health Care	Health for all by 2000
Safe Motherhood Initiative	WHO, UNICEF, UNFPA, World Bank, and others	1987, Nairobi, International Safe Motherhood Conference	Reduce maternal mortality to half the present rate by 2000.
Bamako Initiative	UNICEF, WHO	September 1987, Bamako, Mali, Annual Meeting of African Ministers of Health	Achieve universal maternal and child health coverage at the peripheral level by 2000. Revitalize peripheral public health systems. Supply basic drugs. Establish revolving funds. Involve communities in health care.
Task Force for Child Survival	WHO, UNICEF, World Bank, UNDP, Rockefeller Foundation	March 1998, Talloires, France, Protecting the World's Children, an Agenda for the 1990s	Global eradication of polio. Virtual elimination of neonatal tetanus, 90% reduction in cases of measles and 95% reduction in its fatalities, 25% reduction in fatalities owing to ARI. Reduction of IMR and MMR by half or 50-70/1000, whichever is greater. Reduction of MMR by at least half.
Mother-Baby Package	WHO	Sept 1994, Cairo, International Conference on Population and Development	Reduce maternal mortality to half of 1990 levels by 2000.
			Reduce perinatal and neonatal mortality from 1990 levels by 30%-40% and improve newborn health.
Making Pregnancy Safer	WHO	1999, Safe Motherhood Initiative	Accelerate reduction of high maternal and perinatal mortality and morbidity by refocusing WHO strategies in national and international health sectors.
Millennium Development Goals	WHO	2000-2015	Reduce child mortality Reduce by two-thirds the mortality rate for children <5 years old between 1990 and 2015.
Newborn Care Training	NIH	2010	Essential newborn care training of community-based birth attendants has reduced the stillbirth rate.*
Sustainable Development Goals	WHO	2015-2030	Reduce the under-5 mortality rate by two-thirds between 1990 and 2015. Reduce the maternal mortality rate by three-fourths between 1990 and 2015. Reduce global maternal mortality to ≤70 per 100,000 live births. Reduce neonatal mortality to ≤12 per 1000 live births. Reduce under-5 mortality to ≤25 per 1000 live births.

ARI, Acute respiratory infection; IMR, infant mortality rate; MMR, maternal mortality rate; NIH, National Institutes of Health; UNDP, United Nations Development Program; UNFPA, United Nations Fund for Population Activities; UNICEF, United Nations Children's Fund (formerly United Nations International Children's Emergency Fund); WHO, World Health Organization.

*From Carlo WA, et al. Newborn-care training and perinatal mortality in developing countries. *N Engl J Med*. 2010;362:614.

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child younger than 5 years old.[93] This concept included an emphasis on improved care of newborns. By the end of the twentieth century, a significant decrease in MMR and IMR was reported as one of the top 10 achievements of the century.[91] However, the high IMR and NMR in the LMICs continued to be a major concern to global policymakers. The World Bank initiated the Global Burden of Disease study, which showed that perinatal conditions, including infant mortality, form a significant portion (39%) of the global burden of disease. It showed that developing countries are the major contributors to global perinatal and neonatal mortality. Perinatal mortality constitutes one of the 10 leading causes of death in developing countries. Neonatal mortality is the major part of perinatal mortality. These findings underscore the importance of improving perinatal and neonatal care in developing countries, as declared in the MDGs in 2000.[95]

The Millennium Development Goals (MDGs)

In 2000, the United Nations developed eight MDGs to be achieved by 2015.[95] The targets were measured by preset quantifiable measures. The MDGs focus on some specific health issues but also emphasize social, economic, and public health and health-policy matters that affect the "health" of the people and addressed specific indicator goals for perinatal care (Table 8.2).

In addition to these developments, the series of landmark scientific publications in *The Lancet* provided evidence-based scalable interventions that could reduce NMR and IMR in resource-poor countries.[22,41] These publications generated great interest among researchers and health policymakers around the globe. The Child Survival series examined the potential impact of scaling up 43 interventions that could reduce child mortality by 2015. In 2005, the series on newborn survival provided the first systematic estimates of neonatal deaths by cause and identified simple and cost-effective scalable interventions that could reduce neonatal deaths globally. The impact of some of the suggested interventions is described in the later part of this chapter.

The Sustainable Development Goals

In 2015, the United Nations proposed the Sustainable Developmental Goals (SDGs) to be achieved by 2030.[36,94] These goals were adopted to end poverty, protect the planet, and ensure prosperity for all as part of a new sustainable development agenda. Each goal has specific targets to be achieved over the next 15 years. There are 17 goals (Fig. 8.1).[94] Goal 3 is focused on health and aims to ensure healthy lives and promote well-being for all at all ages. This goal includes specific targets for perinatal and childhood health outcomes. The maternal and childhood targets aim to reduce global maternal mortality ratios to less than 70 per 100,000 live births and end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births. These aspiring goals are ambitious and will require commitment from all stakeholders to achieve them.

Tracking the Global Progress of the Sustainable Development Goals

Worldwide efforts are taking place to implement SDGs and track their impact. There is a need for accurate birth and death data from all participating countries. Unfortunately, collecting accurate NMR, IMR, and under-5 mortality data on a global scale remains a major problem. There are several hurdles to collect these data accurately. Whereas high-income countries have well-established vital statistics of births and deaths, the LMICs do not. Ostergaard and coworkers found that only 60 of the 193 countries studied had fully functioning sources of mortality data[67]; the rest of the countries depend on annual or periodic surveys. There is a need for improvement in accurate vital statistics to establish

TABLE 8.2 Details of Millennium Development Goals (MDG) and Sustainable Development Goals (SDG) Related to Perinatal Care

Goals	Targets	Indicators
MDG Goal 4 Reduce child mortality	Reduce the under-5 mortality rate by two-thirds between 1990 and 2015.	Under-5 mortality rate (deaths per 1000 live births) Infant mortality rate (deaths per 1000 live births) Proportion of 1-year-old children immunized against measles
MDG Goal 5 Improve maternal health	Reduce the maternal mortality rate by three-fourths between 1990 and 2015.	Maternal mortality ratio (deaths per 100,000 live births) Proportion of births attended by skilled health personnel
SDG Goal 3 Good health and well-being	Reduce global maternal mortality to ≤70 per 100,000 live births. Reduce neonatal mortality to ≤12 per 1000 live births. Reduce under 5 mortality to ≤25 per 1000 live births.	Maternal mortality ratio (deaths per 100,00 live births) Neonatal mortality rate (deaths per 1000 live births) Under-5 mortality rate (deaths per 1000 live births)

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• **Fig. 8.1** The Sustainable Development Goals: a plan of action for people, planet, and prosperity. Goal 3 is focused on health. (United Nations. Sustainable Development Goals. United Nations; 2015. www.un.org/sustainabledevelopment/sustainable-development-goals/. Accessed on February 1, 2018. © 2015 United Nations. Reprinted with the permission of the United Nations.)

the true burden of MMR, NMR, and IMR and to develop appropriate strategies to monitor progress.

Global Burden of Maternal and Neonatal Deaths

Maternal Mortality

Maternal mortality has been a major global burden of disease.[51] At the time of and preceding the declaration of MDGs, more than 600,000 women were dying annually from causes related to pregnancy and childbirth.[92] Asia and Africa had the highest MMR and the highest number of maternal deaths, compared with only 4000 deaths per year in HICs. The causes of maternal death include maternal hemorrhage (25%), sepsis (15%), abortion (13%), hypertensive disorders of pregnancy (12%), and obstructed labor (8%). More than 50% of the deaths related to pregnancy and childbirth were estimated to be preventable using simple, well-accepted interventions. The MDG #5 aimed at reducing the MMR by 75% between 1990 and 2015.

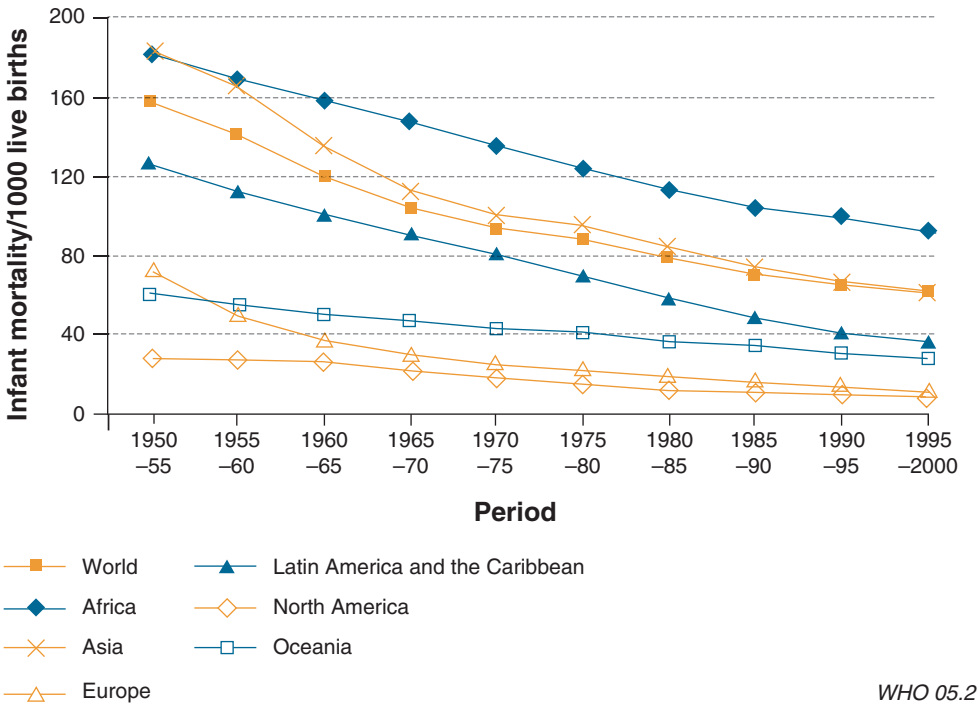
On a positive note, global MMR in 2010 had decreased by 47% (from 400/100,000 in 1990 to 210/100,000), accounting for 287,000 maternal deaths in 2010.[14,58] Although the overall number of maternal deaths has decreased, only 10 countries have reached the goal, 9 countries are "on track," 50 countries are "making progress," 14 countries have made "insufficient progress," and 11 are categorized as having made "no progress" at all. Sub-Saharan Africa (56%) and South Asia (29%) continue to bear the major burden of global MMR (85%), accounting for 245,000 maternal deaths in 2010. Two countries, Nigeria and India, contribute one-third of the global MMR: India at 19% and Nigeria at 14%.

Neonatal and Infant Mortality

There are limited data on NMR or IMR that go back to the early twentieth century, but there were major reductions in mortality. Fig. 8.2 shows global trends in IMR during 1950 to 2000.[60] In the 1950s, there were wide variations in IMR among different regions of the world. Infant mortality rate was lowest in industrialized Western countries (33 per 1000). It decreased to around 5 per 1000 by 2000, a reduction of 85%. In 1950, sub-Saharan Africa had the highest IMR (157 per 1000) and showed the least reduction (only 32%) among all the regions of the world during the next 50 years. South Asia, the Middle East/North Africa, and Latin America/Caribbean showed 53%, 70%, and 74% decreases, respectively. At the end of the twentieth century, IMR continued to remain significantly high: 70 per 1000 in South Asia, 45 per 1000 in the Middle East, and 27 per 1000 in Latin America.

In an analysis of NMR, out of 193 countries from 1990 to 2009, the investigators found that only 38 countries had a system of civil registration of births and deaths.[67] One hundred fifty-five other countries calculated NMR using statistical models. During the two-decade study, 79 million babies died. More than 98% of deaths occurred in LMICs, the majority of these deaths occur in South Asia and sub-Saharan Africa. The annual reduction rate of NMR was twice as high for the period 1999 to 2009 (2.3%) compared with the period 1990 to 1999 (1.1%). There was a lower

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• **Fig. 8.2** Global trends in IMR during 1950 to 2000. Over the past 50 years major demographic changes have affected all regions and countries. As a result of changes in fertility and mortality the world's population has increased from 2.5 billion to 6 billion. Declines in mortality rates, especially during childhood, have been particularly remarkable. (Moser K, Shkolniko V, Leon DA. World mortality 1950-2000: divergence replaces convergence. *Bull World Health Organ*. 2005;83:202-209.)

rate of reduction of NMR in high-income countries (HICs) (1.7% in 1999 to 2009 vs. 3.7% in 1990 to 1999). In spite of these decreases in NMR across the LMICs, the annual rate of NMR reduction was still well below the MDG #4 goal of 4.4% and below the IMR and under-5 mortality rate reductions.[37] Most importantly, NMR varies marginally between countries, with the highest neonatal mortality rates in sub-Saharan Africa and Southeast Asia (Fig. 8.3).

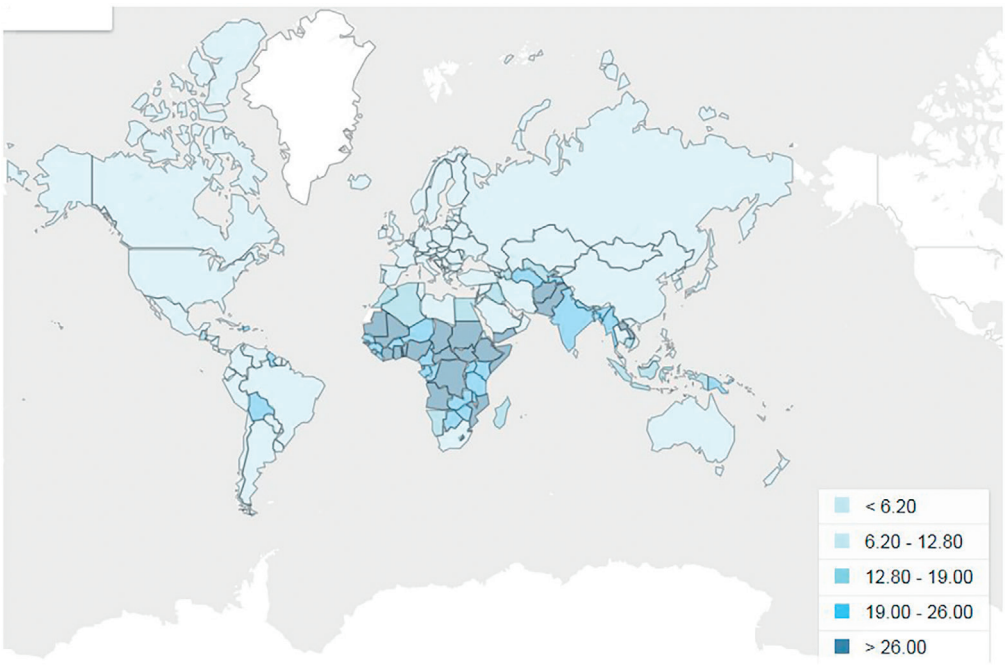
Of the 7.6 million deaths in children under 5 years in 2010, 40% were neonatal deaths (Fig. 8.4).[49] Preterm birth complications (14% of under-5 deaths), birth asphyxia (also called intrapartum-related) complications (9%), and sepsis/meningitis (5%) were the most frequent causes of death in the neonatal period. About 35% of the neonatal deaths occured on the day of birth with another ~35% occurring during the rest of the first week after birth[69] (Fig. 8.5). After a month of age, pneumonia (14%), diarrhea (10%), and malaria (7%) were the most frequent causes of death. To decrease under-5 mortality the most, efforts should concentrate on these causes of death, particularly soon after birth.[48,49,50]

Compared with NMR, the under-5 mortality rate (U5MR) decreased considerably from 1990 to 2010. Fig. 8.6 shows trends in U5MR and NMR in 193 countries from 1990 to 2010.[45] The U5MR showed a steady decrease during the period, whereas the NMR, although decreasing, did so at a slower rate. The NMR thus constituted a higher proportion of U5MR from 2000 to 2010 compared with 1990 to 2000. South Asia accounts for more than half of under-5 deaths. Almost 30% of global neonatal deaths occurred in India. Sub-Saharan Africa accounts for 38% of global neonatal deaths, with the highest NMR (34/1000 live births) and least progress in reducing that rate over the last two decades. Neonatal deaths in sub-Saharan Africa account for about one-third of U5MR (1.1 million neonatal deaths). Taking into consideration the current slow rate of reduction in NMR among the LMICs,[100] the authors also calculated the number of years it will take various countries in different regions to achieve NMR levels similar to those currently in HIC (Fig. 8.7).[67] It is disconcerting to note that for some countries, it will take several decades to reach the low levels of HIC, whereas others may take more than 100 years to reach the low levels of HICs. These disappointing findings underscore the need for serious efforts with a stronger health policy to decrease NMR and IMR in sub-Saharan countries.

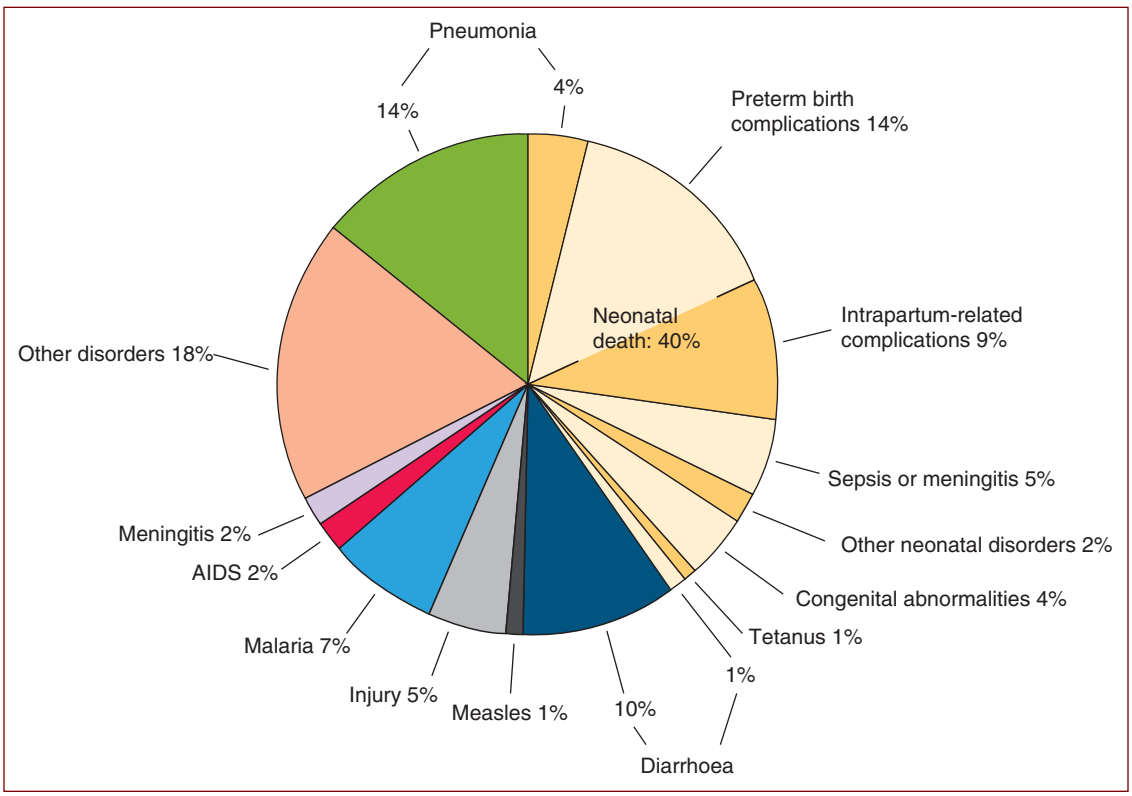
Causes of Global Maternal and Neonatal Mortality

Factors that influence MMR and NMR include commonly known maternal and neonatal medical problems, socioeconomic conditions, gender inequality, environmental factors, and economic and political instability. Socioeconomic factors greatly influence the health of mother and baby, in particular, in LMICs, as discussed in the following section.

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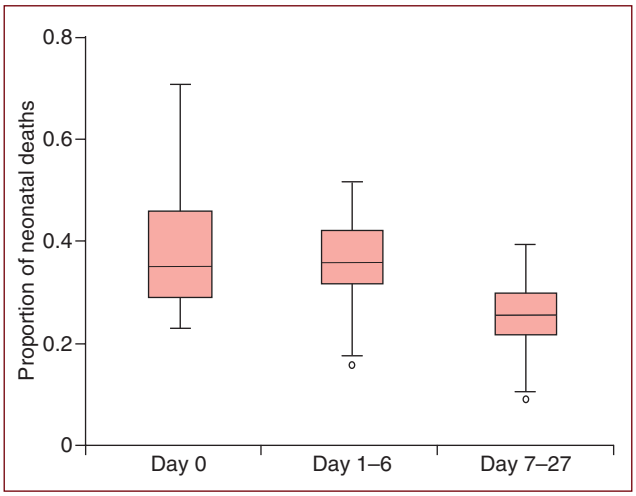


• **Fig. 8.3** Most recent neonatal mortality rate (per 1000 live births) estimates by country. The estimates were developed by the UN Inter-agency Group for Child Mortality Estimation (UNICEF, WHO, World Bank, UN DESA Population Division) and updated in 2017. Countries in sub-Saharan Africa have the highest neonatal mortality rates. Some countries in South and Southeast Asia also have very high neonatal mortality rates. (UNICEF, WHO, World Bank, UN DESA Population Division. https://data.worldbank.org/indicator/SH.DYN.NMRT?view=map and childmortality.org. Accessed February 2, 2018.)

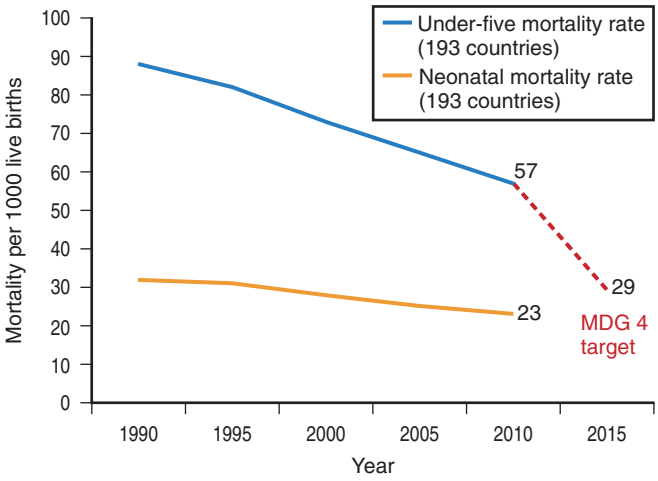


• **Fig. 8.4** Global causes of childhood deaths in 2010. Causes that led to less than 1% of deaths are not shown. Of all infectious disorders, pneumonia, diarrhea, and malaria were the leading causes of death worldwide. Of all deaths in children younger than 5 years, pneumonia caused 1.396 million deaths (uncertainty range [UR] 1189–1.642 million; 18.3% of total deaths), diarrhea caused 0.801 million deaths (UR 0.555–1.182 million, 10.5%), and malaria caused 0.564 million deaths (UR 0.432–0.709 million, 7.4%). (Liu L, Johnson HL, Cousens S, et al. Global regional and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379:2151-2161.)

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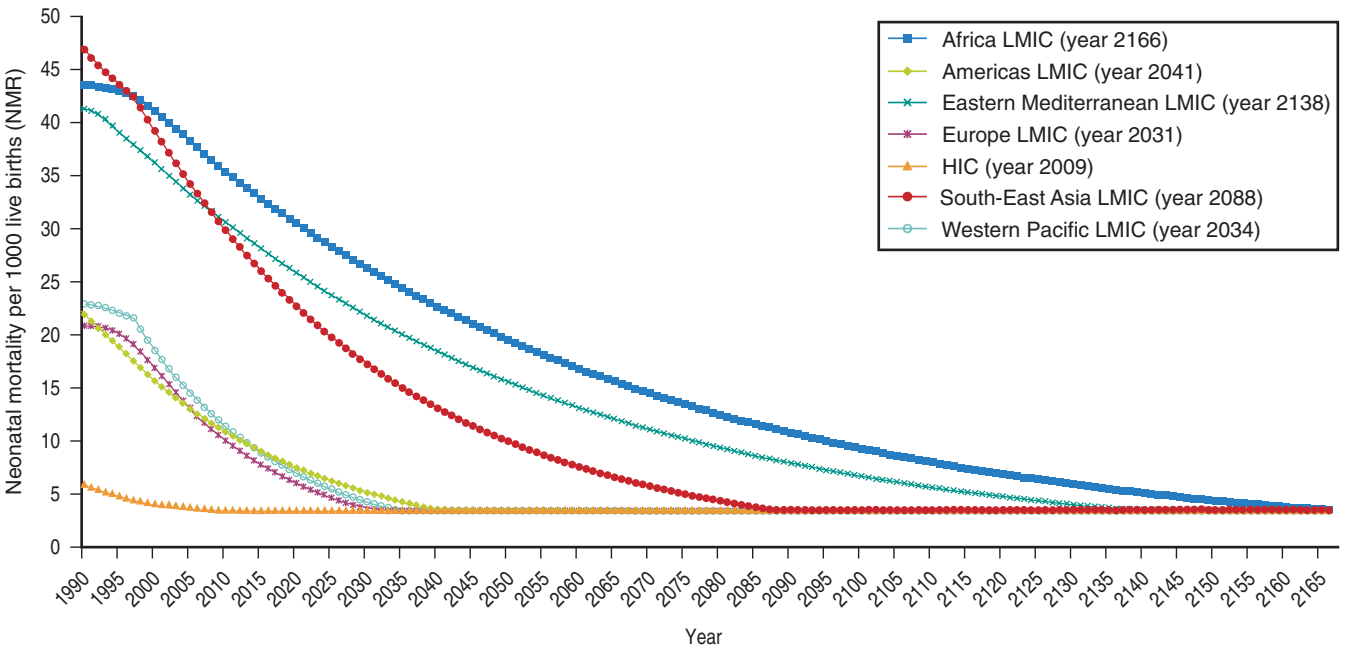


• **Fig. 8.5** Proportion of neonatal deaths for 57 countries with vital registration data on days 0, 1-6, and 7-27. Most deaths occur during the first week after birth. (Oza S, Cousens SN, Lawn JE. Estimation of daily risk of neonatal death, including the day of birth, in 186 countries in 2013: a vital-registration and modeling-based study. *Lancet Glob Health*. 2014;2(11):e635-44.)



Average annual rate of reduction	1990–2010	2000–2010
Under-five mortality rate	2.2%	2.5%
Children 1–59 months mortality rate	2.5%	2.9%
Neonatal mortality rate	1.8%	2.1%

• **Fig. 8.6** Progress towards Millennium Development Goal 4 for child survival showing progress globally (193 countries). (Lawn JE, Kinney MV, Black RE, et al. Newborn survival: a multi-country analysis of a decade of change. *Health Policy Plan*. 2012;27[suppl 3]:iii6-28.)



• **Fig. 8.7** Forecasting the number of years for low- and middle-income regions to reduce neonatal mortality rate (NMR) to the current rate in HICs. The graph illustrates when each region of the world attains an NMR of 3.6 as observed in HICs in 2009—the year each region attains an NMR of 3.6 is specified in parenthesis. Regional NMRs are illustrated as constant from the year they achieve an NMR of 3.6. Forecasting based on average annual changes in the NMR over the 10-year period 1999–2009. (Oestergaard MZ, Inoue M, Yoshida S, et al. Neonatal mortality levels for 193 countries in 2009 with trends since 1990: a systematic analysis of progress, projections, and priorities. *PLoS Med*. 2011;8:e1001080.)

Socioeconomic and Cultural Factors

The socioeconomic factors adversely influencing IMR include gender bias against women, maternal education, and economic dependence. SDG #5 is aimed at eliminating gender inequity. Gender bias against women has a negative effect on every phase of a woman's life, interfering with her education, economic power, and health.[71] Gender-biased discrimination begins its influence early in life, leading to poorer nutrition and health in girls compared with boys.

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Gender inequalities persist worldwide, depriving women and girls of their basic rights and opportunities. SDG #1 aims to end poverty in all its forms everywhere. SDG #4 aims to ensure inclusive and equitable quality education and promote lifelong learning opportunities for all. Evidence shows that a woman with more education has fewer children, better economic status, lower fertility rate, lower IMR, and improved quality of life. Even in developed countries, every additional year of education for women is associated with lower mortality rates at all ages.[26] Education increases earning potential, and higher income is associated with lower mortality. Earning power provides women with economic, social, and political empowerment. In short, education is seen as a means of ensuring health. Health-seeking behavior during pregnancy, childbirth, and the neonatal period is influenced by regional, religious, and ethnic differences and by cultural beliefs. Understanding the cultural beliefs and their influences on care of the mother and infant is crucial to providing appropriate counseling to mothers.[81] Health strategies to improve MMR and IMR in LMICs include implementation of programs that eliminate gender inequities, end poverty, and ensure equitable education will enable women to improve their health and that of their children. In addition, increasing awareness of maintaining health, improving health-seeking behavior, and improving access to health care will improve health outcomes.

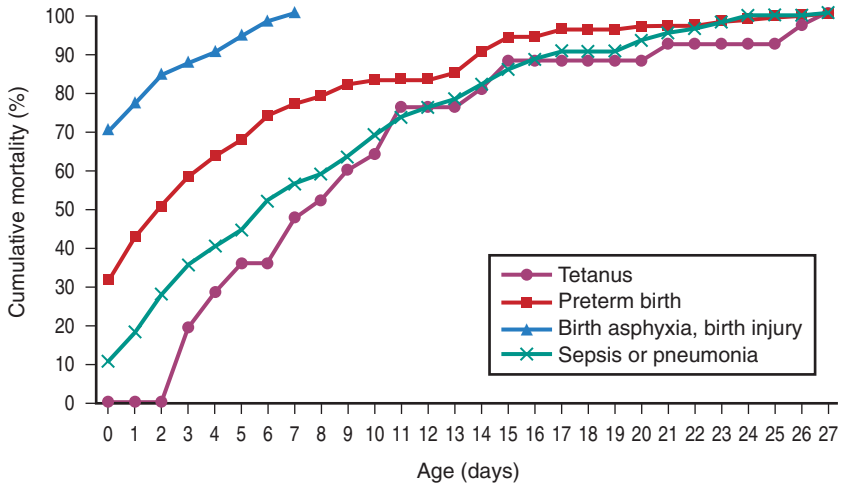
Influence of Political Instability, War, and Conflict

Economic stability alone does not guarantee better health of the mother and child. For example, many oil- and mineral-rich countries in Middle East, Africa, and Latin America with a sizeable global income are a unique group with wide disparities of wealth and health.[12] Despite high gross national product, some of these countries have high IMR, high U5MR, high MMR, and low life expectancy.[60] Although the overall IMR has decreased from ~200 per 1000 in the 1950s to ~50 per 1000 in 2000, in some countries, IMRs are far higher than in Latin America and East Asia.[78]

Women and children account for a disproportionate morbidity burden among conflict-affected populations. Political instability and wars have adversely affected perinatal and neonatal outcome. For example, infant mortality rate and under-5 mortality rate increased during the recent conflict in Syria.[28] Similarly, natural disasters such as Hurricane Katrina and tsunamis call for preparedness to care for pregnant women, parturient mothers, and neonates.[67,68] Pediatricians and neonatologists serving in areas of war conflicts and those working in the armed forces should be well-prepared to manage these situations.

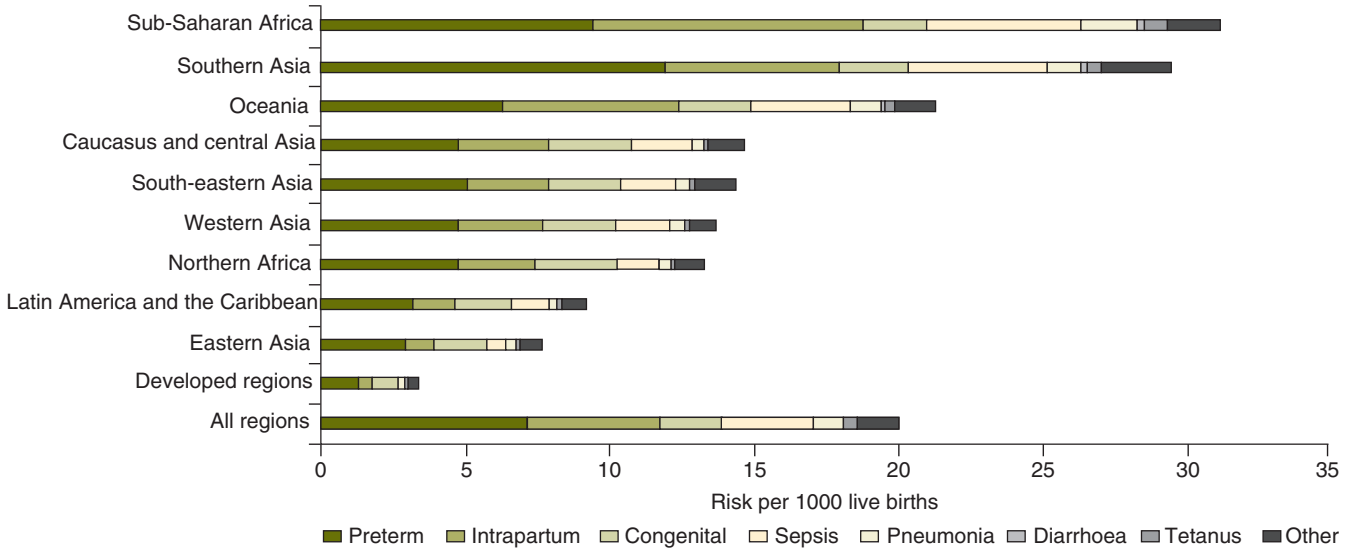
Medical Causes of Neonatal Mortality Rate

In developing countries, prematurity, birth asphyxia, and sepsis/pneumonia continue to constitute a major portion of NMR and IMR (see Fig. 8.4).[49] About 40% of U5MR is due to NMR. Neonatal death due to prematurity is the number one cause of U5MR. Birth asphyxia and sepsis are the other major causes of neonatal mortality.[37,38,49,70] The WHO estimates that 40% to 60% of neonatal deaths are preventable. The time of death is dependent on these causes of death (Fig. 8.8).[5] Furthermore, specific causes of death vary substantially by regions of the world (Fig. 8.9).[70] In contrast to the major contributions of prematurity, birth asphyxia, and sepsis in LMIC settings, congenital malformations and prematurity are the dominant causes of neonatal mortality in HICs. The major causes of neonatal mortality are discussed in detail in the following section.



• **Fig. 8.8** Distribution of deaths by diagnostic categories during the first 28 days of life in a rural population. Lines show cumulative percent deaths for each diagnostic cause. Most deaths in babies with birth asphyxia occur during the first week of life. Prematurity is the second-highest cause of deaths, followed by sepsis and tetanus-related deaths start occurring by the second day of life. (Baqui AH, Darmstadt GL, Williams EK, et al. Rates, timing and causes of neonatal deaths in rural India: implications for neonatal health programmes. *Bull World Health Organ*. 2006;84:706-713.)

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• **Fig. 8.9** Cause-specific risk of neonatal death by Millennium Development Goal (MDG) region in 2013. In every MDG region, preterm birth is the leading cause of neonatal death, with the highest risks in southern Asia (11.9 per 1000 live births) and sub-Saharan Africa (9.5 per 1000 live births). (Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000-2013. *Bull World Health Organ*. 2015;93:19-28.)

Prematurity

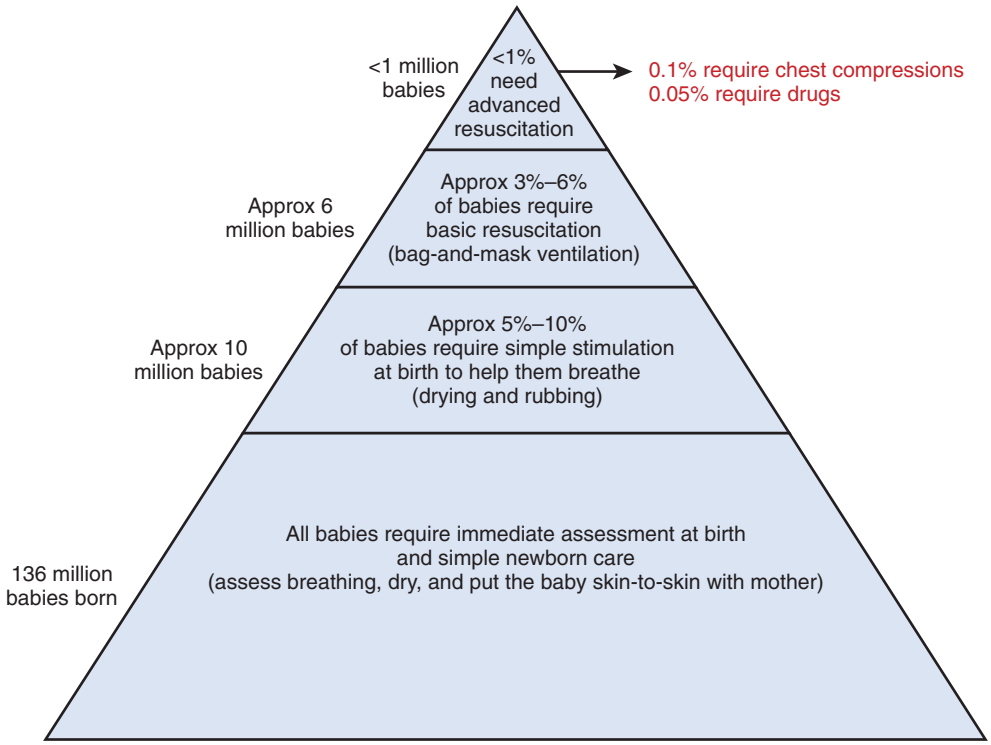
While prematurity is the most frequent cause of death in neonates, the specific cause of death in premature babies worldwide is not known. Respiratory distress syndrome is the most common cause of death in HICs, but in LMICs it is likely that lack of neonatal intensive care accounts for most of the deaths from prematurity. A meta-analysis conclusively demonstrates that surfactant administration reduces mortality in LMIC settings with neonatal intensive care units.[78,79] There are many other effective therapies, such as thermoregulation, nutrition, and prevention and treatment of sepsis, that may have a large impact in LMIC settings. It is likely that most interventions that reduce neonatal mortality in neonatal intensive care units in HICs will reduce neonatal mortality in similar settings in LMICs also.

Birth Asphyxia

Failure to achieve a smooth postnatal transition may lead to various degrees of birth asphyxia. Death due to birth asphyxia is defined as death due to the inability to breathe or sustain breathing soon after birth. Of the 136 million births per year globally, almost 1 million babies die of birth asphyxia. Most of these deaths occur in LMICs where an estimated 4 to 9 million infants per year experience birth asphyxia. Birth asphyxia contributes to 20% to 40% of all neonatal deaths depending on the setting.

The burden of birth asphyxia and the number of babies requiring resuscitation at birth at a global level are shown in Fig. 8.10.[47] It is estimated that of the 136 million annual births, about 10 million (5%–10%) respond to simple stimulation to initiate breathing efforts, 3% to 6% require basic resuscitation with bag and mask (6 million), and only less than 1% (<1 million) require advanced resuscitation (0.1% chest compression and 0.05% require drugs). Causes of birth asphyxia include poor maternal health, inadequate antenatal care, high-risk pregnancies and intrapartum complications, and inadequate care during labor and delivery. Prematurity also contributes to the problem of birth asphyxia. Lack of skilled birth attendants and lack of availability of proper equipment at the time of delivery are the major contributing factors for higher birth-asphyxia–related morbidity and mortality in developing countries. It is heartening to note that in recent years great strides have been made to overcome these deficiencies. Many countries have initiated training programs to improve resuscitation skills at the grass-roots level. In addition to the earlier efforts of WHO and UNICEF, the Neonatal Resuscitation Program (NRP), developed by the American Academy of Pediatrics and American Heart Association, has been adopted in its full or modified form by more than 72 countries worldwide, including India and China. Helping Babies Breathe (HBB) is a simplified version of neonatal resuscitation that advocates proper assessment of baby at birth, stimulation to breathe, and assisted ventilation for all newborns who are not breathing adequately by 1 minute after birth—"The Golden Minute."[84,85] The main life-saving skill is ventilation with a bag and mask. Because of the simplicity of the skill training, it is easily adoptable to train health care workers attending deliveries at a health facility in rural settings. Two large-scale trials that enrolled almost 200,000 deliveries showed that Essential Newborn Care (now simplified as Essential Care for Every Baby and Essential Care for Small Babies) and resuscitation programs reduced early neonatal mortality by over 60%[16] and fresh stillbirth by over 30%,[15] markedly reducing perinatal mortality. These programs are being implemented by many global partners (UNICEF,

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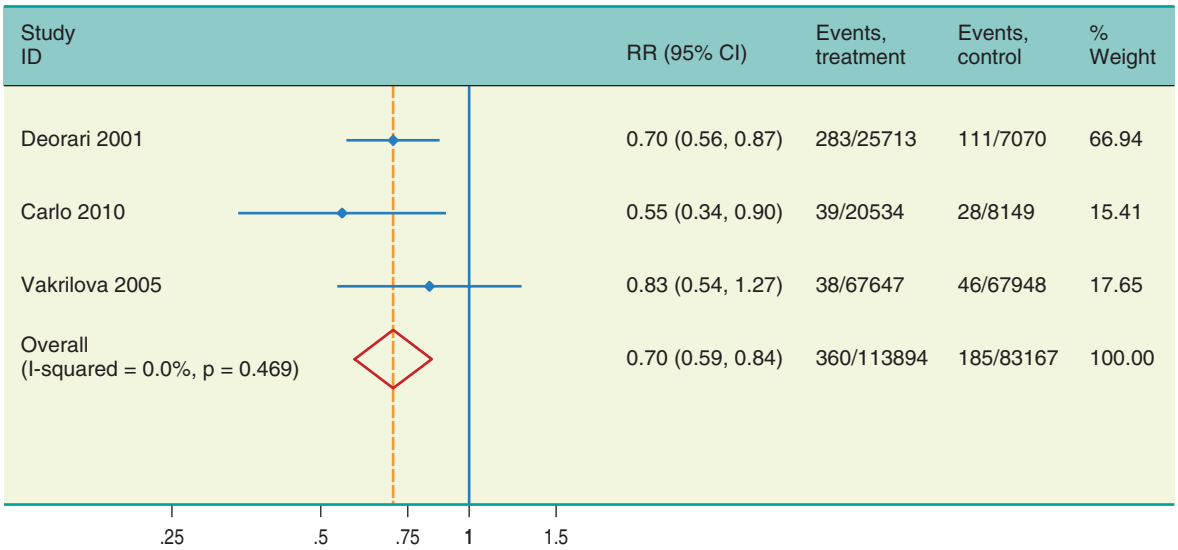
• **Fig. 8.10** The global burden of neonatal resuscitation demonstrating the potential number of babies that require various degrees of resuscitation at birth. Many babies (approximately 10 million) respond to simple resuscitation using skills of "Helping Babies Breathe," and approximately 6 million will need bag and mask ventilation. About 1 million may require intubation and full resuscitation. (Lee AC, Cousens S, Wall SN, et al. Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: a systematic review, meta-analysis and Delphi estimation of mortality effect. *BMC Public Health*. 2011;11[suppl 3]:S12.).

WHO, and USAID) in many LMICs.[102] In India, the NRP has become a standard skill-training module since 1990.[29] A significant reduction in deaths related to birth asphyxia after NRP training of health professional was reported.[30] China also has introduced NRP across the country.[107] It is anticipated that HBB will help further reduce birth-asphyxia–related mortality among LMICs. Lee et al. studied the impact of implementation of neonatal resuscitation on neonatal mortality and morbidity at different facilities around the globe.[47] The investigators identified 24 studies: 20 observational, two quasi-experimental, and two cluster randomized controlled trials. The results showed that resuscitation at birth was associated with significant improvement in overall survival (RR = 0.70, 95% CI 0.59–0.84). They also showed that resuscitation in the delivery room significantly decreased early NMR (see Fig. 8.10).[47] It was estimated that immediate newborn assessment and stimulation would reduce both intrapartum-related and preterm deaths by 10%. Facility-based resuscitation would prevent a further 10% of preterm deaths, and community-based resuscitation would prevent a further 20% of intrapartum-related deaths and 5% of preterm deaths. Many intrapartum deaths are classified as stillbirths who are not included in vital statistics in some countries. Many stillbirths are preventable including with postnatal resuscitation.[15,25,46] Stillbirths are very prevalent worldwide and need to be given a higher priority on the global health agenda.[75,76] These encouraging projections regarding the benefits of training health professionals are supported by the large-scale trials (Fig. 8.11).[15,16] The overwhelming majority of survivors following birth asphyxia in low-resource settings have been found to have normal neurodevelopment.[16] This is likely due to the difficulty in keeping alive the most severely asphyxiated newborns. Therapeutic hypothermia reduces mortality and morbidity from hypoxic-ischemic encephalopathy (HIE) in HICs.[39] Using innovative inexpensive methods, body cooling in HIE is showing promise even in LMICs.[40]

Hypothermia

Neonatal hypothermia is a common and important potentially life-threatening condition.[104] Neonatal hypothermia occurs in 32% to 85% of newborn infants, especially in rural primary health centers.[10,52] The incidence of neonatal hypothermia is substantially higher in LMICs compared to HICs.[19,42,43,44,56,88] Neonatal hypothermia (core body temperature <97.7°F [36.5°C]) is common in LMICs even during summer months. In Ethiopia, 67% of high-risk infants and infants of low birth weight (LBW) were hypothermic on admission. In Nepal, more than 80% of infants became hypothermic at birth and 50% remained hypothermic at 24 hours after birth.[62] Hypothermia is associated with higher risk of neonatal mortality.[62,86] When adequate

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• **Fig. 8.11** Meta-analysis of three studies examining the effect of additional training of health professionals in neonatal resuscitation on deaths of infants not breathing at birth. There is a significant decrease in mortality of "infants not breathing at birth following the training of health professionals in neonatal resuscitation." (Lee AC, Cousens S, Wall SN, et al. Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: a systematic review, meta-analysis and Delphi estimation of mortality effect. *BMC Public Health*. 2011;11[suppl 3]:S12.)

warmth is not provided, both preterm and term infants are at risk of developing hypothermia.

The causes of neonatal hypothermia in LMICs are many, starting from low ambient temperature of delivery rooms. Inadequate clothing and giving routine baths soon after birth are causes of neonatal hypothermia. Newborns may also experience heat losses within the hospital during transport from delivery room to the postnatal ward and during transport home from the hospital or from hospital to hospital. Neonatal hypothermia increases metabolic demand, oxygen consumption, and neonatal mortality. In the absence of sophisticated and expensive incubators, simple techniques can be adopted to abate hypothermia.[101]

To reduce neonatal hypothermia, the World Health Organization (WHO) recommends the "warm chain," a thermoregulation protocol that should be implemented in every nursery and with every newborn during the first several days and weeks after birth. The warm chain includes warm delivery rooms, immediate drying, uninterrupted skin-to-skin contact as much as possible, early breastfeeding, delayed bathing and weighing, appropriate bundling, mother and baby together, warm transportation, warm resuscitation, and training and awareness raising.[105] However, not all the elements recommended in the WHO thermoregulation protocol are practiced routinely in many birth facilities around the world.[53] Plastic bags and wrapping with plastic wrap at birth are effective in decreasing hypothermia in term and preterm infants.[7] This is a very inexpensive and effective method of providing thermal protection to the newborn in the immediate neonatal period. Kangaroo mother care (KMC) is becoming a universal practice,[87] and in addition to keeping the baby warm, the immediate initiation of breastfeeding provides early provision of calories. However, two Cochrane reviews showed that while KMC in preterm and LBW infants reduces mortality at the time of discharge,[21] early KMC did not reduce hypothermia in healthy late preterm or term infants.[59]

Infections

It is estimated that worldwide 20% of newborns die of neonatal infection. The incidence of sepsis is estimated to be 5 to 6 per 1000 live births (600,000 to 750,000) among hospitalized patients. Meningitis accounts for 0.7 to 1 per 1000 live births (88,000 to 126,000 cases per year), and acute respiratory infections account for 800,000 deaths in neonates. Among these deaths are cases of pneumonia, bronchiolitis, and laryngotracheitis. Cord infections and neonatal tetanus are preventable causes of acquired infection. The maternal transmission of HIV to the newborn was a major factor contributing to neonatal deaths in some countries, particularly in sub-Saharan Africa, but effective prevention is largely available.[103]

Burden of Neonatal Sepsis

Infections in the neonatal period can manifest at birth but most often occur within the first few days, peaking at 2 weeks after birth (see Fig. 8.8).[5] Estimating the burden (incidence) of neonatal infections in developing countries is challenging because of several factors: (1) Most births take place at home, and those newborns with sepsis rarely seek medical attention. (2) Hospital-derived information does not represent true incidence of sepsis in the community. (3) Laboratory facilities for cultures are inadequate or nonexistent. Population-based studies from developing countries have reported clinical sepsis rates ranging from 49 to 170

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per 1000 live births.[33] Among 18 studies from developing countries, the median incidence of blood culture–confirmed sepsis was 16 per 1000 live births. A study from Bangladesh found the incidence of clinically suspected neonatal sepsis to be 50 per 1000 live births, and the incidence of culture-confirmed sepsis was 3 per 1000 live births.[18] The incidence of culture-confirmed neonatal sepsis was 5.5 per 1000 live births among neonates presenting to a first-level health facility in rural Kenya.[8] However, the absence of active community surveillance suggests that the true burden is probably higher. A review of early-onset neonatal sepsis in developing countries found only five studies.[34] The incidence of clinical sepsis ranged from 20.7 to 50 per 1000 live births, and the incidence of culture-confirmed early-onset neonatal sepsis ranged from 2.2 to 9.8 per 1000 live births. Only two of these studies reported case fatality rates, of 18% and 19%, respectively. These observations contrast with neonatal culture-confirmed sepsis rates of 1 to 3 per 1000 live births reported from industrialized countries,[13] indicating the huge preventable burden of neonatal infections in LMICs.

Diagnosis of Neonatal Sepsis

As noted, although blood culture is the gold standard for diagnosis of neonatal sepsis, lack of laboratory facilities is a major barrier to diagnosis and treatment of neonatal sepsis in LMICs. Therefore, clinicians and health care workers depend on clinical signs of sepsis for diagnosis and treatment. Several clinical scores have been described to facilitate the diagnosis by health care workers in the field. Bang and co-workers have described a simple set of clinical criteria to recognize sepsis in a rural setting.[4] The Young Infants Clinical Signs Study Group conducted a large multicountry study to identify clinical signs with high sensitivity and specificity for predicting sepsis.[106] They identified seven common clinical signs that could be identified easily by health care workers in primary care settings. Other investigators have used slight modifications of these signs for clinical diagnosis of neonatal sepsis in community-based neonatal programs. The WHO also has developed guidelines for the Integrated Management of Childhood Illnesses for resource-limited countries.[9] Using the aforementioned background information, an algorithm may be used by health care workers in LMICs to assess infants at home or in health facilities, initiate treatment for sepsis, and triage infants to higher levels of care.

Fig. 8.12 shows the elements of observation and action based on common clinical findings: feeding, crying, variations in skin temperature on touch, activity, breathing pattern, and condition of the cord. These findings can be graded from mild to severe. Any two milder forms of distress can be treated and managed at home by the health care worker. Infants showing more severe forms of distress must be treated and transferred to a referral health center. Recent randomized controlled trials by the African Neonatal Sepsis trial group showed feasibility of community-based diagnosis of clinical signs of possible serious bacterial infection and simplified antibiotic regimens including injectable and oral combinations.[1,2]

Evidence-Based Interventions to Reduce Maternal Mortality Rates, Neonatal Mortality Rates, and Infant Mortality Rates

Although the global health policies described in the beginning of this chapter are being adopted by many countries, researchers are also actively investigating the causes of high global maternal and neonatal mortality and gathering information for evidence-based effective interventions that are adoptable and scalable in reducing MMR, NMR, and IMR in LMICs. Three series of landmark publications, popularly known as *The Lancet* series (described earlier), provided evidence-based, scalable interventions that reduced MMR, NMR, and IMR in resource-poor countries.[17,22,41] *The Lancet* Child Survival Series conducted comprehensive reviews of 23 interventions with a focus on under-5 child survival. Interventions were introduced in preconception, antenatal, intrapartum, and postpartum periods. Sixteen major community-based interventions were analyzed for their efficacy in reducing NMR.[23] Increasing coverage of these 16 interventions to 90% of the population could save 590,000 to 1.08 million lives in South Asia annually at an additional cost of US $900 million to $1.76 billion. In sub-Saharan Africa, it could save up to 450,000 to 800,000 lives at a cost of US $680 million to $1.32 billion.

Many antenatal, intrapartum, and neonatal interventions may be very effective in reducing NMR.[6] The 11 major evidence-based effective antenatal and neonatal interventions are listed in Box 8.1. These include two major antenatal interventions, antenatal steroids, and antibiotic therapy for premature rupture of membranes (PROM).

• BOX 8.1 Evidence-Based Cost-Effective Interventions That Increase Neonatal Survival

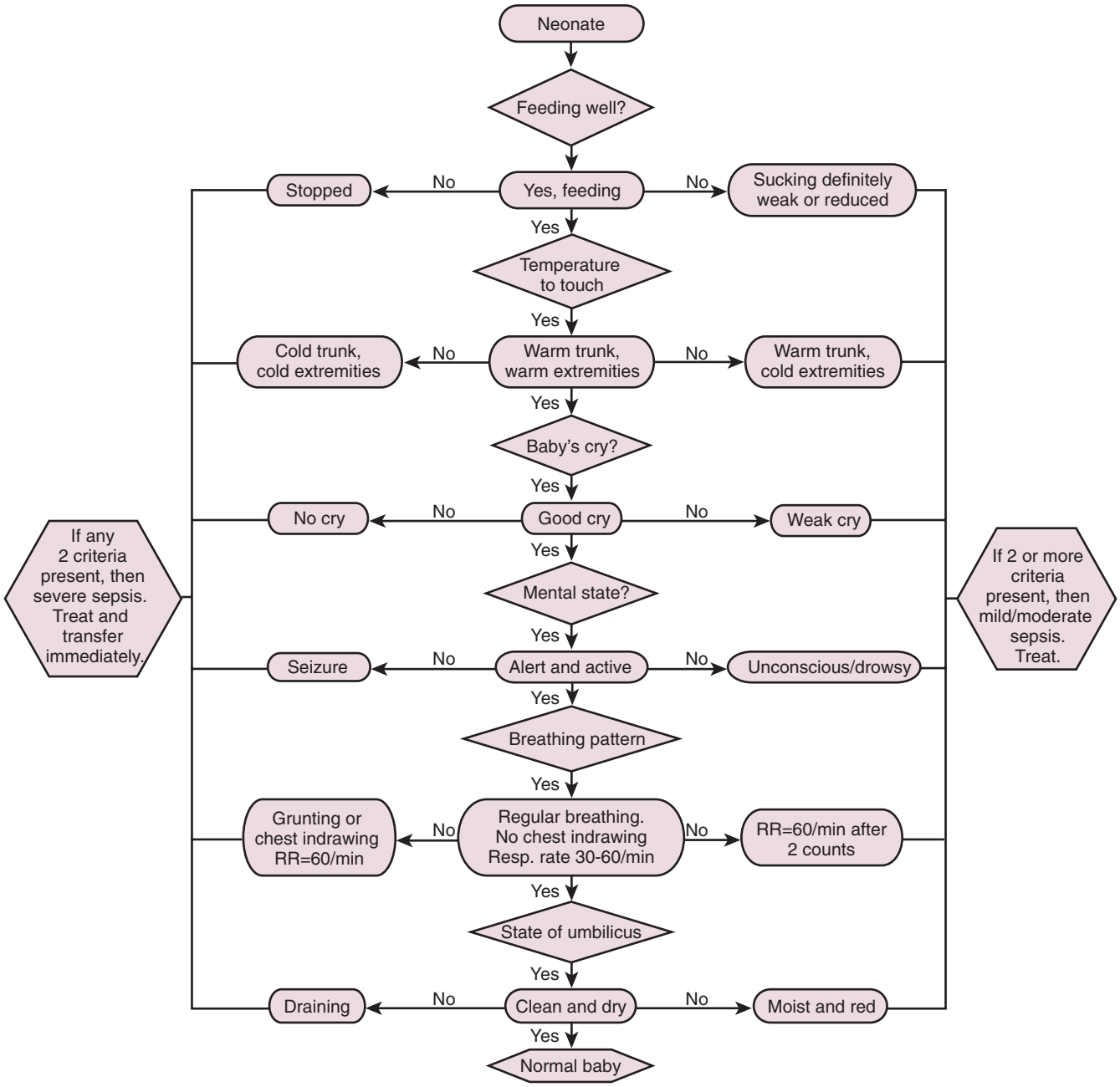
Intrapartum Interventions

- Antibiotics for premature rupture of membranes (PROM)
- Prophylactic antenatal steroids for mothers in premature labor

Neonatal Interventions

- Delayed cord clamping
- Vitamin K supplementation at delivery
- Resuscitation at birth
- Hospital-based kangaroo care
- Early breastfeeding and probiotics
- Thermal care
- Early continuous positive airway pressure (CPAP) in infants with respiratory distress syndrome (RDS)
- Surfactant therapy in RDS
- Case management for sepsis

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• **Fig. 8.12** An algorithmic approach to assessment and management by health care workers of newborns with suspected sepsis.

Also described are nine neonatal interventions, including late cord clamping[89] and neonatal resuscitation.[15,16] After birth, surfactant therapy and application of continuous positive airway pressure (CPAP) reduce mortality in infants with respiratory distress syndrome. Probiotics decrease necrotizing enterocolitis, sepsis, and all-cause mortality in LMICs.[31] These findings are of great clinical importance to practitioners as well as health policymakers because they provide a basis for adoption of new cost-effective interventions in saving many high-risk newborns.

Prematurity is a major cause of neonatal deaths in developing countries, and respiratory distress syndrome (RDS) is the leading cause of neonatal death in this population in HICs. The goal should be to consider preventive antenatal care and proven interventions, such as antenatal steroid therapy in preterm labor, implementation of delivery room neonatal resuscitation, early use of CPAP, and surfactant therapy.[72] Using antenatal steroids as a preventative measure will be the least expensive. Antenatal steroid treatment of mothers in premature labor has been estimated to save 500,000 lives a year.[63] Infants with RDS can be best managed with inexpensive nasal CPAP devices. Evidence suggests that in LMICs, postnatal CPAP followed by surfactant therapy can significantly reduce mortality and morbidity from RDS.[44,99] Use of nasal CPAP as a first choice of treatment decreases the need for surfactant replacement

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therapy and reduces mortality and bronchopulmonary dysplasia (BPD) compared to early surfactant.[77] Therefore, outcomes can be improved by using early CPAP and reducing the use of surfactant for infants who respond to CPAP as is done now in HICs.[20]

The Impact of Progress

With the increased access to neonatal intensive care and improved survival of preterm and VLBW infants, there is a financial burden on families and risk of associated morbidities among survivors. Three major neonatal emerging challenges in developing countries are of great concern. They include (1) BPD, also known as chronic lung disease (CLD);[66] (2) retinopathy of prematurity (ROP)[35,74]; and (3) neurodevelopmental delays.[64,83] All three conditions are related to prematurity, and as survival of preterm infants increases, so does the incidence of CLD, ROP, and neurodevelopmental delays. Data regarding the prevalence of these morbidities in LMICs are lacking.

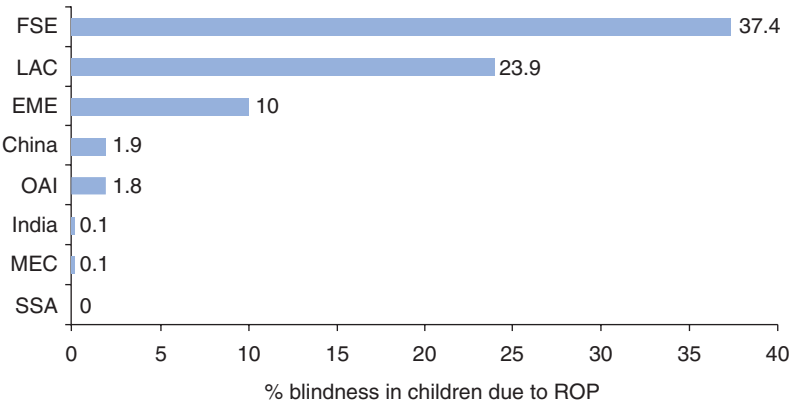
BPD is a newly emerging disease in LMICs.[66] LMICs contemplating the development of modern NICUs should be well-prepared to recognize these complications and associated costs. Strategies need to be developed to minimize the overall burden of disease on the community. In this regard, the application of CPAP as the first approach to managing respiratory distress syndrome is to be encouraged in LMICs.[99]

Retinopathy of prematurity was first encountered in the early 1950s in HICs with the introduction of high oxygen therapy and again with the introduction of ventilator care and increasing survival of extremely premature infants. Although the rate and severity of ROP is decreasing in HICs, it is beginning to increase in LMICs. As NMR is steadily decreasing, it is estimated that globally at least 50,000 children are blind from ROP. This observed large number of ROP worldwide has come to be known as the *third epidemic*.[35] Fig. 8.13 shows the estimated absolute number of ROP-related blind population by global regions. As is seen, ROP is being increasingly reported from India and China, home to more than one-sixth of the world's population. Fig. 8.14 shows the relationship of IMR rate and ROP-related blindness.[35] Blindness caused by ROP begins to rise as the IMR of a country continues to decrease. These data suggest the influence of increased survival of preterm infants with the introduction of NICU care, oxygen therapy,[24,100] and ventilation: the lower the IMR, the higher the rate of ROP-related blindness. Retinopathy of prematurity will soon become a public health issue in these countries unless control activities keep pace with the increased survival of premature babies at risk.

There is a need to develop and implement educational programs to avoid the potentially hazardous practices of high oxygen therapy, to promote early detection of ROP, and to pursue a multidisciplinary approach to prevent ROP. LMICs also have the additional problem of lack of awareness of ROP among pediatricians, whereas ophthalmologists may be inadequately trained in the recognition and management of ROP.[74]

The Burden of the High Cost of Advanced Neonatal Care

The overall cost of neonatal intensive care at the tertiary level in developing countries is very high and sometimes affordable only to middle- and upper-income groups. Bhutta from Pakistan showed that infants with RDS can be successfully managed with ventilator support.[11] In that study, the overall mortality of infants with RDS treated with assisted ventilation was 39%, the average length of stay was 25 ± 21

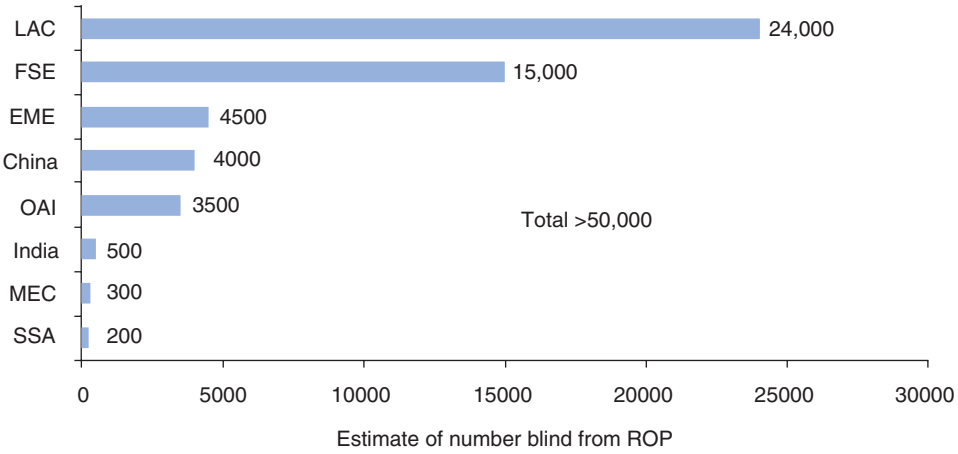


FSE = Former Socialist Economies
LAC = Latin America and the Caribbean
EME = Established Market Economies
OAI = Other Asia and Islands
MEC = Middle East Crescent
SSA = Sub Saharan Africa

Note: Data from South Africa showed that ROP only affected Caucasian and Asian children. As no other countries in the region had any child blind from ROP the proportion for the region has been put as 0%.

• **Fig. 8.13** Retinopathy of prematurity as a cause of blindness (%), by World Bank region, using data on more than 15,000 blind children examined in 43 countries. (Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev*. 2008;84:77-82.)

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MEC = Middle East Crescent
SSA = Sub Saharan Africa

• **Fig. 8.14** Estimates of the number of children who are blind from retinopathy of prematurity by World Bank region. (Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev*. 2008;84:77-82.)

days, and the average cost was US $1391 per survivor. Shanmugasundaram and colleagues in India reported similar costs associated with NICU care.[82] Narang and co-workers reported the per-day cost of NICU care of neonates in a government teaching hospital to be US $125/day, although the family shared 25% of the total cost of NICU care.[65] Profit and co-workers showed that NICU care for infants born at 24 to 26, 27 to 29, and 30 to 33 weeks' gestational age in Mexico prolonged life expectancy by 28, 43, and 34 years and averted 9, 15, and 12 disability-adjusted life years (DALYs) at incremental costs per infant of US $11,400, US $9,500, and US $3,000, respectively, compared to infants with no intensive care.[73] These data provide strong evidence that even in LMICs, provision of NICU care is cost effective in improving survival and decreasing morbidity. Unfortunately, in many LMICs, parents have to bear 80% of hospital costs out of pocket, which may exceed their resources.[57]

Long-Term Neurodevelopmental Outcome

Data on long-term outcomes in LMICs are limited. Lack of a uniform database of surviving infants, lack of expertise in assessing developmental disabilities, and the lack of a support system for needy families and children are the major barriers to develop meaningful information regarding the morbidity of surviving infants. Mwanki and co-workers reviewed 153 studies from around the world suitable for inclusion for analysis of developmental outcome of high-risk newborns.[64] Altogether, there were 2161 survivors of intrauterine or neonatal insults. The overall median risk of at least one sequela in any domain was 39% (interquartile range [IQR] 20% to 55%), with a risk of at least one severe impairment in any insult domain of 18% (8% to 33%), at least one moderate impairment of 5% (0% to13%), and at least one mild impairment of 10% (1% to 18%).

The pooled risk estimate of at least one sequela associated with one or more of the insults studied (excluding HIV) was 37% (95% CI 27% to 48%). The most common deficits were learning difficulties, cognition, or developmental delay ($N = 4032$; 59%); cerebral palsy ($N = 1472$; 21%); hearing impairment ($N = 1340$; 20%); and visual impairment ($N = 1228$; 18%). Only 40 studies included data for multidomain impairments. These studies (26%) included 2815 individuals, of whom 1048 (37%) had impairments, with 334 (32%) having multiple impairments. These findings show that in developing countries, perinatal adverse insults have a high risk of causing substantial long-term neurologic morbidity.

Shillcott and co-workers[83] studied the estimates of long-term disabilities following neonatal illness in a district of Bangladesh. They found that "a significant burden of disability results from neonatal conditions." They also projected that their national newborn project might have averted several years lost to disability.

The preceding two studies provide important information on the impact of advanced care and increasing survival of at-risk infants in LMICs. Comparable cohort studies in other resource-poor regions should be done to assess the burden of long-term outcome effects of improved neonatal survival.

Ethical Dilemmas

The issues of the high cost of hospital care and uncertain outcomes of LBW and critically ill newborns pose ethical dilemmas to practicing neonatologists in LMICs. Most poor populations cannot afford the high cost of care. In these countries, although public sector health care caters to the care of the poor, the private sector is rapidly expanding services to selected families able to afford the cost of NICU care.

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Because of changing economic demographics among LMICs, there will be two divergent situations regarding the care of the sick newborn in the NICU, with one group of families who cannot afford the high cost of NICU care. As stated by Singh, undue emphasis is being placed on saving an individual infant with an uncertain outcome at any cost to the family.[84] He suggests that to ensure the principle of cost-effectiveness in resource-poor countries, the narrow principle of the "best interests" of the child should be replaced by the concept of a broader benefit to the family, society, and state. His point is valid and should be considered when counseling resource-poor families. In recent years, rapid demographic and economic transitions have changed the expectations of middle-class and upper-middle-class families in countries such as India, China, and other LMICs. When the families and parents with adequate economic resources are willing to avail themselves of such care in spite of the high cost, the care cannot be denied. The neonatologist, therefore, has the responsibility to prepare parents with prenatal counseling and provide realistic evidence-based treatment options to parents.[3] There is a need for a larger debate and development of ethical guidelines for practitioners among LMICs.

Strategies to Improve Global Neonatal and Perinatal Outcome

Strategies to reduce perinatal mortality in LMICs should include social and medical programs that are integrated into national plans. Box 8.2 outlines the steps involved in developing a plan to improve neonatal-perinatal outcome. Even though the objectives and goals of the MDG declaration have been universally accepted, strong commitment and leadership on the part of professional groups, nongovernmental organizations (NGOs), and the governments are necessary for successful implementation of programs aimed at reducing NMR.

Schiffman and Sultana noted that the factors that led to national advocacy for newborn health in Bangladesh were both a strong commitment of the government to achieving the MDG targets and donor resources.[80] They note that the emergence of successful policy to improve newborn survival involved interactions between global and national agencies rather than either alone. To quote the authors, "In Bangladesh, newborn survival emerged from obscurity to relative prominence on the government's health policy agenda." These observations are applicable to other LMICs. Many LMICs are developing similar programs to scale up maternal and neonatal services.

Summary

Developing countries continue to share the major burden of neonatal and infant mortality. The major causes responsible for such disparity between HICs and LMICs are a lack of health facilities, lack of skilled personnel, and lack of access to health care. The SDGs declared in 2015 are the single most influential program bringing the world community, governments, scientists, and policymakers together to address the issues of high neonatal and infant mortality in LMICs. The publication of *The Lancet* series also evoked great interest among researchers to explore the causes of high NMR and find evidence-based cost-effective interventions to reduce MMR, NMR, and IMR in LMICs. A review of the literature clearly identified several evidence-based effective antenatal, intrapartum, and neonatal interventions. It remains to be seen how well these interventions will be implemented in LMICs. It is recognized that successful implementation of the MDGs requires both commitment

• BOX 8.2 Strategies to Develop Sustainable Programs to Improve Maternal and Neonatal Health in Low- and Middle-Income Countries

Step I

- Identify a region to be covered.
- Assess the current situation: data gathering on MMR, NMR, and IMR.
- Involve regional governmental and nongovernmental agencies and local stakeholders.
- Develop a local perinatal advisory committee.
- Identify gaps in services.
- Develop programs that provide continuums of care: preconceptual/conceptual/post-delivery services.

Step II

- Improve and achieve optimal perinatal-neonatal coverage with available services.
- Introduce innovative approaches to overcome deficiencies.
- Introduce capacity-building programs for health professionals.
- Improve local health facilities with proper equipment for keeping the baby warm and providing resuscitation at birth.
- Establish links between health facilities within the region: from basic level of care to tertiary-care level for consultation and transport of highest-risk babies.

Step III

- Develop outreach educational services in the community.
- Increase public awareness of the importance of safe motherhood and newborn care.
- Coordinate with other health initiatives in place at local/regional/state levels.
- Systematically scale up the preceding activities as these programs take root.
- Share results with stakeholders, and gain confidence in the program.

Step IV

- Measure impact annually.
- Share information with stakeholders.
- Make innovative changes as needed.
- Continue activities defined in steps II to IV to achieve goals defined in MDG #4 and #5 for the region.

IMR, Infant mortality rate; MDG, Millennium Development Goals; MMR, maternal mortality rate; NMR, neonatal mortality rate.

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of national governments and collaboration of international agencies. It is encouraging to note that some LMICs have reached their targets of MDGs #4 and #5, but many countries have not reached their MDGs. There is lot more to be done in a large number of LMICs. Neonatology is a work in progress in LMICs.

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Key Points

- More than 98% of the neonatal deaths worldwide occur in low- and middle-income countries. The majority of these deaths occur in South Asia and Africa.
- Neonatal deaths constitute approximately 40% of global under-5 childhood mortality, of which the highest proportion is related to complications of preterm birth, intrapartum-related complications, and sepsis.
- Preterm birth complications (14% of under-5 deaths), birth asphyxia (also called intrapartum-related) complications (9%), and sepsis/meningitis (5%) were the most frequent causes of death in the neonatal period.
- The increased attention to improving newborn care at a global level can be traced to the recognition by the World Health Organization of unacceptably high infant mortality in low- and middle-income countries.
- Several large controlled trials have demonstrated the benefits of selected interventions including packages of care such as the Mother-Baby Package, Helping Babies Breathe (resuscitation), and the Essential Newborn Care programs.
- Considerable progress is being made in reducing maternal and child mortality in developing countries; however, many challenges remain. By the end of the twentieth century, a significant decrease in maternal and infant mortality was reported to be one of the top health achievements of the century.
- One of the Sustainable Development Goals metrics aims to reduce neonatal mortality to at least as low as 12 per 1,000 live births.

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9

Social and Economic Contributors to Neonatal Outcome in the United States

RENATE D. SAVICH AND MOBOLAJI FAMUYIDE

Epidemiology of Health Disparities in Neonatal and Perinatal Medicine

While there have been significant improvements in neonatal and infant mortality in the United States over the past 50 years, compared to other high income countries in the world, the United States alarmingly lags behind these other countries in infant mortality rates.[60] Infant mortality and morbidity rates are commonly used as an important indicator worldwide of overall population health. Recent research has focused on why the United States has not seen continued improvements in these public health indices as have other countries, and indeed several markers of US infant health have actually worsened in recent years. It is important to understand recent US trends and contributing factors to provide optimal care and public health planning in the prenatal, perinatal, neonatal, and post neonatal periods to improve these outcomes. One major factor contributing to these poor perinatal and infant outcomes in the United States is the significant health disparities seen among women and infants related to race and ethnicity. Other disparities in health outcomes in the perinatal period in the United States are related to poverty, lack of health care access, and other overall indicators of poor socioeconomic status.

Infant Mortality

While the United States had a steady decline in infant mortality over the past decade, declining 15% from 6.86 deaths per 1000 live births in 2005 to 5.82 per 1000 in 2014,[62] this rate is still almost twice that of other comparable countries in the world.[60] Data comparing infant mortality from 2010 indicated that the United States had 2 to 3 times the infant mortality rate of countries such as Germany and Sweden, in spite of significantly larger health care expenditures in the United States per capita compared to these other countries. Multiple studies have attempted to delineate the factors unique to the United States that might explain this discrepancy. One possible explanation is the high number of infants born and resuscitated at 22 and 23 weeks' gestation in the United States compared to many countries in Europe. However, excluding these infants still indicates a US infant mortality rate twice that of these countries.[60] Addressing prematurity is a significant health and financial priority. Although only 9.1% of birth hospitalizations were among preterm or low birth weight infants, these births accounted for 43.4% of total costs of neonatal care.[6]

Prematurity (infants born at less than 37 weeks) in the United States has a major impact on high infant mortality rates. Studies show that the United States has rates of prematurity up to two times that of other developed countries.[60] Clearly, this is a significant contributor to the high infant mortality seen in the United States. During the 1990s and early 2000s, the US preterm birth rate steadily increased from 10.6% in 1990 to 12.8% in 2006.[39] The United States overall saw a steady decrease in the prematurity rate over the past decade, with a decrease from 10.44% in all births in 2007 to 9.57% in 2014.[40,61] Disturbingly, this trend in the prematurity rate has reversed in recent years with a small but significant increase to 9.63% in 2015 and 9.84% in 2016, primarily due to an increase in late preterm births.[40] It is unclear how this will impact the recent improvements in US infant mortality.

Addressing the causes of prematurity is critical to reducing the US infant mortality rate. However, a higher rate of prematurity alone does not explain the higher US infant mortality rate, as the gestational-age-specific infant mortality rates are also increased above other countries at gestational ages 32 weeks and above, the category with the highest number of preterm births.[60]

It is now well established that major contributors to infant mortality rates in the United States are the significant health disparities. The major health disparity is related to racial and ethnic differences of perinatal health outcomes in all states in the United States, with a wide variation state to state.

Epidemiologic studies have shown that non-Hispanic black infants have an infant mortality rate over two times that of non-Hispanic white infants (10.93 deaths per 1000 live births in 2014 vs. 4.89 per 1000 live births) (Fig. 9.1).[59,62]

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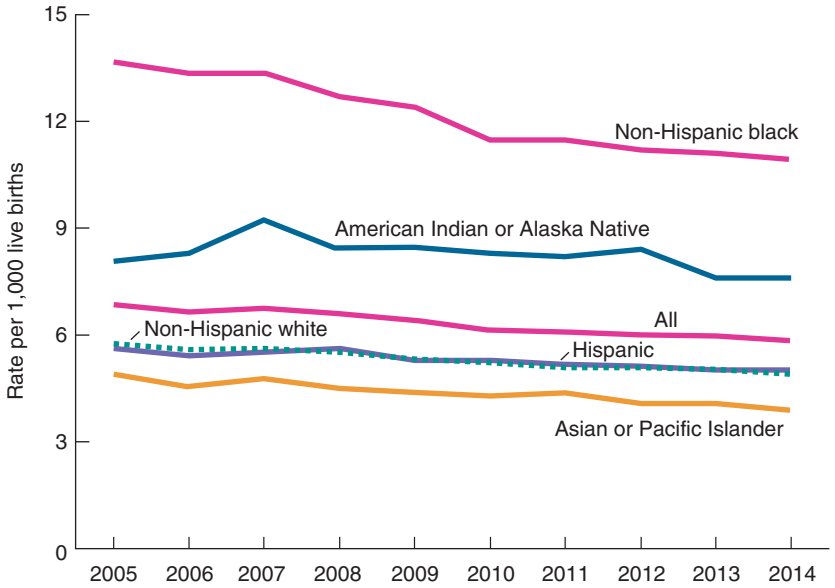
Abstract

While there have been significant improvements in neonatal and infant mortality in the United States over the past 50 years, compared to other high income countries, the United States lags behind in infant mortality rates. Infant mortality and morbidity rates are commonly used as important indicators worldwide of overall population health. One major factor contributing to these poor perinatal and infant outcomes in the United States is the significant health disparities seen among women and infants related to race and ethnicity. Other disparities in health outcomes in the perinatal period in the United States are related to poverty, lack of health care access, and other overall indicators of poor socioeconomic status. In the United States, non-Hispanic black infants have the highest rates of infant mortality and prematurity compared to other races and ethnic groups. Non-Hispanic black mothers also have extremely high rates of maternal mortality and morbidity, as well as obesity, leading to other poor outcomes. Native American/Alaska Natives also suffer from a disproportionate share of infant mortality and prematurity as well as higher rates of sudden unexpected death of infancy. Hispanic mothers also suffer from adverse outcomes such as obesity, yet seem somewhat protected from other neonatal adverse outcomes. In the United States, optimal social determinants of health that are lacking in minority races and ethnicities play a major role in the poor outcomes seen in the perinatal and neonatal period suffered by these groups. Specific interventions targeting racial and ethnic disparities in neonatal mortalities and morbidities will be needed to improve current US perinatal and neonatal outcomes.

Keywords

infant mortality
health disparities
non-Hispanic black
Hispanic
Native American/Alaska Native
prematurity and racial disparities

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• **Fig. 9.1** Infant mortality rates, by race and Hispanic origin of mother: United States, 2005-2014. (Source: NCHC National Vital Statistics System.)

American Indian or Alaskan Native infants also exhibit substantially higher infant mortality rates than non-Hispanic whites.[59,62] Interestingly, Asian or Pacific Islander infants have consistently exhibited the lowest neonatal and infant mortality rates for many years, while Hispanic infant mortality rates track close to non-Hispanic white infant mortality rates in spite of economic disadvantages and poor health care access.[62]

From 2005 to 2014, infant mortality rates overall and for each race or ethnic group had decreased each year.[62] However, in recent years, this decline has plateaued. It appeared that the United States was making great strides in reducing the discrepancies in infant mortality rates related to race with a 16% decline from 2005 to 2011 seen in non-Hispanic black rates compared to the overall US decline of 12% during those years. A closer look at recent US infant mortality data shows disturbingly that from 2013 to 2014, only non-Hispanic whites had a significant 3% decrease; other groups did not show a statistically significant improvement.[62] In fact, the 2015 data indicate that for non-Hispanic black infants the infant mortality rate actually increased from a low of 11.4 per 1000 in 2014 to 11.7 per 1000 in 2015.[75] This is in sharp contrast to the infant mortality rate of 4.8 per 1000 in non-Hispanic white infants in 2015.[59,75] Thus, it appears that in the United States, these disparities by race are worsening. In addition, there are significant differences in infant mortality by state, with the southern states having the highest infant mortality. These are also the states with the highest percentage of non-Hispanic black women in their population (Fig. 9.2).

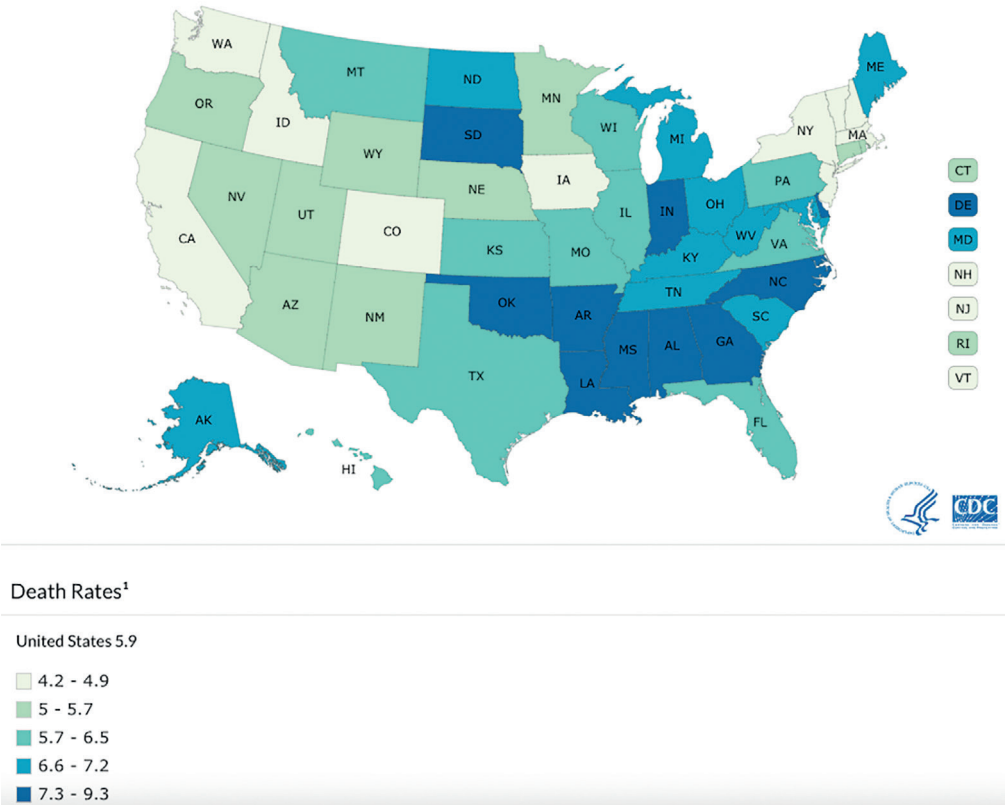
Similar to significant disparities seen in infant mortality, the incidence of prematurity varies greatly by race and ethnicity, with the provisional 2016 percent of births under 32 weeks for non-Hispanic blacks at almost three times that of non-Hispanic whites (3.16% vs. 1.26%)[40] (Table 9.1). Disturbingly, US prematurity rates for less than 37 weeks gestation are slightly increased in 2016 compared to 2015 and 2014 for the United States.

The five leading causes of infant mortality in the United States are congenital malformations, short gestation and low birth weight, SIDS (sudden infant death syndrome) or SUID (sudden unexpected infant death), maternal complications, and unintentional injuries.[62] Data show that these causes of death vary by racial and ethnic group. For example, death due to low birth weight/preterm-related causes is over 3-4 times higher in non-Hispanic blacks compared to non-Hispanic whites. In contrast, the high infant mortality seen in Native Americans and Alaska Natives occurs in those babies born at much higher birth weights and would appear to be less impacted by prematurity.[33] There are also differences in mortality noted within certain ethnic groups. For Puerto Rican infants, the rate of infant mortality due to preterm causes is almost twofold that of non-Hispanic whites and is the highest among all of the Hispanic subgroups.[33,62] This could reflect the longer-term presence of the Puerto Rican population in the United States compared to more recent Hispanic immigrants and the cumulative toxic effect in the United States of low socioeconomic states (SES) over time on adverse pregnancy outcomes.

Congenital anomalies and subsequent infant mortality are also impacted by health disparities. Bassil et al. found that socioeconomic inequities lead to a significant increase in major congenital anomalies in babies born to mothers in areas of highest deprivation.[7] Further analysis revealed that there were higher odds of chromosomal and multiple systems anomalies in the highest deprivation areas. These findings could be explained by higher exposure to teratogens or to poor health of these disadvantaged mothers.

Post-neonatal mortality also exhibits racial and ethnic disparities as seen in SIDS/SUID, a leading and increasing

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• **Fig. 9.2** Infant mortality rates by state, 2015. (Source: National Center for Health Statistics. https://www.cdc.gov/nchs/pressroom/sosmap/infant_mortality_rates/infant_mortality.htm. Accessed November 15, 2015.)

TABLE 9.1 Selected Maternal and Birth Characteristics by Race and Hispanic Origin of Mother, 2016 Provisional Data

	Unmarried (%)	First Trimester Prenatal Care (%)	Late or No Prenatal Care (%)	Gestational Age Under 37 Weeks (%)	Gestational Age Under 32 Weeks (%)	Low Birth Weight (%)	Very Low Birth Weight (%)
TOTAL	39.7	77.2	6.2	9.84	1.59	8.16	1.39
White	28.4	82.3	4.3	9.04	1.26	6.97	1.07
Asian	12.0	80.6	5.4	8.63	1.19	8.43	1.09
Hispanic	52.5	72.0	7.7	9.44	1.45	7.31	1.23
Black	69.7	66.6	10.0	13.75	3.16	13.33	2.94
American Indian/ Alaska Native	68.1	63.0	12.5	11.38	1.74	7.77	1.38
Native Hawaiian or Pacific Islander	47.7	51.9	19.2	11.51	1.79	7.65	1.44

National Center for Health Statistics.[5]

cause of infant mortality. The vast majority of infant autopsies identifying the cause of death due to SIDS or SUID are from infants born at 37-42 weeks.[71] For American Indian or Alaska Natives, the largest difference in mortality outcomes when compared to non-Hispanic whites is the two- to threefold increase in deaths due to SUID (American Indian: 177 per 100,000 live births, non-Hispanic white: 84.5 per 100,000 live births).[71] Non-Hispanic blacks also have an extremely high rate of mortality from SUID (172.4 per 100,000 live births),[71] only slightly lower than the rate for Native American infants. The lowest rate of SUID is seen in Hispanic and Asian/Pacific Islander infants (Hispanic: 49.3 per 100,000 live births, Asian/Pacific Islanders: 28.3 per 100,000 live births), even lower than the non-Hispanic

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white rate. A significant impact on SUID is decreasing gestational age at birth, with infants born at 24-27 weeks having a 3.5–5-fold increase in the rate of SIDS compared to term infants.[70] Again, racial disparities are seen, with an SUID rate in non-Hispanic blacks at less than 28 weeks of 382.3 per 100,000 live births compared to the lowest group, Asian/Pacific Islanders: 126.6 per 100,000 live births at less than 28 weeks.[71] Given that the highest rate of prematurity is seen in non-Hispanic blacks, this contribution to SIDS/SUID also negatively impacts this population and infant mortality. In addition, overall, the SUID group had twice the percentage of African American mothers and was independently associated with this adverse outcome. There are racial and ethnic differences in positioning of babies for sleep, with Hispanic and non-Hispanic black infants and infants in southern states being placed supine much less often than non-Hispanic white infants. Premature infants are also positioned more often in the prone position as well.[46a] Alarmingly, many states have reported a recent increase in deaths due to SIDS/SUID in the non-Hispanic black population for unclear reasons. Again, it is unclear what impact genetic versus cultural factors may play in this adverse outcome. This would imply that both genetic and cultural aspects of race and ethnicity contribute to differing SIDS/SUID outcomes as well as lower SES.

Mirroring the infant mortality rates, fetal deaths and perinatal mortality rates show wide variation by race and ethnicity. Non-Hispanic black fetal mortality rates are twice as high as non-Hispanic white rates, with American Indian or Alaska Native fetal and perinatal mortality rates intermediate.[58] Poorer maternal health and decreased access to prenatal care may have an impact on this.

Maternal Mortality

Maternal mortality related to pregnancy has been steadily increasing in the United States over the past 20 years[56,57] despite significant decreases seen in other high income countries during this same time period.[86] Again, alarming racial and ethnic disparities are seen in pregnancy-related mortality in the United States, with non-Hispanic black women dying at a rate almost four times that of non-Hispanic white women (42/100,000 live births vs. 12/100,000).[9,25,26] While the reasons for the dramatic increase in US pregnancy-related mortality are not clearly understood, underlying poorer maternal health, obesity, lack of prenatal care, teen pregnancies, and single mothers without support systems all are likely contributors to this high mortality rate. All of these indicators of poor health care during pregnancy are significantly higher in non-Hispanic black women and American Indian and Alaskan Native women compared to non-Hispanic white women.[26,61] As a reflection of the increasingly overall poor health of the United States, maternal deaths due to hemorrhage, hypertensive disorders of pregnancy, emboli, and anesthesia complications have declined, while contributions from cardiovascular conditions, cardiomyopathy, stroke, and non-cardiovascular medical conditions have increased.[9,25,26] For non-Hispanic black women over the age of 40, pregnancy is particularly dangerous, with the rate of almost 192 deaths per 100,000 live births, compared to an average mortality ratio of 17 maternal deaths per 100,000 live births for all women at all ages.[26] Racial disparities impact a variety of maternal morbidities, with non-Hispanic black and American Indian and Alaska Native women having the highest rates of blood transfusion, heart failure, shock, eclampsia, and renal failure, as well as an overall rate severe maternal morbidity over twice that of non-Hispanic white women during delivery hospitalization.[23] Pre-eclampsia during pregnancy is a particularly dangerous condition leading to maternal morbidity and death as well as several neonatal complications, especially preterm birth and its associated complications for the neonate. Pre-eclampsia is highest in non-Hispanic black mothers but lower in Hispanics and Asians compared to non-Hispanic white women. A recent study also noted that American Indians/Alaska Natives also had a significant higher pre-eclampsia risk. However, the authors noted that higher pre-pregnancy body mass index (BMI) in American Indians/Alaska Natives may contribute to this morbidity.[89]

Determinants of Prematurity and Adverse Outcomes

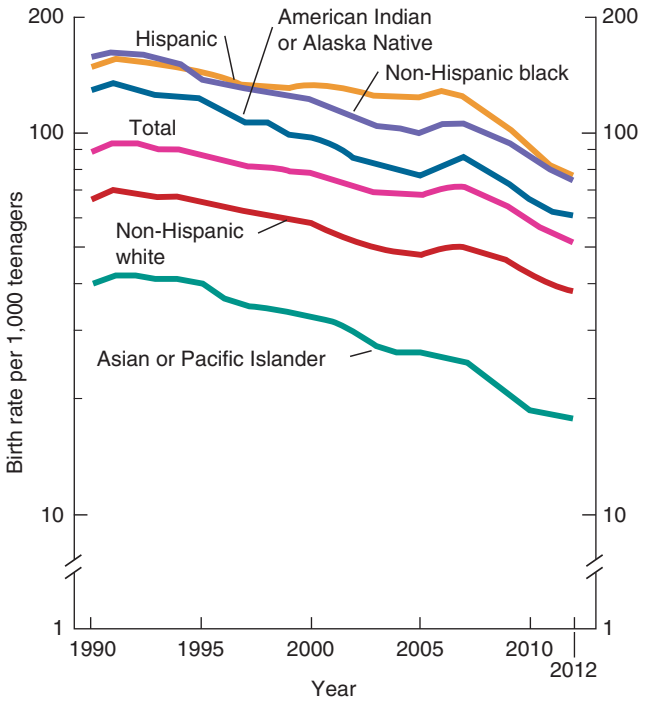
A significant body of research has focused on the high teen pregnancy rate in the United States compared to other high income countries. Encouragingly, rates of teen pregnancies have significantly decreased for all races and ethnicities in the United States[41,61,77,81] (Fig. 9.3). However, two groups with some of the highest teen pregnancy rates, non-Hispanic black women and Native American women, have the highest infant mortality rate and prematurity rate; teen pregnancies may play a factor in these outcomes. There are also significant regional differences in the United States in teen birth rates, with the south having much higher rates of teen pregnancies (Fig. 9.4).

Previous studies have shown that infants born to Hispanic women have outcomes for prematurity and mortality similar to non-Hispanic white women.[59,62,78] Although many Hispanic women are also economically disadvantaged and have poor access to prenatal care, their rates of prematurity and infant mortality are low, suggesting a genetic component and unexplained protective effect of Hispanic ethnicities in birth outcomes. However, even within women who identify as Hispanic, there is large variation in infant outcomes with Puerto Rican infants having much higher mortality rates than other Hispanic infants.[59] In addition, even within race and ethnicity, there may be an additional genetic component, as Hispanic women who identify as black Hispanic have outcomes such as low birth weight, preterm birth, and small for gestational age intermediate of Hispanic and non-Hispanic black women.[8] Interestingly, women of Mexican origin who were born and delivered in Mexico were much less likely to deliver preterm or low birth weight infants compared to US-born

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Mexican-origin women who delivered in the United States. Even those women who delivered in the United States but were born in Mexico appeared to have some protective effect.[45,78]

Prematurity rates vary widely in the United States by state, with those in the Deep South—states with the highest percentage of non-Hispanic black mothers—showing the highest rates of prematurity and infant mortality. The highest mortality states include Mississippi, Alabama, Louisiana, North Carolina, Arkansas, Georgia, Oklahoma, and South Dakota, states with either very high non-Hispanic black or Native American populations. These are also the states with the highest rates of preterm births (see Fig. 9.2). Encouragingly, many of these states in the Deep South also had the biggest recent decreases in infant mortality.[62] This may be partially explained by the state-level progress made by many of the southern states in reducing the black-white infant mortality gap in recent years.[13] However, within the Mississippi Delta, those counties with the poorest health outcomes also have a significantly higher percentage of African American females and low birth weight infants.[37] It is unlikely that poverty and low SES, or higher rates of teen pregnancy alone, can explain the poorer outcomes of low birth weight seen in non-Hispanic black women. A recent study by Coley et al. found that even after adjusting for a multitude of maternal factors encompassed in a "neighborhood risk" score, racial disparities persisted as a cause of low birth weight in North Carolina.[20]

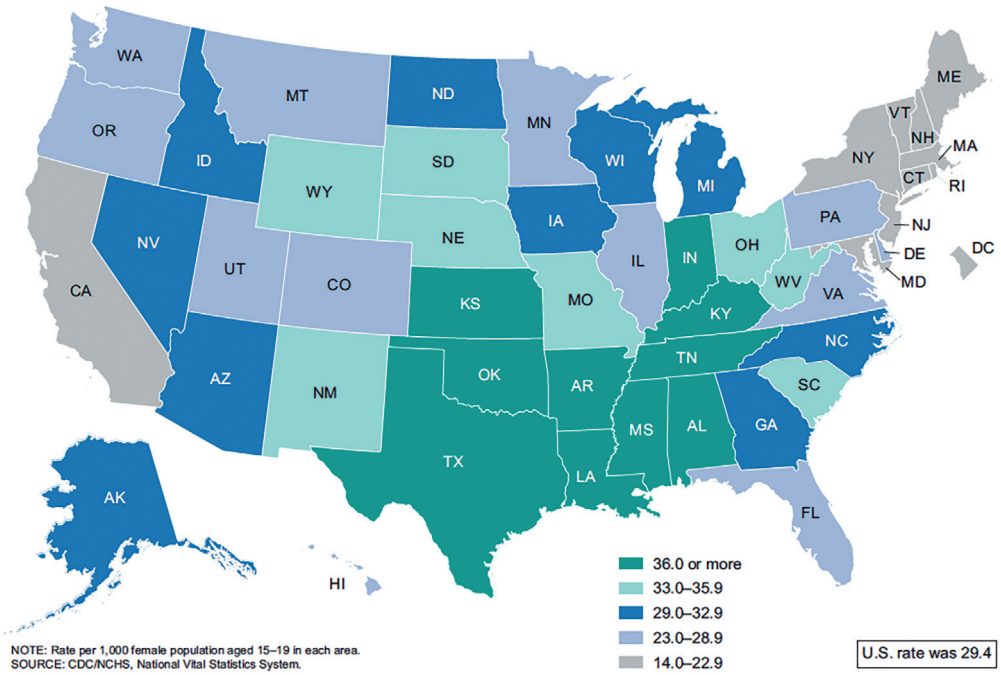


Note: Rates are plotted on a logarithmic scale.
Source: CDC/NCHS, National Vital Statistics System.

• **Fig. 9.3** Birth rates for teenagers aged 18–19, by race and Hispanic origin: United States, 1990–2012.

Social Determinants of Health

Health care disparities are differences in health care quality, access, and outcomes adversely affecting members of racial and ethnic minority groups and other socially disadvantaged populations.[34,67] The World Health Organization (WHO) defines social determinants of health as the conditions in which people are born, grow, live, work, and age.[87] They consist of policies, programs, and other aspects of societal structure, including government and private sectors,



• **Fig. 9.4** Standardized birth rates for teenagers aged 15–19, by state: United States, 2012.

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as well as community factors.[44] Health is determined in part by access to social and economic opportunities; the resources and supports available in homes, neighborhoods, and communities; the quality of schooling; the safety of workplaces; the cleanliness of water, food, and air; and the nature of social interactions and relationships (Box 9.1). These circumstances are shaped by the distribution of money, power, and other resources at global, national, and local levels.[44] Social determinants greatly impact perinatal outcomes[55] and are largely responsible for preventable health inequities.[18,48] Poverty limits access to healthy foods and safe neighborhoods and education resources, a known predictor of better health.[10,18,82]

A "place-based" organizing framework, reflecting five key areas of social determinants of health (SDOH), was developed by Healthy People 2020.[44] These five key areas (determinants) include: (1) economic stability, (2) education, (3) health and health care, (4) neighborhood and built environment, and (5) social and community context.[44] Each of these five areas reflect several critical components/key issues that make up the underlying factors.

The complex history of race and ethnicity in the United States may affect individual responses to medical recommendations for screening tests and adherence to treatment plans, contributing to disparate outcomes along racial lines.[84] Numerous examples exist of racial and ethnic groups being targeted for forced medical procedures or experimentation.[54] These past atrocities in the United States have left a lasting mistrust in minority communities. Distrust of the health care system has not been well studied in the prenatal/obstetric/neonatal context. In other settings, health care system distrust is associated with a greater burden of racial discrimination and not explained by differences in individual socio-demographics, health care access, or residential segregation.[4,35] Experiences of racism and discrimination likely play a role in health system engagement and prenatal care utilization. In a survey of mothers, non-Hispanic black or Hispanic race/ethnicity was associated with almost three times higher odds of discrimination due to race, language, or culture, and uninsured women had nearly twice the odds of experiencing any perceived discrimination.[35]

Creanga et al. noted that non-Hispanic black-serving hospitals performed worse than other hospitals on 12 of 15 delivery-related indicators, highlighting the impact of the access to quality health care as a determinant of delivery outcomes.[24] Adequacy of prenatal care has been found to be significantly associated with infant outcomes, particularly gestational age at delivery and birth weight.[16,19,35] Race and living in a distressed neighborhood are associated with late presentation to prenatal care. Proximity to the hospital is a key mediator in prenatal care utilization, and transportation to appointments and affordability of transportation are key factors in adherence to prenatal care. The impact of the neighborhood of residence on prenatal care disparities has not been explained by provider or physician supply alone. Neighborhood factors are thought to explain up to two-thirds of observed black–white differences in the preterm birth rate.[20,35]

Social determinants such as insurance status, availability of social support in the form of childcare and adequate housing, neighborhood, and transportation likely play some role in prenatal care utilization and ultimately neonatal outcomes.[35] Community-based research has shown that bundling prenatal care with other services such as child care that specifically aimed to reduce known disparities in social determinants improves outcomes.[35] Non-Hispanic black women are three times more likely to be homeless during their pregnancy or preconception period, and prenatal homelessness is associated with higher odds of low birth weight and preterm delivery.[28,83]

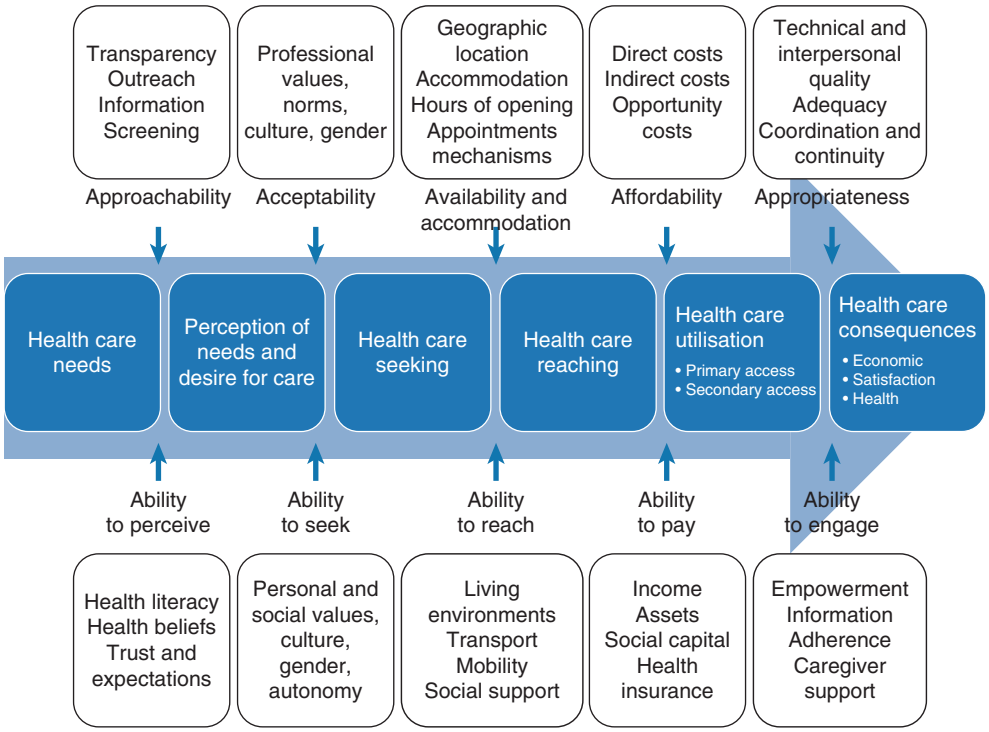
Access to health care is central to the delivery of health care services. Access is defined as the opportunity or ease with which consumers or communities are able to use appropriate services in proportion to their needs. Levesque et al.[53] conceptualized five dimensions of accessibility of services: approachability; acceptability; availability and accommodation; affordability; and appropriateness. Five corresponding abilities of persons interact with these dimensions of accessibility to generate access; these dimensions of abilities include: ability to perceive; ability to seek; ability to reach; ability to pay; and ability to engage. The various dimensions of access identified are not independent constructs (Fig. 9.5).

Although the Children's Health Insurance Program (CHIP) has increased the number of US children with coverage,[31,32] insurance coverage alone does not guarantee access to needed health care. Angier et al. found affordability and lack of availability to be the most commonly reported barriers to health care access in a cohort of parents with incomes less than 133% of the federal poverty level; despite their child having health insurance, parents were unable to receive necessary health care services.[1,2,50] Low socioeconomic status is associated with poor health status before, during, and after pregnancy. Homelessness during pregnancy in particular leads to worse birth outcomes due to a variety of factors.[28]

• BOX 9.1 Examples of Social Determinants of Health

- Availability of resources to meet daily needs: safe housing and local food markets
- Access to educational, economic, job opportunities, health care services, and job training
- Availability of community-based resources for recreational and leisure-time activities
- Transportation options and public safety
- Social support, social norms, and attitudes (e.g., discrimination, racism, and distrust of government)
- Exposure to crime, violence, and social disorder
- Socioeconomic conditions (e.g., concentrated poverty and the stressful conditions that accompany it)
- Residential segregation, language/literacy, and culture
- Access to mass media and emerging technologies (e.g., cell phones, the Internet, and social media)

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• **Fig. 9.5** A conceptual framework of access to health care. (From Levesque J-F, Harris MF, Russell G. Patient-centered access to health care: conceptualizing access at the interface of health systems and populations. *Int J Equity Health*. 2013;12:18.)

The increase in ethnic differences in neonatal mortality may be related to additional inequities in the provision of health care. Alabama's 2011 omnibus immigration law resulted in a reduction in service availability for Latina immigrants and their US and foreign-born children. Affordability and acceptability of care were also adversely affected because of economic insecurity and women's increased sense of discrimination.[85] A mental health diagnosis, poor relationships with health professionals, and environmental barriers can compromise women's utilization of maternity services.[12]

Before the Affordable Care Act (ACA) spurred major expansions in health insurance coverage, non-Hispanic black and Hispanic working-age adults were far more likely than non-Hispanic whites to be uninsured.[43] Uninsured women are 77% less likely to use obstetrical services, have higher rates of severe morbidity, and are more likely to have inadequate prenatal care.[35] Having health insurance makes it easier to gain access to and afford care, but insurance alone is unlikely to eliminate differences in access among all groups.[43] Increased state level Medicaid reimbursement for care increases adequate prenatal care utilization.

Even within the hospital setting, there may be unrecognized and unintended disparities in the delivery of health care to pregnant mothers and neonates. Profit et al. found clinically and statistically significant racial and/or ethnic variation in quality of care between neonatal intensive care units (NICUs) as well as within NICUs.[74] Earlier work in the California Perinatal Quality Care Collaborative suggested that Hispanic mothers, mothers younger than age 20, and those without prenatal care were less likely to receive antenatal steroid treatment for impending preterm delivery.[51] A recent review of three New York hospitals suggested that non-Hispanic white infants were more likely to receive surfactant by 4 hours (85%) than non-Hispanic black infants (61%) or Hispanic infants (67%).[46]

Chronic stress and worry by disadvantaged mothers likely has a significant impact on poor perinatal and neonatal outcomes. Braveman et al. found that non-Hispanic black women reported significantly higher chronic worry about racial discrimination compared to non-Hispanic white women.[11] Surprisingly, rates of worry for non-Hispanic black women were highest in those with higher income and education levels. Those with the highest rates of worry also had the highest rates of preterm birth. Even more intriguing is the evidence for continued generational effects of racial disparities with non-Hispanic black mothers who were small for gestational age or preterm themselves having a higher risk than non-Hispanic white mothers to deliver a subsequent small for gestational age or preterm infant.[17]

Interventions to Reduce Neonatal Health Outcome Disparities

It is unlikely that improving care in the NICU alone will have a dramatic impact on reducing the US neonatal and infant mortality rates. Research has demonstrated the areas of greatest impact that will result in improved neonatal health. First, all women, but especially those at highest risk

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such as non-Hispanic black women and Native American/Alaskan women, must have improved health status even before conception. Programs that can screen and identify women at risk must be easily accessible. This is certainly a challenge in very rural/remote areas where health care access is limited or non-existent. In addition, many urban settings have a maldistribution of health care providers, making access difficult for those most in need.

The massive rise in obesity in the US population over the past years has been well documented. Of significant concern to those in the public health arena is how this has negatively impacted women of reproductive age and their future children. Maternal obesity is another aspect of health disparities in that those races and ethnicities exhibiting worse perinatal and neonatal outcomes also have significantly higher rates of obesity than the general population. Recent data indicate that in the last decade, non-Hispanic black women over the ages of 20 have an extremely high incidence of obesity at 56.9%, compared to non-Hispanic white women at 35.5%.[69] Hispanic women also suffer from this epidemic of increased weight with an incidence of 45.7%. Disparities in the incidence of obesity during pregnancy also are seen in non-Hispanic black women, having the highest rates of prepregnancy obesity in the general population, especially at the highest categories of obesity.[49,52,79] Obesity is known to increase the risk of gestational diabetes from a baseline of 2.8% to a high of 14.6% in pregnant women with class III obesity.[49] Other morbidities of pregnancy such as gestational hypertensive disorders (increasing fourfold at highest obesity classes), infection, cesarean section rates, and cardiovascular events are all higher in obese pregnant women. While obesity has its own risks of increased morbidity on pregnant women, obesity is also associated with increased infant mortality and morbidity. Infant mortality increases with each increase in obesity category.[49] Declerq et al. found that with a normal prepregnancy weight as a reference, the odds ratio (OR) for an infant death rose from 1.32 (95% confidence interval [CI] 1.27–1.37) for mothers in the obese I category up to 1.73 (95% CI 1.64–1.83) for obese III category pregnant mothers.[29] Lemon et al. reported that compared with non-Hispanic white women, non-Hispanic black women were more likely to be obese and experienced a higher rate of stillbirth (8.3 vs. 3.6 stillbirths per 1000 live-born and stillborn infants) and infant death (8.5 vs. 3.0 infant deaths per 1000 live births).[52] In addition, obesity during pregnancy is associated with increased neonatal morbidities such as prematurity,[79] sepsis, large-for-gestational-age infants, and NICU admission.[49] Increasing obesity also results in an increased risk of major malformations in the neonate and were the highest as the severity of obesity increased.[73] Congenital malformations were seen in the cardiovascular system, malformations of the nervous system, and limb defects. It is also likely that to reduce these adverse outcomes, intervention begin before conception.

The causes of obesity are multifactorial, but chronic maternal stress related to racial and ethnic disparities seen in the United States may play a significant role.[72] Screening and health promotion for obesity, diabetes, and hypertension are critical to improving the health of the mother. Current models of physician reimbursement discourage the significant time needed for such interventions. Innovative models, such as mobile clinics, group counseling, and specially trained health care workers have all shown to improve health outcomes in women of child-bearing age. Chronic conditions, such as hypertension and diabetes, must be well controlled over time, with continued and affordable access to medications that are known to be effective. The current dramatic increase in obesity, especially in the south and among non-Hispanic blacks, Native Americans, and Hispanics in the United States, is a particular challenge. Not often recognized is the lack of healthy food available in underserved and rural areas, which contributes to obesity.

Another public health initiative that will have a significant impact on health care disparities in the perinatal and neonatal period is in pregnancy delay and prevention of unintended pregnancies[36] and associated short interpregnancy intervals. Teen births, while significantly decreasing, are still highest in some of the populations at highest risk for prematurity and infant mortality. Improved education about pregnancy prevention, including in schools, as well as easier access to contraception, is critical. In addition, long-acting reproductive contraception (LARC) has been shown to be particularly effective and is reversible at the time of desired pregnancy. Contraception for those that desire it must be more readily available, especially immediately after delivery of a baby. Contraceptive counseling is rarely done during postpartum care, or while a baby is in the NICU, but these are valuable missed opportunities to improve the health of the mother and her future children. Improved access to contraception will increase interpregnancy intervals. Short inter-pregnancy intervals less than 6 months are more common in non-Hispanic black mothers (7.1%) compared to non-Hispanic white mothers (4.1%) and Hispanic mothers (5.0%).[80] The shortest interval of inter-pregnancy conception (less than 6 months) has been shown to have the highest adverse outcomes, especially in teen mothers.[68] Access to contraception, especially for teen pregnancies, of which 75% are unintended, is critical to lengthen interpregnancy intervals and prevent adverse outcomes associated with teen pregnancy. Local legislation will be needed to implement this public health intervention. Because of limited access to contraception, there are racial disparities in abortion rates for women of lower socioeconomic status and women of color. Hispanic women and non-Hispanic black women have 2–3.5-fold higher rates of abortion than non-Hispanic white women.[47] However, efforts to decrease access to abortion for these women may only widen the health disparities for future generations.[30]

As noted above, there are significant disparities in rates of prenatal care related to race and ethnicity, with non-Hispanic blacks overall having the lowest rates of adequate prenatal care and the highest rates of no prenatal care (see Table 9.1). Statewide Medicaid-enhanced prenatal care

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programs have been shown to reduce infant mortality risk.[64,65] Implementation of such a program in Michigan reduced the odds of infant death by 27%, with the highest reduction in black infant mortality (29%). The greatest reduction was seen in those women who fully participated in the program using a population-based home visitation program. For non-Hispanic black women, this program resulted in lower odds of low birth weight (0.76), very low birth weight (0.42) and very preterm birth (0.41) compared with matched nonparticipants.[76]

Access to insurance coverage before, during, and after pregnancy is also a vital piece of health care. Having health insurance reduces racial and ethnic disparities in key measures of health care access and affordability, even after adjusting for income and other factors.

Women often qualify for Medicaid coverage once the pregnancy is identified but cannot access the health care system before the pregnancy to improve their health, thus putting them at greater risk. As noted above, the Affordable Care Act (ACA) has significantly decreased the uninsured rate of people in the United States, with varying improvements in insurance coverage based on the degree of states' Medicaid expansion. This program has also mandated insurance coverage by all health plans for prenatal, postnatal, and infant care. The Children's Health Insurance Program (CHIP) funded by the United States has increased coverage of uninsured children. Survey-based research shows positive associations between CHIP expansions and children's health care utilization. After Oregon's 2009-2010 CHIP expansions, newly insured patients' utilization rates were more than double their pre-expansion rates (adjusted rate ratios [95 % confidence intervals]); increases were 2.10-fold (1.94–2.26) for primary care visits.[5] Thus, continued access to insurance for women and children may have a significant impact on reducing the disparities seen. Unlike other developed countries, the United States has no universal health care and the ACA has been a significant, albeit controversial, improvement in this area. Those in health care, both providers and insurers, must advocate for the most vulnerable in the population to maintain and expand this coverage.

Other modifiable factors must be addressed for women at risk of becoming pregnant. Tobacco, alcohol, and illicit substance use/abuse all have negative impacts on pregnancy outcomes and are often disproportionately used by those at highest risk of adverse outcomes.[66] Culturally specific and appropriate educational materials and interventions must be available in a variety of settings, including schools. Tobacco cessation programs specifically during pregnancy, especially quitting early in pregnancy, have been shown to decrease the risk of preterm birth.[66] Alcohol use and abuse is particularly high among Native American and Alaska Natives and results in high rates of fetal alcohol syndrome.[15] Fetal alcohol syndrome and fetal alcohol spectrum disorder is the largest cause of preventable long-term neurodevelopmental disability in children. Treatment of those ingesting alcohol during pregnancy is particularly difficult. However, intensive interventions have made some impact.[42] Finally, the current opioid epidemic has been well publicized, as has the impact on those at the lowest socioeconomic populations. Pregnant women are often the least likely to get medical help given the highly punitive nature of some state programs, even to the point of arresting and incarcerating pregnant women, especially those women of minorities. However, programs that deal with multiple aspects of maternal drug use with known effective interventions and a less punitive approach have been shown to significantly improve neonatal and maternal outcomes, including more controlled or even cessation of drug use.[88] Other innovative prenatal care programs such as group-based centering, easier access to care during pregnancy, and the use of novel IT platforms for patient access and information also have been shown to have a significant impact on avoiding adverse outcomes of pregnancy.[27]

While the underlying cause of prematurity is multifactorial and not clearly understood, certain interventions have been shown to reduce preterm birth. For those women identified with a singleton pregnancy and a previous history of spontaneous preterm birth, 17 alpha-hydroxyprogesterone caproate (17OHP) has been shown to reduce the risk of subsequent preterm delivery by up to 30%.[22] However, access to this medication requires weekly injections, and the current drug delivery and reimbursement model is problematic for both physicians and women at risk. Many state Medicaid plans are investigating novel methods to deliver this drug to mothers at risk.

Breastfeeding has been shown to have important benefits to both the mother and infant, including decreased breast and ovarian cancer rates, less postpartum depression, and osteoporosis in the mother, as well as fewer infections, less risk of diabetes, heart disease, and asthma in the infant. However, significant disparities exist in the rates of breastfeeding among different races and ethnicities.[63] Non-Hispanic black women have the lowest rates of initiation of breastfeeding, exclusive breastfeeding at 6 months, and any breastfeeding at 12 months.[3] In addition, certain areas of the United States with the highest poverty levels such as the Deep South and Appalachian States have the lowest rates of breastfeeding. Successful implementation of breastfeeding must begin before delivery with targeted and appropriate education. Baby Friendly initiatives in the United States have resulted in increased awareness of the importance of this public health measure but more must be done. Lactation specialists must be available to all mothers immediately after delivery and during the postnatal period to improve initiation of and adherence to breastfeeding.

The American Academy of Pediatrics (AAP) and March of Dimes (MOD) have initiated the Safe Sleep campaign in an effort to reduce SIDS. While the Safe Sleep program is effective, key measures must be stressed, such as the lack of separate sleeping spaces for the infant and co-bedding in minority populations. It is often difficult to intervene in those families with limited finances. Programs such as Back to Sleep and Baby Sleeping Boxes are simple and effective

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interventions. However, continued local and state educational efforts must be maintained and supported.

State Perinatal Quality Collaboratives have been an extremely successful model for health care providers and families interested in improving prenatal and postnatal outcomes, primarily using Quality Improvement methodology. Areas successfully addressed have been increased administration of antenatal corticosteroids to mothers at risk of preterm delivery, decrease in elective late preterm deliveries, and antibiotic stewardship.[38] State collaboratives identify best practices within each state and work together to improve maternal and neonatal outcomes through quality improvement processes.

Finally, improving the overall health and economic status of those most disadvantaged in the United States will result in improved perinatal and neonatal/infant outcomes. In enhanced programs, implementation of measures that increase educational opportunities, job creation, and statewide early intervention programs have been shown to be beneficial in other countries. Canada implemented unconditional prenatal income supplements to mothers already receiving prenatal social assistance and observed reductions in low birth weight (21%), preterm births (17.5%), and increases in breastfeeding.[14] Every baby deserves a first birthday. Effective interventions exist that will help more to reach this goal.

Key Points

- The United States has high infant mortality and prematurity rates compared to other high income countries.
- Health disparities are seen in maternal outcomes with non-Hispanic black mothers having the highest rates of maternal mortality and morbidity, obesity, and teen pregnancy.
- The United States has significant health disparities in measurements of perinatal and neonatal outcomes with non-Hispanic black infants leading in prematurity and infant mortality.
- American Indian/Alaska Native infants suffer from high infant mortality rates compared to non-Hispanic white infants.
- Public health interventions to address health disparity outcomes by race and ethnicity are needed to improve US neonatal outcomes.

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10

Genetic Aspects of Perinatal Disease and Prenatal Diagnosis

SUSAN J. GROSS AND CIPRIAN P. GHEORGHE

The genetic basis of human disorders is a fundamental cornerstone of modern medicine. Recent advances in our understanding of complex genetic disorders coupled with technical developments have allowed genetics to become an invaluable part of clinical practice. This chapter highlights essential concepts regarding the genetic basis of disease and issues surrounding prenatal evaluation and diagnosis. Principles of inheritance, teratogens, genetic screening, and diagnostic modalities are discussed.

Principles of Inheritance

Chromosomal Disorders

In humans, normal gametes are composed of 23 chromosomes each. A normal human somatic cell contains 46 chromosomes. In both genders, 22 pairs of chromosomes, also known as *autosomes,* are identical. Women have a homologous pair of sex chromosomes, known as the X chromosome. Men have a nonhomologous pair, an X and a Y chromosome.

A chromosome is composed of a linear DNA molecule that is complexed with structural proteins known as *histones* to form chromatin. Each chromosome has a centromere, which divides the chromosome into a short arm (the *p* arm) and a long arm (the *q* arm). Where the centromere is located helps describe chromosomes as metacentric, submetacentric, and acrocentric. In *metacentric* chromosomes the arm length is equal, whereas in *submetacentric* chromosomes, one arm is larger than the other. If the p arm contains such small amounts of genetic material that it is almost negligible, the chromosome is considered *acrocentric*. In humans, the acrocentric chromosomes are 13, 14, 15, 21, and 22. The ends of each chromosome are known as *telomeres*. During cell division the chromosomes condense more than 10,000-fold, resulting in compact structures that can segregate.

To analyze chromosomes, a karyotype is produced (Fig. 10.1). The chromosomes are paired and organized according to size. The overall structure and banding pattern is evaluated and is reported according to the International System for Cytogenetic Nomenclature. According to this nomenclature, a karyotype designation includes the total chromosome number followed by the sex chromosome constitution. Females are 46,XX and males are 46,XY. If there are any variants or abnormalities, this is reported after the sex chromosomes (Table 10.1).[35] Chromosome disorders can be either structural or numerical. The consequence of the abnormality depends on the amount of genomic imbalance and the genes involved.

Maternal Age Considerations

Epidemiologic studies suggest that women are having fewer children, often later in life. The National Center for Health Statistics (NCHS) reported that from 2000 to 2014, the proportion of first births to women aged 30-34 rose 28% (from 16.5% to 21.1%), and first births to women aged 35 and over rose 23% (from 7.4% to 9.1%).[19] With the advent of assisted reproductive technology (ART), women in their 50s and 60s can achieve pregnancy. Although it cannot be emphasized enough that the effects of increasing age occur as a continuum, the term *advanced maternal age* has historically referred to pregnant women who will be 35 or older on their expected date of confinement.

Chromosomal analysis of samples from spontaneous abortions, prenatal diagnosis, and live births reveals that there is a steady increase in aneuploidy as a woman ages (Fig. 10.2). The basis for this increase is unknown, although it may be related to a decrease in the number of normal oocytes available or cumulative oxidative stress on the finite number of oocytes with which females are born. Along with chromosomal abnormalities, it has been observed that congenital anomalies increase with increased maternal age. The FASTER trial reported rates of congenital anomalies for women younger than 35 years old as 1.7%; women 35 to 39 years old and 40 years old or older had rates of 2.8% and 2.9%, respectively.[29]

Abnormalities of Chromosome Number

The mere presence of additional genetic material, albeit of normal makeup, can result in clinically significant

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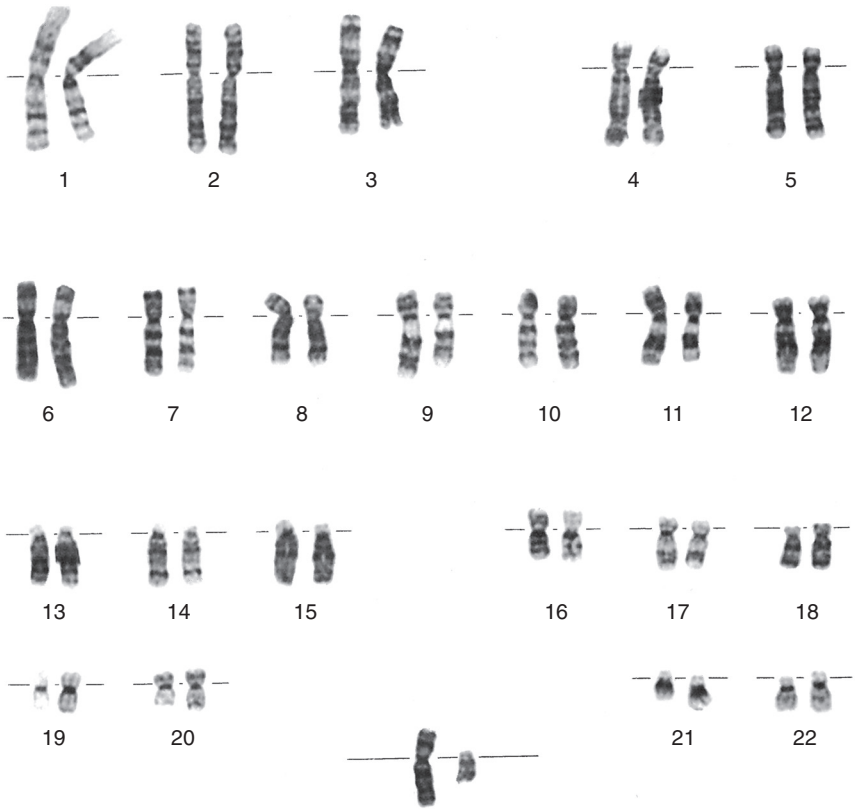
Abstract

The genetic basis of human disorders is a fundamental cornerstone of modern medicine. Recent advances in our understanding of complex genetic disorders coupled with technical developments have allowed genetics to become an invaluable part of clinical practice. This chapter highlights essential concepts regarding the genetic basis of disease and issues surrounding prenatal evaluation and diagnosis. Principles of inheritance, teratogens, genetic screening, and diagnostic modalities are discussed.

Keywords

genetics
prenatal diagnosis
aneuploidy screening
microarray
cell-free DNA screening

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• **Fig. 10.1** Karyotype of a normal male. Notice the presence of an X and Y chromosome and 22 pairs of autosomes.

TABLE 10.1 Abbreviations Used for Description of Chromosomes and Their Abnormalities

Abbreviation	Meaning	Example	Condition
		46,XX	Normal female
		46,XY	Normal male
+	Gain of	47,XX,+21	Female with trisomy 21
–	Loss of	45,XX,–22	Female with monosomy 22
T	Translocation	46,XY,t(2;8)(q22;p21)	Male with balanced translocation between chromosome 2 and 8, with breaks in 2q22 and 8p21
/	Mosaicism	46,XX/47,XX,8	Female with two populations of cells, one with a normal karyotype and one with trisomy 8

From Nussbaum RL, et al. Thompson and Thompson Genetics in Medicine. 7th ed. Philadelphia: Saunders; 2007:66.

phenotypes. Following is a discussion of the various types of numerical abnormalities.

Triploidy and Tetraploidy

Triploid fetuses have three sets of chromosomes for a total number of 69. Triploid fetuses are rarely born alive; when they are, survival is poor. Most triploidy is the result of fertilization by two sperm. Tetraploids, fetuses with 96 chromosomes, are usually miscarried in the first trimester.

Aneuploidy

In humans, the term *aneuploid* is used to describe any genotype in which the total chromosome number is not a multiple of 23. Most aneuploid patients have either a monosomy (only one representative of a particular chromosome) or a trisomy (three copies of a particular chromosome). As a rule, monosomies tend to be more deleterious than trisomies. Complete monosomies are generally not viable except for monosomy X (Turner syndrome). Trisomies for chromosomes 13, 18, 21, X, and Y are compatible

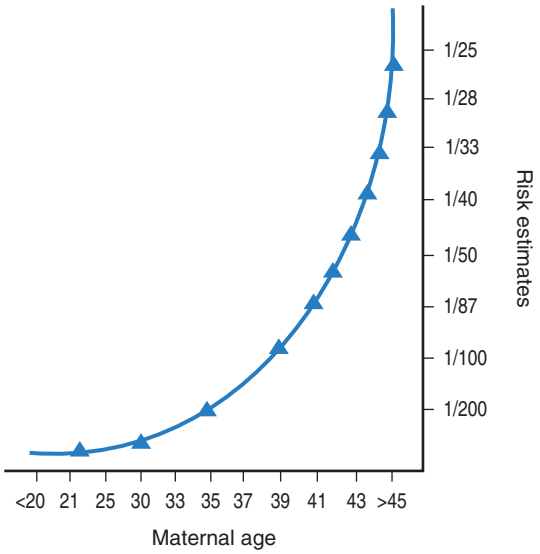
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with life, with trisomy 21 (Down syndrome) being the most common trisomy in live-born infants.

The most common mechanism for aneuploidy is meiotic nondisjunction, in which a pair of chromosomes fails to separate during either of the meiotic divisions (Fig. 10.3). Nondisjunction can rarely occur during a mitotic division after the formation of the zygote. If this happens early in cleavage, mosaicism may occur. In this situation, two or more different chromosome complements are present in one individual. The clinical significance of mosaicism is difficult to evaluate and depends on the developmental timing when the mosaicism occurred, the tissues affected, and the proportion of tissue affected.

Abnormalities of Chromosome Structure

Chromosomal structural abnormalities are the result of chromosome breakage followed by anomalous reconstitution.



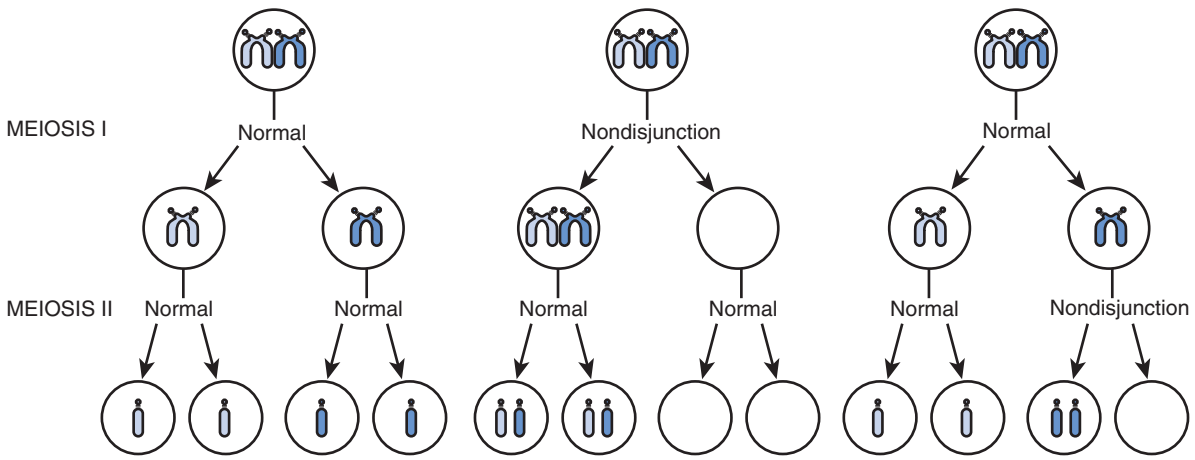
• **Fig. 10.2** Risk of fetal aneuploidy as a function of maternal age.

Rearrangements result spontaneously or are due to inducing agents, such as ionizing radiation. Structural abnormalities can be divided into two categories—balanced and unbalanced. Balanced rearrangements have the normal complement of chromosomal material. Also, a balanced rearranged chromosome must have a functional centromere and two functional telomeres. Unbalanced rearrangements are either missing or have additional genetic information.

Structural rearrangements include deletions, insertions, ring chromosomes, isochromosomes, and translocations (Fig. 10.4). One unique type of translocation is the Robertsonian translocation, in which two acrocentric chromosomes lose their short arms and fuse near the centromeric region. Because the short arms of acrocentric chromosomes contain only genes for ribosomal RNAs, loss of the short arm is rarely deleterious. The result is a balanced karyotype with only 45 chromosomes, including the translocated chromosome, which comprises the long arms of two chromosomes. Carriers of Robertsonian translocations are phenotypically normal but have the risk of producing unbalanced gametes. The main clinical relevance of a Robertsonian translocation is that one involving chromosome 21 could result in a child with Down syndrome. About 4% of cases of Down syndrome have 46 chromosomes, one of which is a Robertsonian translocation between chromosome 21 and another chromosome.

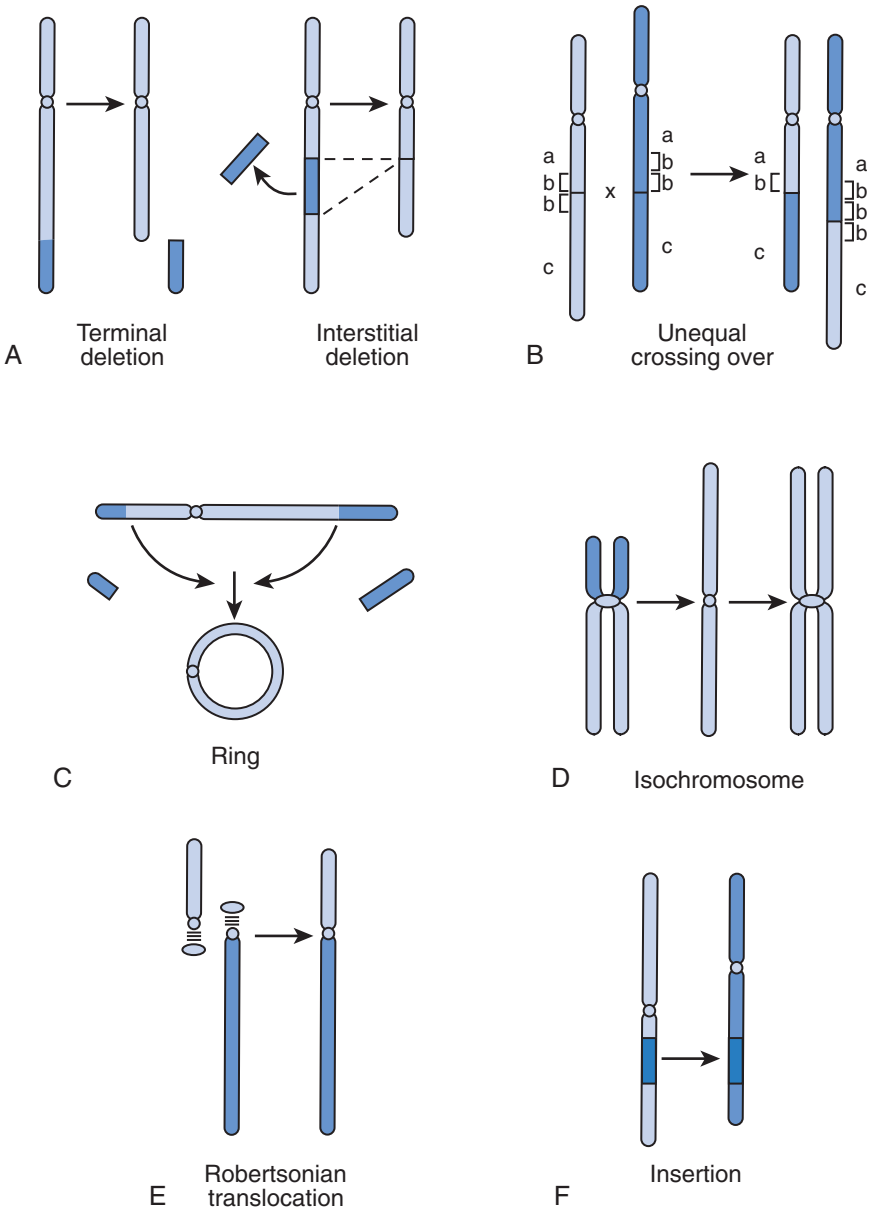
Single-Gene Disorders

Mendel studied the offspring characteristics of garden peas and observed that certain phenotypic characteristics occurred in fixed proportions. Single-gene traits for which mutations cause predictable disease are described as exhibiting *Mendelian inheritance*, because they follow the rules that he originally described. Currently, almost 4000 diseases are known to exhibit Mendelian patterns of inheritance.



• **Fig. 10.3** Consequences of nondisjunction at meiosis I (*center*) and meiosis II (*right*) compared with normal disjunction (*left*). If the error occurs at meiosis I, the gametes either contain a representative of both members of the chromosome 21 pair or lack chromosome 21 altogether. If nondisjunction occurs at meiosis II, the abnormal gametes contain two copies of one parental chromosome 21 (and no copy of the other) or lack chromosome 21. (From Nussbaum RL, et al. *Thompson and Thompson Genetics in Medicine*. 7th ed. Philadelphia: Saunders; 2007:68.)

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• **Fig. 10.4** Structural rearrangements of chromosomes. **A,** Terminal and interstitial deletions, each generating an acentric fragment. **B,** Unequal crossing over between segments of homologous chromosomes or between sister chromatids (duplicated or deleted segments indicated by *brackets*). **C,** Ring chromosome with two acentric fragments. **D,** Generation of an isochromosome for the long arm of a chromosome. **E,** Robertsonian translocation between two acrocentric chromosomes. **F,** Insertion of a segment of one chromosome into a nonhomologous chromosome. (From Nussbaum RL, et al. *Thompson and Thompson Genetics in Medicine*. 7th ed. Philadelphia: Saunders; 2007:69.)

Among hospitalized children, 6% to 8% are thought to have single-gene disorders.

Variants of a gene are called *alleles*. For many genes, there is one prevailing allele, which is referred to as the *wild-type* allele. The other versions of the gene are *mutations,* not all of which may cause disease. Mutations can be inherited or de novo, meaning that neither parent possessed the mutation. Instead, the mutation occurred as a random error during gametogenesis. To distinguish between benign and deleterious mutations, the professional genetics community now calls the latter pathogenic variants.

Autosomal Dominant Disorders

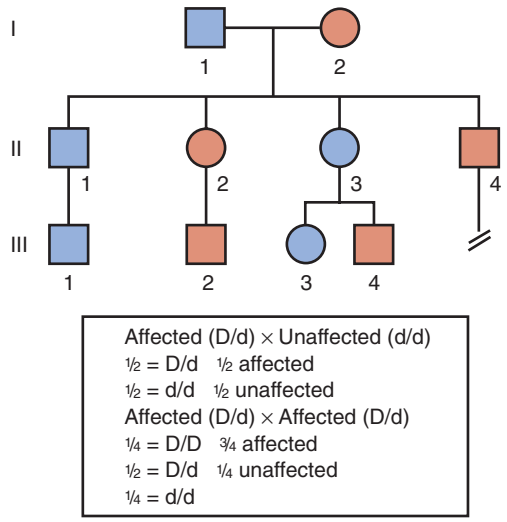
Approximately half of Mendelian disorders are inherited in an autosomal dominant fashion. Inheritance usually exhibits a vertical pattern of transmission, meaning that the phenotype appears in every generation, with each affected person having an affected parent (Fig. 10.5). For each offspring of an affected parent, the risk of inheriting the mutated allele is 50%. An example of a disorder inherited in an autosomal dominant fashion is osteogenesis imperfecta. Biochemical defects in either the amount or the

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structure of collagen result in various clinical phenotypes depending on the mutation.

Advanced Paternal Age

The link between advanced maternal age and genetic abnormalities has been well-established. The role of advanced paternal age, defined as 40 or older, is not as clear. It has been established that the rate of base substitution mutations during spermatogenesis increases as a man ages. The risk of de novo autosomal dominant disorders in offspring of fathers 40 years old or older is estimated at 0.3% or lower.[26] Some evidence has suggested that advanced paternal age is associated with an increased risk for complex disorders such as schizophrenia, autism, and congenital anomalies. The relative risk for these conditions is 2% or less. Although there may be slightly increased risk for a range of disorders associated with advanced paternal age, the overall risk remains low. No screening or diagnostic tests target conditions associated with advanced paternal age. Pregnancies that are fathered by men 40 years old or older should be treated according to standard guidelines established by the American College of Medical Genetics (ACMG) and the American College of Obstetrics and Gynecology (ACOG).[38]



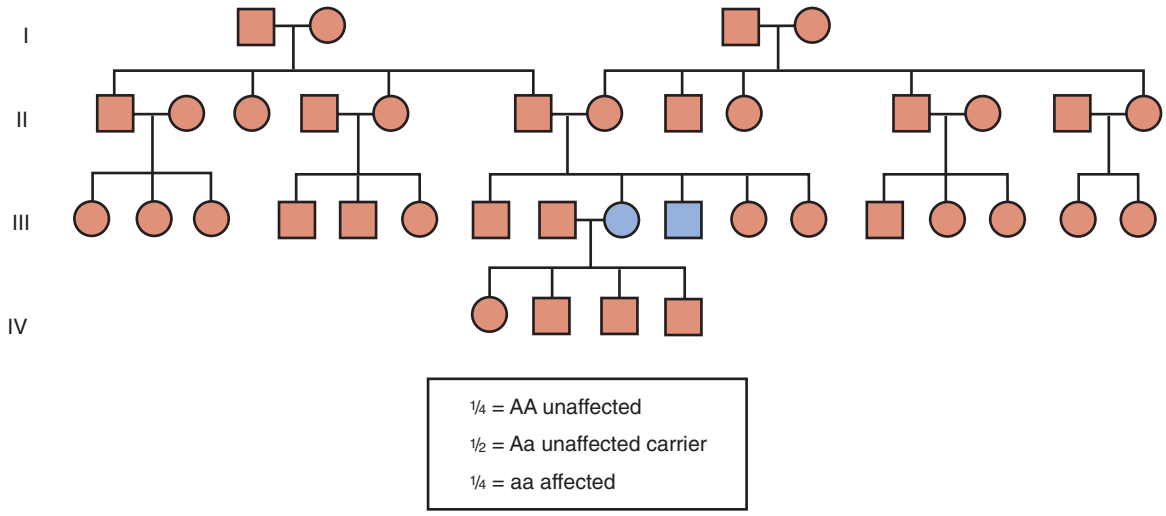
• **Fig. 10.5** Pedigree showing the typical inheritance of an autosomal dominant disorder. ■ affected male; ● affected female; ■ unaffected male; ● unaffected female.

Autosomal Recessive Disorders

An autosomal recessive condition occurs when an individual possesses two mutant alleles that were inherited from heterozygous parents. For autosomal recessive diseases, an individual with one normal allele does not manifest the disease, because the normal gene copy is able to compensate. Autosomal recessive disorders exhibit horizontal transmission, meaning that if the phenotype appears in more than one family member, it is typically in the siblings of the proband, not in parents, offspring, or other relatives (Fig. 10.6). If both parents are carriers of a mutated allele, 25% of offspring have the autosomal recessive disease. Consanguineous unions (mating between individuals who are second cousins or closer) are at increased risk for an autosomal recessive disorder, because there is a higher likelihood that both individuals carry the same recessive mutation. A common autosomal recessive disease is cystic fibrosis. Carrier screening and prenatal implications are discussed in a later section.

Sex-Linked Disorders

X chromosome inactivation is a normal process in females in which one X chromosome is randomly inactivated early in development. Females are normally mosaic with respect to X-linked gene expression. Disorders of genes located on the X chromosome have a characteristic pattern of inheritance that is affected by gender. Males with an X-linked mutant



• **Fig. 10.6** Typical pedigree showing autosomal recessive inheritance. Unaffected carrier (A/a) × Unaffected carrier (A/a). ■ affected male; ● affected female; ■ unaffected male; ● unaffected female. (From Nussbaum RL, et al. *Thompson and Thompson Genetics in Medicine*. 7th ed. Philadelphia: Saunders; 2007:123.)

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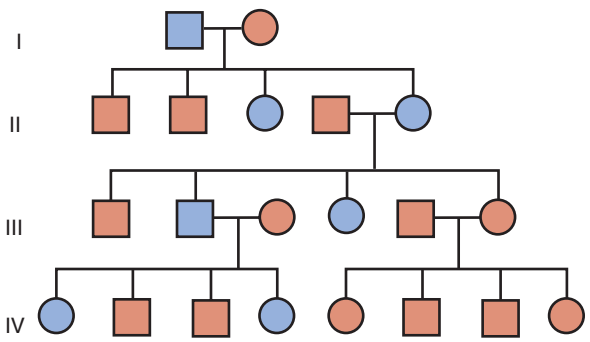
allele are described as being hemizygous for that allele. Males have a 50% chance of inheriting a mutant allele if the mother is a carrier. Females can be homozygous wild-type allele, homozygous mutant allele, or a heterozygote.

An X-linked recessive mutation is phenotypically expressed in all males but is expressed only in females who are homozygous for the mutation. As a result, X-linked recessive disorders are generally seen in males and rarely seen in females. An example of such a condition is hemophilia A. X-linked dominant disorders may manifest differently among heterozygous females in the same family because of different patterns of X chromosome inactivation. X-linked inheritance is classically characterized by the lack of male-to-male transmission, because males transmit their Y chromosome to their sons, not their X chromosome (Fig. 10.7).

Non-Mendelian Patterns of Inheritance

Mitochondrial Inheritance

Mitochondrial DNA (mtDNA) is organized as a 16.5-kb circular chromosome located in the mitochondrial organelles of a cell, not the cell nucleus. mtDNA contains 37 genes that encode for important proteins, including proteins involved in oxidative phosphorylation.



• **Fig. 10.7** Pedigree pattern showing X-linked dominant inheritance. ■ affected male; ● affected female; ■ unaffected male; ● unaffected female. (From Nussbaum RL, et al. *Thompson and Thompson Genetics in Medicine*. 7th ed. Philadelphia: Saunders; 2007:133.)

Mitochondrial inheritance has a few distinct features that differ from Mendelian inheritance: maternal inheritance, replicative segregation, and heteroplasmy. Because sperm mitochondria are eliminated from the forming embryo, mtDNA is inherited entirely from the maternal side, with very rare exception. At cell division, the mitochondria sort randomly between two daughter cells, a process known as *replicative segregation*. A cell containing a mix of mutant and wild-type mtDNA can distribute variable proportions of mutant or wild-type DNA to daughter cells. By chance, a daughter cell may receive all wild-type or all mutant mtDNA, a state known as *homoplasmy*. Heteroplasmic daughter cells can result in variable penetrance and expression depending on the amount of mutant mtDNA present.

More than 100 different mutations in mtDNA have been identified to cause disease in humans and with new technologies, that number is growing.[10] Most of these involve the central nervous system or musculoskeletal system (Table 10.2).

Mitochondrial disease typically manifests as dysfunction in high energy-consuming organs such as the brain, muscle, heart, and kidneys. Poor growth, muscle weakness, loss of coordination, or developmental delay not explained by more common causes should alert a neonatologist or pediatrician to the possibility of a mitochondrial disease. When a mitochondrial disease is suspected, the child should be referred to a specialized medical center wherein comprehensive evaluation, including genetic studies, can be performed.

Epigenetics and Uniparental Disomy

Epigenetics refers to modification of genes that determines whether a gene is expressed or not (see Chapter 16). These modifications, an example of which is methylation, affect the expression of a gene, but not the primary DNA sequence itself. *Imprinting* refers to a phenomenon in which genetic material is differentially expressed depending on whether it was inherited from the father or the mother. A different phenotype can result depending on the parent of origin,

TABLE 10.2 Common Mitochondrial Diseases and Their Manifestations

Name	Abbreviation	Disease Characteristics
Myoclonic epilepsy associated with ragged red fibers	MERRF	Progressive myoclonic epilepsy, short stature, clusters of diseased mitochondria accumulated in subsarcolemmal region of muscle fiber (appear as "ragged red fibers" when stained)
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke	MELAS	Muscle weakness, headaches, loss of appetite, seizures, lactic acidosis, stroke
Neuropathy, ataxia, and retinitis pigmentosa	NARP	Numbness and tingling in limbs, muscle weakness, ataxia, deterioration of light-sensing cells of retina
Leber hereditary optic neuropathy	LHON	Acute onset of visual loss and optic atrophy usually in early young adulthood
Myoneurogastrointestinal disorder and encephalopathy	MNGIE	Ptosis, progressive external ophthalmoplegia, diffuse leukoencephalopathy, gastrointestinal motility dysfunction

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because for certain genes, only the allele from one parent is transcriptionally active.

Uniparental disomy is the inheritance of a pair of homologous chromosomes from one parent rather than the normal scenario in which one chromosome is inherited from each parent. This situation is thought to arise most commonly by a process called *trisomy rescue,* during which a trisomic cell is converted into a disomic cell. It is a matter of chance as to which chromosome drops out. When trisomy rescue occurs, both chromosomes are from one parent a third of the time.

Classic examples of disorders related to genomic imprinting are Prader-Willi and Angelman syndromes. Both these syndromes involve the long arm of chromosome 15 (15q11-15q13). At birth, Prader-Willi syndrome is characterized by hypotonia, low birth weight, and almond-shaped eyes. During childhood, other features such as short stature, obesity, indiscriminate eating habits, small hands and feet, mental retardation, and hypogonadism develop. In most of these cases, there is paternally derived deletion, which means that all the genetic information in the region is maternal in origin. Angelman syndrome, characterized by mental retardation, short stature, abnormal facies, and seizures, is the opposite situation, in which the deletion is maternally derived, and the genetic information in the region is paternal only in origin. Approximately 30% of Prader-Willi cases and 5% of Angelman cases are the result of uniparental disomy. In this scenario, there is no cytogenetically detectable deletion. Because of imprinting, Prader-Willi syndrome results from uniparental disomy in which both chromosomes derive from the mother. The loss of the paternal contribution results in Prader-Willi syndrome. Paternal uniparental disomy in the same region results in Angelman syndrome because of the loss of maternal contribution of genes in the 15q11-q13 region.

Another aspect of epigenetics that has become an exciting avenue for research is the fetal origin of adult disease hypothesis. This is also known as the Barker Hypothesis, named after British epidemiologist David Barker, who proposed that intrauterine stress in the form of growth restriction and prematurity can predispose the individual to hypertension, cardiac disease, and diabetes. The initial evidence was provided by epidemiologic data that correlated low birth weight with poor health outcomes in adulthood.[7] Since then, several animal and human studies have shown that a harsh intrauterine environment can lead to a host of changes in DNA methylation and ultimately influence gene expression and metabolic dysregulation in adulthood.[27]

Trinucleotide Repeat Expansion

Most mutations, when they occur, remain unchanged as they get passed from one generation to the next. There is a subset of disorders, however, for which an expansion of an area of DNA containing repeating units results in disease. In this case, as the gene is passed on, the number of repeats (usually consisting of three nucleotides each) can increase to beyond polymorphic range and begin to affect gene function. Although the mechanism of how this expansion occurs is not completely elucidated, it is thought to be the result of a slipped mispairing mechanism in which an insertion occurs when a newly synthesized strand temporarily dissociates from the template strand. A dozen or so diseases, including congenital myotonic dystrophy, Huntington disease, Friedreich ataxia, and fragile X syndrome, are the result of unstable repeat expansions.

Fragile X syndrome, the most common hereditary form of mental retardation, has an incidence of approximately 1 in 4000 births. The normal number of triplet repeats in the Xq27.3 region (*FMR1* gene) is less than 45; a full mutation is considered to be greater than 200 repeats. Individuals with 45 to 54 repeats are referred to as intermediate carriers—these individuals are not at risk for any phenotypic abnormalities and are not at risk for expansion to a full mutation in their offspring. Individuals with 55 to 200 repeats are known as premutation carriers. Besides the risk of having an offspring with the full mutation, these premutation carriers are also at risk for adult-onset cerebellar dysfunction (known as fragile X-associated tremor/ataxia syndrome) and premature ovarian failure.[25]

Individuals who have any family or personal history of developmental delay, mental retardation, ovarian dysfunction, or tremor should be offered screening for fragile X syndrome. There has been increasing adoption of prenatal screening for fragile X in the general population, despite not being recommended by professional bodies.[13]

Multifactorial Inheritance

There are disorders that affect certain families more than others but do not follow Mendelian patterns of inheritance or fit into the non-Mendelian inheritance phenomenon. These disorders are thought to be the result of interplay between genetic and environmental factors and gene–gene interactions. Known as *multifactorial* or *complex* inheritance, these disorders have a greater incidence than disorders secondary to chromosomal or single-gene mutations. These disorders provide unique genetic counseling dilemmas regarding recurrence risks, because although genotypes predisposing to disease may aggregate in families, the phenotypic expression is discordant, owing to differences in nongenetic exposures.

An illustrative example of multifactorial inheritance is the occurrence of neural tube defects (NTDs). Spina bifida and anencephaly are NTDs that cluster in families and are a leading cause of fetal loss and handicap. Spina bifida is the result of incomplete fusion of vertebral arches and manifests in various degrees of severity. Anencephaly is a devastating condition in which the forebrain, overlying meninges, bone, and skin are absent. Most fetuses with anencephaly are stillborn. Although some NTDs can be explained by teratogens, amniotic bands, or chromosomal disorders, most are multifactorial. Decreased levels of maternal folic acid have been inversely correlated with the risk of NTDs. Folic acid levels are affected by two factors—dietary intake and enzymatic processing. Folic acid levels are detrimentally affected by

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a mutation in the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR). Fifteen percent of the population is homozygous for the mutation. It has been shown that the mothers of infants with NTDs were twice as likely to have MTHFR mutations than controls. Preconceptual supplementation of folic acid has been shown to decrease the risk of NTDs.[42] All reproductive-age women should consume 0.4 mg of folic acid daily. Prenatal screening for NTDs is discussed later in this chapter.

Teratogens

Environmental exposures—medications, maternal conditions, or infections—are the etiology of malformations in 10% of cases. The impact of the agent relates to the timing and amount of exposure (duration and dosage). The susceptibility of a fetus depends on its stage of development when an exposure takes place (Fig. 10.8)[34] (see Chapter 14).

Exposure during the first 2 weeks after conception usually either is lethal to the embryo or has no adverse effect. This window is known as the "all-or-none" period. During organogenesis, teratogenic exposure may result in major morphologic abnormalities because of disruption of the forming organ systems.

Most commonly prescribed medications can be used with relative safety during pregnancy. For the medications that are suspected or known teratogens, genetic counseling should emphasize relative risk. That is, risk increases should be presented in relation to a woman's baseline risk of a birth defect, which is 2% to 3%. The possibility that certain medical conditions if left untreated pose greater threat to the fetus than the medications used to treat the condition should be addressed. The US Food and Drug Administration, in 2014, removed the letter categories for drugs in pregnancy, and labeling now includes information on whether a drug is absorbed systemically and relevant information to help providers manage and counsel patients.[20]

Use of these drugs in pregnancy ultimately requires expertise and access to up-to-date databases specializing in teratogenesis, available through a prenatal genetics service. Certain drugs may be a significant risk, but only during a particular trimester. Trimethoprim-sulfamethoxazole should be avoided in the third trimester to avoid kernicterus in the newborn but may be used in the first and second trimesters. Likewise, a certain drug may be a genuine teratogen, but the risk of stopping the drug would be of even greater consequence. Lithium use during the first trimester of pregnancy has been associated with cardiac malformations, including Ebstein anomaly. Although efforts should be made to avoid lithium during the first trimester, if an alternative therapy is inappropriate, the lowest possible lithium dose should be used. Finally, certain drugs are known teratogens, but the underlying disorder may contribute to birth defects independently. Women with epilepsy are at increased risk of fetal malformations such as orofacial clefts, independent of whether or not they are taking anticonvulsant therapy.

Diagnostic Imaging

Radiographic imaging modalities are widely used in inpatient and outpatient settings. Safety of ionizing radiation exposure in pregnancy is an important concern because of the association of ionizing radiation with prenatal death, malformation, and carcinogenesis. It is necessary to weigh the risk of exposure versus the risk to the mother and fetus of a delayed diagnosis. With proper test selection, shielding, and procedure modifications, fetal risk can be significantly reduced or eliminated.

Common radiologic studies such as chest or dental x-rays typically expose the fetus to much less than 5 rad of radiation (Table 10.3). At these levels, there has been no evidence of increased risk of mental retardation, fetal anomalies, or pregnancy loss. The risk of childhood leukemia with an exposure of 1 to 2 rad increases to 1 in 2000, a 1.5-fold increase above the baseline risk of 1 in 3000.[14]

Exposure greater than 10 rad has been associated with an increased risk of malformations. Diagnostic imaging rarely, if ever, exposes the fetus to this level of radiation, however. Iodinated contrast materials can cross the placenta and produce transient effects in the developing fetal thyroid. Although not contraindicated, iodinated contrast material should be used with great care.

Magnetic resonance imaging (MRI), which uses electromagnetic radio waves to generate images, has not been associated with any harmful effects to the developing fetus. Gadolinium, the contrast agent most commonly used in MRI, crosses the placenta. There has been limited evaluation of its safety, and it is not recommended for use in pregnancy.

Ultrasonography is an important tool in obstetrics. Although there has been some concern regarding elevation of tissue temperature with prolonged use, there is no reliable evidence of harm to the human fetus as a result of standard, medically indicated ultrasonography. When used appropriately, ultrasonography can provide important information regarding gestational age and fetal anatomy. The casual use of ultrasonography for fetal pictures or sex determination is not justified.[1]

Airline Flights

The amount of cosmic radiation received during commercial flights is much less than the levels associated with fetal risk and is considered negligible. Air travel should be avoided if the woman suffers from a condition that may require emergency care. Pregnant women should keep well hydrated and move their lower extremities when possible to avoid venous stasis and thromboembolic events.[2]

Congenital Anomalies and Ultrasonography

Ultrasonography has become an important tool in obstetrics and gynecology over the past two decades. Geneticists

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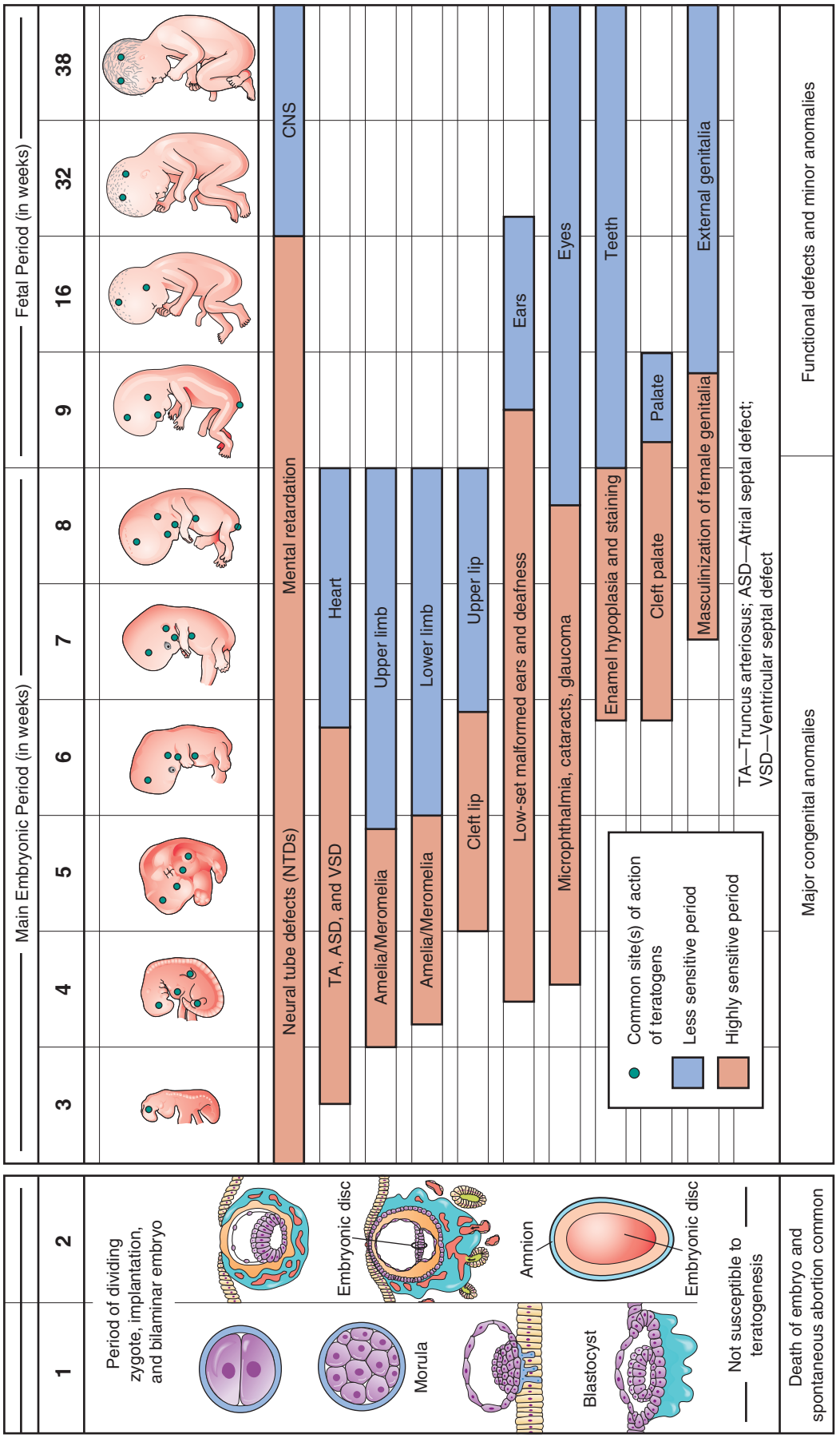


Fig. 10.8 The developing embryo in stages. Bars indicate when the organ system is susceptible to teratogenic exposure. CNS, Central nervous system. (From Moore KL. *The developing human: clinically oriented embryology*. 10th ed. Philadelphia: Saunders; 2016.)

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TABLE 10.3 Estimated Average Fetal Exposure From Select Imaging Studies

Procedure	Fetal Dose (mrad) for an Average Study
Chest x-ray (PA and lateral)	<1
Abdominal plain film	200-300
Intravenous pyelogram	400-900
Barium enema	700-1600
Cervical spine x-ray	<1
Dorsal spine x-ray	<1
Lumbar spine x-ray	400-600
Lumbosacral area x-ray	200-600
Upper GI series	50-400
Dental x-rays	0.01
Mammography	Negligible
CT scan of chest	30
CT scan of abdomen	250
Perfusion lung scan with Tc 99m	6-12
Ventilation lung scan	1-19
Pulmonary angiography via femoral route	221-374
Pulmonary angiography via brachial route	<50

CT, Computed tomography; GI, gastrointestinal; PA, posteroanterior.
From Nussbaum RL, et al. *Thompson and Thompson Genetics in Medicine*. 7th ed. Philadelphia: Saunders; 2007:449.

use ultrasonography as a way to characterize dysmorphology in utero.

Congenital abnormalities occur in 3% to 4% of live births and have several causes—single-gene defects, chromosomal abnormalities, teratogens, multifactorial, or unknown reasons. Congenital anomalies can be divided into three categories depending on the mechanism underlying the defect: malformations, deformations, and disruptions. Malformations involve intrinsic abnormalities in the genetic programs controlling development. The syndactyly that is associated with Apert syndrome is the result of a mutation in a gene encoding for fibroblast growth factor receptors. Conversely, deformations are caused by extrinsic factors physically impinging on otherwise normal tissue. An example of this is arthrogryposis, or contractures of the extremities. This condition can be caused by a prolonged leakage of amniotic fluid, resulting in fetal crowding. Disruptions, the final category, are the consequence of fetal tissue destruction. They can be the result of vascular insufficiency or mechanical damage. Amniotic band syndrome results in the partial amputation of a limb.

Assessment of an infant with birth defects requires a careful review of prenatal exposures and maternal illnesses. When evaluating birth defects, it is important also to consider whether a defect occurred in isolation or is part of a pattern, which may suggest a syndrome. Imaging studies or laboratory examinations may also help elucidate the underlying pathophysiology of an anomaly.

Ultrasound examinations fall into three categories: limited, standard, or specialized. A limited examination is one that is performed to address a specific question, such as placental location, or to confirm fetal cardiac activity. It cannot replace a standard ultrasound examination, which is ideally performed between 18 and 20 weeks' gestation. A specialized ultrasound examination, which may include fetal echocardiography, fetal Doppler studies, or additional biometry, is performed when an anomaly is suspected based on family history, laboratory aberrations, or discovery during standard ultrasound examination. An abnormality seen on ultrasound examination is a common reason that patients opt to undergo invasive prenatal diagnosis.

An example of the utility of ultrasonography is the case of fetal pyelectasis, or hydronephrosis. Defined as a renal pelvic diameter of greater than or equal to 4 mm, this finding is present in up to 3% of euploid fetuses and is a relatively common finding. Postnatal evaluation shows that although most cases resolve, conditions such as ureteropelvic junction obstruction and vesicoureteral reflux may be identified in some infants.[44] The fact that the potential issue can be identified prenatally and results in postnatal follow-up obviates the possibility of a child with chronic renal impairment owing to silent infection and inflammation.

In a review of 36 published studies including 900,000 fetuses, the overall sensitivity for detecting fetal anomalies was 40% (range 15% to 80%), indicating that these detection rates greatly depend on the incidence of anomalies in the population studied and sonographer experience. It has been observed that 50% of fetuses with Down syndrome have no findings on prenatal ultrasound examination. When an examination is performed, the patient should be counseled regarding the benefits and limitations of ultrasonography.

First-trimester ultrasonography has been traditionally used to confirm an intrauterine pregnancy, to estimate gestational age, and to evaluate pelvic anatomy. Since the introduction of first-trimester aneuploidy screening, there has been interest in screening for structural anomalies in the first trimester. There is now extensive literature on the use of first-trimester testing in the detection of fetal anomalies and, in expert hands, a very thorough examination is possible. Older studies had shown a 44% to 50% detection rate of major anomalies in the first trimester[17] with the latest reports indicating that 95% of the common aneuploidies could be detected with detailed sonography between 11 and 13 weeks.[39] First-trimester sonography is becoming more widely adopted among centers with appropriate expertise, although in the United States, detailed anatomy is still preferentially assessed in the second trimester.

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TABLE 10.4 Elevation and Depression of Parameters Used in First-Trimester and Second-Trimester Screening Tests

	First-Trimester Screen			Second-Trimester Screen			
	Nuchal Translucency	PAPP-A	Free β-hCG	uE3	AFP	Free β-hCG	Inhibin
Trisomy 21	Increased	Decreased	Increased	Decreased	Decreased	Increased	Increased
Trisomy 18	Increased	Decreased	Decreased	Decreased	Decreased	Decreased	Unchanged
Trisomy 13	Increased	Decreased	Decreased	Decreased	Decreased	Decreased	Unchanged
Neural tube defect	NA	NA	NA	Unchanged	Increased	Unchanged	Unchanged

AFP, α-fetoprotein; β-hCG, human chorionic gonadotropin β subunit; NA, not applicable; PAPP-A, pregnancy-associated plasma protein A; uE_3, unconjugated estriol.

Three-dimensional ultrasonography has some unique advantages over two-dimensional ultrasonography. Its ability to acquire and manipulate an unlimited number of planes allows for the quantification of organ volume and the ascertainment of images inaccessible by two-dimensional technology. Despite these technical advantages, however, consistent utility has not been determined. Potential areas of clinical benefit include evaluation of NTDs and facial anomalies.

Screening Modalities

Screening for Aneuploidies

Current guidelines from ACMG and ACOG recommend that all pregnant women, regardless of age, have the option to undergo invasive diagnostic testing for fetal aneuploidy. After reviewing the benefits and limitations of screening and diagnostic modalities with their health care provider, patients have the option to undergo screening tests for fetal aneuploidy and NTDs (Table 10.4).

First-Trimester Screening

First-trimester screening, which involves an ultrasound examination and ascertainment of serum markers, is performed between 10 0/7 weeks and 13 6/7 weeks' gestation. The ultrasound examination involves measurement of the nuchal translucency, a fluid-filled space behind the fetal neck. An increased nuchal translucency is significantly associated with aneuploidy, including Down syndrome. The ACOG recommends that patients with a fetal nuchal translucency of 3.5 mm or greater be offered targeted ultrasonography with or without echocardiogram. Detection of Down syndrome with nuchal translucency alone is 70%. When combined with two serum markers, pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG), the detection rate increased to 82%-87%. Results are reported as an adjusted risk for Down syndrome. It is recommended to offer maternal serum alpha-fetoprotein (AFP) as an isolated test in the second trimester to screen for NTDs (see later).

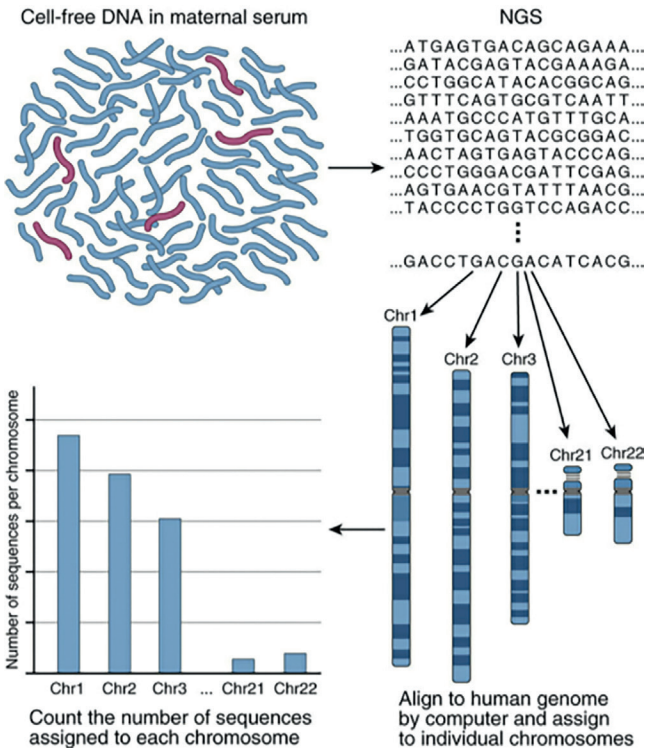
Second-Trimester Screening

The second-trimester maternal serum screen for aneuploidy, particularly trisomies 18 and 21, and NTDs is performed between 15 0/7 weeks and 22 6/7 weeks of pregnancy. Maternal serum AFP, hCG, and unconjugated estriol, known as the "triple screen," has an aneuploidy detection rate of 65%. With the addition of a fourth marker, inhibin-A, to create the "quad screen," the detection rate increases to approximately 80%. The detection of NTDs is discussed subsequently. Results are reported as age-adjusted risks and, similar to first-trimester screening, should be reported to patients to make decisions regarding their desire for invasive testing.

Cell Free DNA Screening

Fetal DNA of placental origin is present and detectable in maternal blood. Taking advantage of this biologic phenomenon, fetal DNA can be isolated and screened for aneuploidy using either sequencing or SNP detection methods (Fig. 10.9). A recent meta-analysis has shown that cell free DNA (cfDNA), also known as non-invasive prenatal screening (NIPS), performs best in detecting trisomy 21 (99% detection and a false positive rate <1%), while performing less well for trisomy 18 and 13. Multiple recent studies have demonstrated superior performance of NIPS compared to standard screening. In a major multi-centered, blinded, prospective study, a positive NIPS result was correct 80.9% of the time compared to only 3.5% using traditional first-trimester screening. Most labs offer NIPS for trisomy 21, 18, and 13, with the option of sex chromosome screening as well. The ACOG now recommends that "no one test is superior for all test characteristics and not every test is available at all centers. Each test has advantages and disadvantages that should be discussed with each patient, with the appropriate test offered based on her concerns, needs, and values." NIPS is not yet a universal first-line test due to issues related to cost and accessibility, but uptake continues to grow rapidly. It is important to note that the ACOG still recommends that all women, regardless of risk, have the option of invasive testing if they so choose.

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• **Fig. 10.9** NIPS screening using next generation sequencing. Cell free fetal DNA is isolated and sequenced using next generation sequencing technology. Output consists of short sequences that are then counted and aligned to known sequences in the reference genome. Sequences are then counted and loss or gain of genetic material is determined by number of probes counted.

Initially, the excellent sensitivity and specificity of NIPS led to some confusion that this new technology is a diagnostic test when in fact it is simply an improved screening modality. In the prospective study mentioned above, despite excellent sensitivity and overall performance compared to standard testing, the positive predictive value (PPV—the chance that a positive test is truly positive) in a general population was only 80.9% and not 100%. In a large retrospective study of 712 women, while testing for trisomy 21 still performed well with a positive predictive value (PPV) of 85%, trisomy 13 was only diagnosed correctly in 45% of cases, trisomy 18 in 77%, monosomy X (Turner syndrome) in 26%, and 47,XXY (Klinefelter syndrome) in 86% of cases. These findings underscore the importance of properly interpreting screening results and following professional guidelines that universally call for confirmatory testing of all positive NIPS results prior to initiating any clinical management plan.

The other limitation is that the circulating DNA originates from placental trophoblast, which can have isolated placental mosaicism and does not always reflect the true fetal phenotype. For this reason, there has been some controversy regarding the best way to confirm a positive NIPS test. A chorionic villus sampling (CVS) procedure samples the same tissue that is the origin of the circulating DNA, while a karyotype from an amniocentesis is fetal-derived. An unfortunate example of not being attuned to the implications of placental mosaicism is reflected in a case report of a positive trisomy 13 on NIPS. The NIPS result was confirmed via rapid aneuploidy analysis using fluorescence in situ hybridization (FISH) probes and consequently, a termination of a fetus was performed. The final fetal karyotype was normal. A systematic study has shown that after a high-risk NIPS result for trisomies 21, 18, 13, and monosomy X (Turner syndrome), there is still a substantial likelihood of finding CVS mosaicism and need for amniocentesis. Chromosomes 13 and X in particular seem to have a higher rate of placental mosaicism and, therefore, especially for positive trisomy 13 and monosomy X results, amniocentesis is the preferable confirmatory approach. Other confounding factors that can lead to false positives are maternal occult malignancy or undiagnosed translocations as well as the vanishing twin phenomenon.[10,32] Trophoblast tissue can remain viable following a demise of one twin, which is more likely in the twin with an abnormal karyotype. Thus, DNA reflecting an abnormal karyotype (or sex in the case of Y chromosome) may be detected by NIPS, resulting in a false diagnosis. In summary, while NIPS performance characteristics are far superior to traditional screening approaches for common aneuploidies, this technology cannot yet replace prenatal diagnosis.

To summarize, although the benefits of a non-invasive method of sampling fetal DNA are easy to grasp, certain caveats must be pointed out. NIPS is a screening test, therefore, the patient must be counseled regarding the inherent limitations compared to diagnosis. There are multiple other chromosomal anomalies aside from basic aneuploidies that will not be detected with NIPS, even if the test had a perfect detection rate. For women who want to know not just about trisomy 21 but all clinically detectable chromosomal anomalies, invasive testing may be a better option.

Future Directions for Non-Invasive Screening and Diagnosis

Microdeletions

While NIPS covers the majority of clinically significant aneuploidies, this technology can also detect microdeletions and larger genomic deletions and duplications. Although an advance over previous standard screening methodologies that cannot detect these changes, screening performance for microdeletions is substantially inferior to that of the standard aneuploidies. In a retrospective review, detection rates were as low as 0% for Cri-du-chat syndrome and as high as 21% for 22q11.2 deletion syndrome.[36] It is possible that NIPS screening for microdeletions and structural rearrangements perform better in higher risk populations. However, currently there are no clinical validation or utility studies to support the use of NIPS for these chromosomal anomalies. Guidelines may differ on the use of NIPS for microdeletions, but ACOG and SMFM have come out clearly that until there are appropriate population-based studies, NIPS is not recommended as a screening test for fetal microdeletions.

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The Role of First-Trimester Ultrasound

The fetal medicine community has been concerned that if NIPS continues to move forward as a first-line test, the benefits of the first trimester ultrasound used in standard screening may be lost. An approach that may be adopted in the future is a detailed anatomic fetal ultrasound in the first trimester for all pregnant women. Those who have an ultrasound finding would be referred to a fetal medicine center. The remaining women would have NIPS and, if positive, referred to a high-risk center as well. A recent study looked at this strategy and found that this new approach had a significant reduction in the false positive rate compared to standard screening for trisomy.[23] While this study may not be sufficient to advocate for a new screening mechanism, it does give a window into what the near future may look like for prenatal aneuploidy screening.

Non-Invasive Prenatal Diagnosis (NIPD)

Several technological advances have shown promise in moving the field from NIPS to NIPD. If fetal or placental cells could be derived in a non-invasive way, they could be tested using the same genetic analyses currently used for blood, CVS, or amniocentesis. A new technique has been proposed that allows for direct isolation of circulating fetal cells and subsequent amplification and analysis of the fetal DNA. This technique eliminates the risk of maternal contamination of the sample and allows for more granular analysis such as microdeletion detection.[24] Researchers have isolated fetal trophoblast from a cervical scraping akin to a Pap smear.[8] This technique would eliminate the procedural risks associated with CVS but suffers from the same limitation of not being able to distinguish an aneuploidy from a placental mosaicism. However, with multiple research centers and technologies that allow for precise cell sorting as well as single cell analyses, NIPD that assesses the fetal genome may soon be a reality.

Screening for Multifactorial Disorders

Serum Alpha-Fetoprotein

Maternal serum AFP is an important tool in screening for NTDs; AFP is a fetal-specific molecule that is synthesized by the fetal yolk sac, gastrointestinal tract, and liver. The maternal serum AFP concentration is usually significantly lower than in fetal plasma or amniotic fluid and generally offered to women between 15 and 20 weeks.

Although it is intended as a screening test for open NTDs, other abnormalities such as ventral wall defects may also cause an increase in maternal serum AFP. Results from the examination are reported as multiples of mean (MoM) based on gestational age. A value greater than 2.5 MoM is considered abnormal, although cut-offs may vary based on the laboratory. Clinicians may opt to repeat the test after one moderately elevated result, because one-third are below the threshold on repeat analysis. If this occurs, a return to below threshold has not been associated with an increase in false-negative results.[16]

If the value remains persistently elevated or if the clinician opts not to repeat the test, the next step is to perform a detailed ultrasound examination and discuss the option of amniocentesis with the patient. Amniotic fluid AFP and amniotic fluid acetylcholinesterase (AChE) are the two main analytes evaluated for detection of NTDs. An elevation of AFP and AChE values suggests an open fetal NTD with 96% accuracy, with a false-positive rate of 0.14%. Contamination of the amniotic fluid sample with blood accounts for half of false-positive results.[40] Fetal karyotype should also be performed using the amniotic fluid obtained. An elevated maternal serum AFP in the second trimester that cannot be explained by a fetal structural abnormality or underlying maternal condition is associated with poor fetal outcome, including increased risk of intrauterine fetal demise, placental abruption, and preeclampsia.[33] In some centers, with appropriate equipment and expertise, ultrasound is being used as the first-line screening test for NTDs.

Screening for Mendelian Disorders

Preconceptual and prenatal parental carrier screening is an effective way to prevent or prepare for neonatal diseases. Discussions of testing strategies for common Mendelian disorders follow.

Screening for Hemoglobinopathies

As part of routine obstetric care, all women in the United States have a complete blood count early in pregnancy. This simple test helps identify women at risk for hemoglobinopathies and thalassemias. According to ACOG guidelines, women with an MCV <80 and normal iron indices should have a follow-up hemoglobin electrophoresis (if normal, follow-up testing may still be needed to rule out alpha-thalassemia). A baseline hemoglobin electrophoresis should be performed in women from high-risk groups (African, Middle Eastern, Southeast Asian, West Indian, and Mediterranean ancestry). If a hemoglobin variant or thalassemia is discovered, the woman's partner should be evaluated. When the father is determined also to be a carrier or is unavailable for testing, the patient should be offered genetic risk assessment and prenatal testing.

Carrier Screening for Cystic Fibrosis

Cystic fibrosis, the most common autosomal recessive disease in live-born infants, is a multisystem disorder that is the result of mutations of a large gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The condition is characterized by chronic pulmonary disease, pancreatic insufficiency, and liver disease. CFTR is a complex gene, with more than 2000 mutations identified (800 additional mutations were added

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TABLE 10.5 Cystic Fibrosis Detection and Carrier Rates Before and After Testing

Racial or Ethnic Group	Detection Rate	Carrier Rate Before Testing	Carrier Risk After Negative Test Result
Ashkenazi Jewish	94%	1/24	1/380
Non-Hispanic white	88%	1/25	1/200
Hispanic white	72%	1/58	1/200
African American	64%	1/61	1/170
Asian American	49%	1/94	1/180

From ACOG Committee Opinion #691. Available at https://www.acog.org/-/media/Committee-Opinions/Committee-on-Genetics/co691.pdf?dmc=1&ts=20170309T1313372850. Accessed December 9, 2017.

to the database since this book's last publication) and the frequencies of certain deleterious mutations vary based on ethnicity. Likewise, the carrier rate differs based on ethnic origin; individuals of Asian descent have the lowest and Ashkenazi Jewish and non-Hispanic white individuals have the highest carrier rates (Table 10.5).[15] The ACOG recommends that carrier screening be offered to all couples regardless of ethnicity. It is important for providers to discuss with their patients that a negative screen decreases the risk of being a carrier, but does not eliminate it completely because screening does not test for all possible mutations. Expanded screening beyond the usual 23 mutations tested by the ACMG panel can be offered to improve sensitivity, especially in non-Caucasian populations. Finally, guidelines recommend that complete sequencing of the *CTFR* gene should not be routinely offered but can be performed in specific cases: family or personal history of CF, newborn with CF that had negative maternal screening, or males with congenital bilateral absence of the vas deferens.

Jewish Carrier Screening

The *founder effect* refers to the overrepresentation of specific alleles in an inbred population. This mechanism has been documented in the Jewish community, particularly individuals of Ashkenazi heritage (eastern European). Tay-Sachs disease is the most well-known of these disorders. Because of communal efforts and professional guidelines, the incidence of this disease has declined remarkably, however, to the point that most children born with this disorder are not of Jewish heritage. Carrier screening, prenatal diagnosis, and culturally sensitive marital planning in regard to this autosomal recessive disease all were applied in this effort dating back to the 1970s. Since that time, the underlying genetic mutations are now known for several more similar diseases known collectively as the *Jewish genetic disorders*. As a group, the carrier frequency is very significant—one in four Ashkenazi Jews carries a mutation for one of these autosomal recessive disorders.

Culturally sensitive preconceptual and prenatal carrier screening is an important tool in preventing or preparing for these devastating diseases. The current recommendation from ACOG is to offer carrier screening to individuals who identify their background as Ashkenazi Jewish for at least the following diseases: cystic fibrosis, Canavan disease, familial dysautonomia, and Tay-Sachs disease. Screening should be considered for mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, Gaucher disease type I, familial hyperinsulinism, glycogen storage disease type 1, Joubert syndrome, maple syrup urine disease, and Usher syndrome. In couples with one partner of Ashkenazi Jewish background, that partner should be screened first, and if he or she is found to have a positive result, the other partner (regardless of background) should be screened for that disorder. One Ashkenazi Jewish grandparent is sufficient to offer someone testing. As mentioned in the above discussion on CFTR, expanded panels well beyond guidance recommendations have arrived for Jewish ethnicity panels as well.

Carrier Screening for Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a progressive neuromuscular disease resulting from degeneration of spinal α motor neurons. Childhood SMA is divided into three clinical groups, types I, II, and III SMA, depending on age of onset and clinical sequelae. With a live birth rate of 1 in 10,000, SMA is the second-most common fatal autosomal recessive disorder after cystic fibrosis. The SMA-determining gene, *SMA1,* is located on 5q13. The carrier rate of an abnormal allele varies widely between races. In 95% of cases, this abnormality is a deletion in exon 7 of *SMA1*. In a recent change, the ACOG has joined the ACMG and recommends that SMA carrier testing be offered to all couples regardless of race or ethnicity.[13] The sensitivity of the carrier screening test is approximately 95% in Caucasians and as low as 71% in African Americans, although with new molecular tests, false negative rates are improving.[28] A negative screening test for both partners reduces the possibility of an affected offspring significantly but does not eliminate it entirely, as 2% of cases result from de novo mutations.[43] Because of advances in genetic science, there have been some recent SMA treatment breakthroughs, including a medication, nusinersen, that is now FDA approved. In addition, researchers have just reported a successful gene therapy study. Of note, neither approach is curative, but research is ongoing and more advances are expected in the future.

Diagnostic Modalities

The ACOG recommends that all women, regardless of risk, have the option of invasive prenatal diagnosis. However, the

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majority of tests are still performed in a high-risk setting. After genetic counseling, some couples may opt to undergo diagnostic testing as opposed to prenatal screening. Others choose diagnostic testing after an abnormal screening result or ultrasound finding.

Chorionic Villus Sampling (CVS)

CVS involves procuring a small sample of the placenta for genetic diagnosis. Although not fetal tissue, the placenta is embryologically derived from the same trophoblastic cells as the fetus and most often has the same karyotype as the fetus. Usually performed between 10 and 13 weeks' gestation, CVS is an ambulatory procedure. Using ultrasound guidance, the placental villi can be obtained through a transcervical or transabdominal approach depending on placental location. Chorionic villus sampling enables diagnosis of genetic disorders in the first trimester, giving patients more time to make decisions about the pregnancy, including the opportunity for first-trimester termination if they choose.

When the villi have been obtained, the medium is placed onto a plastic tissue culture dish to evaluate the sample. If the sample appears inadequate, the operator may opt to take a second pass to obtain more villi. Blood clots and maternal decidua can be separated from the villi, and these cleaned villi can be transferred to different media for further evaluation, including FISH studies and long-term culture. Alpha-fetoprotein testing cannot be performed on CVS tissue samples. It is impossible to assess risk of NTDs through CVS.

The most serious complications associated with CVS are damage to the fetus and pregnancy loss. It has been associated with an increased risk of transverse limb and oromandibular defects. It is hypothesized that these defects are caused by disruption of the vascular system. The overall risk for transverse limb defects after CVS is approximately 1 in 3000, with most defects occurring if CVS is performed before 9 weeks' gestation.[9] Women contemplating CVS can be reassured that if performed after 9 weeks' gestation, the risk of limb defects associated with CVS is low and approaches the baseline population risk.[4]

The pregnancy loss rate after CVS is complicated by the fact that the background risk of pregnancy loss in the first trimester is greater than in the second trimester. Operator experience, number of insertions, and gauge of catheter used all play a part in determining the procedure-related risk of CVS. More recent data suggest that the pregnancy loss rate attributable to both CVS and amniocentesis is quite low and is no more than 0.1%-0.3% in skilled hands.[5]

An important concept related to CVS is that of confined placental mosaicism, discussed earlier in the section on NIPS. Culture of mesenchymal cells of CVS samples reveals the existence of trisomies not present in the conceptus in approximately 1% of cases. In this scenario, an amniocentesis is warranted to confirm the fetal karyotype. Patients should be informed of the small risk of an inadequate sample or the need for additional testing secondary to placental mosaicism during their genetic counseling session, before opting for diagnostic testing.

Amniocentesis

Amniocentesis, a procedure to withdraw amniotic fluid from the uterine cavity, is most commonly performed either for prenatal genetic studies or for evaluation of fetal lung maturity (performed in the third trimester). It can also be used as a diagnostic tool for evaluation of intra-amniotic infection or as a therapeutic procedure to remove excess amniotic fluid. The rest of this section focuses on amniocentesis for the purposes of genetic diagnosis.

Although technically possible after 11 weeks' gestation, an amniocentesis is usually performed between 15 and 22 weeks' gestation. Before 14 weeks' gestation, the complication rate, particularly orthopedic malformations, is higher because of incomplete fusion of the amnion, chorion, and decidua parietalis. After 22 weeks, two potentially serious scenarios exist: (1) the procedure provokes labor or rupture of membranes resulting in a periviable delivery, or (2) abnormal results arrive after the fetus has entered into the 24th week of gestation, eliminating the option of termination in most states.

Similar to a transabdominal CVS, the patient is placed in supine position. An ultrasound survey is done to assess viability, fetal position, placental location, and a gross anatomic survey is performed before the procedure. Amniotic fluid, 20 to 30 mL, is aspirated into sterile syringes. The amniocytes and desquamated fetal cells floating in the amniotic fluid provide a source of mitotically active cells for cytogenetic evaluation and culture. Levels of AFP and AChE in the amniotic fluid can help identify fetuses at high risk for NTDs. Results of FISH (see Technical Advances in Molecular Cytogenetics) are usually available in 2 days, whereas results from cell culture take approximately 7 to 14 days.

The fetal heart rate is assessed and documented after the procedure. It is normal for a patient to experience uterine cramping during the procedure, but cramping should resolve soon after the procedure is over. Patients are encouraged to keep themselves well hydrated and to avoid strenuous physical activity, including intercourse, for 2 days.

Fetal loss is the most devastating potential complication. As mentioned above, data strongly suggest that procedure-related loss is low at 0.1%-0.3% for otherwise normal pregnancies. Increased maternal age, a history of bleeding associated with pregnancy, and abnormal serum screening results all increase the risk of fetal loss. Patients are cautioned regarding fetal injury, although this is an extraordinarily rare event with the advent of ultrasound guidance. Leakage of fluid can occur in approximately 1% of cases; however, in contrast to spontaneous rupture of membranes that occurs outside the setting of amniocentesis, 90% are self-limited and resolve spontaneously within 1 week. If a patient reports leakage, a conservative approach—one that

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monitors amniotic fluid volume, fetal growth, and signs of infection—should be adopted because the prognosis is excellent. Overall, long-term follow-up on offspring of women who underwent amniocentesis did not show a significantly higher rate of major disabilities compared with matched controls.[6]

Cordocentesis

A third and much more infrequently used modality of diagnostic testing is cordocentesis, also known as *percutaneous umbilical blood sampling*. This procedure involves puncturing the umbilical vein under ultrasound guidance to obtain fetal blood cells for genetic analysis. Usually performed after 18 weeks, the procedure-related pregnancy loss rate is approximately 1 in 100 when the procedure is performed for genetic diagnosis.[30] Given the high loss rate compared with CVS or amniocentesis, use of this test for genetic diagnostic purposes is limited to further evaluation of chromosomal mosaicism discovered on a CVS or amniocentesis result. Instead, most cordocenteses are performed in the setting of fetal transfusions to evaluate and treat fetal anemia, especially in the case of Rh sensitization.

Technical Advances in Molecular Cytogenetics

Molecular and cytogenetic diagnostics are an important part of genetic counseling. Increasing understanding of the human genome has led to the development of efficient, accurate testing modalities. Following is an overview of the most commonly used diagnostic tools.

Chromosomal analysis, or karyotyping, is best performed when the cell is in prometaphase or metaphase and the chromosomes are condensed. The most common staining technique, a Giemsa stain, results in a distinct pattern of alternating light and dark bands that is dependent on the composition of the underlying DNA sequence. Each chromosome has a unique banding pattern. Analysis of this banding pattern can show structural abnormalities. The disadvantage of this technique is that the sensitivity of banding is limited, which means that small structural abnormalities or mutations would go undiagnosed. The advantage of this technique is that the whole genome is visualized at one time.

As a diagnostic tool, FISH has better resolution than traditional chromosomal banding. After denaturation, a DNA probe labeled with a fluorochrome is directly hybridized onto cells that have been fixed onto a glass slide. The fluorescent signal is immediately visible by fluorescence microscopy. A double signal corresponds to one signal on each chromosome pair. Cells with one nuclear signal are monosomic for the chromosomal region being evaluated. Conversely, trisomic cells have three nuclear signals.

The advantage of FISH is that it can be applied to nondividing and dividing cells. It can identify several different types of mutations—deletions, duplications, and aneuploidy. Its major disadvantage is that structural abnormalities are missed, because the DNA probe detects only the presence of a genetic sequence, not its location. Although FISH is a rapid test, its use is currently limited to a few aneuploidy and deletion syndromes. However, FISH is an important tool for patient care in labor and delivery and the neonatal intensive care unit when quick decision making is required. Because of its limitations, however, a full karyotype is still performed before formulating a definitive report.

Polymerase chain reaction (PCR) is a process to amplify a single DNA molecule into thousands of copies in a matter of hours. The double-stranded DNA of interest is heated to separate into two single strands. Single-stranded primers, usually 20 to 30 nucleotides in length, are mixed in to allow them to anneal to the opposite DNA strands of the desired target. Next, a thermostable DNA polymerase and single nucleotides are introduced, and the complementary strand is synthesized using the primers as sites of initiation.

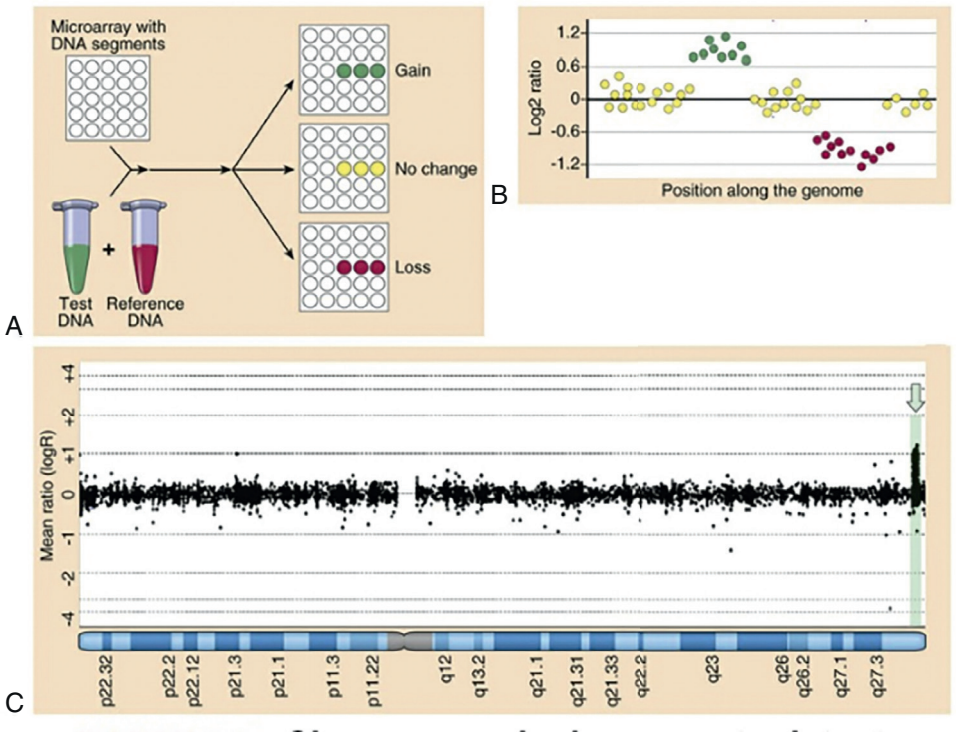
The advantage of PCR is that it is fast and extremely sensitive, meaning that PCR can amplify DNA from a single cell. Because of this sensitivity, however, contamination with even small amounts of other DNA can produce an erroneous result. To design appropriate primers, the nucleotide sequence information of the target region must be known.

Quantitative PCR is a newer application of standard PCR in which the accumulation of PCR products over time is measured directly with the use of fluorescent probes that hybridize to the target sequence. This probe begins to fluoresce when the DNA polymerase cleaves it. The fluorescent signal increases proportionally to the amount of PCR product, and this signal is quantified by comparing the cycle number at which the sample reaches a predetermined level of fluorescence with a standardized curve of a control. In some countries, this technique is preferred over FISH analysis.[25]

Microarray Technology

Since their development in the 90s as research tools for gene expression analysis, microarray technologies have quickly become important clinical tools. They allow for quick and thorough interrogation of chromosome structure and integrity. The technology consists of two array types: comparative genomic hybridization (CGH) arrays and single nucleotide polymorphism (SNP)–based arrays. The major benefit of microarrays is that they can provide important information on copy number variants (CNVs). These are the gains and losses of "pieces" of chromosomes that can have significant clinical implications. A routine karyotype can only detect losses or gains of up to 5 MB (megabases), while microarrays can detect much smaller changes (Fig. 10.10). 22q11.2 Deletion syndrome (also known as DiGeorge syndrome) is an important example of a common disorder that would be missed on karyotype without microarray, as the common deletion is only 3 MB in size. A detailed review of the

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• **Fig. 10.10** NIPS screening using array comparative genomic hybridization (aCGH). **A,** Fetal DNA and a reference DNA are both labeled with different fluorescent dyes and co-hybridized to an array containing probes aligned along all chromosomes. **B**, An excess of fetal sequence represents a DNA gain such as a triploidy and a loss represents a monosomy. **C**, The sequences are then aligned according to their position along the chromosome and excess or loss of genetic material can be seen as points above or below the median.

various technologies is beyond the scope of this overview but can be found elsewhere.[37]

Clinically, the benefit of microarrays has been demonstrated by several studies. A landmark study of 4340 fetal microarray samples showed that they correctly identified all aneuploidies and unbalanced translocations identified by traditional karyotyping. The researchers identified additional clinically relevant deletions and duplications in 6% of samples from fetuses with ultrasound anomalies and 1.7% of fetuses referred for advanced maternal age.[41] Due to the technical limitations of the microarray platform, they could not identify balanced translocations.

Additionally, a meta-analysis of 17 studies demonstrated that in fetuses with an increased nuchal translucency, microarray analysis provided clinically valuable information in 5% of fetuses over conventional karyotyping.

The question remains regarding where microarray fits within the various modalities available for prenatal diagnosis. The SMFM published guidelines in 2016 that recommend that it be offered in cases of fetal malformations or stillbirth and should replace conventional karyotyping in these situations. The guidelines also allow for the consideration of microarrays even in the setting of normal fetal anatomy due to the 1.7% detection rate beyond karyotype in this population. The other recommendations involve best practices such as appropriate counseling regarding the limitations of the technology in regard to the non-detection of single gene disorders and the potential detection of fetal variants of uncertain significance or cases of non-paternity.

One constant issue that has plagued microarray studies is the large quantity of data that can be difficult to interpret. Variants that are not associated with a known disorder or do not cover a known coding region of the genome are often detected, and their interpretation can be challenging. With further research, some of these have been reclassified as benign or likely pathologic, but the problem will likely persist into the foreseeable future and continue to pose a dilemma for the clinician and the parents presented with these results.

Future Directions for Prenatal Diagnostic Testing

Next generation sequencing (NGS) is a technology that has revolutionized medicine. There is now the capability to sequence all 3 billion base pairs of the human genome. While whole genome sequencing (WGS) is used only sporadically by clinicians, its role in research laboratories is well established and critical to identifying new pathogenic variants or multiple variants that together may result in disease. Whole exome sequencing (WES), however, is a key technology used to identify causative pathogenic variants in children with undiagnosed syndromes or to screen adults at risk

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for cancers. There are studies that are currently ongoing regarding the use of WES and WGS in the prenatal setting as well as a new approach to newborn screening.[18] The benefit of these technologies is the ability to detect genetic changes that would be missed otherwise. Conversely, the additional data can also result in the same problems clinicians are struggling with when it comes to microarrays—providing an abundance of data that may not be actionable or even interpretable. Currently, guidelines do not recommend the use of these technologies in the prenatal period if outside the parameters of a clinical trial.

Assisted Reproductive Technologies (ART)

More than 60,000 infants born in the United States each year are conceived through ART. The outcomes of techniques such as in vitro fertilization (IVF) and intracytoplasmic sperm injection have been well examined. The risks of ART can be divided into two categories—obstetric risks and fetal risks.

Thirty percent of ART pregnancies are twins or higher order multiples, which inherently carry an increased risk of premature delivery. Even when compared to spontaneous twinning, IVF twins carry a higher risk of preterm birth (RR of 1.23) and low birth weight (RR or 1.14).[31] Singleton IVF pregnancies are at an increased risk of preterm delivery and perinatal mortality when compared with spontaneously conceived singleton pregnancies. Singleton IVF pregnancies also have increased risk for other morbidities, including abnormal placentation, preeclampsia, and cesarean delivery.

There is an overall increase in birth defects associated with ART (1.32 RR).[22] The risk of de novo chromosomal abnormalities seems to triple, however, if intracytoplasmic sperm injection is performed. It has been observed that pregnancies that are the result of ART are at an increased risk for rare imprinting disorders, such as Beckwith-Wiedemann syndrome, suggesting that epigenetic changes may occur as a result of ART.[18,44]

Although there may be increased morbidity related to ART, there is some evidence that couples suffering from infertility that end up conceiving spontaneously also have an increased rate of birth defects, which points to potential underlying conditions leading to both issues.[45]

As a result, couples contemplating IVF must be informed of the small increased risk of birth defect and pregnancy complications associated with IVF and must receive appropriate screening and close evaluation during the pregnancy.[3]

Genetic Evaluation and Counseling

Genetic counseling is an ever-evolving field that has become an important part of clinical practice. Full of ethical and practical challenges, genetic counseling focuses on assessing a patient's genetic risk to provide individualized information and options. Some level of genetic counseling is provided by health care professionals in all fields of medicine. Obstetricians spend time with their pregnant patients discussing prenatal screening and diagnosis, whereas oncologists review hereditary cancer susceptibility. Patients can also be referred to genetic counselors, formally trained professionals who have received a Master's level degree and are certified by the American Board of Genetic Counseling. Genetic counselors are trained not only in pedigree construction and analysis, but also in communication education and counseling skills, and are a distinct discipline from medical geneticists who are certified by the American Board of Medical Genetics after completing a residency program. Although such physicians also provide counseling, their focus is more on diagnosis, treatment, and management of genetic disease.

In many centers, physicians and counselors work as a team to provide comprehensive genetic services. Indications for referral are varied but include (1) family history of early-onset cancer, (2) personal or family history of known or suspected hereditary disease, (3) ethnic background associated with an increased risk of a heritable disorder, (4) teratogen exposure during pregnancy, (5) abnormal prenatal ultrasound or abnormal first-trimester or second-trimester screening results, and (6) recurrent pregnancy loss. Any pregnancy at risk of birth defects warrants such a referral.

A genetic counseling visit entails obtaining a detailed medical and family history, including the age and health status of first-degree, second-degree, and third-degree relatives. For the prenatal patient, additional information such as genetic screening results, ultrasound findings, and possible teratogenic exposures is discussed. This information allows for a targeted discussion regarding the likelihood of developing disease, testing options for the condition, the impact that an illness could have on the patient and family, and the possible interventions available to modify the disease.

Ideally, genetic counseling is provided in a nondirective manner; emphasis is placed on educating the patient on his or her options and the consequences of those options. Before initiating any testing, a provider should ensure that proper consent is obtained. It is up to the provider to ensure that the patient understands the nature of the test, its limitations, and its potential sequelae. This becomes more complex when testing of children or adolescents is considered. In this situation, the benefits of timely genetic testing should be the primary justification. The American Society of Human Genetics (ASHG) suggests that "counseling and communication with the child and family about genetic testing should include advocacy on behalf of the interests of the child." Generally, if there is no immediate benefit to the child, testing is usually deferred until adulthood, when the individual can make his or her own choices.[11]

Another ethical dilemma of genetic testing that clinicians face is the balance between maintaining patient confidentiality and the duty to protect other family members who might be affected. An individual's genetic testing results have implications for an entire family. The ASHG encourages voluntary disclosure by the person tested (proband) whenever possible. If this does not happen, the ASHG recommends that the degree of disclosure to other family

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members depends on the magnitude and immediacy of risk faced, stating that disclosure is acceptable if "harm is likely to occur, and is serious, immediate, and foreseeable."[12]

A concern that many patients have is the impact of their genetic testing results on future employment and ability to obtain health insurance. In 1995, the Equal Employment Opportunity Commission issued guidelines that individuals discriminated against based on their genetic testing had the right to sue. A year later, the Health Insurance Portability and Accountability Act was enacted to prevent insurance companies from denying coverage based on genetic testing. On a federal level, the Genetic Information Nondiscrimination Act (GINA) was passed in early 2008.[21] It prohibits US insurance companies and employers from discriminating on the basis of information derived from genetic tests. Insurers and employers are not allowed under law to request or demand a genetic test. The GINA prevents insurance companies from discriminating through reduced coverage, and it prohibits employers from making employment decisions based on an individual's genetic code. State laws that have an impact on the provision of genetic services also exist, and there may still be issues with respect to procurement of life insurance despite the aforementioned laws.

Key Points

- An understanding of the genetic basis of disease and the tools available for prenatal genetic evaluation is vital in the management of patients and their offspring in the peripartum and newborn period.
- Reproductive genetic counseling and diagnostic techniques are a vital means of defining a potential clinical dilemma, allowing for seamless coordination between obstetricians and neonatologists.
- Medical genetics is a rapidly evolving field, with new advances and discoveries reported frequently. However, the underlying genetic core principles and the clinician's respect for patient autonomy to make good choices based on complete information have remained unchanged.

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11

Perinatal Ultrasound

NOAM LAZEBNIK, NANCY E. JUDGE, AND PE'ER DAR

Ultrasound has permanently changed imaging in perinatology, increasing expectations of success and improving outcomes in maternal and neonatal care. The method is safe, real time, relatively inexpensive, and readily available in hospitals and clinics worldwide.[19] Fetal imaging is the most common ultrasound study. Identifying anomalies related to fetal and placental development or dating errors is crucial. Sonographic genetic screening, cervical assessment, Doppler vascular measurements, and three-dimensional (3D) examinations have evolved from investigational techniques to accepted diagnostic tools. In the past two decades, magnetic resonance imaging (MRI) has joined sonography for the prenatal diagnosis of a broad spectrum of disorders.

Ultrasound Equipment

In an ultrasound exam, a transducer (probe) is placed directly on the skin, inside the vagina or other body cavity, or directly on the organ of interest intraoperatively. A thin layer of water-based gel acts as a coupling agent to potentiate sound wave transmission.

Obstetric studies may be performed by either the transabdominal or transvaginal approach, using transducers of the appropriate frequency, usually between 1.5 and 10 MHz. Choice of transducer is a trade-off between penetration with lower frequencies (essential in the obese patient) and resolution at the higher end (required for the smallest fetal structures).

Fetal Imaging Techniques

Real-time ultrasound, in which image brightness varies with the intensity of returning signals (B-mode), is the standard method of fetal imaging (Fig. 11.1). It is required for confirmation of cardiac activity and fetal movement in living gestations. Brief signal bursts are followed by relatively long receptive intervals (1 : 10 ratios or greater); lower signal frequencies encounter less interference but reflect from fewer informative interfaces. Image quality varies with distance to the target, structure size, movement relative to the signal, and tissue transmission characteristics. Ideally, the transducer is close to its target; the transvaginal approach is preferable in early gestation for cervical studies and for gynecologic investigations. Suboptimal images are common with obesity, limited fluid interfaces, intervening structures, gas-filled viscera, scar tissue, and poor positioning relative to the sound beam. Diagnostic difficulty arises when different materials have similar echo characteristics, as do blood, urine, ascites, and the contents of many cysts.

M-mode ultrasound is a direct representation of beam reflection by moving edges (e.g., in cardiovascular imaging). Interpretation requires standardized, often hard-to-achieve, stable views. M-mode is useful in assessing arrhythmias, myocardial contractility, and pericardial effusions. M-mode "snapshots" efficiently document cardiac activity and rate (Fig. 11.2).

Doppler ultrasound uses the frequency shift that occurs when sound beams are reflected off moving objects to demonstrate the presence, velocity, and direction of blood flow (Fig. 11.3). Direct calculations from narrow, tortuous fetal and uterine vessels lack accuracy; to compensate, prenatal Doppler findings ideally are obtained at beam angles less than 35 degrees relative to umbilical vessels and 15 degrees for middle cerebral arteries. The flow indices are generally expressed as ratios, relative to median values. Color Doppler semiquantitatively assigns direction to blood flow; by convention, warm colors (red) denote movement toward the transducer, and saturation is keyed to velocity. Color Doppler illuminates cardiac, arterial, and venous structures (Figs. 11.4 and 11.5). Color Doppler energy (power Doppler) reflects signal intensity; amplitude corresponds to blood cell motion. Power Doppler is sensitive to very low flow and effective independent of angulation; it is helpful for mapping vascular beds and for quick visualization of any fetal vessel (Figs. 11.6 and 11.7).

Three-dimensional ultrasound analyzes returning echoes along a third axis. Images are manipulated electronically to render surfaces and volumes from multiple perspectives, both as static and real-time ("four-dimensional") views. Surface rendering of subtle organ details enhance detection of anomalies, partially overcoming positional limits of standard scans and permitting a comprehensive review of fetal organs and skeleton (Fig. 11.8). Three-dimensional studies have improved volume calculations, facilitated analysis of complex spatial relationships, and have better explained

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Abstract

The field of perinatal imaging and diagnosis has been exponentially growing for the last 30 years using both ultrasound and magnetic resonance imaging (MRI). It has revolutionized diagnosis of fetal anomalies in different organ systems, enables fetal well-being assessment, accurately determines gestational age, and uncovers potential uterine, placental, and ovarian disorders that might negatively affect maternal and fetal outcome. Apart from imaging, other techniques, for example, DNA analysis from chorionic villus samples, amniocentesis, and free fetal DNA circulating in the maternal blood can be used to diagnose specified fetal anomalies. The aim of this chapter is to share with pediatrician and neonatologist the current modalities of prenatal imaging as well as its limitations. The chapter includes descriptions of abnormalities paired with their sonographic images. The template includes a brief description of the anomaly, the relevant findings, and information regarding management and prognosis.

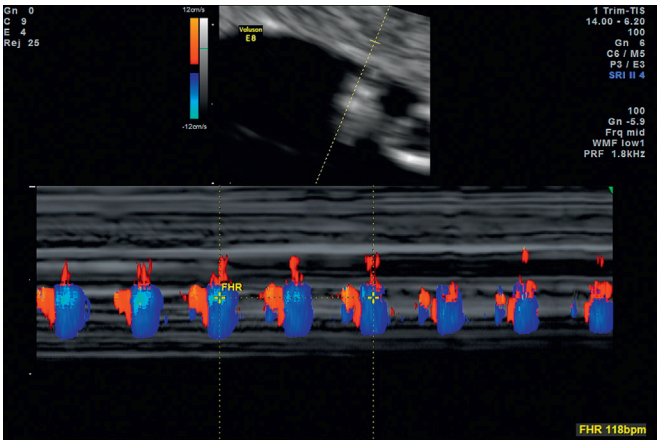
Keywords

fetal imaging
ultrasound
magnetic resonance imaging (MRI)
prenatal diagnosis
fetal anomalies

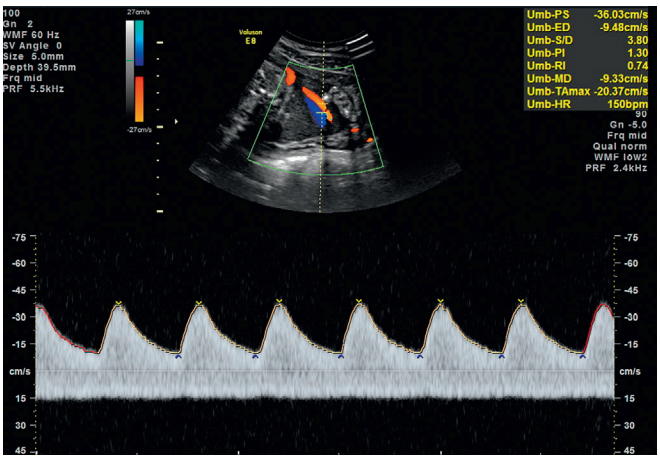
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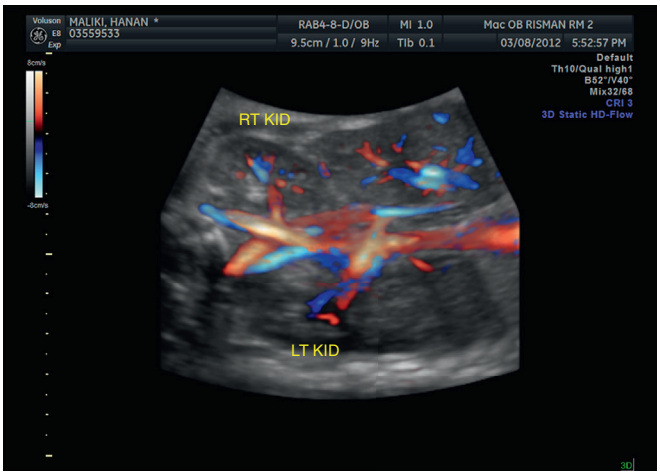
• **Fig. 11.1** Transabdominal B-mode, two-dimensional scan. Profile of 20-week fetus.



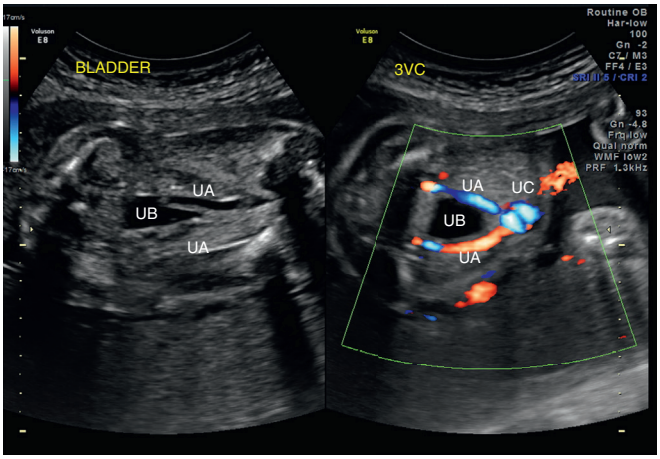
• **Fig. 11.2** Transvaginal M-mode demonstration of embryonic cardiac activity at 5 5/7 weeks' gestation. Upper frame: Embryo with cursor across thorax. Lower frame: M-mode display of wall movement during two cardiac cycles, 114 beats per minute (between vertical lines).



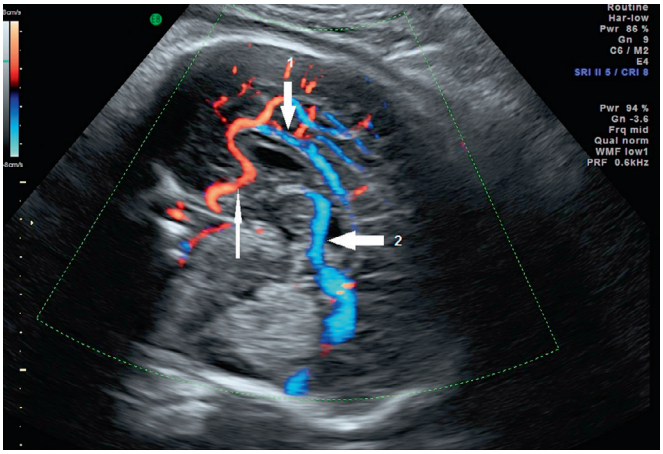
• **Fig. 11.3** Upper frame: Color Doppler highlights a segment of the umbilical cord (*trapezoid*). The gate (*transverse parallel lines*) identifies the sampling site within the umbilical artery. Lower frame: Pulse Doppler waveform recorded from the umbilical artery.



• **Fig. 11.4** Color flow Doppler demonstration of a right pelvic kidney, descending aorta, and inferior vena cava in a 28-week fetus. Flow toward the transducer is the color of the upper bar; flow away corresponds to the lower bar colors.

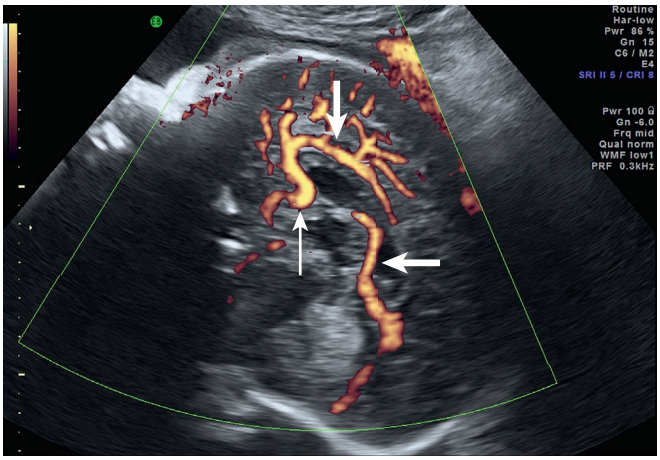


• **Fig. 11.5** Transverse view of fetal pelvis, umbilical cord (UC), and urinary bladder (UB) with color Doppler showing bifurcation of the umbilical arteries (UA).

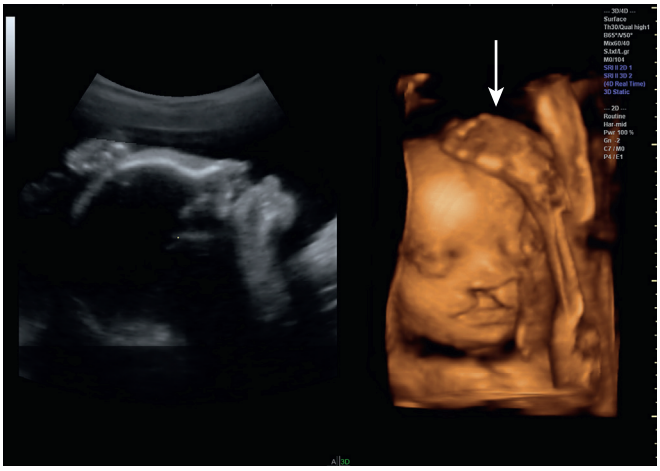


• **Fig. 11.6** Color Doppler demonstration of the anterior cerebral, pericallosal, and vertebral arteries (*thin*, *first thick*, and *second thick arrows*). Lower velocities are shown as more saturated hues. Turbulent flow and flow more rapid than the scale parameters demonstrate aliasing (mixture of colors). Compare with Fig. 11.7, power Doppler of same structures.

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• **Fig. 11.7** Power Doppler demonstration of the anterior cerebral, pericallosal, and vertebral arteries.

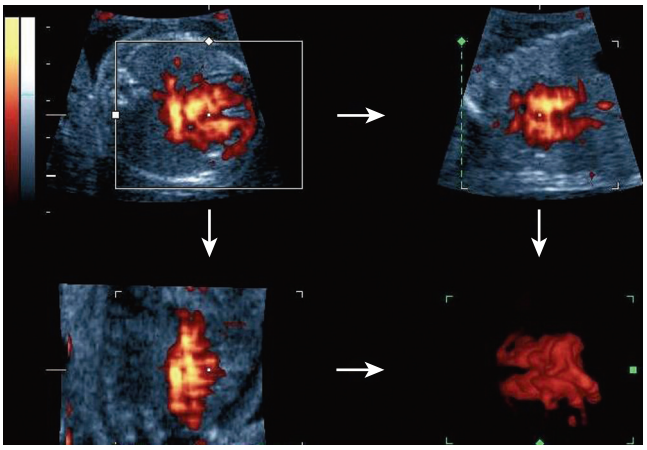


• **Fig. 11.8** Two-dimensional profile (compare with normal profile in Fig. 11.1) and three-dimensional coronal rendering of a 26-week fetus with a large, right-sided cleft lip and palate. The fetus is in a frank breech position with the foot (*arrow*) visible on the head.

abnormal findings.[5] Spatiotemporal correlation (by a database managing both space and time inputs) of heart movement with color and power Doppler augments standard cardiac imaging (Fig. 11.9).

In spite of challenges, the most clinically mature applications for volume ultrasound technology are within the realm of obstetrics. The ability to reorient the active view for optimal visualization permits rapid identification of normal and abnormal structures. Advantages to volume imaging also include presentation of recognizable fetal anatomy and anomalies to parents, aiding informed decision-making, and aid in maternal-infant bonding.

Magnetic resonance studies of pregnancies are usually performed after the first trimester, in spite of lack of identified biologic adverse effects.[48] Maternal oblique positioning prevents undesirable inferior vena cava compression, and images are obtained with ultrafast sequences in less than 1 second; claustrophobia can be difficult for some patients, even after sedation or anxiolytic use. The wide field of



• **Fig. 11.9** Spatiotemporal color flow imaging of normal four-chamber heart at 18 weeks. Transverse chest with four-chamber view. Upper left: Cardiac apex facing right. Upper right: Axial view. Lower left: Coronal view. Lower right: Cardiac apex facing left (three-dimensional).

view, extremely high resolution, excellent soft tissue contrast, and multiple potential planes of construction make MRI an appealing imaging modality, particularly useful when ultrasound studies are compromised by obesity or oligohydramnios.[29]

MRI is often used to elucidate problems initially identified by ultrasound examinations. Images are acquired in the axial, coronal, and sagittal planes relative to the fetus or orthogonal to the maternal pelvis. Gadolinium is placentally transferred and is contraindicated during pregnancy because of its exceptional persistence in tissue and known potential for adult renal injury. Its use rarely may be justified for assessment of placenta accreta or serious maternal disease.[48]

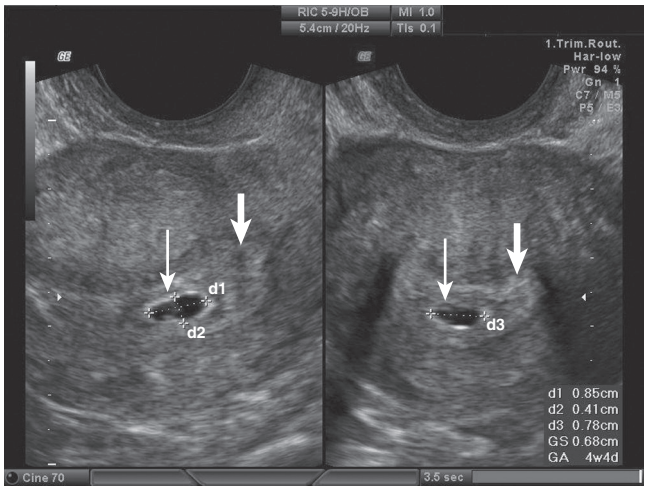
Bioeffects and Safety

As part of the Food and Drug Administration's (FDA's) initiative to reduce unnecessary radiation exposure from medical imaging, health care providers are advised to consider techniques with little or no ionizing radiation, for example, ultrasound or MRI, and only if medically appropriate.

Diagnostic ultrasound energy has the potential for affecting tissues (bioeffects); two recognized mechanisms are heating and cavitation.[38] Data collected during routine studies show that "gray-scale" B-mode ultrasound is associated with a negligible rise in temperature.[40] To date, there has been no convincing evidence of harm to the human fetus.

By definition, ultrasound is inaudible to humans; moreover, oncogenic effects have not been identified. At nonclinical levels, ultrasound energy causes cell lysis, intracellular shearing, streaming effects, altered membrane permeability, and abnormal chromosome function. Heat exposure triples with each change in modality: from 2- or 3D, B-mode to M-mode, then color flow, before peaking during pulsed Doppler. Harmful levels should not be attained routinely but might occur during focal cranial pulsed Doppler

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• **Fig. 11.10** Transvaginal longitudinal and transverse axis ultrasound images of a 4 4/7-week intrauterine pregnancy, showing a small yolk sac (*thin arrows*) within the gestational sac (*calipers*) and echogenic surrounding decidual reaction (*thick arrows*). The embryo is not yet visible. Note MI and TI notations at top center.

interrogation or in a febrile patient, without unusually long exposures. Mechanical disruption from cavitating gas bubbles is improbable in the fetus. Both temperature and disruption risks are now displayed on equipment (Fig. 11.10); thermal index (TI), a ratio between transducer output and the energy needed to warm up tissue temperature by 1°C, with a desired value below 2, is also categorized by tissue type: TI soft tissues, TI cranial structures, and TI bone. Mechanical index (MI) references pulse amplitude effects of compression and decompression, ideally maintained below 0.4 in fetal studies. Publication standards now usually require that these indices be displayed on submitted images. For safety, only medically essential examinations should be performed; settings and duration should be the minimum required to achieve adequate views.

Strong magnetic fields and radiofrequency waves are used in MRI with no known harmful effects, but large longitudinal studies are lacking. As with ultrasound, heat delivery to the fetus is a recognized hazard; in MRI, however, the maternal surface receives the greater thermal exposure. Noise from the magnetic coils (up to 120 dB) is, in theory, capable of causing acute hearing damage; fortunately, maternal tissue attenuation decreases fetal intensities by 25% to relatively safe levels. Direct magnetic bioeffects remain unproven; the FDA states that safety to the fetus "has not been established."

The FDA has recommended that health care providers attempt to minimize exposure while maintaining diagnostic quality when using ultrasound. The lowest possible ultrasound exposure settings that obtain adequate image quality and gain the necessary diagnostic information should be used, following the as-low-as-reasonably-achievable (ALARA) principle.[20] Spectral or "flow" Doppler should not routinely be used to "auscultate" the fetal heart rate in the first trimester because of its higher energy delivery; instead, adequate documentation of viability can be obtained with use of M-mode or conventional two-dimensional real-time ultrasonography with video or cine archiving.

Who Should Perform Fetal Ultrasound Examination?

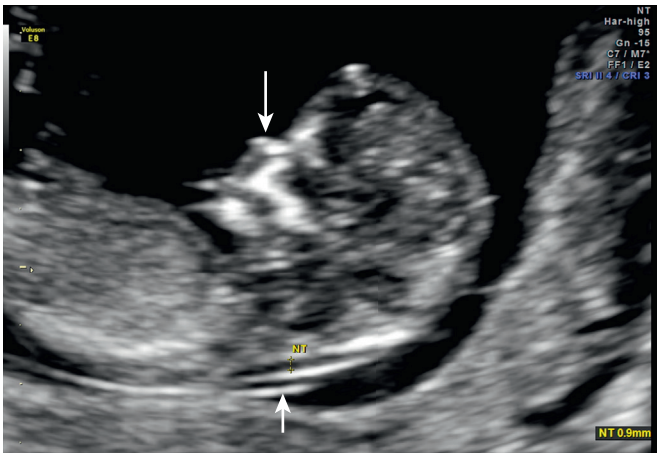
Evaluating the unborn fetus is an enormous responsibility. A true hazard of performing obstetrical ultrasound studies lies in the potential for error in image interpretation. Either under- or over-diagnosis may trigger a chain of events with tragic consequences. Some radiologists who perform ultrasound studies may have had relatively limited exposure during training to obstetrical imaging; in contrast, obstetrical services may offer extensive bedside experience but fewer didactic hours, particularly for complex cases. As a result, many practitioners prefer to delegate the task of scanning to sonographers, themselves of variable competencies, choosing instead to emphasize image interpretation and case management.

All practitioners who perform or supervise the performance of obstetric ultrasonography should be licensed medical practitioners, with specific training in obstetric ultrasonography; this is especially necessary when providing specialized obstetric ultrasound examinations.[49] Certification programs, continuing education and credentialing for both sonologists and the interpreting sonologists, are important steps toward improving safety and diagnostic accuracy. To ensure the highest quality and accuracy in interpretation of obstetric imaging, the American Institute of Ultrasound in Medicine and the American College of Radiology offer ultrasound facility accreditation. The process involves a review of submitted case studies, practice volume, equipment use and maintenance, report generation, image storage, and qualifications of all providers. Practices, not individuals, are accredited for obstetrics, gynecology, or both; practices maintaining ultrasound accreditation have been shown to demonstrate improved compliance with published standards and guidelines for the performance of ultrasound examinations.

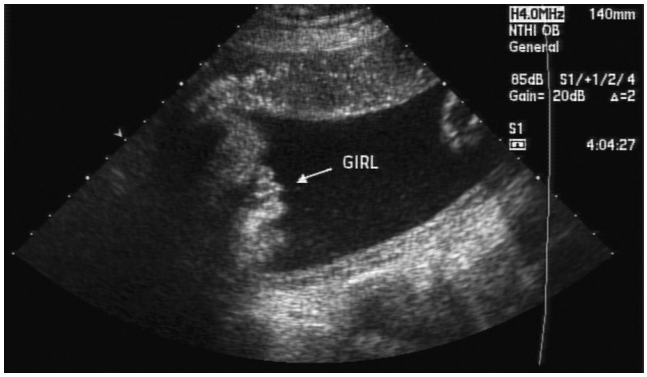
Ethical Considerations

The education of physician sonologists encompasses visual recognition and interpretative tasks common to diagnostic imaging but also demands mastery of specific mechanical skills (or, at least, an ability to assess the latter in sonographers). Both ultrasound and MRI have rapidly evolved; clinically relevant frontiers are often explored by collaborators with pooled data, prerelease technology, and funding for staff and statistical analysis. Nuchal translucency measurement, a deceptively simple sonographic method for aneuploidy screening, provides a cautionary example (Fig. 11.11).[41] Its orderly dissemination, including certification courses, ongoing audits, professional society, and laboratory coordination, stands in sharp contrast to the viral dissemination of most techniques, yet erosion of competency, once achieved, remains a concern.

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• **Fig. 11.11** Nuchal lucency measurement (*calipers*) in a 13-week fetus. The nasal bone is visible (*down arrow*), and the amnion (*up arrow*) is clearly distinguished from the skin fold.



• **Fig. 11.12** Vulvar skin folds (*arrow*) of normal female fetus in the midtrimester.

Ethical practitioners should be candid when informing patients of their ability to provide a requested service and assiduous in improving their skills. Professional judgment remains paramount in deciding how and when to incorporate new developments into personal clinical practice. The ability to conduct a knowledgeable, balanced discussion regarding interventions both local and international is essential when counseling patients overwhelmed by online information.

Prenatal identification of fetal sex for the purpose of selective termination is available for serious X-linked disorders but has been more widely applied to abort normal female fetuses because of a lower perceived value (Fig. 11.12).[53] The addition of preimplantation genetic evaluations and non-invasive prenatal screening has redistributed the onus without fully resolving the problem.

Nonmedical fetal ultrasound (also known as "keepsake" ultrasound) uses ultrasound to provide nondiagnostic pictures or to determine the sex of a fetus (for a "reveal" party) without a practitioner referral, directly paid for by the patient. Notwithstanding governmental and professional guidelines and warnings regarding ultrasound safety, the popularity with prospective parents, evident profitability, and absence of proven harm have provided keepsake businesses with the impetus for rapid expansion. A number of ethical issues are raised, including conflicts of interest for the commercial enterprise, the fetus, and the parents with respect to long-term effects. Current epidemiologic evidence is not synchronous with advancing ultrasound technology; a lack of evidence of harm is not the same as lack of harm. Applying four major theories of ethics and principles (the precautionary principle, theories of consequentialism and impartiality, duty-based theory, and rights-based theories) leads to the conclusion that obstetric ultrasound practice is ethical only if the indication for use is based on medical evidence, rendering "keepsake studies" ethically unjustifiable.

Multiple gestations may result in a number of ethical dilemmas. Advances and regulation in assisted reproductive technology (ART) have decreased the incidence of multifetal pregnancies, but fetal reduction remains a painful choice for parents facing the prospect of extreme prematurity in higher order multiples. Management of twin–twin transfusion syndrome (TTTS), anomalous co-twins, discordant growth, or distress far from term also necessitates choosing among unsatisfactory alternatives. An excellent review of the psychosocial consequences and the ethical issues associated with selective termination of pregnancy has been published.[25]

Non-diagnostic studies, varying prognoses for a given diagnosis, and the inherent limitations of ultrasound and MRI studies lead to ethical issues in management and counseling. Patients and physicians alike may share unrealistic expectations for the predictive accuracy of targeted diagnoses.

Anomalies and variants linked to Down syndrome and other serious conditions (sonographic "markers") identified during routine studies present patients and caregivers with unanticipated, unwelcome options, particularly if patients had previously explicitly refused serum screening or direct genetic testing.[19] Ideally, informed consent discussions addressing risks, benefits, consequences, alternative strategies, and limitations of ultrasound and MRI should be provided to all patients before performing such imaging. Given the irreversible nature of both birth and abortion, prospective parents must ultimately judge for themselves their tolerance for uncertainty in diagnosis and for imperfection in their offspring.

Classification of Fetal Sonographic Examinations

A. First-Trimester Examination

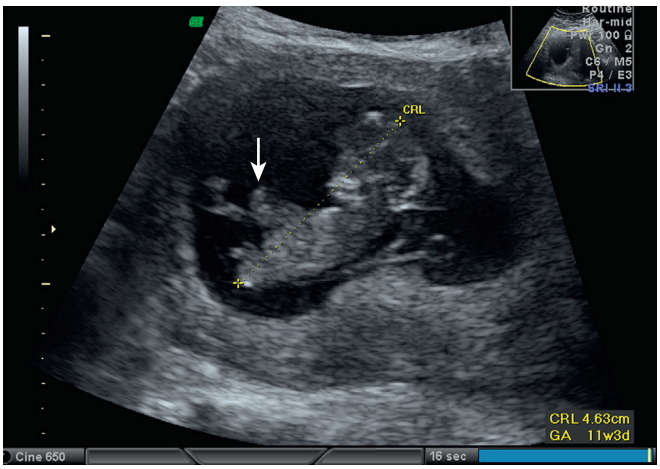
First trimester transvaginal scans exclude ectopic implantation by demonstrating an intrauterine asymmetric or "double sac" gestational sac with yolk sac or embryo, ideally with visible cardiac activity; identifiable embryos in the fallopian tubes are uncommon. Heterotopic pregnancy occurs in less than 0.1% of spontaneous conceptions, leading to the pragmatic conclusion that finding an intrauterine pregnancy excludes an ectopic one, except after assisted reproductive technic (ART). Nevertheless, careful study of the

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adnexa, ovaries, and cervix is generally prudent. A "double sac" is usually seen transvaginally at levels of 1000-1500 international units of human chorionic gonadotropin before 5 1/2 menstrual weeks (see Fig. 11.10); but serum human chorionic gonadotropin (hCG) and visualization thresholds are variable. Finding a yolk sac or embryo confirms an intrauterine site, with growth of the gestational sac diameter of about 1 mm daily in early pregnancy. The embryonic disc is usually visible transvaginally once sac diameters exceed 15 mm. Embryonic length also increases daily by 1 mm; transvaginally identified cardiac activity is customary by the end of the sixth week (4 mm embryonic length) and obligatory by the seventh. Current practice postpones diagnosing a failed pregnancy until well past the accepted normal thresholds for appearance and progressive development of these structures.

Embryonic heart rates, slower at initiation, increase to more than 160 beats per minute (bpm) by the 9th week, declining slightly through the 13th week. Persistent rates below 100 bpm have been linked to risk for missed abortion, aneuploidy, and anomalies.[15] When an embryonic heart rate (below 80 bpm) is detected between 6 and 7 weeks, a first-trimester demise is anticipated in approximately 25%, even if the rate subsequently normalizes. In such pregnancies, a follow-up scan is warranted. Prior to 6 weeks, an embryonic heart rate below 100 bpm is not necessarily indicative of a poor prognosis. Likelihood of survival into the second trimester is also significantly higher when there is concordance between biometrically calculated gestational age and menstrual dating.[3]

Embryonic anatomic surveys are limited and necessarily provisional; however, early fetal period scans diagnose a number of entities accurately (Fig. 11.13). First-trimester screening for early detection of abnormalities decreases the need for invasive testing (previously offered to every woman over 35 years old, thereby missing abnormal pregnancies in younger women), the associated risk of miscarriages, and enabled first-trimester invasive testing and diagnosis in high-risk pregnancies using chorionic villi sampling rather than a second-trimester amniocentesis. It also allowed the safer and more private option of first-trimester termination of an abnormal pregnancy before the pregnancy was visible, decreased anxiety, and provided reassurance about pregnancy well-being in both high-risk and low-risk situations. Progress in the field of first-trimester sonography continues in two intertwined directions: One is finding additional sonographic markers that increased the accuracy and sensitivity of detecting chromosomal abnormalities, especially Down syndrome. The other is improving the early detection of congenital anomalies. Midtrimester confirmation continues to be prudent for the majority of first-trimester findings (see Fig. 11.13). Later studies retain advantages with respect to the natural history of many anomalies and for visualization of heart, spine, and other problematic structures.



• **Fig. 11.13** Eleven-week embryo with a thickened nuchal lucency and an omphalocele (*arrow*) containing fetal liver. The fetal liver does not undergo physiologic herniation. A study at 18 weeks identified a lumbosacral spina bifida in addition to confirming the omphalocele.

B. Standard Second- or Third-Trimester Examination

A standard second- or third-trimester sonogram includes an evaluation of fetal number, presentation, cardiac activity, fetal biometry, amniotic fluid and placental characteristics, and fetal organ survey. Second trimester transvaginal cervical measurement is encouraged for patients at risk for prematurity; however, the role of universal screening remains controversial. Examination of the maternal pelvic structures is otherwise performed transabdominally at this time, if feasible.

C. Limited Examination

A limited examination is performed to investigate a specific concern, usually under exigent circumstances. For example, a limited examination might identify fetal cardiac activity in the presence of bleeding or confirm presentation in early labor. Abbreviated sonographic studies are more acceptable when there has been a prior complete study; pragmatically, a full examination should be documented once the acute situation has stabilized for ongoing pregnancies.

D. Specialized Examinations

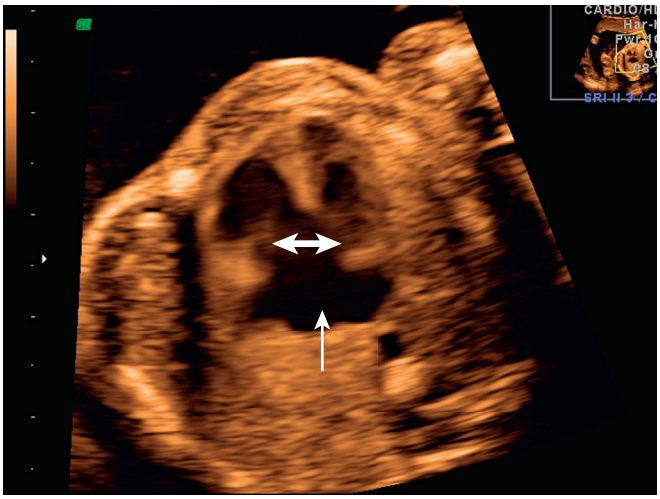
A detailed "targeted" anatomic examination is performed when an anomaly is suspected on the basis of history, biochemical or genetic results, or findings on prior scans. Other specialized examinations include fetal Doppler ultrasound, 3D imaging, biophysical profile, fetal echocardiogram, detailed neurosonography, and additional biometry or evaluation of organs not usually imaged on routine studies.

Applications of Ultrasound Studies

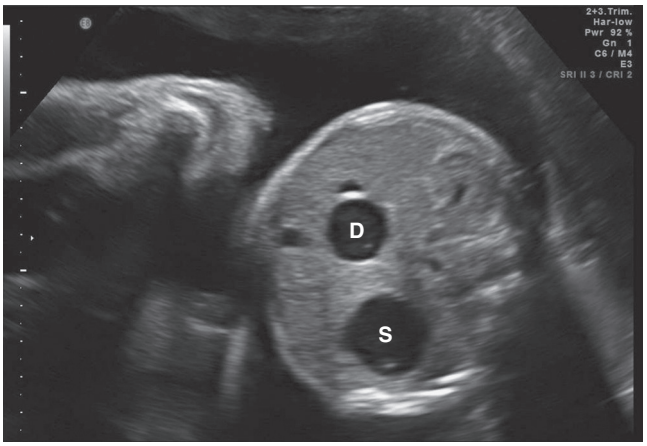
Genetic Screening

Genetic screening combines ultrasound study and biochemical testing to enhance the detection of chromosomal abnormalities. This approach has resulted in greater scrutiny of younger patients and less frequent age-based invasive

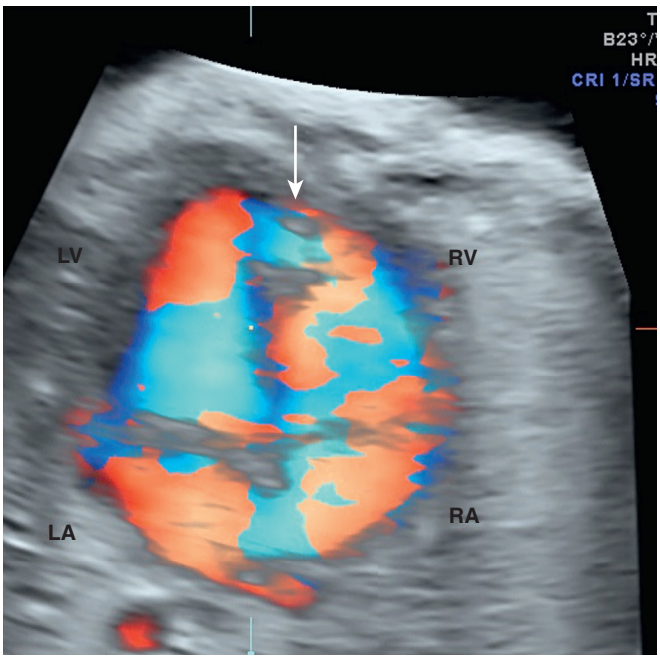
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• **Fig. 11.14** Fetus with trisomy 21 and large atrioventricular canal defect on transverse thoracic view. Note the absence of a normal crux. Common atrium (*thin arrow*) connecting into a common ventricle (*thick, double-headed arrow*) can be seen.



• **Fig. 11.15** "Double bubble" sign of duodenal atresia in a 35-week pregnancy, with the dilated stomach (S) and the obstructed proximal duodenum (D) seen on transverse abdominal view, spine to right of image. The finding is uncommon before the late second trimester.

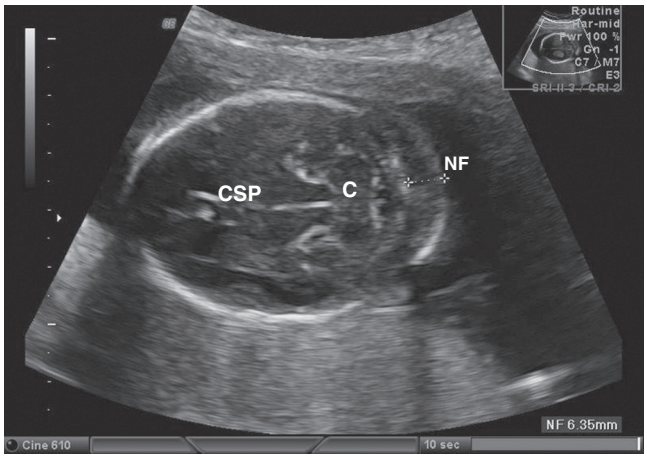


• **Fig. 11.16** Ventriculoseptal defect (*arrow*) demonstrated by color flow Doppler in 28-week fetus. LA, Left aorta; LV, left ventricle; RA, right aorta; RV, right ventricle.

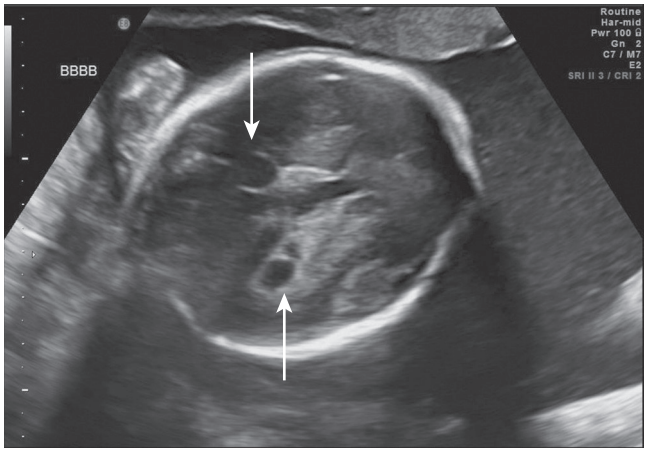
testing.[2] Presently, noninvasive screening for fetal aneuploidy (trisomies 13, 18, 21) is encouraged for all low-risk patients. Common noninvasive screening options include: (1) first-trimester screening (nuchal translucency measurement and maternal serum biochemical marker algorithm), (2) first- and second-trimester cell-free fetal DNA fragment analysis from maternal blood, (3) second-trimester serum screening (maternal age and serum biochemical marker algorithm), or (4) two-step integrated screening, which includes first- and second-trimester serum screening with or without nuchal translucency (integrated prenatal screen, serum integrated prenatal screening only, contingent and sequential screening variations). Different algorithms noticeably affect sensitivity, specificity, and predictive values; cost or convenience may factor in choosing a strategy.[12] Analysis of cell-free fetal DNA, found at concentrations almost 25 times higher than those from intact nucleated fetal blood cells extracted from similar volumes of maternal blood. Cell-free fetal DNA (cfDNA) noninvasive prenatal screening is now in wide use for specific targeted chromosomal abnormalities, especially trisomy (an extra copy of a chromosome) or monosomy (a missing chromosome), and numerous commercial products are currently marketed for this indication.[42] Patient acceptance has been high, perhaps in part because of early identification of fetal sex. Insufficient fetal fractions and indeterminate results appear more frequently in obese patients but may also occur with chromosomal abnormalities. Direct prenatal diagnosis by chorionic villus biopsy or amniocentesis should be routinely recommended for at-risk individuals on the basis of age, family history, abnormal screening, or ultrasound findings.

One-third of fetuses with Down syndrome will have anomalies, characteristically endocardial cushion defects (Fig. 11.14), duodenal atresia (Fig. 11.15), and more subtly, small atrioseptal and ventriculoseptal cardiac defects (Fig. 11.16). Two-thirds may have second-trimester sonographic markers: for example, increased nuchal lucency, hypoplastic or absent nasal bones, and abnormal cardiovascular Doppler patterns in the first trimester, thickened nuchal fold (Fig. 11.17) and nasal hypoplasia, ventriculomegaly, choroid cysts (Fig. 11.18), hypoplasia of the fifth digit, decreased long bone ratios, enhanced echogenicity of papillary muscles and bowel, and renal pyelectasis (Fig. 11.19). The predictive value of screening components is affected by ethnicity, habitus, maternal diet, and fetal sex, as well as by device and operator-dependent detection rates. The permutations may confound counselors attempting to elucidate (and patients trying to grasp) the difference between screening and diagnosis, and basic descriptions of risks

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• **Fig. 11.17** Thickened nuchal fold (NF) (*calipers*) at a level demarcated by the cavum septum pellucidum (CSP) and the cerebellum (C), here noted at 18 weeks, is considered a marker for trisomy 21 (Down syndrome) and cardiac and other anomalies. The finding is infrequent, even in affected infants, limiting its utility.

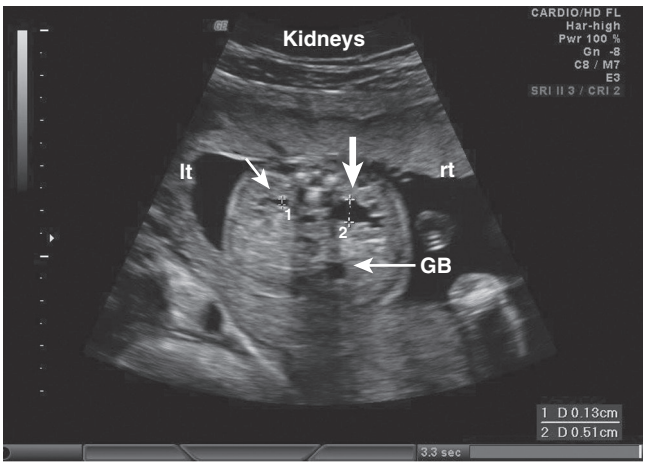


• **Fig. 11.18** Choroid plexus cysts. Coronal view of the brain shows bilateral choroid plexus cysts (*arrows*).

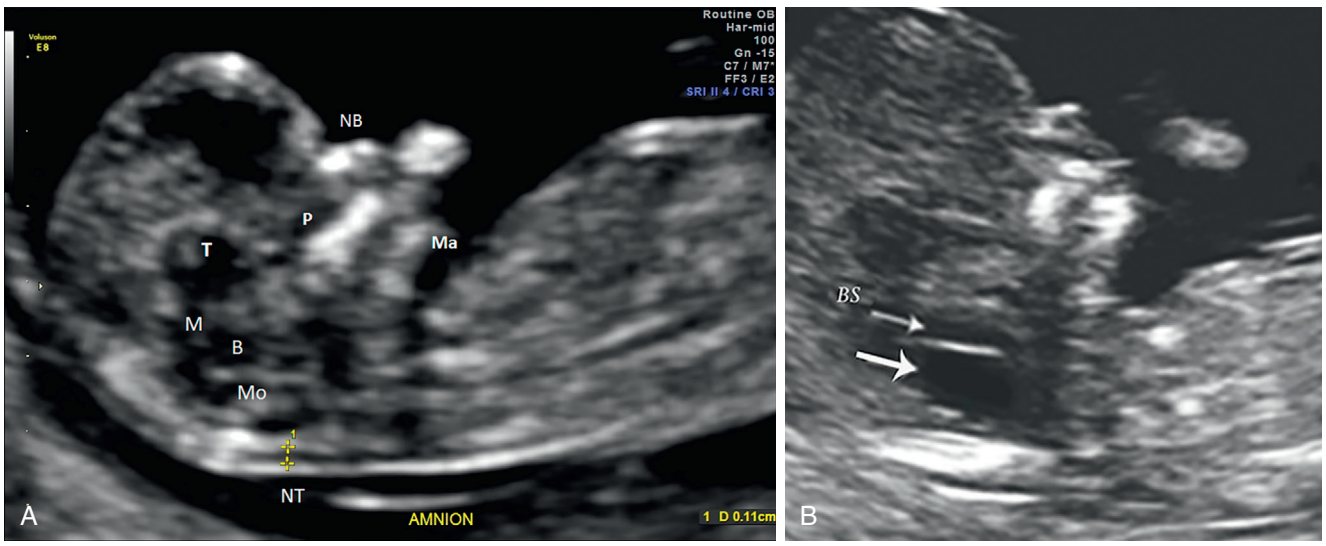
and benefits. Recently described first-trimester evaluation of the posterior brain (intracranial translucency) provides an additional screening tool for open neural tube defects and other intracranial abnormalities (Fig. 11.20*A* and *B*).[21] Second-trimester sonographic follow-up and genetic evaluation may add critical information to the assessment of these abnormal findings. First-trimester identification of tricuspid regurgitation and increased ductus venosus resistance seems a promising, albeit technically challenging, addition to early screening protocols.[26]

Assisted Reproduction

Ultrasound is essential for timing and guiding oocyte retrieval and helpful in embryo transfer; its role in judging



• **Fig. 11.19** Transverse abdominal view, backup. Gallbladder (*arrow GB*) at right, with asymmetric renal pelves (*calipers*) illustrating the normal left renal appearance (1) (*short, thin arrow*) and right pyelectasis/caliectasis (2) (*thick arrow*). Between 1% and 5% of normal fetuses have pyelectasis, limiting its utility as an isolated marker.



• **Fig. 11.20** **A,** Ultrasound image in the mid-sagittal plane of the fetal profile showing the nasal bone (NB), palate (P), mandible (Ma), nuchal translucency (NT), thalamus (T), midbrain (M), brainstem (B), and medulla oblongata (MO). **B,** Mid-sagittal ultrasound images of fetal brain in a case of Dandy–Walker malformation at 12 weeks' gestation; note only two posterior brain spaces (*arrows*) and enlarged brainstem (BS).

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endometrial receptivity is less clear. Saline ultrasound studies prior to fertility treatments routinely complement or replace hystero-salpingogram in assessment of the uterus and adnexa. Use of MRI may play an expanded role in structural and functional evaluation in the future.

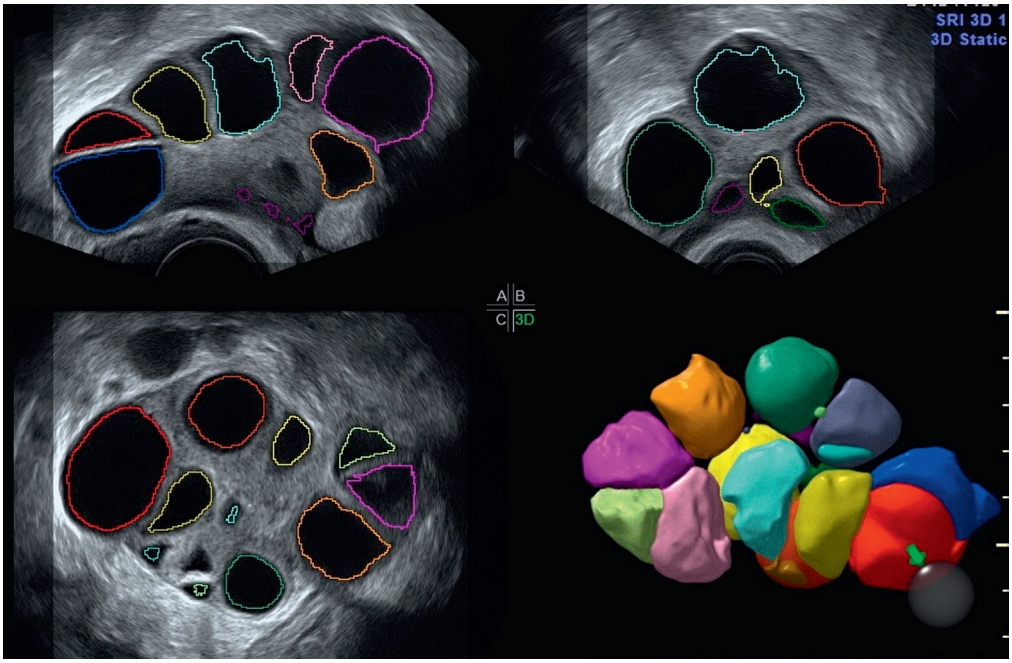
Assisted reproductive technology results in more twins and higher-order multiples; early ultrasound study of embryos, amnionicity, and chronicity is essential to subsequent management. With the increasing popularity of ART, obstetricians and radiologists are more likely to encounter associated complications, especially in an emergency setting. These complications include ovarian hyperstimulation or torsion, ectopic or heterotopic pregnancy, and pregnancies of unknown location or undetermined viability. Ovarian hyperstimulation syndrome may occur following ovulation induction or ovarian stimulation and is characterized by bilateral ovarian enlargement, by multiple cysts, and third-spacing of fluids (Fig. 11.21). Additional clinical findings may range from gastrointestinal discomfort to life-threatening renal failure and coagulopathy. Ovarian torsion should be excluded in any woman undergoing ART who presents with severe abdominal pain. Ectopic pregnancy resulting from ART has a relatively increased frequency of rarer and more lethal forms, including interstitial and cervical locations. Heterotopic pregnancies, simultaneous intrauterine and ectopic implantations, are more common in ART patients.

Ultrasonography is the first-line choice for identifying ART complications, although lack of specific symptoms may first trigger other approaches. Familiarity with characteristic strengths and limitations of these and other techniques will facilitate accurate, timely diagnosis and avert potentially serious consequences.

Multiple Gestations

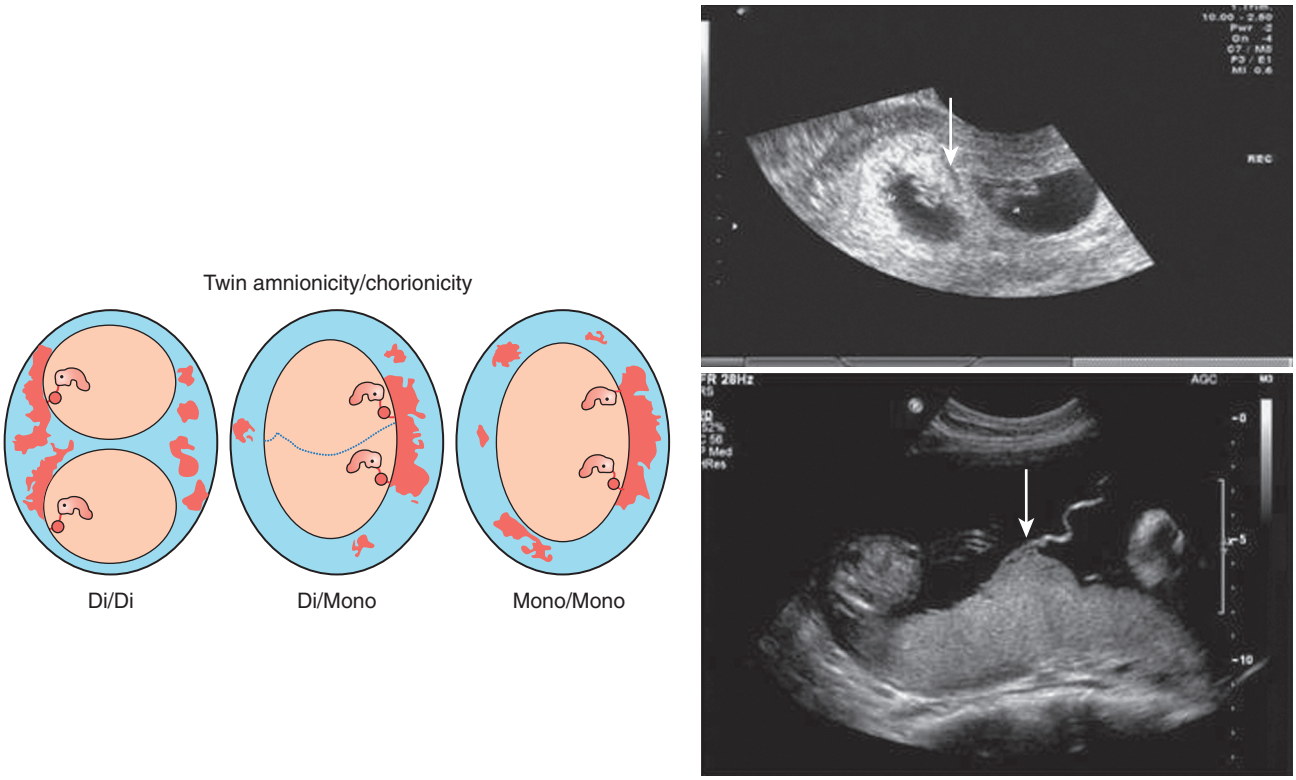
Multiple gestation accounts for about 3% of all pregnancies. With an increase in the number of fetuses, scans become more complex, time consuming, and error prone; additionally, determination of zygosity is essential. The management of anomalous, discordant, or moribund co-twins differs significantly based on chorionicity (Fig. 11.22). Monochorionic twins occur with a relatively constant frequency (1:250 pregnancies), unlike dichorionic twinning that may be influenced by race, heredity, maternal age, parity, and ART. Ultrasound assignment of chorionicity is most accurate for different-sexed dizygotic twins, but by evaluating sac appearance in early gestation, approaches this accuracy in gender-concordant pairs. Successful identification may occur throughout gestation by examining the dividing membranes at their placental origin. Dichorionic diamniotic twins are usually (95%) dizygotic, with independent risks for anomalies and placental malfunction. Monochorionic pairs are predictably monozygotic; attrition rates exceed 30% from early abortion, anomalies, and prematurity. Matched and isolated anomalies are both more common in monochorionic gestations; because of shared vasculature, loss of a co-twin may kill its sibling outright or produce severe neurologic damage in up to one-third of survivors.[27]

Monochorionic TTTS, more common in females, is characterized by unbalanced, shared perfusion that restricts



• **Fig. 11.21** Three-dimensional color-enhanced volume rendering of seven follicles in the right ovary. The echo-free follicles are outlined by the operator in orthogonal planes. The generated volumes are then displayed in the three-dimensional rendering (*lower right*) with color correlation.

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• **Fig. 11.22** Diagram (*left*) of variations in appearance of the dividing membrane for dichorionic, monochorionic, and monoamniotic twins. Upper-right image shows typical thick first-trimester appearance of the chorion (*arrow*) in dichorionic diamniotic twins. Lower image shows the peaked dividing membrane (*arrow*) of dichorionic twins in the latter half of pregnancy.

growth and amniotic fluid production in the donor and causes volume overload, cardiac dysfunction, and polyhydramnios in the recipient. Ultrasound staging has been used to time and to guide a variety of vascular ablation strategies. Serial amniocentesis may be helpful in milder cases. Management by these approaches has been modestly effective in decreasing stillbirths and prematurity in TTTS. Monoamniotic twins rarely experience TTTS but routinely encounter cord entanglements, resulting in high lethality rate of both fetuses (Fig. 11.23). Management usually consists of a scheduled preterm cesarean prior to onset of labor. For all multiple gestations, serial ultrasound monitoring of growth, well-being, placental performance, and cervical length is common practice.

Twin reversed arterial perfusion (TRAP) sequence is another complication of monochorionic twinning, complicating approximately 1% of monozygotic pregnancies.[32] Placentation among TRAP cases has been predominantly reported to be monochorionic diamniotic and to a lesser degree monochorionic monoamniotic twins. The proposed pathogenesis is the association of paired artery-to-artery and vein-to-vein anastomoses through the placenta combined with delayed cardiac function of one of the twins early in pregnancy. This situation allows blood pumped from the healthy twin "pump twin" to perfuse retrogradely the heart of the other twin, also known as the "acardiac" twin or "parabiotic twin." Thus, flow in the artery and vein are



• **Fig. 11.23** Monochorionic monoamniotic twins with entangled umbilical cords at 10 weeks' gestation.

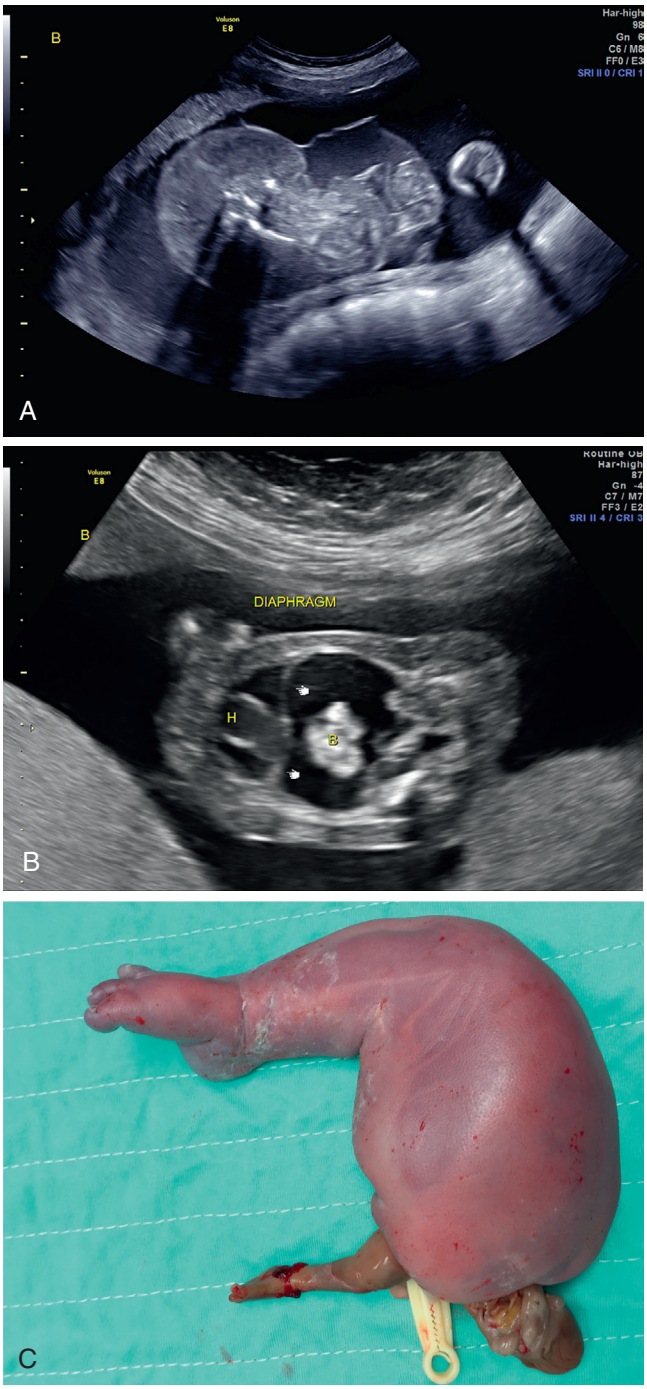
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reversed in the umbilical cord of the acardiac twin, giving rise to the acronym TRAP. Retrograde perfusion interferes with normal cardiac development, which rarely goes beyond the stage of tubular heart. Common abnormal findings in the "acardiac twin" include impaired or absent development of the cephalic pole, rudimentary or absent heart, abnormal or absent upper limbs, relative preservation of the lower limbs although clubbing and abnormal toes are common, abnormal viscera, and single umbilical artery. A common finding is massive edema around the upper body including the neck of the acardiac twin (Fig. 11.24*A-C*).

Pregnancy Evaluation

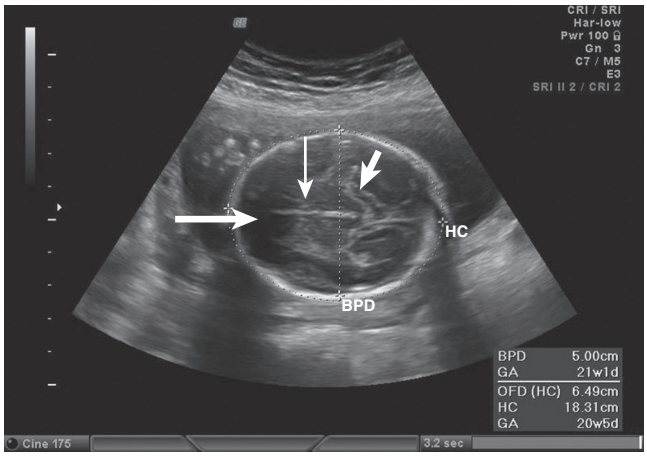
One of the most powerful applications of prenatal ultrasound is using biometrics to establish or confirm gestational age.[9] Through 22 weeks of gestation, most genetically normal individuals cluster closely on normographic curves. Sonographic measurements of fetal ultrasound parameters are the basis for accurate determination of gestational age and detection of fetal growth abnormalities. It has been shown that a fixed error of about 8% (plus or minus) can be anticipated when determining gestational age by ultrasound, consistent with the observation that the earlier gestational age is determined, the lower the margin of error in days. If accelerated or restricted growth supervenes, however, biometric markers are generally compromised accordingly.

Selection of the most useful single parameter depends on the timing and purpose of measurement and is influenced by specific limitations. Commercial equipment has a variety of preinstalled normograms, biometry-based dating, and weight estimation formulae. Embryonic pole and crown-rump lengths are considered most precise for early dating of pregnancy, becoming more variable with fetal flexion effects at the end of the first trimester. Biparietal diameter (BPD), obtainable after parietal bone calcification in week 12, maintains the closest correlation with gestational age in the second trimester. BPD is measured from the outer to the inner table of the skull, perpendicular to the parietal bones and central falx cerebri. The proper plane contains the cavum septum pellucidum, thalami, third ventricle, and tentorial hiatus, within the bony table of a complete head circumference (Fig. 11.25). In cases of variation in the shape of the skull, a head circumference (HC) measurement obtained in the same plane may be an effective alternative. Microcephaly may be suspected when the HC measurement is more than 3 standard deviations (SD) below the mean but is rarely diagnosed prenatally. Additionally, antenatal sonographic estimation of HC is associated with significant underestimation compared with the actual postnatal HC. This discrepancy may have important clinical implications and should be taken into account in the interpretation of sonographically measured HC.[30] BPD and HC are relatively spared in nutritional and perfusional disorders of growth, although cranial measurements may also be distorted by compression effects. The abdominal circumference (AC), measured along the outer margin of the abdominal skin line at the level of the gastric bubble and the intrahepatic portion of the umbilical vein at the bifurcation of the portal veins, is the best single predictor of growth aberrations but is less helpful for dating (Fig. 11.26). Femoral length (FL) is the fourth measurement commonly included in biometric

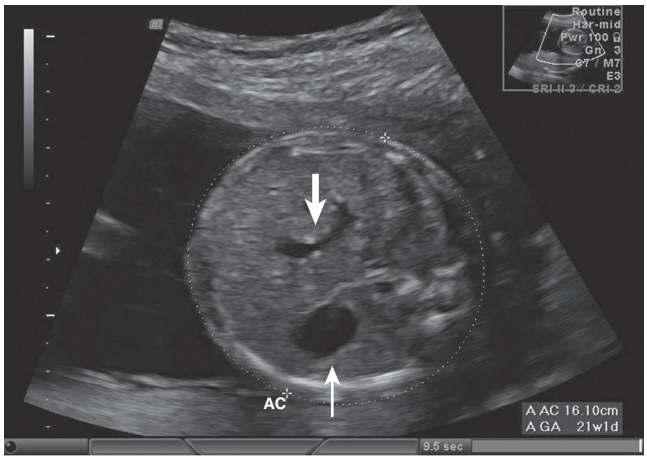


• **Fig. 11.24** **A,** Monochorionic diamniotic parabiotic (acardiac) twin. Note the massive edema and abnormal and disorganized organs. **B,** Parabiotic twin with massive pleural effusion and ascites. Note the presence of a completely dysfunctional heart (H) and echogenic bowel (B). The diaphragm is clearly seen (*pointing hands*). **C,** The same fetus following premature delivery at 34 weeks. The upper portion of the body has never been formed.

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• **Fig. 11.25** Measurement of the biparietal diameter (*vertical calipers*) and head circumference. The required landmarks include the midline falx cerebri (*long thick arrow*), the cavum septum pellucidum (*thin arrow*), and the thalami (*short thick arrow*). The BPD calipers are placed on the upper outer table and the inner margin to compensate for signal scatter.



• **Fig. 11.26** The abdominal circumference indirectly reflects hepatic glycogen stores. The correct level should include the gastric bubble (*thin arrow*) and the junction of the portal veins (*thick arrow*); the circumference should be fitted to the outer diameter of the skin line. AC, Abdominal circumference.

formulae, less affected by hypoperfusion but potentially influenced by familial stature. Extraocular and transcerebellar diameters, humeral and pedal lengths are common additional dating parameters. Special curves are available for non-Caucasian ethnicity and multiple gestations, although not universally accepted as essential.

Use of multiple predictors improves the accuracy of estimates, with an individualized approach recommended for fetal growth assessment. The various epidemiologic factors influencing fetal growth should be considered. Clinical application of fetal biometry is of utmost importance in recognizing dating errors, growth abnormalities, chromosomal anomalies, and skeletal dysplasias.

Fetal Growth

Serial measurements over time are the best way to judge fetal growth. The sac and embryo grow perceptibly each day; by the second trimester, intervals of 2 or 3 weeks between studies are more reliable. Problems arise when attempting simultaneously to assign age and weight percentile without reliable dating. The abdominal circumference (AC) is a better indicator of decreased perfusion or increased glycogen storage than the cranial measures; ratios of AC to the HC and FL amplify differences but have poor sensitivity and specificity. Strategies to identify small-for-date fetuses have included risk panels, Doppler ratios, amniotic fluid volume, placental scores, and biometry-based weights; none have had completely satisfactory results, although outcomes appear to have improved.

Correctly identifying fetal growth abnormalities remains an elusive goal despite their major contribution to adverse perinatal outcomes and stillbirth. Current clinical screening relies on the symphyseal–fundal height measurement, but fewer than 25% of small-for-gestational-age (SGA) infants will be identified using this methodology in a low-risk population. Routine third-trimester ultrasound study for growth assessment has a better detection rate, ranging from 50% to 80%, but the impact on perinatal outcome is unclear.[43]

Several common findings, in addition to risk panels, underlying maternal diseases (particularly with vascular components) and prior stillbirth or growth-restricted outcomes may raise concern for fetal growth restriction.[11] These include a modest size–dates discrepancy (within method error) on a first-trimester study, abnormal maternal serum levels of pregnancy-associated plasma protein-A (PAPP-A), and free β-human chorionic gonadotropin at 9-13 weeks, usually obtained as part of genetic screens; early elevation of maternal blood pressure and abnormal uterine artery resistance by Doppler at 11 0/7 to 13 6/7 weeks; a hypoglycemic response to glucose testing may be an early third-trimester observation. By combining uterine artery Doppler findings and baseline maternal characteristics, detection rates for early-onset fetal growth restriction have reached clinically acceptable levels. Unfortunately, fetal growth restriction developing later in pregnancy still goes largely undetected.[7]

Placental Abnormalities

Placental conditions affecting the mother and/or fetus include gestational trophoblastic diseases, placental hematoma, chorangioma, abruption, placenta previa, placenta accreta/increta/percreta, vasa previa, choriocarcinoma, chorioamnionitis, viral and parasitic villitis and placentitis, decidual and thrombotic vasculopathies, infarction, polyps, and retained products of conception. Although gross inspection and histopathology provide the ultimate diagnosis, ultrasonography is the definitive prenatal modality for the evaluating the majority of these conditions. MRI

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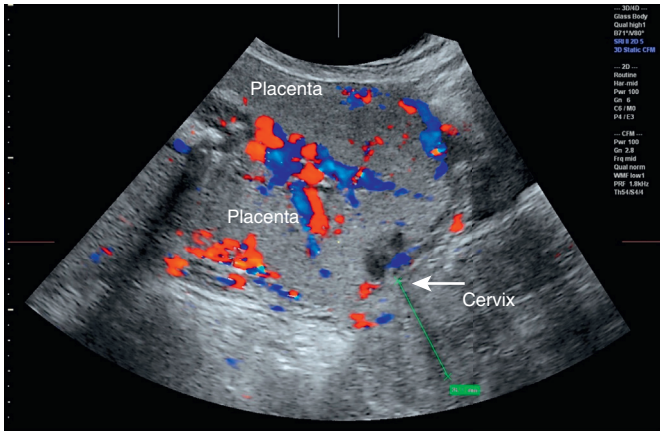
and computed tomography are infrequent adjunctive measures, with the latter occasionally helpful in tumor staging or trauma cases.[31]

Placental Location

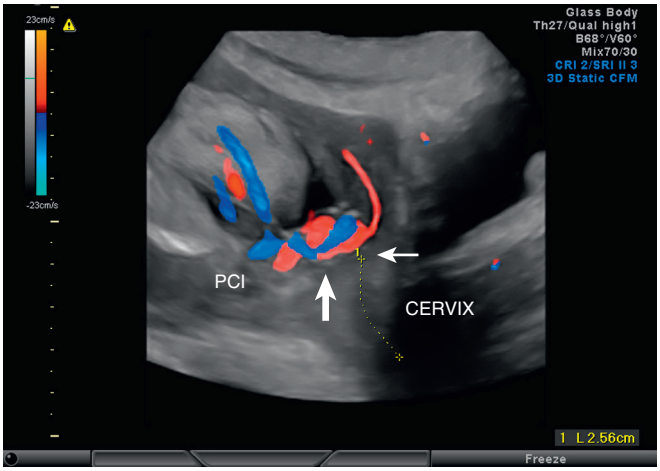
Placental location can be confidently established by abdominal and transvaginal ultrasound studies. Low-lying placentation, present in up to 60% of early second-trimester studies, persists as placenta previa in only 1% to 2% of patients at term (Fig. 11.27). Fetal vessels near the cervix can be visualized using color Doppler, facilitating the diagnosis of funic (umbilical cord) presentation and vasa previa (fetal vessels overlying the os) (Fig. 11.28). Normally inserted centrally in the placenta, the umbilical cord may later, as a result of asymmetric placental growth, be located marginally or even on adjacent membranes; in the latter position, traumatic lacerations, hemorrhage, and compression-linked heart rate changes are potential consequences.

Abnormally invasive placenta is a spectrum disorder encompassing the histopathologic diagnoses of placenta accreta (a small focus or more generalized muscular invasion), placenta increta (deeper myometrial invasion up to the uterine serosal layer), and placenta percreta (through the serosa to adjacent visceral or vascular structures). It is potentially life threatening, as forced removal of an abnormally invasive placenta can lead to catastrophic maternal hemorrhage; management of all but the most circumscribed lesions usually requires hysterectomy (Fig. 11.29*A* and *B*).

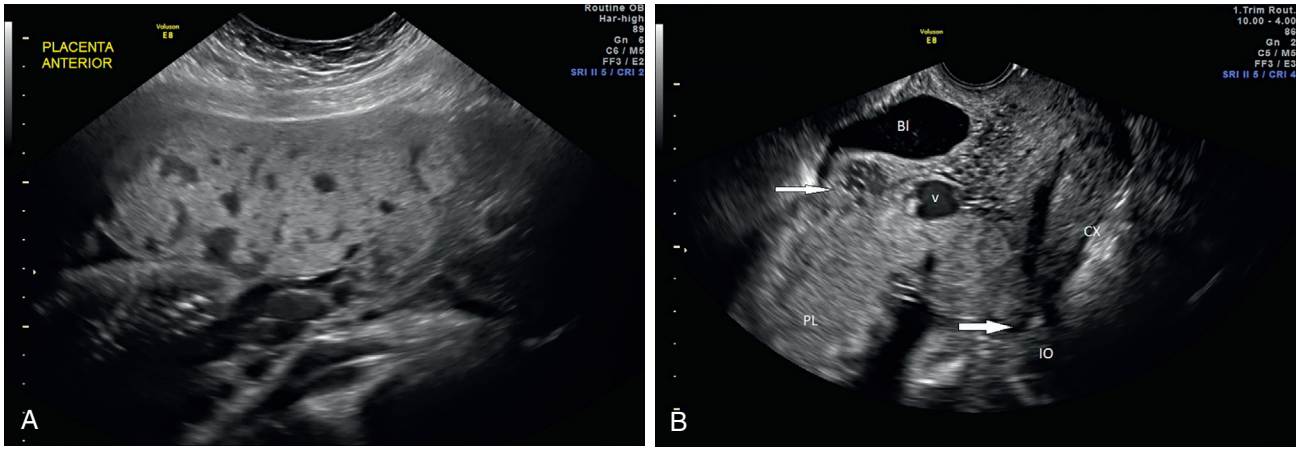
Invasive placentation was previously diagnosed only when failed attempts to remove the placenta were followed by massive bleeding. Placental accretion is significantly more likely in women with the combination of placenta previa and a history of one or more cesarean sections,[36] after myomectomy or curettage, and with high parity.[18] The frequency of accretion, now complicating 1/2500



• **Fig. 11.27** Placenta previa: the internal os (*arrow*) is completely covered by the placental tissue (P) in this transabdominal view.



• **Fig. 11.28** Fetal vessels (*thick arrow*) within the membranes overlying the internal os (*thin arrow*) are termed vasa previa. Rupture of the vessels can rapidly exsanguinate the fetus; artificial membrane rupture and labor are contraindicated.



• **Fig. 11.29 A,** Anterior placenta accreta showing multiple cysts (vascular lacunae). The hypoechoic interface between the placenta and the myometrium is not seen. **B,** Anterior wall placenta previa and percreta. The wall of the maternal bladder (Bl) is invaded by placental vessels (*narrow arrow*). A sizable venous lake (V) is seen where one would normally expect to view the placental myometrial interface. The placental margin covers the internal cervical os (IO) (*wide arrow*). Cx, Cervix.

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deliveries, has increased more than 10-fold in the past 20 years, echoing rising cesarean rates.[50] Sonographic criteria for placenta accreta were developed using conventional gray-scale, 2D, and 3D color and power Doppler transabdominal and transvaginal ultrasonography. The sonographic characteristics identified are loss/irregularity of the echo-free "clear space" between the uterus and the placental basal plate; thinning or interruption of the hyperechoic interface between the uterine serosa and the bladder wall (increasing concern for percreta), and Doppler findings that included the presence of turbulent placental lacunae with high-velocity flow, as well as hypervascularity of the uterine serosa–bladder wall interface and irregular intraplacental vascularization. Diagnostic ultrasound findings of indistinct placental margins, attenuated myometrium, and large turbulent placental vessels (mainly veins) have sensitivity and specificity for accretion in the range of 85%.[18] The presence or absence of the listed findings has been shown to be very helpful in diagnosing placental accretion and in differentiation of placenta accreta from percreta.[8] In a recent study, the European Working Group on Abnormally Invasive Placenta sought to increase diagnostic capabilities of abnormally invasive placenta.[10] The researchers have suggested a total of 10 sonographic findings detected by 2D gray-scale and color Doppler study to be very helpful in diagnosing an abnormally invasive placenta. Similar sonographic findings with 81% sensitivity and 98.9% specificity were recently reported.[35]

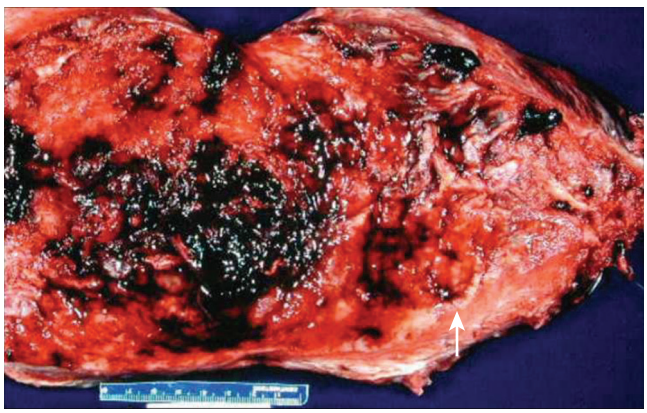
Antepartum diagnosis of abnormal attachment permits multidisciplinary planning for prematurity management, anesthesia, transfusion, hemostatic and uterotonic medications, balloon tamponade, arterial embolization, or scheduled preterm (around 34 weeks) cesarean-hysterectomy prior to onset of labor (Fig. 11.30). MRI mapping is most helpful when there is posterior placentation, suspected lateral extension, after myomectomies, for evaluation of adjacent viscera with percreta, or when ultrasound findings are ambiguous.[35]

The diagnosis of placental abruption remains a clinical one. The role of imaging in this disorder is to exclude placenta previa, an equally common source of severe third-trimester bleeding. Subchorionic hematomas are often noted on transvaginal scans early in gestation; symptomaticity, size, and persistence have been linked to poorer outcomes.[17] Later abruptions are more difficult to visualize; acute bleeding is isoechoic with placenta and can be mistaken for placentomegaly. Hypoechoic fluid collections and hyperechoic infarcted areas appear in more chronic presentations.

Grading placental appearance to detect disturbed growth or maturation is of limited benefit. Persistent immaturity is linked to hydrops fetalis, although not as often as increased echogenicity and thickening. Precociously mature placentas may presage growth restriction (Fig. 11.31).

Amniotic Fluid Volume

Amniotic fluid is initially secreted by the amnion; by the 16th week of pregnancy, fetal renal production accounts for the majority, with nearly complete turnover during a 24-hour period. Malformations of the esophagus and upper gastrointestinal tract, inhibited fetal swallowing, aneuploidy, intermittent renal obstruction, maternal diabetes, twin–twin transfusion syndrome, some forms of dwarfisms, and fetal hydrops are associated with marked polyhydramnios. Severe growth restriction with polyhydramnios carries a poor prognosis. Polyhydramnios is idiopathic in almost half of the cases; associated complications include maternal respiratory compromise, premature membrane rupture, preterm labor and delivery, malposition, abruption, cord prolapse, preeclampsia, amniotic fluid embolism, and puerperal hemorrhage. Maximum vertical pocket or summed depths across quadrants conveniently serve as proxies for volume calculation in clinical settings (Fig. 11.32). Oligohydramnios may occur after membrane rupture; after fetal renal compensation for placental hypoperfusion; from functional or obstructive urogenital anomalies; with maternal dehydration; or following exposure to some medications, including indomethacin and angiotensin-converting-enzyme inhibitors. Maternal obesity is associated with underestimation of amniotic volumes. Amniotic fluid measurements may be

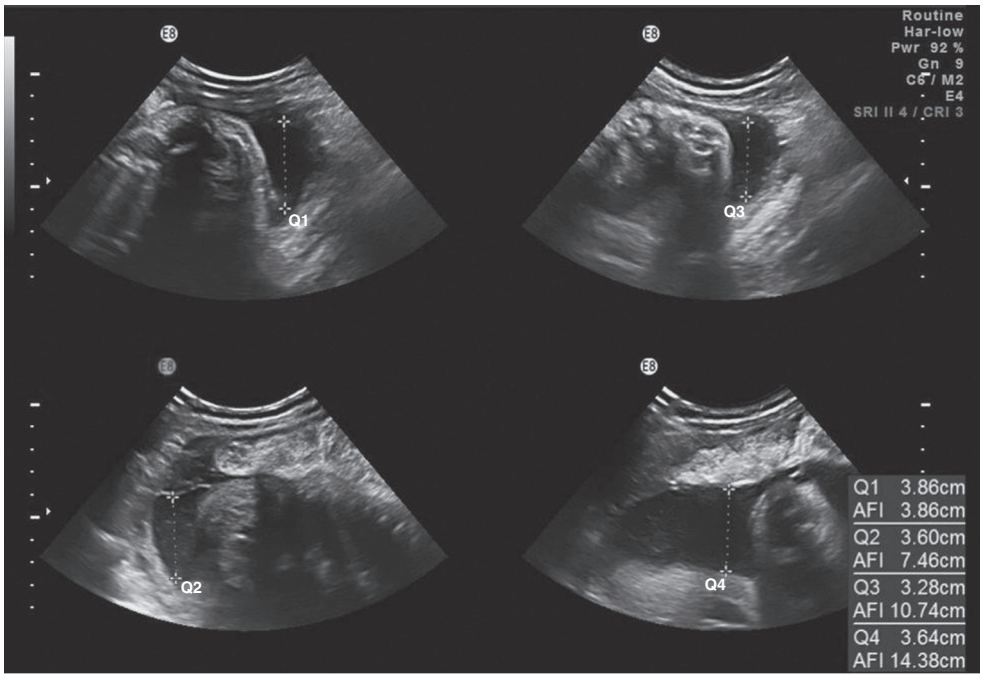


• **Fig. 11.30** Hysterectomy specimen with placenta accreta. There is no visible distinction between the uterine muscle and the placental tissue, with the exception of a small area in the lower right (*arrow*).



• **Fig. 11.31** Grade III placenta, characterized by echogenic outlines of the cotyledons with hypoechoic centers.

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• **Fig. 11.32** Four quadrant vertical pocket assessment of amniotic fluid; other techniques include measurement of the single greatest vertical pocket or identification of a 2 × 2 cm cord-free area.

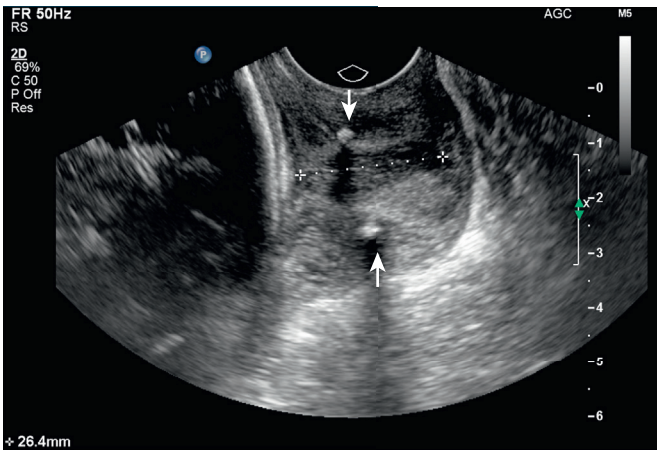
combined with non-stress and fetal biophysical testing to provide reassurance of fetal well-being.

Cervical Length and Pelvic Structures

Cervical length and appearance is frequently assessed during routine antenatal ultrasound; transvaginal measurements (Fig. 11.33) are more reliable and reproducible than transabdominal views. The closed endocervical canal length is positively correlated with duration of gestation in a continuous fashion. Moreover, once values fall below 25 mm, preterm deliveries increase. In patients with prematurity risks, shorter cervical length is strongly predictive of delivery before 36 weeks; in combination with fetal fibronectin and other biomarker assays, ultrasound aids in identifying those at highest risk for imminent delivery.[6]

Attempts to prevent premature births by tocolysis have been ineffective; postponing delivery for 48 hours to permit steroid enhancement of lung maturity has proven more feasible. First-trimester ultrasound prediction of the need for cervical cerclage has not been reliable. Specific candidates may benefit from either preventive or "rescue" cerclage procedures on the basis of midtrimester cervical lengths. Progesterone prophylaxis against prematurity by intramuscular injection or vaginal preparation has increased in recent years; the former has supporting evidence for effectiveness after a short cervix has been noted by ultrasound.[6]

The gravid uterus is conveniently studied by ultrasound. Congenital Müllerian anomalies, including duplications and septations, occur in about 0.5% of the population (Fig. 11.34). Patients with bicornuate uteri may experience irregular bleeding in early pregnancy, altered cervical



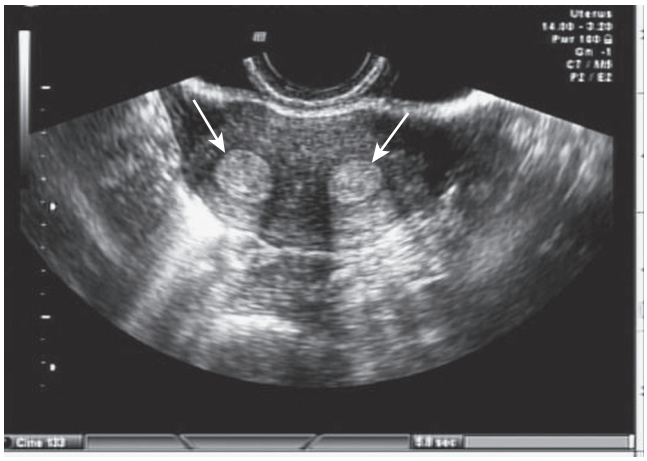
• **Fig. 11.33** Transvaginal study showing cervix (*dotted line*) with MacDonald cerclage (*arrows*) in situ.

competency, and, rarely, torsions or ruptures of the horn in which the gestational sac is located. Poorly vascularized septations are etiologically associated with abruption and pregnancy failure. Myomas complicate 1% to 2% of pregnancies with more frequent cesareans and prematurity, abruption, degeneration, and fetal malpresentation; less common complications include fetal deformation, dystocia (7.5%), puerperal hemorrhage, and hysterectomy.[22] Adverse obstetric outcomes are rare; studies are confounded by age, ethnicity, and other differences in those who develop myomas. Generally good maternal and neonatal outcomes are expected in most pregnancies with uterine fibroids.[22]

Normal adnexal structures are not palpable after the first trimester; ultrasound is the first choice for ovarian

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evaluation during pregnancy, although often augmented by MRI and computed tomography (CT). Ovarian torsion is a rare but acute surgical emergency; it is more likely with ART, ovarian cysts, and adnexal masses, favoring first-trimester or puerperal onset. Once an adnexal mass has been discovered by ultrasound, better characterization by MRI may be essential in avoiding unnecessary surgery during pregnancy. Asymptomatic lesions, even when quite large, are now generally expectantly managed until delivery or the postpartum period if malignancy is not suspected. Ultrasound is frequently sufficient for a secure diagnosis of corpus luteal cysts, benign cystic teratomas, and endometriomas. Use of MRI for atypical lesions can confirm the presence of fat, key to the diagnosis of teratoma and the exclusion of endometrioma. MRI aids in identification of hydrosalpinges and nongynecologic lesions. Expectant management of many adnexal masses past delivery is now more common, based on benign ultrasound, Doppler, and MRI characteristics.[51]

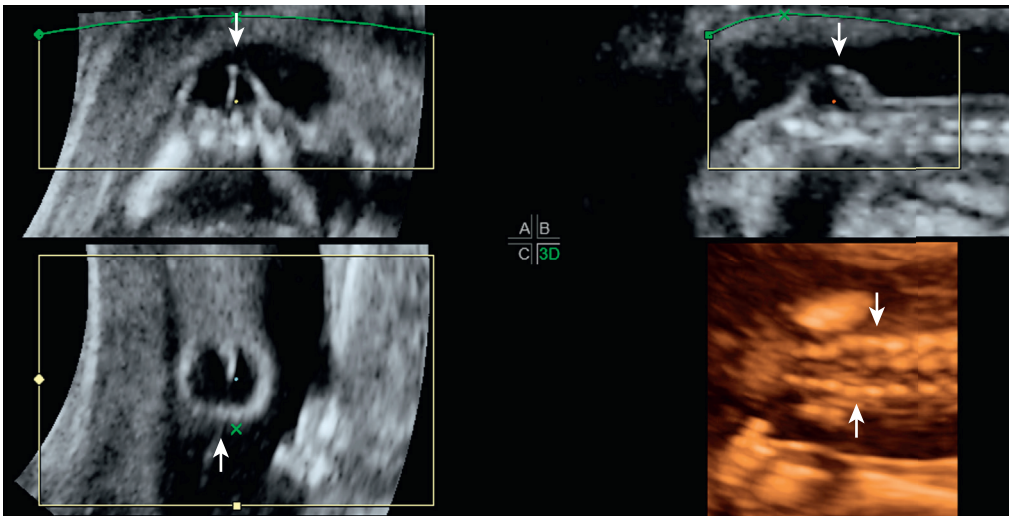


• **Fig. 11.34** Müllerian anomaly: Bicornuate uterus in transverse view with two decidualized cavities (*arrows*) and indented external contours.

Second-Trimester Ultrasound Study of the Fetus

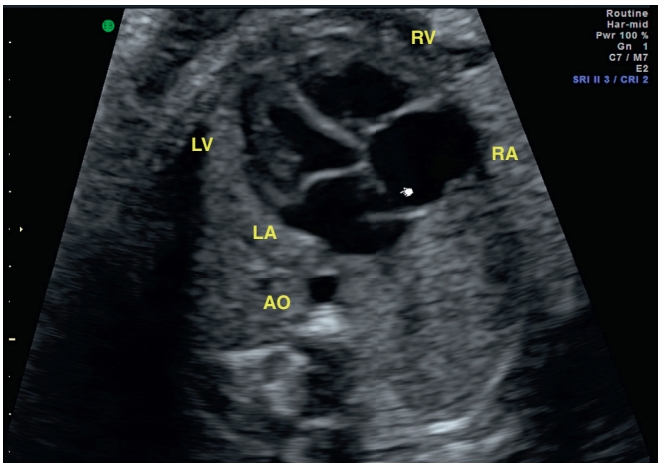
During second-trimester studies, a number of normal fetal structures are routinely identified and anomalies excluded. Basic anatomic surveys usually include documentation of fetal cranial integrity and central nervous system anatomy: midline brain structures, cavum septum pellucidum and thalami, lateral and third ventricles, choroid plexus, cerebellum, and posterior fossa.

Views confirming facial symmetry, intact orbits, clear lenses, paired nares, intact lips and hard palate, and normal profile are part of comprehensive studies. Fetal swallowing, respiratory movements, and nuchal structures may be noted. The spinal column is normally imaged in the long-axis, transverse, and coronal views. Distinct advantages in the visualization of the facial features, small parts, and spine are provided by 3D imaging (Fig. 11.35). Views of the thorax, including the axis, site, and relative proportions of cardiac and mediastinal structures with respect to the lungs and pulmonary vessels, yield indirect support for the integrity of the diaphragm. Over time, the basic cardiac examination has expanded from obtaining the axis, laterality, and rate to requiring symmetric four-chamber apical views and, as feasible, images of normal outflows, ductal and aortic arches, and additional arterial and venous tracts (Fig. 11.36). Prenatal echocardiography adds M-mode rhythm, color flow Doppler, and structural studies capable of details and diagnostic accuracy approaching those of postnatal examinations, subject to predictable limitations. Fetal abdominal views confirm the closure of the ventral wall; presence, normal size, and site of hepatic, gastric, splenic, pancreatic, vascular, and choledochal structures; renal and adrenal contours; normal bowel dimensions and echogenicity; bladder filling; and umbilical cord appearance. Accuracy of fetal sex assignment exceeds 99% by the midtrimester (Figs. 11.12 and 11.37). Fetal digits, small parts, cerebellar vermis, and



• **Fig. 11.35** Three-dimensional rendering of the fetal spine permits localization of the neural tube defect (*arrows*). Compare with the MRI in Fig. 11.39.

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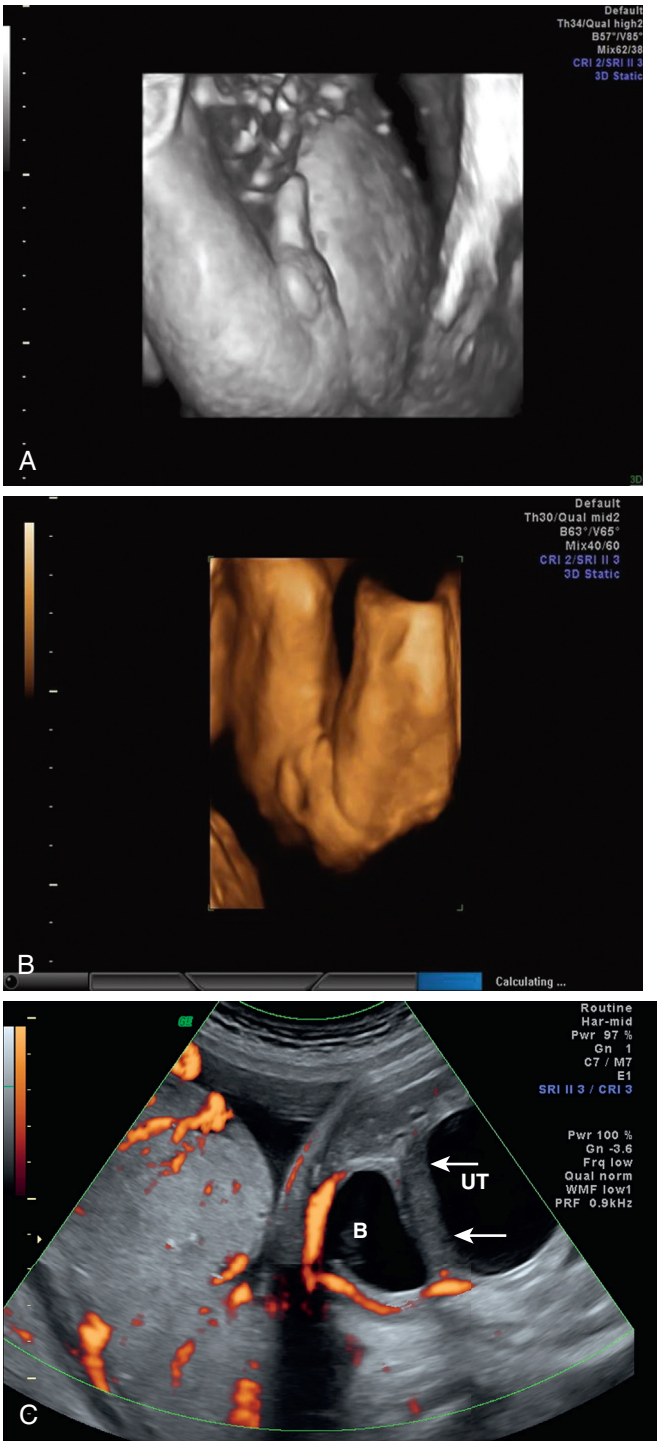
• **Fig. 11.36** View of the thorax showing a normal four-chamber heart; apex is up and to the left of the picture. The right and left atria (RA, LA) and corresponding ventricles (RV, LV) are seen in the transverse plane of the fetal chest.

palatal components are often imaged by a combination of 2D and 3D. As gestation progresses, neurosonography may identify additional features of intracranial architecture and cerebral maturation.

Doppler Ultrasound

Initially considered revolutionary, obstetric Doppler has been hampered by costs, time constraints, safety concerns, and lack of clear utility for most patients. Currently accepted applications, originally employed in research and referral centers, commonly include identification and localization of blood flow, resistance to flow, vessel patterns, and directionality and velocity in cardiopulmonary structures and in a wide range of additional vessels, most commonly the uterine arteries, umbilical vessels, ductus venosus, and middle cerebral artery.

Uterine blood flow patterns reflect both maternal vascular resistance and placental site. Abnormal Doppler results in these and other vessels precede growth restriction and maternal hypertensive complications. Paired umbilical cord arteries are readily shown by color Doppler to bifurcate around the bladder (see Fig. 11.5). Absence of one umbilical cord artery may have associated cardiac and renal anomalies, aneuploidies, or growth restriction. Abnormally high umbilical artery resistance is more often characteristic of uteroplacental constraints on fetal growth than of anomalies or aneuploidy. Doppler findings may suggest the origin of a size/date discrepancy, but weight estimation more reliably identifies the small-for-gestational-age fetus. Persistent absence or reversal of end-diastolic flow, albeit rare, is associated with severe growth restriction, and perinatal morbidity and mortality. Middle cerebral artery resistance and umbilical venous patterns usually change later in the course of compromised perfusion; paradoxical ductus venosus and umbilical venous patterns are considered premorbid. Schemes combining clinical risks, biometry, Doppler

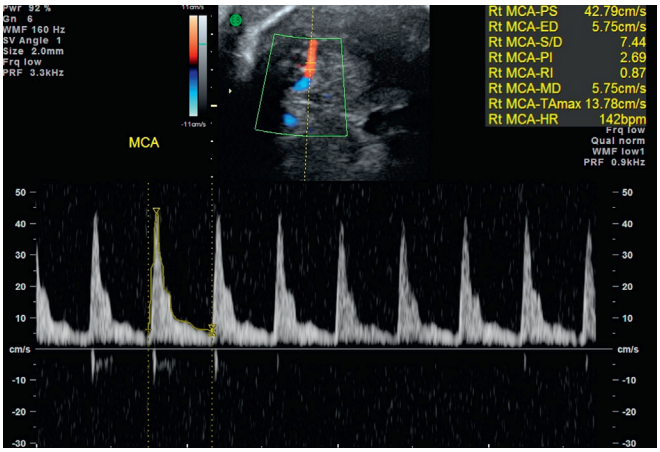


• **Fig. 11.37** The male fetus (**A**) can reliably be distinguished from the female fetus (**B**) by ultrasound after the first trimester. **C**, A female fetus with hydrometrocolpos. The arrows point to sediment of red blood cells in the uterus. B, Bladder; UT, uterus.

measurements of the umbilical and middle cerebral vessels, and biophysical testing appear to have improved outcomes for growth-restricted fetuses while reducing the frequency of iatrogenic prematurity.[2]

Doppler measurement of peak systolic velocity in the middle cerebral artery has become integral to detection of fetal anemia and management of isoimmunization

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• **Fig. 11.38** Middle cerebral artery (*in trapezoid*) Doppler flow velocity in a fetus with Rhesus sensitization. The peak systolic velocity (PSV shown in lower portion) increases as fetal anemia progresses. Doppler measurements in the fetus are often expressed as ratios to compensate for inaccuracies introduced by narrow, tortuous vessels.

(Fig. 11.38). Previously, discovering hydrops or elevated maternal erythrocyte antibody levels triggered obligatory cord blood sampling or amniocentesis. The former is complicated by technical challenges, prematurity, and fetal losses; the latter is informative for only some hemolytic anemias. Peak velocities of the middle cerebral artery by noninvasive Doppler, relatively easily obtained, are inversely correlated with hemoglobin values. At a cutoff of 1.5 multiples of the median, the sensitivity for clinically significant anemia approaches 100%, with a false-positive rate from 0% to 28%; reliability decreases near term.[28] Severe growth restriction may contribute to false-positive results but is usually distinguished by clinical context.

Color flow Doppler distinguishes between cystic and vascular lesions, confirms the presence or site of organs, and aids in evaluating brain, cardiac, and pulmonary vasculature. When combined with 3D, color flow generates dramatic virtual vascular casts, although with more limited prenatal applications.

Doppler Studies of the Growth-Restricted Fetus

Placental dysfunction leading to fetal growth restriction (FGR) is an important risk factor for neurodevelopmental delay. Observations clarify that FGR evolves prenatally from a preclinical phase of abnormal vascular, nutrient, and endocrine milieu to a clinical phase differing in characteristics in preterm versus term pregnancies. Relating childhood neurodevelopment to prenatal characteristics may aid in identifying mechanisms and timing of critical insults. Based on available studies, lagging head circumference, degree of FGR, gestational age, umbilical artery (UA), aortic and cerebral Doppler parameters may be independent prenatal predictors of infant and childhood neurodevelopment. Head circumference is meaningful independent of gestational age, but a generalized growth delay has greater impact in early-onset FGR. Gestational age at delivery becomes the chief determinant of neurodevelopment before 32 to 34 weeks' gestation. Doppler evidence of placental resistance to flow is increasingly important after 27 weeks, with maximum concern when flow reversals are noted in the umbilical artery, aorta, ductus venosus, or the umbilical vein. These findings predominate in early-onset FGR; cerebral vascular impedance changes, sometimes expressed as a ratio between the pulsatility indices of the middle cerebral and umbilical arteries, are important in later FGR. Abnormal motor and neurologic delays occurring in preterm FGR give way to cognitive effects and abnormalities related to specific brain areas as gestation advances, suggesting different pathophysiologies or evolving vulnerabilities of the fetal brain. Current studies do not suggest that fetal deterioration has an independent effect on neurodevelopment in early-onset FGR; the role of intervention in late FGR requires more research: risks for damage and patterns of deterioration may differ in the third trimester.[49]

Ultrasound-Guided Procedures

Real-time ultrasound is well suited by virtue of safety, economy, and convenience for guiding placement of needles, cannulae, catheters, and other devices used in fetal diagnosis and therapy. The range of procedures includes oocyte retrieval and embryo transfers, embryonic and fetal reduction, chorionic villus sampling, placental and skin biopsies, amniocentesis and amnioreduction, cord blood sampling, intrauterine transfusion, aspiration of fluid from various fetal and maternal sites, and an adjunct to fetoscopy and vascular ablation. The effectiveness as well as complications from procedures are often apparent in real time. Determinations of fetal status; relative fetal and umbilical cord positions during external version for malpresentations, labors, and immediately before transfusions; surgical interventions; and the EXIT (EX utero intrapartum treatment) procedure are important accepted applications.

Fetal Well-Being Assessment

A tenet of antepartum testing is that more accurate predictions of fetal wellness are achieved in proportion to the number of variables considered. See also Chapter 12. The biophysical profile (BPP) is a noninvasive ultrasound-based clinical tool that integrates levels of dynamic biophysical activities into a usable standard. The BPP attempts to predict the presence or absence of fetal asphyxia to prevent progression to metabolic acidosis and fetal death. The BPP seeks to identify four parameters in a 30-minute period, each of which is assigned two points: (1) observation of continuous tidal fetal breathing for 30 seconds, (2) a vertical amniotic fluid pocket of at least 2 cm (or 2 cm in 2 planes), (3) three obvious fetal movements, and (4) fetal tone, manifested by brisk flexion of small parts or hands. Death or injury within 1 week is more likely with scores below six, with loss of tone considered a late finding. Conversely, scores of eight

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are considered highly reassuring for well-being during the same period. A fetal non-stress test, sometimes included for an additional 2 points (total score of 10), does not usually affect the predictive value of the BPP.

Antepartum testing by BPP should not be performed prior to viability or when fetal or maternal conditions preclude successful intervention. Cautious interpretation is appropriate for extreme fetal prematurity; in the presence of anomalies; maternal metabolic abnormalities; during labor; and with some drugs, including opiates, sedatives, and antenatal corticosteroids.

Fetal Anomalies

Neonatal outcomes can be optimized by forewarning and timely preparation when fetal abnormalities are present. Unfortunately, more than one-third of birth defects remain unrecognized prenatally. False-positive diagnoses are less frequent, but up to 10% discordancy with autopsy findings highlights the inherent uncertainties of prenatal diagnosis. Familiarity with imaging pitfalls associated with common anomalies is imperative to avoid misdiagnosis. Suspected structural defects should always be visualized in the correct plane with attempted confirmation in other planes. Precise measurements using specific criteria, appropriate gain settings, and additional modalities may be required for correct interpretation and management. Expert second opinions by patient referral or image review are available for most findings. Despite acknowledged limitations, prenatal ultrasound is the standard method for recognition of fetal anomalies.

Central Nervous System

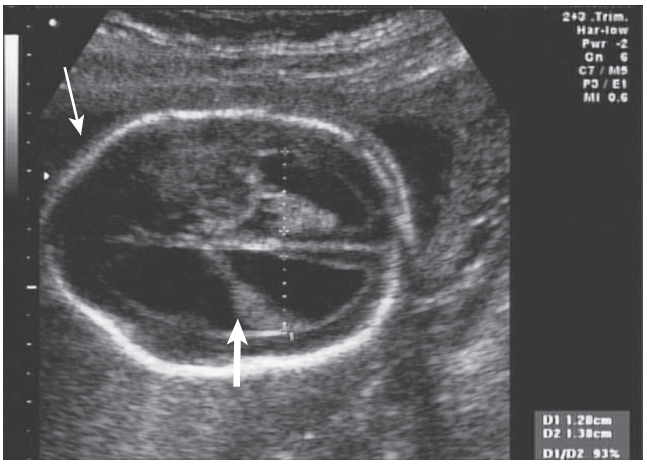
Fetal Ventriculomegaly

Hydrocephalus and ventriculomegaly are not strictly synonymous. Hydrocephalus connotes raised intracranial pressure, a functional observation not directly amenable to ultrasound. Prenatal enlargement of lateral ventricles (Fig. 11.39) may occur without altered pressure because of developmental abnormalities. Enlargement of the atria and posterior horns of the lateral cerebral ventricles (colpocephaly) may be associated with agenesis of the corpus callosum or type II Chiari malformations. Dilated lateral ventricles may also result from obstructed cerebrospinal fluid flow by hemorrhage or from brain destruction by a variety of causes, including ischemia and infection (e.g., cytomegalovirus, toxoplasmosis, or Zika virus). A single measurement over 10 mm at the level of the posterior atria of the lateral ventricles defines ventriculomegaly.

Atrial widths tend to decrease slightly during pregnancy. Choroid plexus positioning is gravity-dependent; on axial views, the choroid, attached at the level of the foramen of Monro, rests on the dependent wall of the lateral ventricle, marking the limit of the lateral ventricle, even when the wall cannot be visualized. A "dangling" choroid plexus conveys the extent and severity of ventricular enlargement (Fig. 11.40).



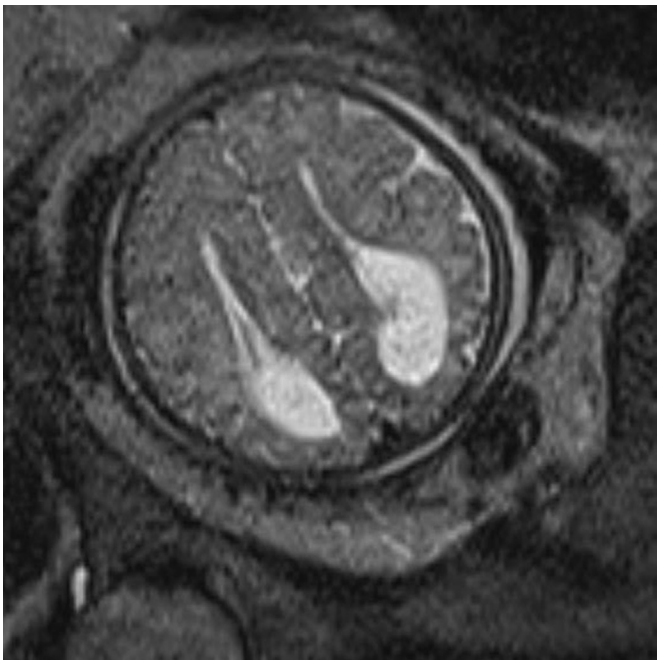
• **Fig. 11.39** Fetal MRI at 23 weeks' gestation. Massive enlargement of the lateral ventricles with a thin rim of remaining brain parenchyma.



• **Fig. 11.40** "Dangling choroid" (*thick arrow*) with bilaterally dilated lateral ventricles secondary to an open neural tube defect. The latter is signaled by the frontal depression "lemon sign" (*thin arrow*) in up to 90% of cases.

Clinical outcomes of severe ventriculomegaly (atrial size greater than 15 mm) are discouraging; survivors are often mentally and physically impaired. Hydrocephalus associated with arachnoid cyst, atresia of Monro, absence of the corpus callosum, or minor intracranial hemorrhage may have a better prognosis. By contrast, hydrocephaly seen with holoprosencephaly, encephalocele, congenital syndromes, or infection generally leads to loss or greater disability. Formal diagnostic and management algorithms, combining ultrasound, MRI, genetic diagnosis, and infectious disease screening play an essential role in counseling and care when hydrocephaly is identified.[52]

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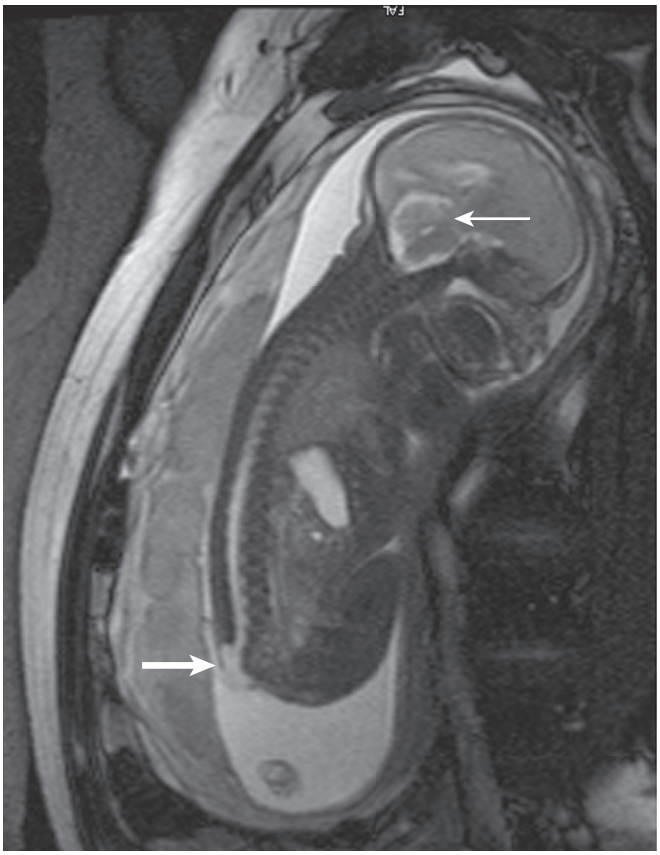
• **Fig. 11.41** Fetal MRI at 35 weeks' gestation demonstrating agenesis of corpus callosum. Axial scan shows parallel lateral ventricles enlarged posteriorly (colpocephaly) in a teardrop shape.

In utero shunting has no current role in the treatment of prenatal ventriculomegaly. Asymmetric or rounded lateral ventricles and mild ventriculomegaly (widths between 10 and 12 mm) convey an uncertain prognosis, as most infants are normal, particularly when resolution occurs; slightly wider dimensions (12-15 mm) carry an intermediate prognosis.

Agenesis of the corpus callosum can be isolated but is commonly associated with other anomalies of abnormal neuronal migration. Midtrimester diagnosis of many brain lesions is hampered by ongoing differentiation and growth of the central nervous system; third-trimester transvaginal cranial ultrasound and MRI are particularly helpful in assessing the progressive development of gyri and sulci of the brain (Fig. 11.41).

Meningomyelocele and (Type II) Chiari Malformation

Meningomyelocele (Fig. 11.42) may be associated with a Chiari II malformation, that is, downward displacement of the hindbrain, as well as with other brain anomalies, including ventriculomegaly (Fig. 11.43). Often, hydrocephalus does not develop in children with neural tube defects (NTD) until after birth or lesion repair. Open NTD (Fig. 11.44) is usually accompanied by markedly elevated alpha fetoprotein levels in both maternal serum and amniotic fluid. A meningomyelocele appears on ultrasound as splaying or divergence of the posterior ossification centers, best appreciated on axial spinal views. A fluid-filled sac may be seen and the integrity of the overlying skin can be visibly disrupted on axial and sagittal images. The level



• **Fig. 11.42** MRI of sacral meningomyelocele (*thick arrow*) at 21 weeks' gestation; normal posterior fossa including cerebellum and fourth ventricle (*thin arrow*).



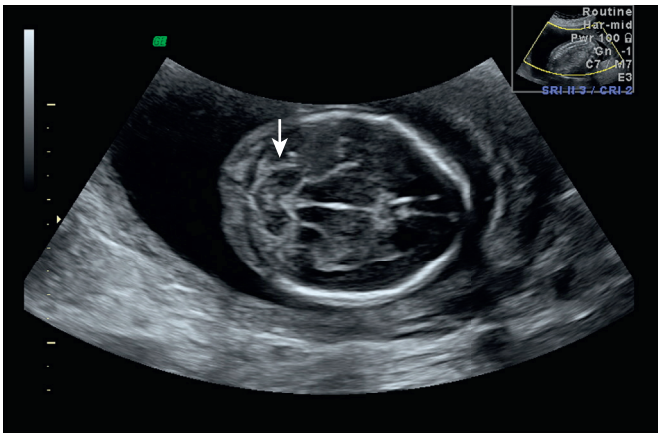
• **Fig. 11.43** Fetal MRI at 19 weeks demonstrates Chiari II malformation. Note dilated lateral ventricle (*straight arrow*) and communication between lower lumbar spinal canal and amniotic fluid–open neural tube defect (*curved arrow*).

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of the meningomyelocele can be ascertained more accurately with 3D ultrasound and MRI (see Figs. 11.35 and 11.42), helpful for predicting the outcome in affected children. Severe cases may be associated with kyphoscoliotic spinal deformity or clubbing of one or both feet. Prenatally, extremity movement may seem to be preserved; however, absence of normal activity better correlates with postnatal motor function.

The Skull and Brain in Spina Bifida

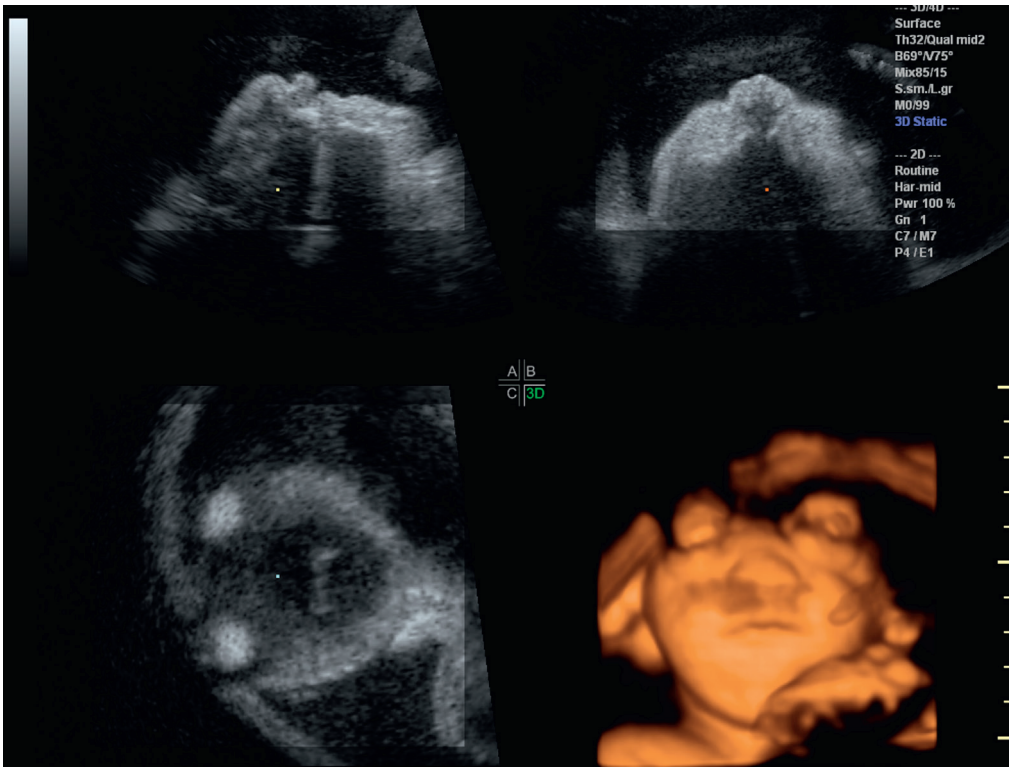
The "lemon sign" refers to the altered appearance of the calvarium, similar in shape to a lemon, on an axial view of the skull and brain (see Fig. 11.40). Biconcave frontal bones produce the calvarial distortion. The sign is best demonstrated between 18 and 24 weeks but is not specific, appearing sometimes in otherwise normal children. The "banana sign" refers to abnormal cerebellar positioning, curled in a crescent (banana-like) around the brainstem (see Fig. 11.44). Obliteration of the cisterna magna and cerebellar distortion are secondary to type II Chiari malformation. One or both signs are seen in the majority of spina bifida cases during the midtrimester and should prompt a more detailed examination of the spine. Prenatal surgical closure of defects may improve outcome in appropriate candidates, particularly with respect to preservation of motor function and prevention of hindbrain displacement.



• **Fig. 11.44** Open neural tube defects may be associated with an obliterated posterior fossa "banana sign" (*arrow*) in 60% of cases.

Anencephaly

Anencephaly, the absence of normal brain and calvarium superior to the orbits, can be detected as early as 10 weeks but is recognizable throughout gestation (Fig. 11.45). Maternal serum alpha fetoprotein is usually very elevated. About half of cases have associated anomalies, for example, meningomyelocele, cleft palate, or clubfoot. Occasionally, the typical appearance is altered by the presence of echogenic material superior to the orbits, identified pathologically as angiomatous stroma ("area cerebrovasculosa"). Polyhydramnios and malpresentation are common later findings. Abnormal prolongation of pregnancy may occur, presumably secondary to lack of fetal neurohormonal cues for labor. Anencephaly is considered incompatible with



• **Fig. 11.45** Three-dimensional orthogonal image of anencephaly at 17 weeks' gestation. The cranial vault is absent above the orbits.

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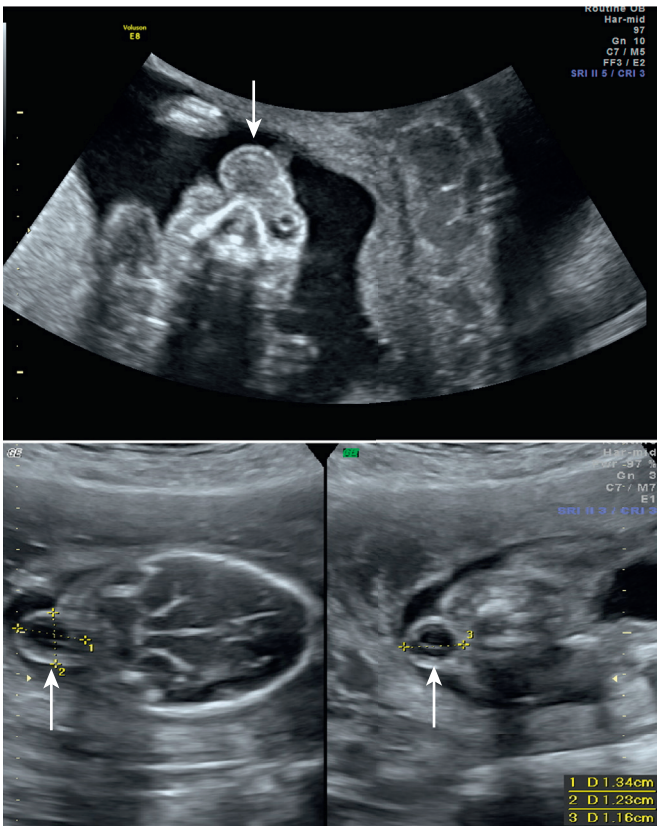
meaningful survival; most affected live-borns succumb in the immediate neonatal period. Intervention for purely fetal indications is futile and is not recommended.

Encephalocele

The extracranial protrusion of brain tissue within a meningeal sac is a straightforward ultrasound diagnosis, although dependent on site and size of lesion and appropriate visualization. Most encephaloceles in the Western world are occipital and midline and should be distinguished from soft tissue edema or lymphangiomata of the neck. The identification of a calvarial defect allows a specific diagnosis (Fig. 11.46). Encephaloceles may be isolated or associated with amniotic band syndrome (when off midline) and genetic syndromes such as Meckel-Gruber. Prognosis is affected by site, size/amount of extruded tissue, and adversely affected by ventriculomegaly, microcephaly, and syndromic etiology. Anterior sites are more common in Asian populations; small nasal or frontoethmoidal encephaloceles may initially elude even postnatal detection.

Holoprosencephaly

Holoprosencephaly, a malformation resulting from early failure of division of the embryologic prosencephalon or forebrain, is frequently associated with facial abnormalities (Fig. 11.47*A*). Its incidence ranges from 0.6 to 1.9 per 10,000 live births, although this is likely an underestimate because many cases spontaneously abort and milder variants can be unrecognized. In cases without chromosomal abnormalities, recurrence risk is estimated to be 6%. The etiology of holoprosencephaly is heterogeneous and not fully known with most cases being sporadic. Environmental, mechanical, and genetic factors have all been implicated. Several chromosomal disorders are linked to this anomaly, most notably trisomy 13, with 70% exhibiting holoprosencephaly. Holoprosencephaly in association with extra-cephalic malformations strongly suggests aneuploidy; there are also autosomal dominant and recessive familial forms. The condition has been induced by a variety of teratogenic agents in animal models. In alobar holoprosencephaly, the most severe form, there is a complete failure of cleavage of the forebrain into two hemispheres. The cerebral hemispheres are fused and enclose a single prosencephalic ventricle. In addition to a single ventricular cavity, the thalami are fused, and the cavum septum pellucidum (CSP), corpus callosum, falx cerebri, optic tracts, and olfactory bulbs are all absent. The alobar condition is often associated with fetal loss; the vast majority of live-borns experience severe neurologic dysfunction or death in early infancy; less severe variants have a wider, less predictable range of outcomes. Partial cleavage results in semilobar holoprosencephaly, with posterior separation of the cerebral hemispheres, variable degrees of thalamic fusion, and absent olfactory bulbs and corpus callosum. In lobar holoprosencephaly, the abnormalities may be confined to absence of the CSP and corpus callosum with fusion of the lateral ventricles and cingulate gyrus; hemispheres are separated anteriorly and posteriorly. The mildest form, septal optic dysplasia, lacks only the CSP. Severe forms of holoprosencephaly may exhibit cyclopia (median mono-ophthalmia) with or without proboscis, cebocephaly (ocular hypotelorism and a blind single nostril), ethmocephaly (ocular hypotelorism with proboscis) (see Fig. 11.47*B*), and median facial clefts. The diagnosis of holoprosencephaly was typically made during the midtrimester anatomic survey by noting fused lateral ventricles and thalami and the absence of normal midline structures. Early prenatal detection of holoprosencephaly can occur between 11 and 14 weeks' gestation by obtaining transverse cranial images in which the normal "butterfly sign" of choroid and ventricles is absent (see Fig. 11.47*C*).

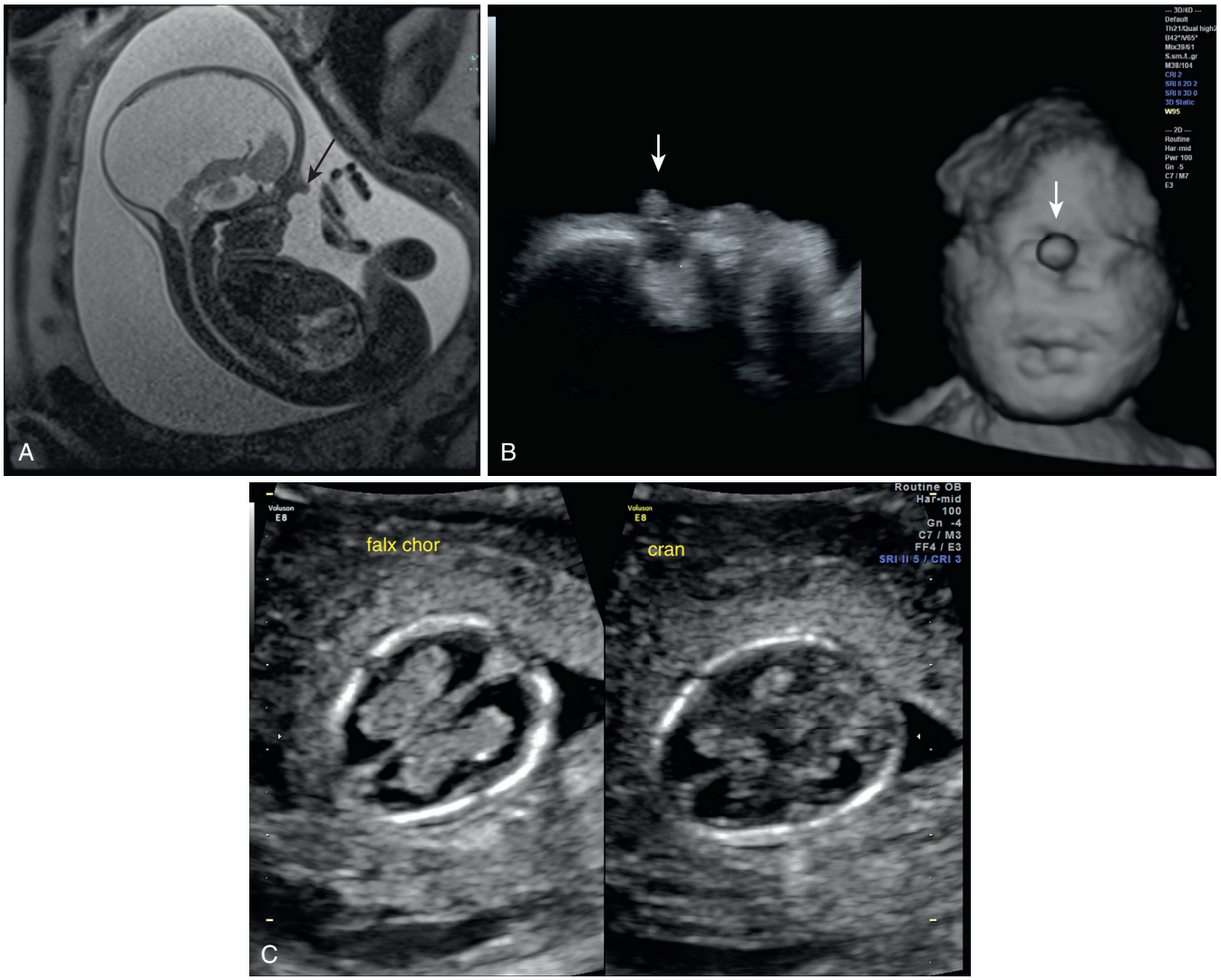


• **Fig. 11.46** Upper image: Occipital encephalocele with herniation of meninges through the defect (*arrow*). Lower images: Posterior encephalocele with meninges and neuronal tissue.

Dandy-Walker Malformation

The Dandy-Walker malformation is a fluid-filled posterior fossa cyst, with variable occurrence of lateral ventriculomegaly; the posterior fossa is always enlarged and the tentorium uplifted.[46] The cerebellar hemispheres, separated by the cyst, are rudimentary. Agenesis of the cerebellar vermis is difficult to confirm before 20 weeks because wide variations in developmental timing mean that full formation may not yet be present. The Dandy-Walker variant consists of direct communication between the fourth ventricle and cisterna magna, without posterior fossa enlargement and with only mild hypoplasia of the inferior vermis. The subtle ultrasound findings can be associated with serious abnormalities

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• **Fig. 11.47 A,** Fetal MRI at 24 weeks. Alobar holoprosencephaly. Profile of the face demonstrated no orbits or nose but a proboscis (*arrow*). Massive single ventricle with little remaining brain. **B,** Reconstructed three-dimensional image of a fetus with alobar holoprosencephaly. A proboscis (*arrows*) is seen but no orbits. **C,** The fetal choroids are seen to be symmetrical and intact in this 12-week fetus.

of neuronal migration; confirmation from MRI is helpful (Fig. 11.48).

Choroid Plexus Cyst

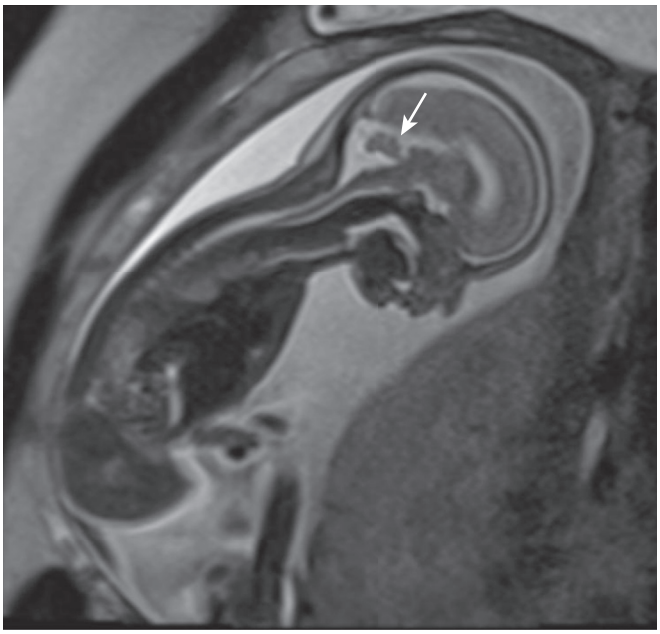
Cysts in the choroid plexus, noted in 1% to 2% of normal second-trimester pregnancies, usually resolve by the early third trimester (see Fig. 11.18). Cyst number, size, or persistence impart no additional clinical significance. Isolated choroid plexus cysts are generally associated with normal karyotype, do not require follow-up to confirm resolution, and do not affect postnatal development.[14] Choroid cysts have been associated with trisomy 18.

Spine

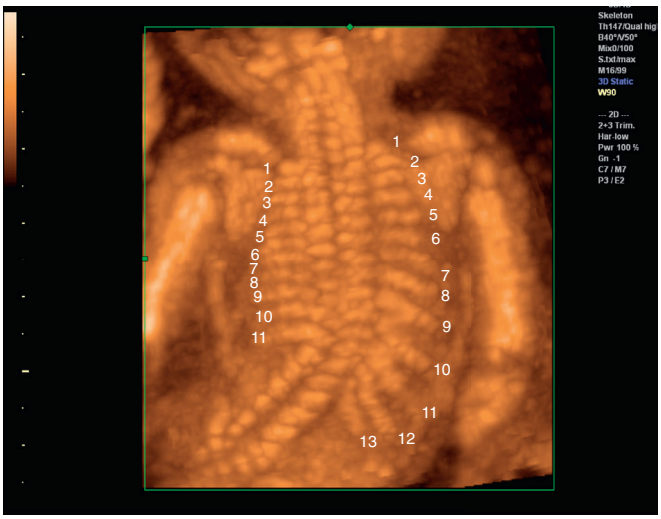
3D imaging is extremely useful for studying fetal spine, vertebrae, ribs, pelvic bones, and spinal cord. Operators can simultaneously visualize three orthogonal planes, scroll through volumes along any given orientation, and precisely locate abnormalities by use of stable anatomic reference points (Fig. 11.49).

Sacrococcygeal teratomas (SCTs) are congenital germ cell tumors, usually benign but often large, arising posteriorly at the medial spinal base. Posterior bony elements of the lumbosacral spine are typically intact. Often SCT is associated with polyhydramnios, prematurity, and more rarely with anemia, high output cardiac failure, and hydrops. Maternal serum alpha fetoprotein is usually elevated. Generally, SCTs are not related to aneuploidy, although rare cases of chromosomal abnormalities have been reported. The typical teratoma is a complex cystic and solid mass protruding from the fetal rump, with arterial and venous flow seen by color Doppler. Uncommonly, it may be entirely cystic or solid, extend into the fetal pelvis (Fig. 11.50) and abdomen, or undergo malignant degeneration. Some SCTs have unique characteristics, including those found

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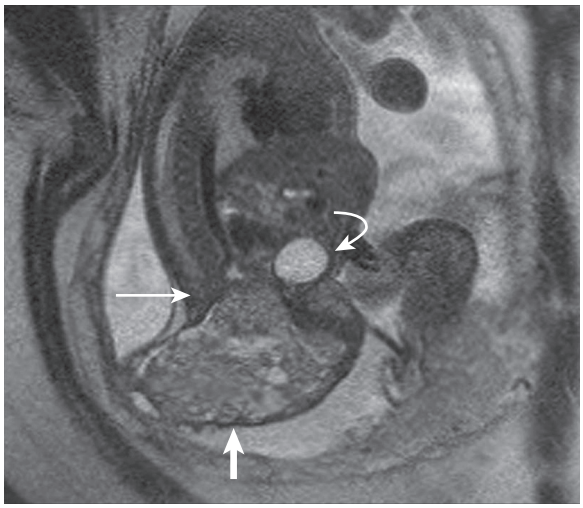


• **Fig. 11.48** Fetal MRI of Dandy-Walker variant at 22 weeks' gestation. Note communication of the fourth ventricle with the cisterna magna and uplifting of the upper cerebellum.

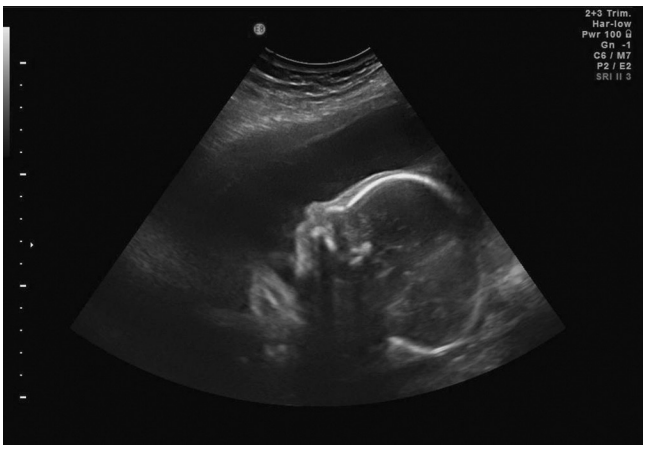


• **Fig. 11.49** Coronal view through the fetal spine showing hemivertebra and an uneven number of ribs.

in the Currarino syndrome (presacral SCT, sacral malformation, and anorectal anomalies, with or without associated Hirschsprung disease and cloacal anomalies). Prenatal diagnosis is extremely important in planning timing and route of delivery, given tumor size and potential for hemorrhage, and in anticipation of postnatal surgery. Critically ill fetuses distant from term may benefit from referral to a fetal surgery center. Emergency delivery may be precipitated by tumor hemorrhage, mass effects, or by obstetric mirror syndrome, a rare maternal complication simulating severe preeclampsia. The prognosis for uncomplicated SCT is generally excellent, although anterior extension and high levels of circulating AFP and other markers, particularly in



• **Fig. 11.50** Fetal MRI of sacrococcygeal teratoma at 27 weeks' gestation. Tumor (*thick arrow*) extends into fetal pelvis between the spine (*thin arrow*) and the urinary bladder (*curved arrow*).



• **Fig. 11.51** Fetal retrognathia (recessed chin) is a feature of a variety of syndromes and aneuploidies, as noted in this fetus with trisomy 18.

immature teratomas, convey elevated risks for recurrence or malignancy.[33,34]

Head and Neck

After 14 weeks, visualization of the nose, nares, orbits, forehead, lips, eyes, and ears is feasible. Orbits are clearly seen axially; the ocular diameters, and interocular and binocular distances (defining hypertelorism and hypotelorism) are measurable. The profile reveals the forehead, nose, and jaw sagittally (contrast Fig. 11.1 with Fig. 11.51). The coronal view, best for facial structures, includes the orbits (and lenses), eyelids, nose, and lips. Coronal and 3D views identify facial clefting, including cleft lip and palate; clefts may be central or lateral, unilateral or bilateral, involving nasal structures or, more subtly, the soft palate. Sagittal views should include the nasal bones; nasal bone hypoplasia or absence is associated with an increased risk for Down syndrome. The complex anatomy of the fetal face is shown exquisitely by 3D sonography. The distinction between

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normal and abnormal facial features can be seen clearly by comparing Fig. 11.8 with Fig. 11.52.

Cystic hygroma is a septate, cystic mass arising from the neck and occipital region secondary to lymphatic malformation; it may extend over the entire trunk (Fig. 11.53*A*). Posterior septation of the nuchal ligament and bony integrity distinguish this lesion from neural tube defects. Associated aneuploidies, particularly monosomy X (45,X), are common. When associated with generalized edema, cystic hygromas carry a grim prognosis; when small, isolated, and with normal karyotype, more favorable outcomes, including regression, are well documented. Less common neck lesions include teratomas, hemangiomas, branchial cleft cysts, and anteriorly, thyroid goiters and thymic absence.

Increased nuchal translucency (see Fig. 11.11) and nuchal fold thickness (see Fig. 11.17) are associated with aneuploidies, including trisomies 21 and 18, cardiac malformations, diaphragmatic herniation, dwarfisms, a wide range of other anomalies and genetically inherited disorders (Noonan syndrome), lymphatic obstruction sequence, and fetal loss. With normal karyotypes and reassuring midtrimester surveys, outcomes are generally good.[47]

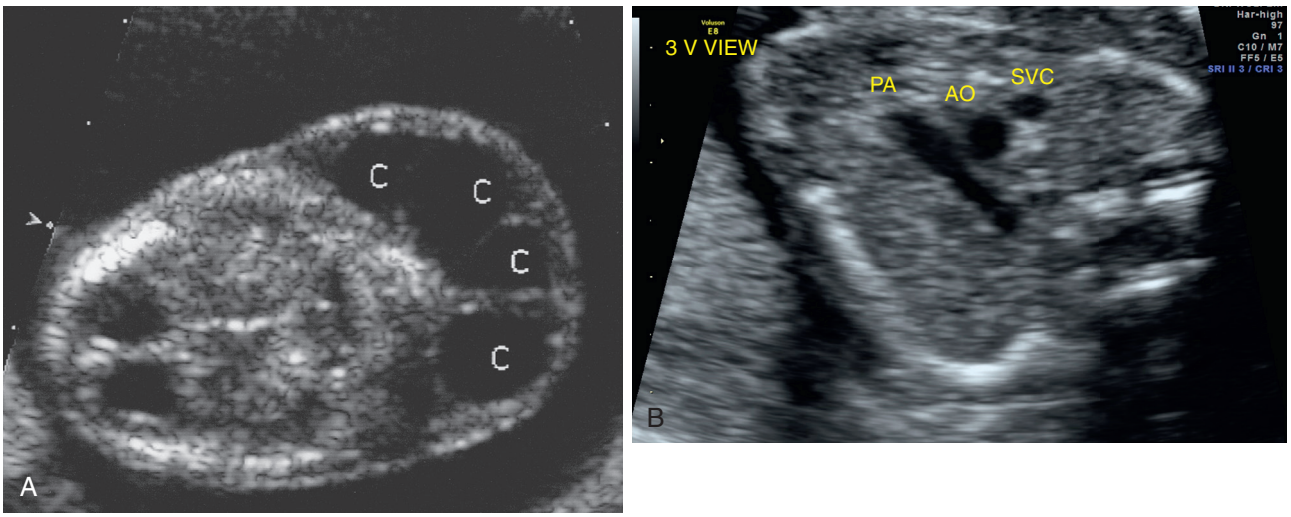


• **Fig. 11.52** Unremarkable fetal face shown on 3D imaging at 34 weeks' gestation. Views are optimized by adequate fluid interface, lack of fetal movement, limited maternal adipose and scarring tissues, and posterior placentation.

Heart

Optimal timing of the fetal heart study is a compromise between finding defects as soon as possible and accurately assessing complex anatomy, recognizing that some lesions manifest late in pregnancy. Basic heart evaluation is now an integral part of anatomic surveys at 18 to 22 weeks' gestation. Initial appreciation of first-trimester cardiac anatomy is feasible by either a transvaginal or transabdominal approach, augmented by color Doppler; however, the best timing for early imaging of the four chambers and great arteries is usually at 13 to 14 weeks. In experienced hands, first-trimester fetal echocardiography is quite sensitive for the detection of major structural cardiac abnormalities. Some features useful in combination with nuchal measurements for aneuploidy screening include abnormal flow patterns in the ductus venosus and tricuspid valve; these are also early markers for cardiac abnormalities and should prompt more detailed assessment. A focused cardiac examination should be performed for known medical or historical risks, with teratogen exposures, and when any significant extra-cardiac anomaly or chromosomal defect has been identified. Cardiac defects should also be excluded in the presence of an aberrant right subclavian artery or other vascular anomalies.[47]

Screening for fetal cardiac abnormalities was introduced more than 30 years ago, yet prenatal detection remains challenging. Most major congenital heart defects are amenable to prenatal identification, with tertiary centers reporting high diagnostic accuracy; however, overall detection rates remain low and highly operator dependent. Pregnancies



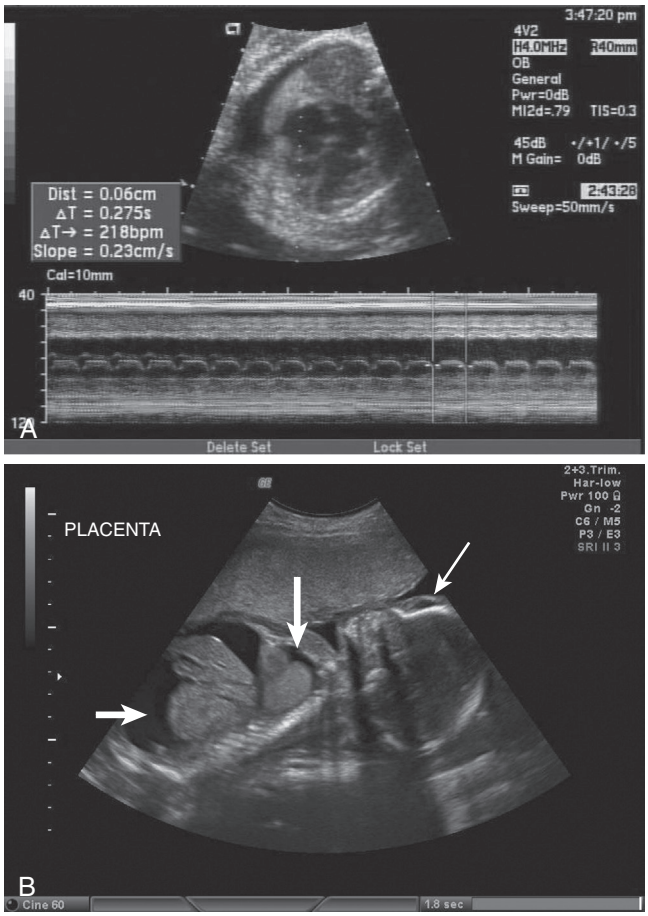
• **Fig. 11.53 A,** Transverse image through the head showing a posteriorly located cystic hygroma with multiple septate cysts (C). **B,** Three-vessel view of the fetal heart. The pulmonary artery (PA), aorta (AO), and the superior vena cava (SVC) can be seen.

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with predisposing factors are usually referred for echocardiogram, but most cases of congenital heart disease occur in low-risk pregnancies. Prenatal diagnosis, particularly for babies at risk for acute cardiovascular collapse, for example, with ductal dependent or restrictive lesions, could reduce both morbidity and mortality.[39]

Basic cardiac studies attempt to obtain symmetric, appropriately oriented four-chamber views of the fetal heart (see Fig. 11.36), showing pulmonary veins, atrioventricular valves, intra-atrial and intraventricular septa, as well as aortic and ductal arches and normal outflow views that link the aorta and neck vessels with the left ventricle and the bifurcating pulmonary artery with the right. The echocardiographic three-vessel view (see Fig. 11.53*B*) allows assessment of the superior vena cava, ascending aorta, and main pulmonary artery. These views aid in identification of transposition of the great arteries, tetralogy of Fallot, truncus arteriosus, and some aortic abnormalities.

Fetal arrhythmias may also be analyzed (Fig. 11.54). Sensitivity for complex cardiac lesions exceeds that for isolated septal defects; accurate diagnosis remains dependent on experience and the absence of obstacles posed by poor resolution or unfavorable fetal position.



• **Fig. 11.54** Fetal arrhythmia by M-mode (**A**), consistent with paroxysmal atrial tachycardia at 218 bpm. Sustained rates greater than 200 bpm may be associated with fetal hydrops (**B**). The fetus has ascites (*short arrow*), pleural effusion (*long arrow*), and skin edema (*thin arrow*).

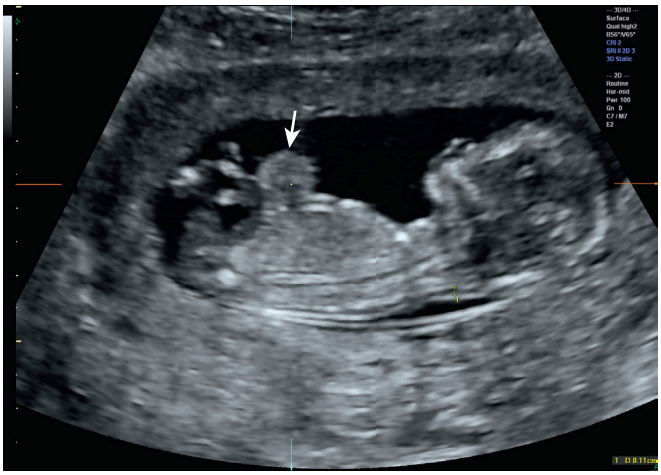
Gastrointestinal Tract

Normal Bowel Appearance

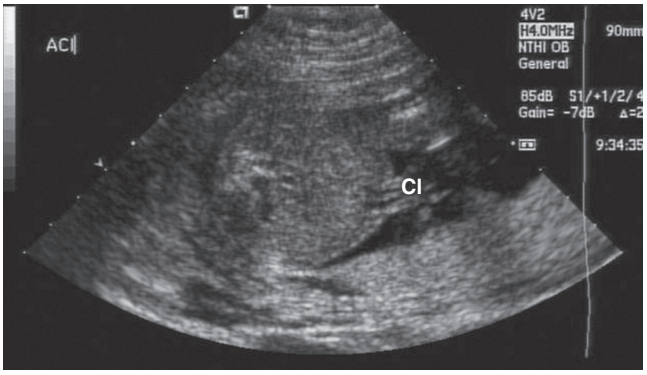
Physiologic migration of the gut into the proximal umbilical cord occurs between gestational weeks 7-10 and may be seen on first-trimester scans (Fig. 11.55) up to 12 weeks. The normal liver always remains intra-abdominal; bowel migration should not be mistaken for a ventral abdominal wall defect.

The fetal stomach, seen transvaginally by 9-10 weeks of gestation, is an echo-free structure in the upper left abdomen, varying in size as it empties and fills.

Fetal small bowel is not undifferentiated in appearance early in gestation but appears as central abdominal fluid-filled loops by the late second trimester (Fig. 11.56). Fetal colon is clearly evident by the third trimester as a hypoechoic, haustrated tube at the abdominal periphery. Meconium in the large bowel is normal in the third trimester; second-trimester meconium normally may have transiently increased echogenicity. Hyper-echogenic bowel, bright as adjacent osseous structures, is a concerning but nonspecific finding associated with trisomy 21, cystic fibrosis,

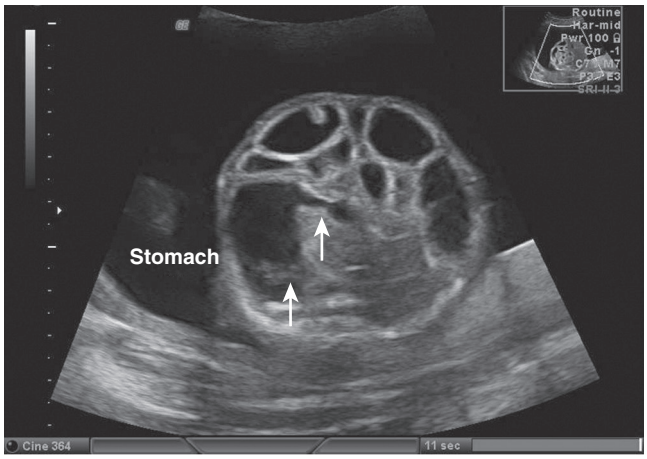


• **Fig. 11.55** An 11-week fetus within its gestational sac. Physiologic midgut herniation occurs from week 8 to week 12.

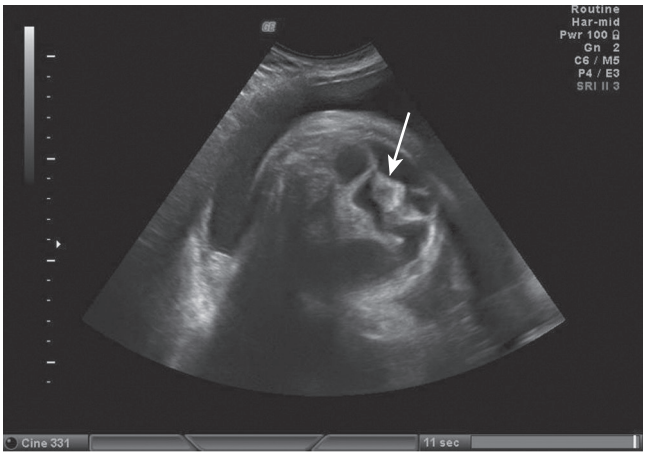


• **Fig. 11.56** Cross section of the abdomen at the level of the umbilical vessels, demonstrating heterogeneous-appearing, nondistended, fluid-filled loops of normal small bowel. The abdominal walls are clearly intact adjacent to the cord insertion (CI).

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• **Fig. 11.57** Massive dilation of bowel loops secondary to in utero volvulus with obstruction. The stomach and duodenal bulb are marked with arrows. Polyhydramnios is present.



• **Fig. 11.58** Dilation of small bowel loops associated with ileal obstruction and perforation. The echogenic material (*arrow*) is a meconium pseudocyst.

bowel atresia, congenital infections (e.g., cytomegalovirus), growth restriction, placental abruption, and poor outcome.[1]

Gastrointestinal tract obstruction can often be diagnosed by ultrasound. Blockage of the proximal alimentary canal interferes with normal amniotic fluid regulation by fetal swallowing and gut absorption. In complete proximal obstructions, assuming intact membranes and normal renal production, polyhydramnios is invariable.

Esophageal Atresia and Tracheoesophageal Fistula

A nonvisualized fetal stomach combined with polyhydramnios should alert the examiner to the possibility of esophageal atresia. Unfortunately, these signs coincide in only 40% of cases. Nonvisualization of the stomach is not specific for esophageal atresia; proximal esophageal pouches are rarely visualized. Polyhydramnios, although present in two-thirds of cases, may not develop until the third trimester. The VACTERL complex consists of vertebral, anal, cardiovascular, tracheal, esophageal, renal, and limb malformations; these systems should be scrutinized if tracheoesophageal fistula is suspected. The stomach may also fail to fill when there is little fluid to swallow (e.g., as in oligohydramnios, or secondary to neuromuscular conditions like Pena-Shokeir syndrome that interfere with swallowing).

Small Bowel Obstruction

In duodenal atresia, the distended stomach and proximal duodenum produce a "double-bubble" sign akin to the neonatal radiologic finding (see Fig. 11.15). A strong (25%) association with trisomy 21 warrants genetic testing when duodenal atresia is suspected. Other etiologies include annular pancreas, duodenal web, malrotation, and severe duodenal stenosis. Ileal and jejunal atresias usually cause multiple distended bowel loops, often exhibiting exaggerated peristalsis (Fig. 11.57). More distal obstruction, as seen in meconium ileus, Hirschsprung disease, and anal atresia, may not result in visible bowel dilation until third trimester or postpartum. Meconium peritonitis, a sterile but morbid chemical response to intrauterine bowel perforation, is characterized by echogenic peritoneal calcifications and free intraperitoneal fluid (Fig. 11.58); some cases progress to echogenic pseudocysts.

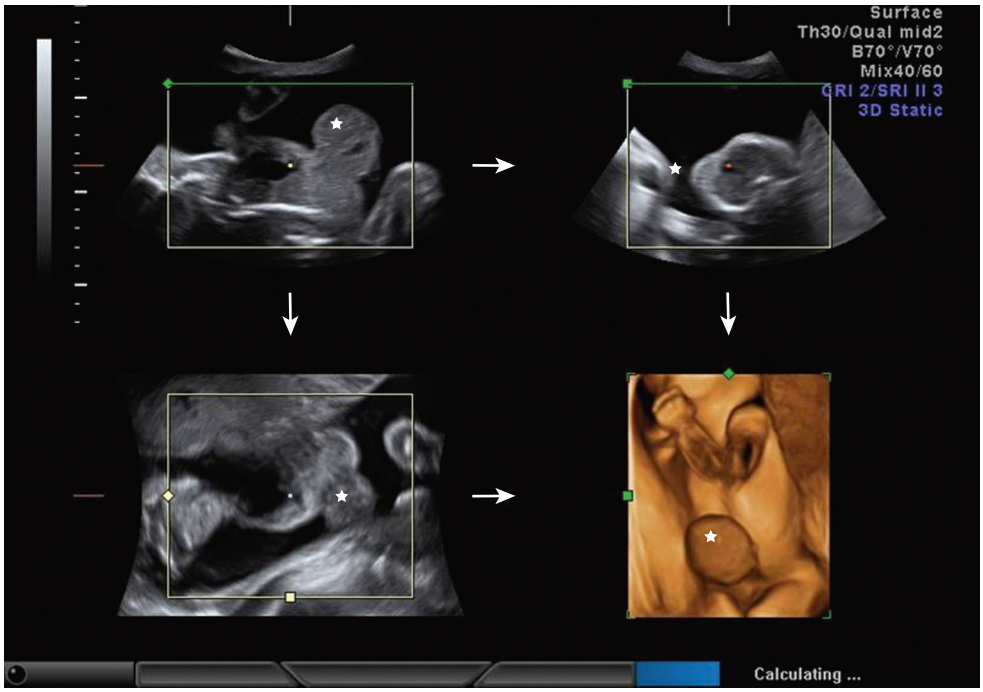
Anterior Abdominal Wall Defects

A midline ventral abdominal wall defect involving the base of the umbilical cord is characteristic of omphalocele (Fig. 11.59). A sac surrounds the herniated viscera and may include the liver (Figs. 11.60 and 11.61). Omphaloceles are often associated with other anomalies (Beckwith-Wiedemann syndrome, pentalogy of Cantrell) and aneuploidies (trisomies 13 and 18). In gastroschisis, herniated bowel loops float freely in the amniotic cavity without a covering membrane (Fig. 11.62). Defects are usually to the right of the umbilical insertion; aneuploidy, extra-intestinal abnormalities, familial forms, and recurrence are not customary with gastroschisis. Gastroschisis is thought to be caused by a vascular accident with wall infarction; young maternal age, use of vasoactive substances, and NSAIDs have been related to increased risk for this lesion.

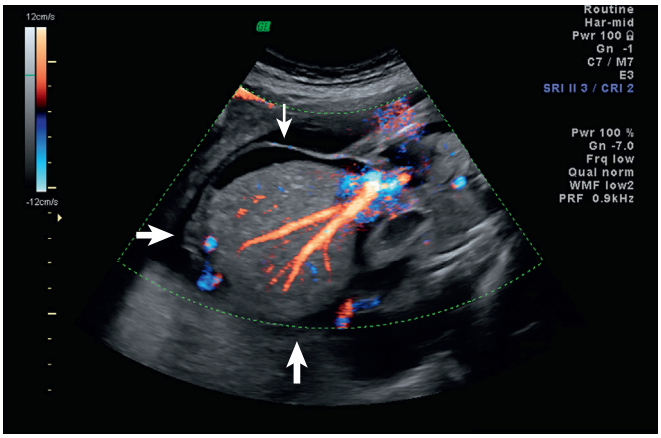
Diaphragmatic Hernia and Thoracic Lesions

Congenital diaphragmatic hernia (Fig. 11.63) is diagnosed when abdominal organs (usually stomach and bowel) are seen in the thorax. Fluid-filled intrathoracic bowel loops with visible peristalsis help confirm the diagnosis. Associated congenital heart disease, other structural defects, and chromosomal abnormalities worsen a guarded prognosis. Hernia contents produce a mass effect, shifting the mediastinum and compressing the lungs (Fig. 11.64); the resulting pulmonary hypoplasia and secondary pulmonary hypertension are major determinants of mortality. Polyhydramnios and lagging abdominal circumference are common associations. Estimation of lethality is usually based on lung measurements at the level of the four-chamber heart (expressed as

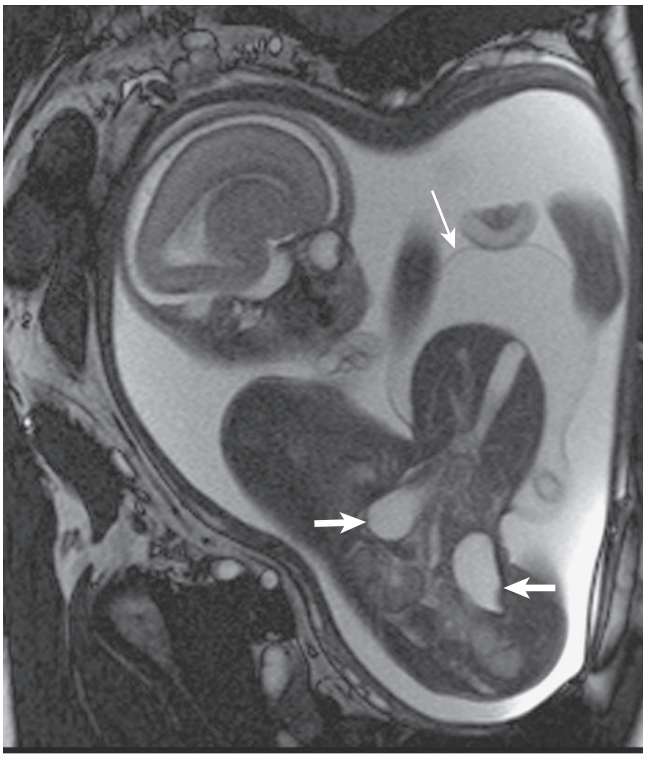
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• **Fig. 11.59** Three-dimensional views of an omphalocele (*star*) at 18 weeks' gestation.



• **Fig. 11.60** Color Doppler view of a massive omphalocele (*outline*) that includes the liver and hepatic vessels (*color*). The extruded portion and the sac are almost equal in diameter to the torso (*to the right*).

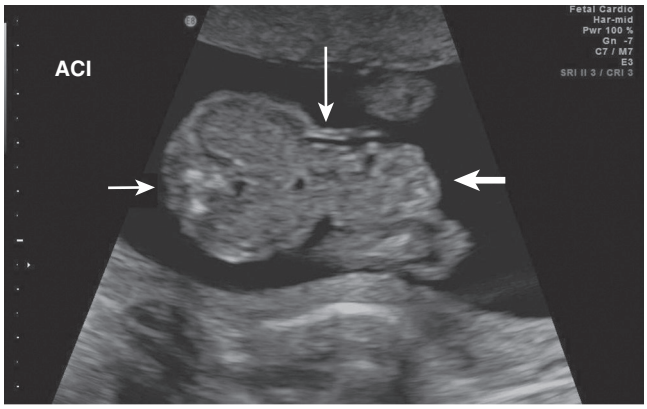


• **Fig. 11.61** Fetal MRI of omphalocele at 24 weeks' gestation. Note membrane (*thin arrow*) covering the omphalocele that includes the liver. Fetal stomach and bladder are shown by *thick arrows*. Note normal smooth brain surface at 24 weeks without gyri or sulci.

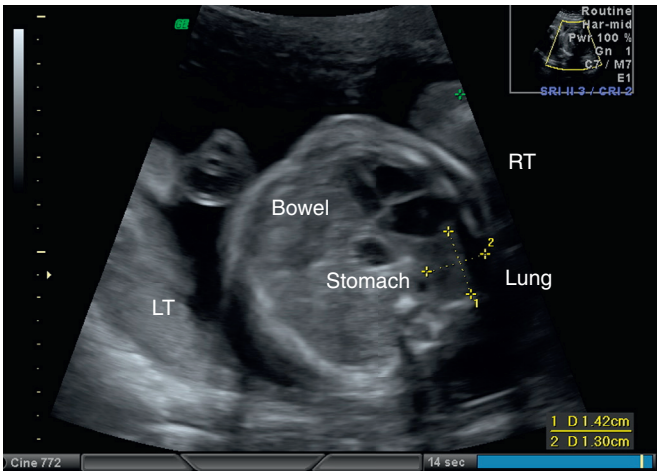
observed to expected lung/head circumference); the process is unreliable, largely because most lesions are in an intermediate prognostic category. Calculated 3D lung volumes by ultrasound study and MRI provide more precise measurements of the lungs but with only minor impact on prognostic accuracy. Liver herniation into the chest (Fig. 11.65) is common but carries a worse prognosis; right-sided hernias are harder to recognize and may also increase mortality. Bilateral herniation is generally lethal with few documented exceptions.

Congenital pulmonary adenomatoid malformations (Fig. 11.66) may have cysts with a similar appearance to bowel but lack peristalsis and displacement of identified abdominal organs. Microcystic forms are echogenic and resemble sequestrations; the latter usually have systemic arterial feeding vessels (Fig. 11.67), although blended forms have been described. Growth is variable, with spontaneous regression during pregnancy commonly reported. "Vanishing" lesions, not identified by postnatal x-rays, are always present on chest CT. Fetal hydrops may develop; fetal surgery

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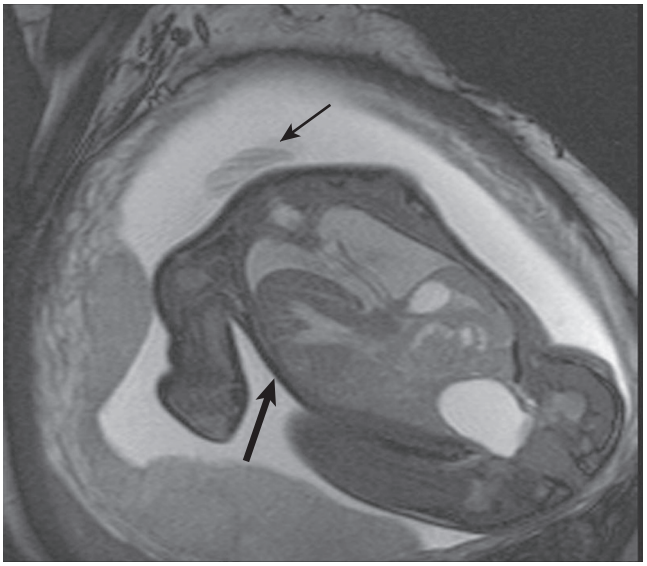
• **Fig. 11.62** Gastroschisis. Transverse abdominal image of the spine (*left, short arrow*) demonstrates free bowel loops (*thick arrow*) to the right of the umbilical cord insertion (*long arrow*). This lesion is more common in younger gravidas and is usually isolated.



• **Fig. 11.64** Fetal ultrasound image of the chest. Left-sided diaphragmatic hernia results in shifting of the mediastinum to the right. Loops of bowel are seen in the left thorax. Note the small compressed right lung marked by the calipers.



• **Fig. 11.63** MRI of posterior Bochdalek diaphragmatic hernia at 28 weeks' gestation. Note the loops of bowel occupying the left hemithorax and compressing the lung.



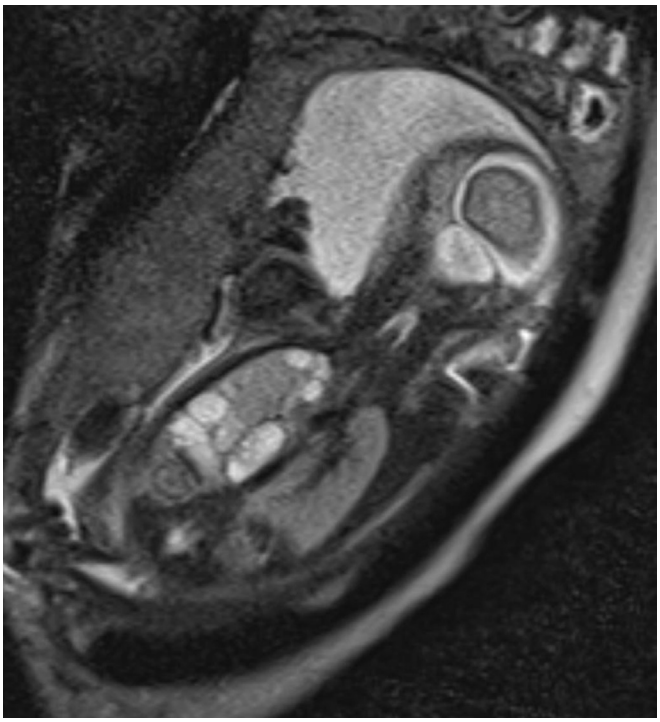
• **Fig. 11.65** Fetal MRI of right-sided diaphragmatic hernia at 32 weeks' gestation. Liver (*thick arrow*) has herniated into right thorax with compressed right lung. *Thin arrow* shows incidental nuchal cord.

may be indicated to avert this potentially fatal complication. Gestational age-normalized congenital pulmonary airway malformation volume and congenital cystic adenomatoid malformation volume ratios have been proposed as methods for anticipation of hydrops. The latter ratio has been used to identify the need for fetal intervention. In predominantly microcystic lesions, maternal betamethasone therapy has been reported to lower risks for polyhydramnios and fetal hydrops.[13]

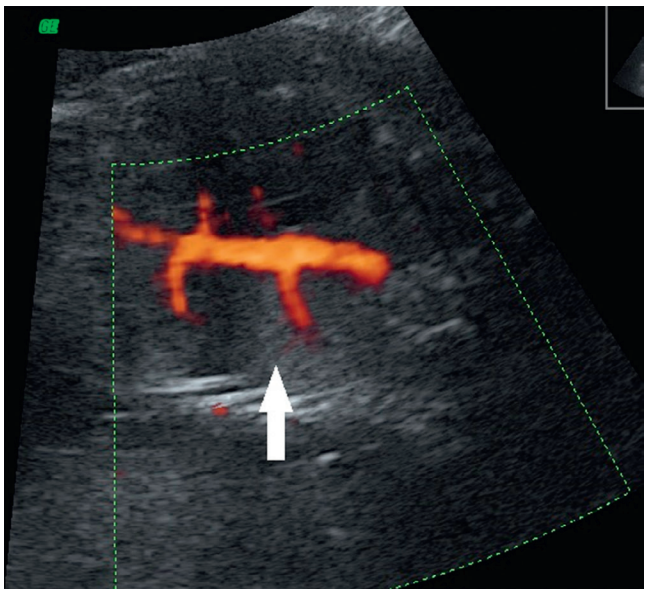
Gallbladder and Bile Ducts

A choledochal cyst is a localized circular dilation of the biliary system, often involving the common bile duct and located in the upper right abdominal quadrant, separate from the gallbladder. Echogenic gallstones and sludge are noted in the gallbladder lumen on third-trimester scans (Fig. 11.68) in one out of every 200 fetuses. The prognosis of fetal gallstones and biliary sludge is favorable. Follow-up studies in neonates generally confirm resolution once separated from the maternal hormonal milieu; infants are usually asymptomatic. The fetal gallbladder can often be seen after 14 weeks' gestation; its rare absence, suspected by persistent nonvisualization, is associated with a variety of abnormal conditions, most notably biliary atresia and cystic fibrosis.[16]

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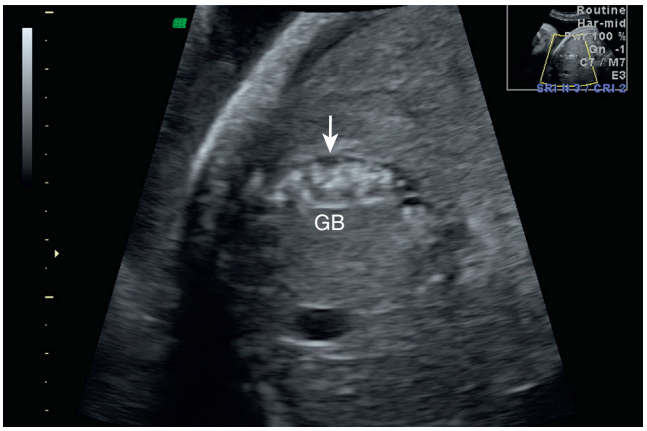
• **Fig. 11.66** Congenital pulmonary adenomatoid malformation. MRI at 26 weeks in the fetal coronal plane showing both lungs. Multiple large fluid-filled cysts are present.



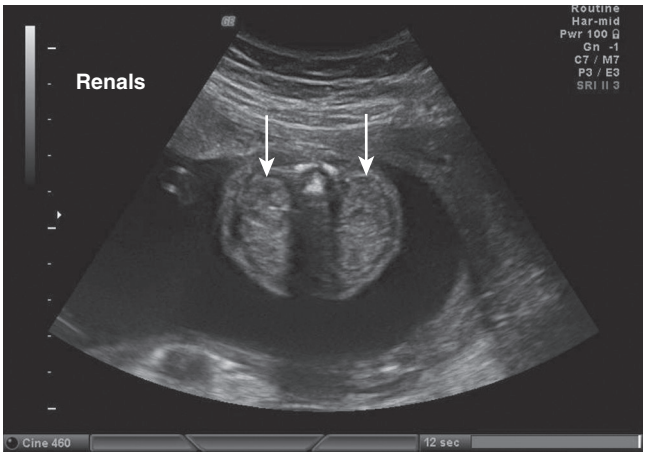
• **Fig. 11.67** Pulmonary sequestration is shown. Power Doppler highlights the feeding vessel (*arrow*).

Genitourinary Tract

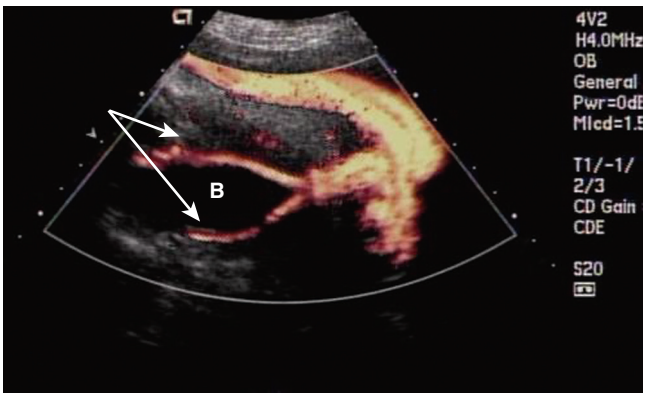
The kidneys, readily visible by 12-14 weeks' gestation, are located lateral to the fetal spine (Fig. 11.69) below the diaphragm and prominent fetal adrenal glands. Normal renal size and volume can be plotted against gestational age. By the late third trimester, fat deposition creates an echogenic border, enhancing visualization. The bladder, may be seen by 11 weeks of gestation, flanked by paired umbilical



• **Fig. 11.68** Fetal gallbladder (*GB*) (*arrow*) with echogenic sludge and small calculi in the third trimester. Findings usually resolve once maternal hormonal levels decrease. Compare with normal echo-free appearance in Fig. 11.19.



• **Fig. 11.69** Transverse view of the fetal abdomen, spine up, demonstrating the normal renal appearance (*arrows*).



• **Fig. 11.70** Power Doppler demonstration of two umbilical cord arteries (*arrows*) outlining the fetal bladder (B).

arteries (Fig. 11.70). Normal fetal ureters are not visible by ultrasound. Fetal adrenal glands are usually identifiable because of a relatively large cortex and unique, contrasting echo textures.

Lethal renal malfunctions, including bilateral multicystic dysplasia, bilateral agenesis, and some cases of congenital

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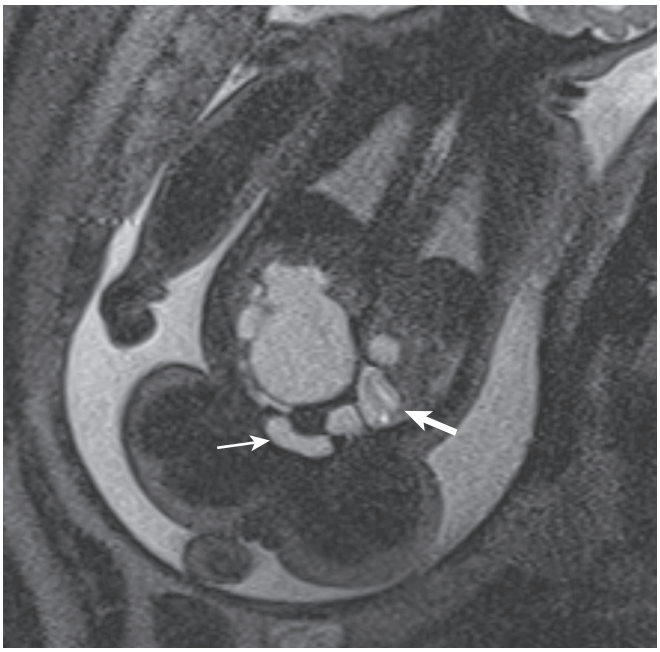
autosomal recessive polycystic kidney disease result in failure of fetal urine production. After 16 weeks, amniotic fluid is almost entirely fetal urine, but oligohydramnios may not become apparent until 18-20 weeks of gestation. Infants born after prolonged oligohydramnios have a characteristic facial appearance, limb deformities, and pulmonary hypoplasia, termed Potter syndrome (or sequence). The finding of oligohydramnios should direct attention to the fetal urinary tract with rescanning at 30-minute intervals for confirmation if the fetal bladder is not initially visualized. Anhydramnios (no measurable fluid), a persistently empty bladder, and an inability to identify fetal kidneys or renal arteries are strongly suggestive of bilateral renal agenesis. Unfortunately, absence of amniotic fluid may impede making a secure diagnosis with its associated implications for management, particularly because fetal adrenal glands, losing their normal angulation in renal agenesis, may be mistaken for kidneys. Fetal MRI can be ideal in establishing this lethal diagnosis. Care must be exercised when suspecting unilateral renal agenesis to exclude renal ectopy (pelvic kidney); color Doppler may reveal the aberrant course of the renal artery (see Fig. 11.4).

Pyelectasis (dilation of the renal pelvis), occurring in up to 5% of pregnancies, is a variant that should not be misinterpreted as hydronephrosis. Pyelectasis is considered a minor marker for trisomy 21 but when isolated is not usually an indication for amniocentesis; transient urinary reflux is a common underlying cause. Measurements of anteroposterior views of the kidneys and renal pelves in the transverse plane are used to identify both pyelectasis and hydronephrosis. Upper limits of 4 mm and 7 mm in second and third trimesters respectively define pyelectasis, with normalization by the third trimester routinely anticipated. Pelvic dilation above 1 cm is suspicious for hydronephrosis, particularly with calyceal involvement. Vague correlation exists between the magnitude of fetal renal pyelectasis and renal abnormalities. Persistent pyelectasis should be confirmed neonatally and followed until either resolved or an etiology established.[44]

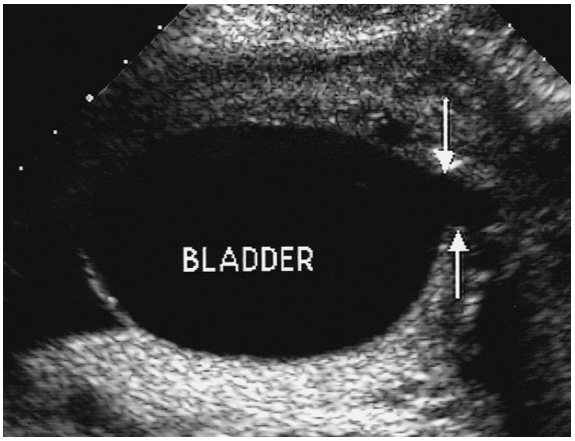
Urinary tract obstruction may have a variable sonographic appearance, depending mainly on timing of onset. Renal dysplasia, sometimes with cyst formation, is the consequence of early obstruction; obstruction occurring later in gestation is more likely to result in dilation of the collecting system (Fig. 11.71).

Hydronephrosis may be unilateral, resulting from obstruction of the ureteropelvic or ureterocystic junctions, or bilateral, secondary to lower tract obstruction by posterior urethral valves or urethral agenesis. A distended, thick-walled bladder may be seen in males with posterior urethral valve, along with hydroureters; urinary ascites may occur as a result of calyceal or bladder rupture with intraperitoneal accumulation of urine. "Keyhole" dilation of the posterior urethra helps in distinguishing this lesion from Eagle-Barrett (prune-belly) syndrome (Fig. 11.72).

Multicystic dysplastic kidney disease (MCDKD) is commonly an incidental unilateral finding on prenatal examination. Bilaterality is less frequent but lethal. In unilateral cases, abnormalities of the contralateral kidney are common.[24] Associated nonrenal abnormalities occur frequently with both unilateral and bilateral MCDKD, increasing risks for chromosomal abnormality. Males predominate in unilateral MCDKD (ratio of 2.4:1), but females are four times more likely to have chromosomal abnormalities and twice as likely to have nonrenal anomalies or lethal bilateral disease.[24] The option of chromosomal analysis should be discussed whenever there are extrarenal abnormalities or bilaterality. Unilateral isolated MCDKD with normal amniotic fluid is not associated with abnormal genetic studies and usually has a favorable outcome; however, a neonatal work-up to exclude reflux in the unaffected kidney should be performed.[37]

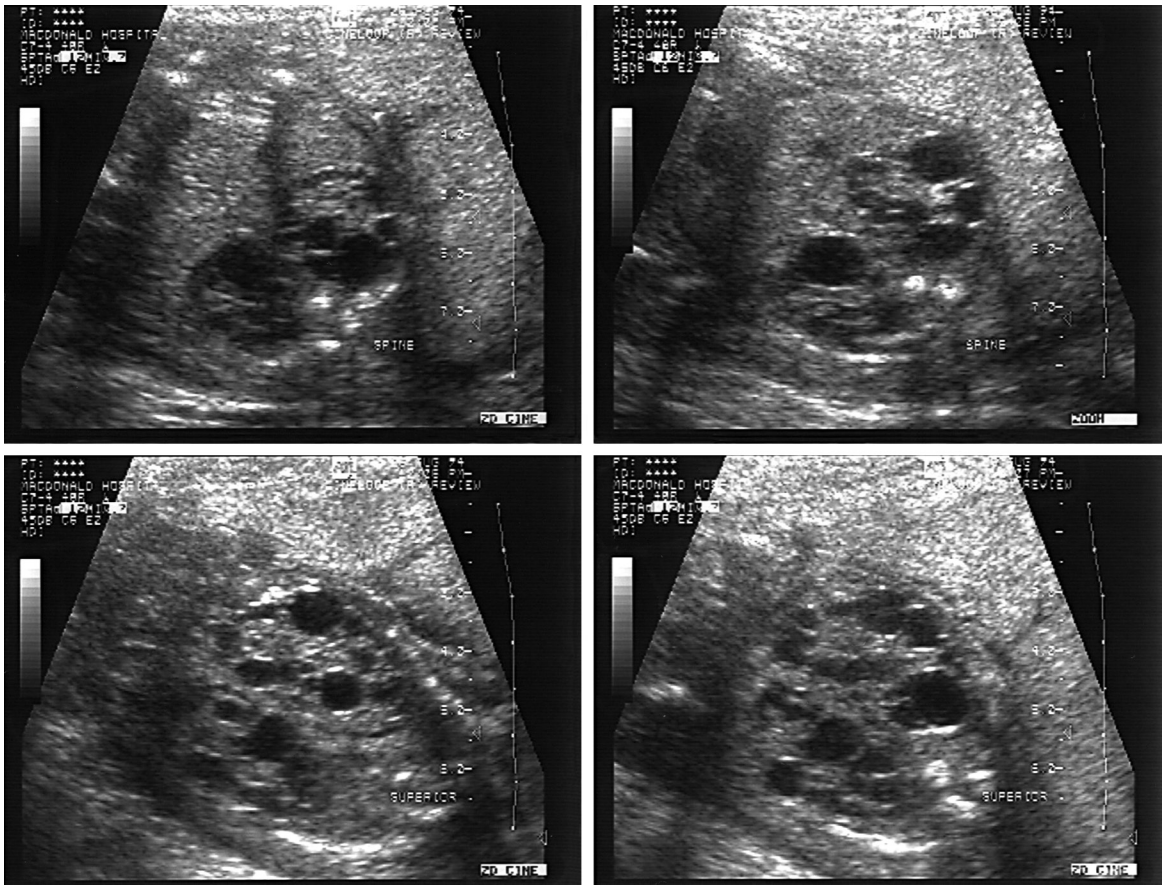


• **Fig. 11.71** Fetal MRI at 35 weeks' gestation. Note massive hydronephrosis with dilated tortuous ureter on contralateral side (*thick arrow*). Fetal urinary bladder is shown (*thin arrow*).



• **Fig. 11.72** Posterior urethral valve. Coronal scan of the fetal pelvis shows an enlarged bladder and dilated posterior urethra. Arrows are proximal to the posterior urethral valves. Note the oligohydramnios.

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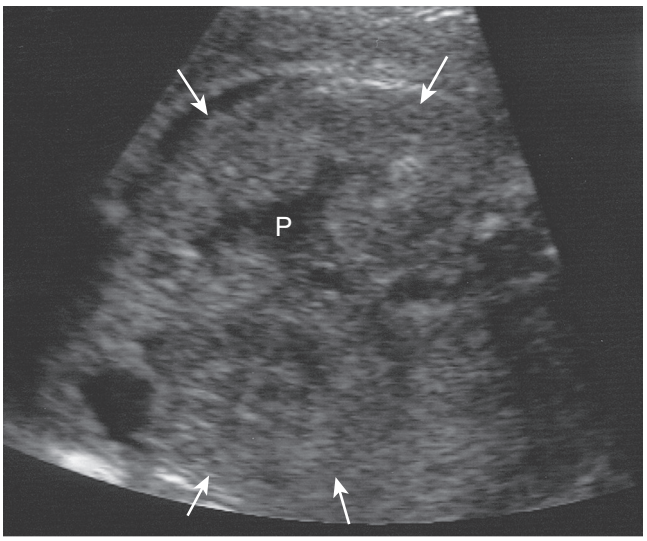


• **Fig. 11.73** Multiple views of bilateral multicystic dysplastic kidneys. This diagnosis is considered incompatible with postnatal survival and is always associated with severe oligohydramnios in the second half of gestation. Note lack of fluid interface.

Severe hydronephrosis, in contrast to MCDKD, is an orderly arrangement of the enlarged renal pelvis with connecting, dilated calyces. Bilateral renal anomalies (including bilateral secondary multicystic renal dysplasia) are common (4%) in the fetus (Fig. 11.73). Dilated ureters occur in ureterovesical junction obstruction, primary megaureter, or secondary to reflux. Infantile autosomal recessive polycystic kidney disease causes bilaterally enlarged, echogenic reniform kidneys (Fig. 11.74). Other renal and urogenital anomalies identified prenatally include cysts, masses, duplicated collecting systems, and bladder exstrophy; in the last, a nonvisualized bladder coincides with normal amniotic fluid and renal appearance. A short or bifid male phallus is sometimes associated.

Reliable identification of male and female sex is anticipated after 16 weeks' gestation (see Fig. 11.37) by external genital examination, with interposition of uterus noticeably separating the fetal bladder from the rectum. Fetal ovarian cysts, fluid-filled or septate, are often abdominal and hard to distinguish from gastrointestinal and other lesions. Hydrometrocolpos may also produce a complex fluid-filled pelvic structure (see Fig. 11.37*C*).

Identification of genes involved in sex differentiation, noninvasive prenatal genetic screening, measurements of



• **Fig. 11.74** Congenital infantile polycystic kidney disease. Transverse abdominal scan shows echogenic, enlarged kidneys filling the fetal abdomen (*arrows*). The renal pelvis (P) is seen in the superior kidney. Oligohydramnios is present.

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key mediating hormones, combined with ultrasound, have allowed multidisciplinary teams to identify cases of ambiguity, conduct detailed prenatal evaluations, and provide informed parental counseling.

Following the characterization of the sex-determining region on the Y chromosome in 1990, there have been a number of genes found to play a role in sex development. The most common disorders of sex development (DSD) result from disruption of androgen levels and activity affecting later embryonal development, for example, congenital adrenal hyperplasia and androgen insensitivity syndrome. Available powerful genetic techniques can interrogate the entire genome for causative changes; it is important to critically assess the flood of genetic data for meaningful information. Recent discoveries have clarified roles of various transcription factors in DSD, including SOX9, SF1, and WT1 genes. Disruption of signaling molecules, such as hedgehog, WNT, cyclin-dependent kinase, and Ras/MAP kinase is known to cause some DSD. Dosage dependence of genes involved in gonadal development is a recurrent theme; genetic changes in promoter and repressor regions are being probed by microarray analysis and other techniques. Multiple phenotypes result from deletion, duplication, homozygous, heterozygous, and regulatory region changes in the same gene. Ongoing studies may yield clinically applicable insights into DSD and its underlying genetic basis.[23]

Musculoskeletal System

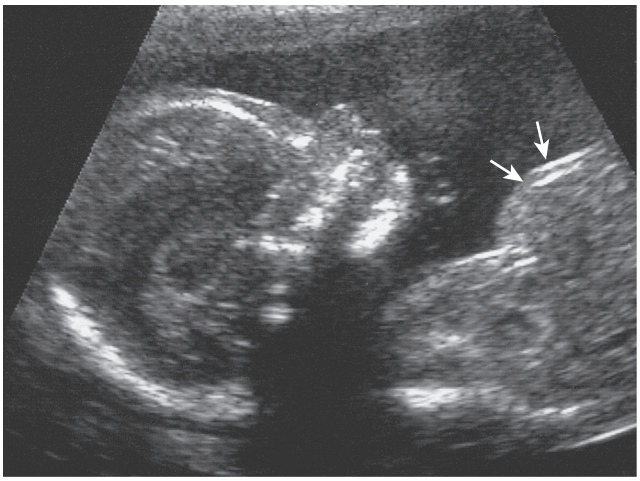
Examination of all four extremities and determination of femur length is routine in prenatal studies. Normograms exist for all fetal long bones, feet, and many other skeletal components. Measurements falling more than three standard deviations below the mean for age are very suspicious for skeletal dysplasia. Because normal individuals by definition populate the fifth percentile, it is reassuring that most skeletal dysplasias are dramatic; an abnormal femur-to-foot ratio (<0.89) provides additional diagnostic support. The biparietal diameter usually continues to reflect gestational age unless the skull is also involved.

Careful measurement of all bones in the peripheral skeleton is required in suspected cases, first to define the category of dysplasia and then, if possible, to make a diagnosis. Extreme generalized limb reduction or absence is termed *phocomelia*; overall limb shortening is *micromelia*; *rhizomelia* refers to proximal (femurs and humeri) reduction; *mesomelia* to more distal (forearms and lower legs); and *acromelia* to the most distal (feet and hands) dysplasias. Fractures and curvatures; altered bone density; the appearance of the spine, skull, and ribs; and extraskeletal anomalies may be keys to more specific diagnoses. Polyhydramnios may also be present and is often a poor prognostic sign.

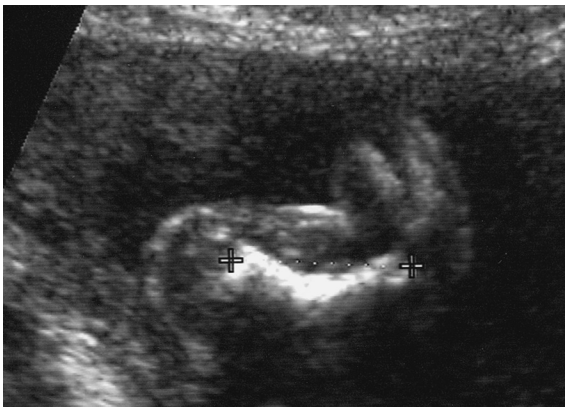
Pulmonary hypoplasia from restrictive thoracic deformation is often the cause of death in severe skeletal dysplasias. Lung volume can be assessed by MRI or by 3D imaging, but a ratio of FL/AC below 0.16 functions as a convenient proxy for more cumbersome estimators for lethality.[37]

Thanatophoric dysplasia is uniformly fatal and relatively common, often recognizable in utero by severe micromelia, curved femurs, and narrow thorax (Fig. 11.75). Useful for diagnosis, when present, is a cloverleaf-shaped skull. Achondrogenesis, also lethal, manifests severe micromelia with poor vertebral ossification. Lethal type II osteogenesis imperfecta presents with short, angulated fractures of long bones and ribs (Fig. 11.76). Bone density, particularly calvarial, is decreased. Fatal forms of hypophosphatasia may have similar severe demineralization with strikingly clear resultant central nervous system imaging and easy compressability of the skull. Short-ribbed polydactyly syndrome, also lethal, is characterized by a small chest with hypoechoic truncated ribs, postaxial polydactyly, and polyhydramnios (Fig. 11.77).

Heterozygous achondroplasia is the most common nonlethal skeletal dysplasia; homozygous status is incompatible with survival. Shortening of the femur, frontal bossing, trident hand shape and increased amniotic fluid volume characterize this autosomal dominant rhizomelic disorder, rarely apparent prior to the third trimester. Prenatal genetic diagnosis is limited to known carriers. Eighty percent of

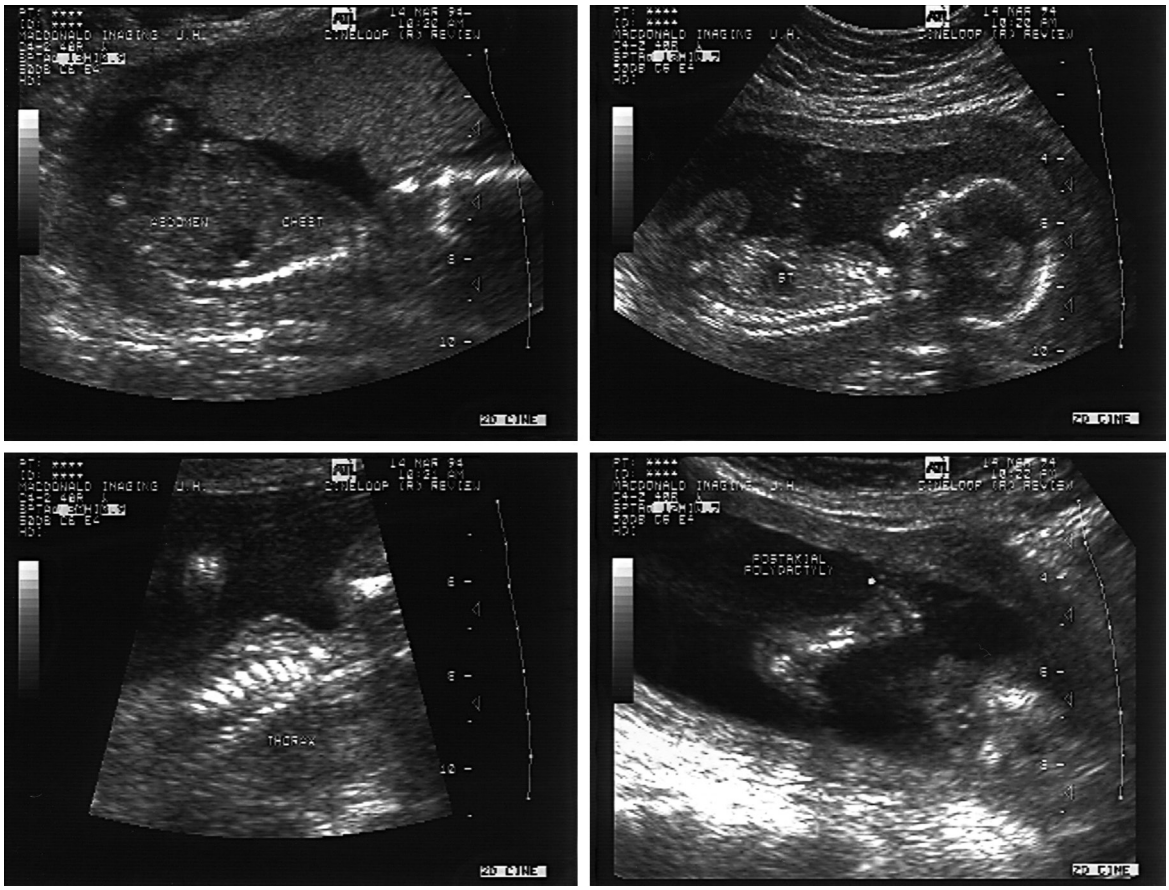


• **Fig. 11.75** Thanatophoric dysplasia. Sagittal view of the fetus reveals severe deformation of the rib cage with protrusion of the abdomen (*arrows*).



• **Fig. 11.76** Osteogenesis imperfecta. The humerus is shortened and abnormal in shape secondary to multiple fractures, indicated by cursors.

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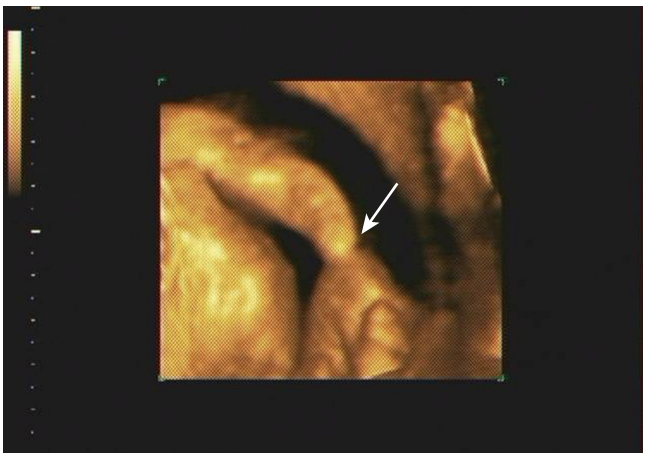


• **Fig. 11.77** Fetus with short-ribbed polydactyly syndrome. Multiple images show a small chest with hypoechoic ribs, large amounts of amniotic fluid, and postaxial polydactyly.

cases are new mutations; some are associated with advanced paternal age.

Other abnormalities of the musculoskeletal system include the malformation or absence (dysostosis) of various skeletal portions; for example, limb reduction anomalies including radial-ray syndromes (hypoplasia or absence, often affecting thumb development) and hemimelia. Amniotic band syndrome (Fig. 11.78) asymmetrically amputates or truncates an extremity, although the narrow strand may not persist. Valgus deformities of the feet (Fig. 11.79) may be isolated, familial, positional, or secondary to central nervous system and spinal cord abnormalities.

Pitfalls in the diagnosis of skeletal dysplasia are appreciable. Complete current classification from the International Skeletal Dysplasia Society is available online.[45] Classification of skeletal dysplasias is constantly being altered by new genetic information.

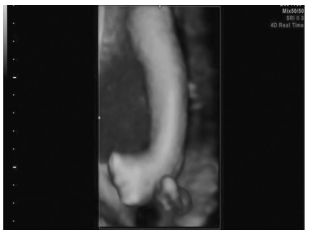


• **Fig. 11.78** Truncated fetal arm (*arrow*) secondary to amniotic band.

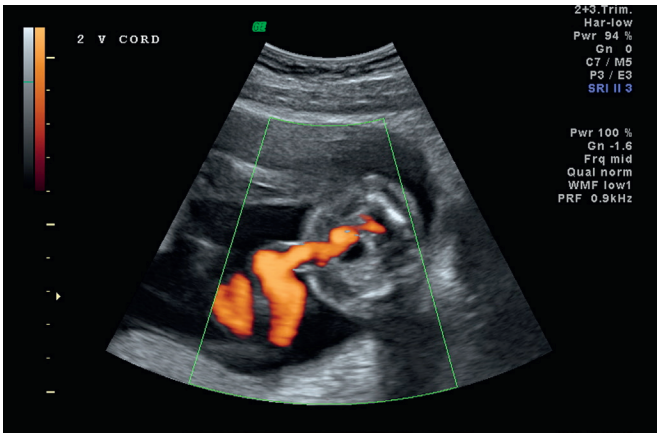
Two-Vessel Umbilical Cord

A single umbilical artery may be identified on transverse views of free cord loops or at the bladder bifurcation based on color Doppler (Fig. 11.80). Single umbilical arteries have been linked to other anomalies, unfortunately without a consistent pattern. Lack of normal coiling and short cords are also linked to abnormalities, particularly those affecting movement. It is unclear whether an isolated single umbilical artery is associated with aneuploidy, nor does the laterality of the absent vessel have significance. Being small-for-gestational age is more common in neonates with single umbilical artery. Counseling, selective use of amniocentesis, and serial third-trimester examinations to document fetal growth may be helpful in management.

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• **Fig. 11.79** Valgus deformity of the fetal foot may be isolated, familial, positional, or secondary to central nervous system and spinal cord abnormalities.



• **Fig. 11.80** Single umbilical artery. A transverse scan of the umbilical cord shows the vein and a single artery. On color flow, one of the branches of the normal "Y" shape will be absent (see Fig. 11.5).

Summary

As sonography nears maturity, it has had gratifying success in fulfilling its early potential. Initial limitations have yielded to advances in technology and technique or have been augmented by genetic and biochemical breakthroughs. MRI is now well established as a versatile partner to ultrasound in prenatal diagnosis. The future of imaging holds immense promise for continued progress in improving neonatal outcomes.

Key Points

- All practitioners who perform or supervise the performance of obstetric ultrasonography should be licensed medical practitioners, having received specific training in obstetric ultrasonography.
- Gray-scale B-mode ultrasound is associated with a negligible rise in temperature. Strong magnetic fields and radiofrequency waves are used in MRI with no known harmful effects. Large longitudinal studies confirming the safety of ultrasound and MRI are lacking.
- A standard ultrasound study should follow the guidelines published by the American Institute of Ultrasound in Medicine.
- An important application of prenatal ultrasound is using biometrics to establish gestational age and the utility of the biophysical profile to confirm fetal well-being.
- Genetic screening of the fetus should combine ultrasound study and biochemical testing or cell-free fetal DNA to enhance the detection of chromosomal abnormalities.
- Neonatal outcomes can be optimized by forewarning and timely preparation when fetal abnormalities are present.
- Nondiagnostic studies, varying prognoses for a given diagnosis, and the inherent limitations of ultrasound and MRI studies might lead to ethical issues in management and counseling.

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12

Estimation of Fetal Well-Being

DAVID N. HACKNEY

In high-risk populations at increased risk of perinatal mortality, antenatal fetal surveillance is often employed in an attempt to prevent stillbirth. Pregnancies at risk for progressive deterioration of placental function leading to fetal hypoxemia and acidosis are most likely to benefit from the methods currently in use. The various modalities, including non-stress test (NST), contraction stress test (CST), biophysical profile, and Doppler velocimetry, rely on fetal biophysical parameters that are significantly associated with the presence or absence of fetal hypoxemia. Because all tests are associated with a false-positive rate, each test result should be interpreted within the clinical context presented by the patient.

Despite the inherent stress of labor, most fetuses are able to tolerate the transient episodes of hypoxemia without harm. Rarely, the process of labor and delivery places a fetus in jeopardy of long-term neurologic damage or death as a result of profound hypoxemia and metabolic acidosis. Since the 1970s, electronic FHR monitoring has emerged as the most common technology to monitor fetuses during labor in the hopes of identifying at-risk fetuses to achieve delivery before permanent harm. Although not without benefit, monitoring has also likely resulted in a dramatic increase in cesarean deliveries without reducing the rate of cerebral palsy. Strategies to prevent fetal harm while reducing the incidence of cesarean delivery have been difficult to achieve, although potential benefits can be derived from standardization of practice.

Introduction

Antepartum testing entails the evaluation of fetal health through a variety of modalities, including fetal heart rate monitoring and ultrasound, occurring at points in pregnancy that are remote from delivery, as opposed to *intrapartum* testing, which is performed in the patient experiencing labor. A false-negative test will be one that fails to identify a fetus at risk of death or major morbidity, which could have been prevented by delivery. False-positive results, however, can lead to iatrogenic preterm birth, which itself can be associated with significant morbidity. Even if testing does not lead to delivery, positive results can also generate significant maternal anxiety and stress, as well as cost. The optimal antepartum fetal testing strategy would appropriately identify an at-risk fetus prior to an irreversible event while minimizing maternal anxiety, cost, and iatrogenic prematurity. Such optimization, however, has been difficult to achieve.

Antepartum Fetal Surveillance

Indications for Surveillance

Intrauterine fetal death may result from a wide range of potential etiologies, including congenital structural malformations, genetic abnormalities, fetomaternal hemorrhage, infection (TORCH and chorioamnionitis), umbilical cord obstruction, placental abruption, and uteroplacental insufficiency.[20] The methods commonly used for antenatal fetal surveillance rely on fetal biophysical parameters that are sensitive to hypoxemia and acidemia, such as heart rate and movement. Thus, it is primarily useful in a fetus at risk for hypoxemia specifically because of chronic uteroplacental insufficiency. Intrauterine demise from sudden catastrophic events, such as abruption, maternal trauma, or cord occlusion, is likely not predictable by antepartum monitoring.

The indications for antenatal testing are those that increase the risk of uteroplacental insufficiency, many of which are listed in Table 12.1. The optimal antenatal testing strategy for each of these would be beyond the scope of a single chapter, and additionally in many circumstances the exact strategy is controversial, because there is often little or no prospective or randomized data from which to determine an optimal approach. Many conditions for which testing has been suggested are those for which epidemiologic studies have identified an increased risk of intrauterine demise. However, in some circumstances the risk of stillbirth, although achieving statistical significance in large studies, may remain small in actual magnitude. Additionally, an association between a particular risk factor and stillbirth alone does not necessarily demonstrate that there is a benefit from antenatal surveillance, because that would require a specific study of antepartum testing for the given risk factor. For example, maternal obesity is associated with an increased risk of stillbirth,[4] but because there are few or

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Abstract

In high-risk populations at increased risk of perinatal mortality, antenatal fetal surveillance is often employed in an attempt to prevent stillbirth. Pregnancies at risk for progressive deterioration of placental function leading to fetal hypoxemia and acidosis are most likely to benefit from the methods currently in use. The various modalities, including non-stress test (NST), contraction stress test (CST), biophysical profile, and Doppler velocimetry, rely on fetal biophysical parameters that are significantly associated with the presence or absence of fetal hypoxemia. Because all tests are associated with a false-positive rate, each test result should be interpreted within the clinical context presented by the patient.

Keywords

antepartum testing
intrapartum testing
biophysical profile
fetal heart rate
electronic fetal monitoring

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TABLE 12.1 Indications for Antenatal Surveillance

Maternal Conditions	Pregnancy-Related Conditions
• Antiphospholipid syndrome • Hyperthyroidism (poorly controlled) • Pre-gestational diabetes mellitus • Cyanotic heart disease • Systemic lupus erythematosus • Chronic hypertension • Chronic renal disease • Hemoglobinopathies (hemoglobin SS, SC, or S-thalassemia)	• Pre-eclampsia • Decreased fetal movement • Oligohydramnios • Polyhydramnios • Intrauterine growth restriction • Complicated multiple gestation • Gestational diabetes with poor control • Premature rupture of membranes

From American College of Obstetricians and Gynecologists. *Antepartum Fetal Surveillance, ACOG Practice Bulletin 9*. Washington, DC: ACOG; 1999.

no prospective interventional studies, exact recommendations for monitoring are not available from professional societies.[19]

Of note, uterine contraction monitoring (tocometry) is performed simultaneously with electronic fetal cardiac monitoring as part of the non-stress and contraction stress test. This is primarily to allow for the interpretation of fetal heart rate decelerations relative to uterine contractile activity. Uterine contraction monitoring alone as a method of identifying patients at increased risk of preterm birth is of low clinical utility.

Physiologic Basis for Antenatal Surveillance

The application and interpretation of antepartum fetal monitoring necessitates an understanding of the progressive fetal changes that occur secondary to increasing placental insufficiency progressing to intrauterine demise. In experiments involving animal and human fetuses, hypoxemia and acidosis have been shown consistently to alter fetal biophysical parameters such as heart rate, movement, breathing, and tone. The fetal heart rate (FHR) is normally controlled by the fetal central nervous system (CNS) and mediated by sympathetic or parasympathetic nerve impulses originating in the fetal brainstem. The presence of intermittent FHR accelerations associated with fetal movement is believed to be an indicator of an intact fetal autonomic nervous system. In historic studies of fetal blood sampling of pregnancies resulting in healthy neonates, Weiner and colleagues established a range of normal fetal venous pH measurements.[22] In this population, the lower 2.5 percentile of fetal venous pH was 7.37. Manning and colleagues showed that fetuses without heart rate accelerations had a mean umbilical vein pH of 7.28 (±0.11), and fetuses with abnormal movement had a mean pH of 7.16 (±0.08).[16] These and similar observations were the basis for the development of antenatal fetal testing modalities that are currently in use.

Patient Assessment of Fetal Movement

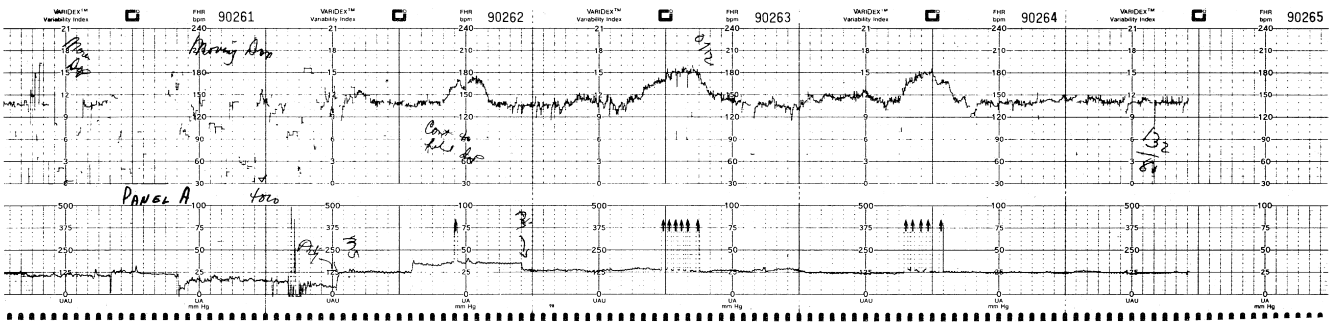
The patient's own subjective assessment of the fetal activity is perhaps the simplest and most universal of antepartum surveillance methods, although its subjective nature leads to difficulty in quantification and empiric evaluation. As described above, fetal movement decreases with increasing hypoxia, which also serves as the physiologic basis of the biophysical profile as described below. As a result, a decrease in subjective fetal movement should usually be evaluated. Beyond this generalized recommendation, various formalized strategies of fetal monitoring (colloquially referred to as "kick counts") have been proposed. One of the more common is to determine the time it takes for the perception of 10 movements during a period of specific, restful evaluation and to contact one's provider if the duration is 2 hours or more. However, systematic reviews have identified neither an optimal strategy nor clear evidence that routine, quantified fetal movement assessment can prevent stillbirth.[14]

Non-Stress Test

In most institutions, the first-line assessment tool for fetal surveillance is the non-stress test (NST). In the outpatient setting, the patient typically rests in a reclining chair with a lateral tilt or semi-Fowler. Ideally she should have not recently smoked. Although commonly provided in antepartum testing units, the maternal ingestion of juice or food has not been demonstrated to increase the probability of a reactive non-stress test. The FHR is monitored with an external transducer for up to 40 minutes and observed for the presence of accelerations above the baseline. A reactive test is one in which there are at least two accelerations that peak 15 beats/min above the baseline and last (not at the peak) for at least 15 seconds before returning to baseline (Fig. 12.1), colloquially referred to as "15 × 15." Most NSTs are reactive within the first 20 minutes. For tests that are not, possibly because of a fetal sleep cycle, an additional 20 minutes of monitoring may be needed. A nonreactive NST is one in which two such accelerations do not occur within 40 minutes.

The optimal gestational age at which to begin antenatal surveillance depends on the clinical condition. In making this decision, the physician must weigh the risk of intervention at a premature gestational age against the risk of intrauterine fetal death. Initiation at 32-34 weeks' gestation is reasonable for most at-risk patients, with the acknowledgment that some situations may warrant testing earlier at 26-28 weeks of gestation. FHR variability and reactivity vary with gestational age, with an increasing frequency of tracings that lack "15 × 15" accelerations with decreasing gestational age under 32 weeks. Thus, prior to 32 weeks, non-stress tests are considered reactive if there are two

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• **Fig. 12.1** Reactive non-stress test showing accelerations occurring with fetal movement. Note the arrows on the contraction channel. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981.)

accelerations that peak 10 beats/min above baseline and last for at least 10 seconds ("10 × 10"). Of note, the magnitude of accelerations in fetuses less than 32 weeks can vary normally over time, thus a fetus at less than 32 weeks is reactive by 10 × 10 criteria even if it had previously demonstrated 15 × 15 accelerations.[9]

Although the NST is noninvasive and easy to perform, it is limited by a high false-positive rate. Normal fetuses often have periods of nonreactivity because of benign variations such as sleep cycles. Vibroacoustic stimulation may be used safely in the setting of a nonreactive NST to elicit FHR accelerations without compromising the sensitivity of the NST. In this situation, the operator places an artificial larynx on the maternal abdomen and activates the device for 1-3 seconds. This technique is often useful in situations in which the FHR has normal beat-to-beat variability and no decelerations but does not show any accelerations. If the test remains nonreactive, further evaluation with a biophysical profile or contraction stress test (CST) is warranted as long as the FHR is otherwise reassuring. However, if the tracing is overtly concerning (see Category III later in this chapter), additional testing may need to be deferred in favor of delivery depending upon the exact gestational age and clinical circumstance.

Contraction Stress Test

The CST is designed to evaluate FHR response to maternal uterine contractions. The principles that are applied to the evaluation of intrapartum FHR monitoring (see FHR Monitoring) are used here. In response to the stress of the contraction, a hypoxemic fetus shows FHR patterns of concern, such as late decelerations.

Similar to the NST, for the CST the patient is placed in a recumbent tilted position, and FHR is monitored with an external fetal monitor. The FHR pattern is evaluated while the patient experiences at least three contractions lasting 40 seconds within a 10-minute period. If the patient is not contracting spontaneously, contractions may be induced with nipple stimulation or intravenous oxytocin. Nipple stimulation can be self-administered by the patient or a breast pump can be used. If no late or significant variable decelerations are noted on FHR tracing, CST is considered to be negative. If there are late decelerations after at least 50% of the contractions, CST is positive. If late decelerations are present less than 50% of the time, or if significant variable decelerations are present, the test is considered to be equivocal. Contraindications to the performance of CST include clinical situations in which labor would be undesirable (e.g., placenta previa or previous classic cesarean section).

• BOX 12.1 Biophysical Profile Scoring System

1. Fetal breathing movements (one or more episodes lasting at least 30 seconds)
2. Fetal movement (three or more discrete body or limb movements)
3. Fetal tone (one or more episodes of active extension with return to flexion of a limb or trunk, or the opening and closing of a fetal hand)
4. Amniotic fluid volume
5. Reactive non-stress test

Biophysical Profile

The biophysical profile is based upon the general principle that a progressively hypoxic fetus will be less likely to engage in elective activities such as breathing or body motions, while an active fetus is likely also healthy. As originally described, it combines NST with four components evaluated by ultrasound (Box 12.1). In a 30-minute period, either 2 or 0 points are assigned depending upon if the criteria are fulfilled or unfulfilled. The final score will thus range from 0-10 with no odd numbers (either 0 or 2; 1 point is never awarded for each criteria). A combined score of 8 or 10 indicates fetal well-being. A score of 6 is considered to be equivocal; it usually merits delivery if the pregnancy is at term or additional or repeat (24 hours) testing if the pregnancy is preterm. A score of 4 or less is considered to be abnormal, and in the absence of reversible causes, consideration would need to be given to delivery except in uncommon extenuating circumstances. Of note,

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one of the five criteria in the BPP is the amniotic fluid volume. This can complicate interpretation of the testing in situations where the fluid volume is low for reasons that are independent of placental function, such as membrane rupture or congenital anomalies of the urinary tract.

Of note, fetal breathing is not usually present during active labor, to the extent that the absence of fetal breathing on ultrasound had previously been evaluated as an assessment tool for the presence of "true" preterm labor. Thus, biophysical profiles are not performed in patients who are actively laboring.

Amniotic Fluid Volume Assessment

Amniotic fluid volume is commonly estimated by ultrasound via one of two primary methods. The amniotic fluid index (AFI) is calculated by measuring and adding the maximal vertical pockets of fluid (without loops of umbilical cord) in each of the four quadrants of the maternal abdomen as demarcated by the umbilicus (Fig. 12.2). Alternatively, the single deepest vertical pocket of fluid alone can be measured. Decreased amniotic fluid volume, or oligohydramnios, is defined as either an AFI of 5 cm or less or no single measurable vertical pocket greater than 2 cm. Gestational age-specific nomograms are also available although are less commonly used. Neither AFI nor single deepest pocket is perfectly sensitive or specific for the detection of oligohydramnios.[13] Oligohydramnios can occur secondary to a range of causes including rupture of the fetal membranes and congenital fetal anomalies of the urinary tract. In the absence of membrane rupture or congenital anomalies, however, the most concerning etiology would be decreased fetal urine production secondary to the shunting of blood flow away from the fetal kidneys in the context of uteroplacental insufficiency.

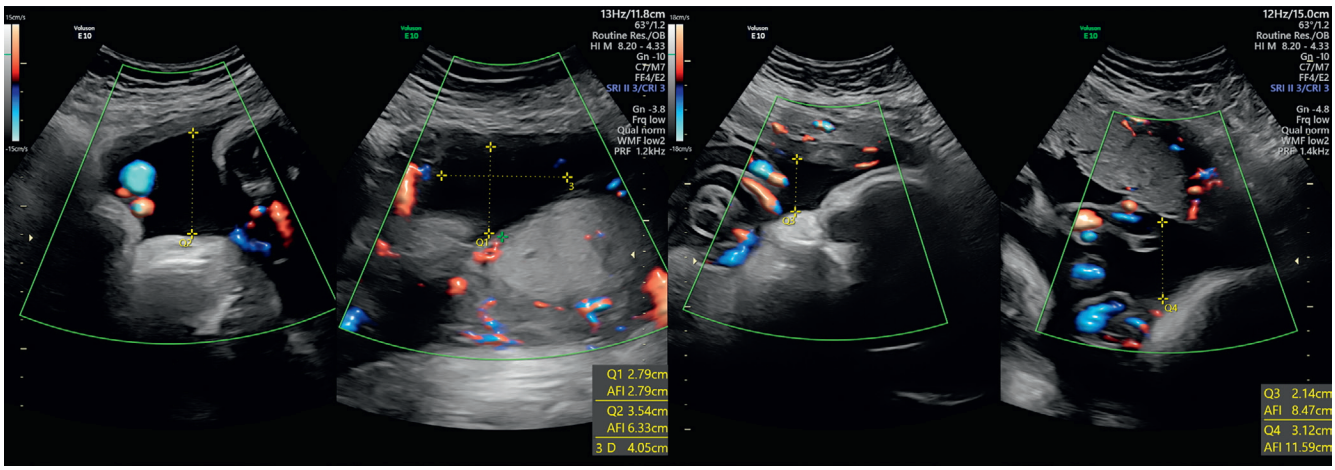
When oligohydramnios is diagnosed, the first step is to rule out membrane rupture and congenital anomalies and, if not present, assess the fetus for other evidence of uteroplacental insufficiency, including fetal biometric measurements to assess growth restriction. Delivery is usually performed for oligohydramnios at term, although at preterm gestations, delivery decisions will involve multiple factors, including the exact gestational age and presumed etiology of the decreased fluid, with conservative management being reasonable in many circumstances. More information on the management of amniotic fluid disorders is covered in Chapter 24.

Doppler Flow Velocimetry

Quantitative evaluation of maternal and fetal blood vessels by Doppler sonography has been the focus of intense research over the last several years and is continuing to evolve rapidly. The list of clinical scenarios in which it has been utilized includes the evaluation of the fetal middle cerebral artery in cases of red blood cell isoimmunization, monochorionic twins with twin–twin transfusion syndrome, the screening and diagnosis of congenital cardiac anomalies, and the diagnosis of congenital vascular anomalies. These indications will likely continue to expand. However, the primary utility of Doppler sonography is in the evaluation of a fetus with possible intrauterine growth restriction. In normal pregnancies or when the fetus has demonstrated normal growth, there is no current role for Doppler sonography of fetal vessels, because they have not been found to convey benefit in a low-risk population. Use of Doppler velocimetry in the setting of intrauterine growth restriction is presented in Chapter 15.

Interpretation of Test Results

The realistic goal of antepartum testing is to decrease the risk of intrauterine fetal demise or perinatal mortality in the tested population so that it approaches the rate for a low-risk population without an excessive or unacceptable false-positive rate that may result in unnecessary intervention. The false-negative rate for commonly employed antepartum tests is very low, with residual stillbirth rates after reassuring



• **Fig. 12.2** Ultrasound image of the maximal vertical pocket measured as part of either the biophysical profile or the amniotic fluid index. Note the absence of umbilical cord in the measured pocket.

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testing approximating those of the general population. The false-positive rate, however, is more difficult to ascertain because a positive test usually results in obstetric intervention, significantly decreasing the likelihood of intrauterine death. However, babies delivered after abnormal testing do not always demonstrate abnormal findings such as acidemia or low Apgar scores. For example, Manning et al. reported on a cohort of 913 infants delivered after biophysical profile score of 6 or less.[15] Nearly 40% of infants with scores of 6 showed no markers of fetal compromise at delivery, as defined by fetal distress in labor, admission to the neonatal intensive care unit, a 5-minute Apgar score of 7 or less, or an umbilical cord pH less than or equal to 7.20. There was a significant inverse linear association, however, between biophysical profile score and these markers, and all fetuses with scores of 0 had at least one of these markers at delivery.

In a clinically stable situation, reassuring tests (reactive NST, negative CST, and biophysical profile of 8 or 10) are considered reliable for 1 week, and so testing is usually performed on a weekly basis. Labile conditions may merit more frequent testing; the frequency is left to the discretion of the physician. In certain high-risk populations, the false-negative rate of NST may be unacceptably high. The stillbirth rate within 1 week of a reactive NST is markedly higher for patients with diabetes mellitus and fetal growth restriction. Boehm and co-workers found that the stillbirth rate decreased from 6.1 per 1000 to 1.9 per 1000 in their high-risk population when the frequency of testing was changed from once weekly to twice weekly.[5] For this reason, testing twice weekly may be appropriate in certain populations, such as those described.

Clinically, one should always give consideration to maternal illness as a cause of nonreassuring fetal status. For example, if the mother is acidemic from any etiology, placental equilibration will eventually lead to acidemia in an otherwise healthy fetus, which in turn can lead to abnormal antenatal testing results. A classic example is maternal diabetic ketoacidosis. In such circumstances, the appropriate course of action is to correct the maternal condition first and not to necessarily directly intervene on behalf of the fetus despite the nonreassuring antenatal testing. The fetal status will improve as the maternal status is improved, thus avoiding iatrogenic delivery, and cesarean sections or other efforts to deliver the fetus may not be safe if the mother is critically ill.

Evaluation of the Intrapartum Fetus

The process of labor and delivery is a period of significant metabolic stress for both the laboring mother and her baby, although in the great majority of cases these stressors are easily tolerated, and labor results in a healthy mother and child. In some cases, however, the process is tolerated poorly, and the fetus develops a degree of acidosis that places it at risk of multiorgan dysfunction or even death. Thus, in the 1970s, FHR monitoring during labor was introduced, with the hope of identifying heart rate patterns that were predictive of adverse outcomes and would allow for intervention prior to irreversible events. Subsequently, continuous electronic FHR monitoring during labor has been used in the majority of laboring patients in developed countries for the last several decades. The initial hopes and promises of continuous FHR monitoring, however, have not been fulfilled during this time. The incidence of cerebral palsy has remained stable, whereas the cesarean section rate has progressively increased, in part because of operative deliveries being performed for FHR patterns that may or may not be sufficiently predictive of adverse outcomes.[11] The contemporary practitioner utilizing FHR monitoring during labor must thus be cautious to both intervene prior to an irreversible event and to avoid iatrogenic operative delivery. This has proved to be a difficult balance.

Intrapartum Oxygenation and Neurologic Morbidity

The strongest correlate to adverse outcomes is decreased tissue concentrations of oxygen (*hypoxia*) and decreased tissue pH (*acidosis*). What is more easily and often evaluated, however, is decreased oxygenation or pH in the peripheral blood, referred to respectively as *hypoxemia* and *acidemia*. These are what is measured when the blood from the umbilical artery and vein is sampled after delivery, and thus serve as common surrogate outcomes in clinical research. Although significant hypoxemia will eventually lead to tissue-level hypoxia and acidosis, the presence of the former does not necessarily guarantee the latter. Although hypoxemia and acidemia can be easily evaluated by laboratory methods, determining the presence or absence of hypoxia or acidosis is more complex and often involves physical and clinical more so than laboratory assessments.

Another important differentiation is between respiratory and metabolic acidosis in the fetus and neonate. The concept of a "respiratory" acidosis in a fetus may seem unusual, because they are not literally using their lungs to exchange air, although the same concepts that are useful outside of the uterus can be applied to the transplacental exchange of oxygen and carbon dioxide. A respiratory acidosis occurs when carbon dioxide accumulates secondary to impaired clearance by the lungs or, in the case of a fetus, the placenta. A fetal metabolic acidosis will be the result of a prolonged or severe deprivation of oxygen, triggering lactate production in fetal tissue. A respiratory or metabolic acidosis, although often occurring in combination, can be differentiated from one another by the measurement of base deficit, with a high base deficit indicating a metabolic process. Metabolic processes are more concerning than respiratory ones for several reasons. First, an umbilical artery acidemia with an increased base deficit strongly implies excess tissue lactate generation. Thus there is probable acidosis and not just acidemia. Additionally, a respiratory acidemia can rapidly correct itself once normal ventilation is established and excessive carbon dioxide is cleared, whereas the correction

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of a metabolic acidosis requires the cessation of lactate generation at a tissue level and is thus delayed relative to the onset of appropriate oxygenation. Clinically, the newborn with an isolated respiratory acidosis (or acidemia) will have a low umbilical cord pH at birth and low 1-minute Apgar score, although once ventilation is established, will enjoy rapid clinical improvement and a subsequent uneventful newborn period. By contrast, the neonate who remains clinically depressed through the first several minutes of life despite adequate ventilation is more likely to have a metabolic acidosis and an increased umbilical artery base deficit.

As discussed previously, various findings in the FHR patterns have been correlated with fetal hypoxemia and acidemia. The outcomes of hypoxemia and acidemia, however, are in and of themselves surrogate outcomes. Although fetal risks increase with increasing metabolic derangements, many fetuses with hypoxemia and acidemia, especially if it is a purely respiratory process, will subsequently have a normal newborn course. If an operative delivery is performed in a fetus that has hypoxemia or acidemia but that would have, if left alone, delivered vaginally without permanent neurologic injury, then the intervention has not been clearly beneficial. The most meaningful clinical question then is if continuous FHR monitoring can predict the fetus that will not survive the labor process or survive with permanent neurologic injury secondary to intrapartum events. Given the multitude of complex factors that contribute to neurologic injury, it is perhaps not unsurprising that an evaluation of FHR alone has not proved to be sufficiently predictive in this regard. Using cerebral palsy as an endpoint, the positive predictive value of FHR monitoring is very low.

The overall determination of neonatal health following the stress of delivery is not determined by a single laboratory value, but a combination of laboratory and clinical evidence of metabolic acidemia with a clinical course that is consistent with a hypoxic event. For the child who is subsequently diagnosed as having cerebral palsy, a multitude of other potential etiologies (anatomic, infectious, genetic, thrombotic, and metabolic, among others) needs to be ruled out as well, because intrapartum hypoxic events account for only a small percentage of cases of neonatal neurologic injury. To provide guidance in these complicated issues, the American College of Obstetricians and Gynecologists and American Academy of Pediatricians convened a joint task force that in 2003 established criteria to define an acute intrapartum event as having been sufficient to cause cerebral palsy[17] with an update in 2014.[18] These criteria are outlined in Box 12.2, and the evaluation of neonatal encephalopathy is covered in detail in Chapter 54. In the absence of these explicit criteria, it is not optimal for a provider to ascribe neurologic outcomes to a potential intrauterine event, and appropriate caution should always be applied to the potentially inappropriate use of the expressions *asphyxia*, *newborn encephalopathy*, and *hypoxic-ischemic encephalopathy* in the medical records.

• BOX 12.2 Criteria to Define an Acute Intrapartum Event as Sufficient to Cause Cerebral Palsy

- Apgar score of less than 5 at 5 minutes and 10 minutes
- Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH <7 and base deficit ≥12 mmol/L)
- Evidence of acute brain injury on neuroimaging
- Multisystem organ failure consistent with neonatal encephalopathy
- A sentinel hypoxic event occurring immediately before or during labor and delivery
- Cerebral palsy of the spastic quadriplegic or dyskinetic type
- Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders

Adapted from *Neonatal encephalopathy and cerebral palsy: defining the pathogenesis and pathophysiology*. Washington, DC: American College of Obstetricians and Gynecologists; 2003.

Continuous Versus Intermittent Fetal Heart Rate Monitoring

Two options for fetal monitoring are available for laboring women: continuous and intermittent fetal monitoring. Provider and patient opinions vary regarding which is optimal, although for low-risk patients guidelines exist for both, and both options are considered acceptable and within usual standards of care. A meta-analysis by the Cochrane Collaborative identified 12 studies that compared continuous electronic FHR monitoring to either no monitoring or intermittent monitoring during labor.[1] The use of continuous FHR monitoring was not associated with a decreased risk of perinatal mortality or cerebral palsy. There was, however, a significant reduction in neonatal seizures. This benefit was balanced against a significant increase in the risk of undergoing either cesarean section or operative vaginal delivery. Thus, the optimal mode of fetal monitoring is unclear. The occurrence of neonatal seizures, low Apgar scores, and hypoxemia at the time of birth can all cause significant emotional distress for new parents even in the absence of clear differences in long-term neurologic outcomes or survival, and many parents would potentially be willing to accept an increased risk of operative delivery to prevent neonatal seizures. On the other hand, many patients are highly motivated to have a spontaneous vaginal delivery and would be willing to accept a risk of transient neonatal seizures if there are no significant differences in longer-term neurologic outcomes. For low-risk patients who would be candidates for either approach, the most optimal approach may be to discuss the relative advantages and disadvantages of either early in pregnancy and allow the patients to then make the choice that works best for them.

Continuous electronic FHR monitoring may be performed externally or internally. Telemetry units are available so that a patient need not be confined to a bed to be monitored. Additionally, many modern units are waterproof and

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would thus allow for continuous monitoring while a patient is laboring in a bath or tub. Most external monitors use a Doppler device with computerized logic to interpret and count the Doppler signals. Internal FHR monitoring may be performed in circumstances in which external monitoring is technically difficult, such as maternal obesity. Internal monitoring uses an electrode that is attached to the fetal scalp, and contraindications to fetal scalp puncture (transmittable maternal infections such as hepatitis or HIV) are likewise relative contraindications for internal fetal monitoring. Internal monitoring also necessitates rupture of the fetal membranes. If the membranes are intact and internal monitoring is determined to be necessary, they can be artificially ruptured to facilitate monitoring, although this can carry a risk of umbilical cord prolapse if the fetal presenting part is not engaged.

Internal fetal scalp electrodes also have the advantage of overcoming monitoring difficulties secondary to maternal obesity. The rates of obesity have been steadily increasing throughout the world and present technical difficulties for external Doppler monitoring when the amniotic membranes are still intact. However, electrohysterography (EHG) and fetal electrocardiograms are expanding alternate technologies that can provide similar degrees of monitoring through maternal abdominal electrodes and are less sensitive to differences in maternal habitus.[7,8]

Interpretation of Continuous FHR Recordings

Baseline Fetal Heart Rate

Baseline FHR is the average FHR rounded to increments of 5 beats/min during a 10-minute segment, excluding periodic or episodic changes, periods of marked variability, or baseline segments that differ by more than 25 beats/min. In any given 10-minute window, the minimal baseline duration must be at least 2 minutes or the baseline is considered indeterminate. A normal FHR baseline rate ranges from 110-160 beats/min. If the baseline FHR is less than 110 beats/min, it is termed *bradycardia*. If the baseline FHR is greater than 160 beats/min, it is termed *tachycardia* (Fig. 12.3). Of note, although rates of 110 and 160 beats/min are the accepted cutoff values for FHR, many fetuses with heart rates above or below these values will be otherwise healthy outliers. For example, a fetus that is experiencing otherwise uncomplicated labor with a fetal heart rate tracing that is perfectly reassuring other than a baseline in the 100s is likely normal.

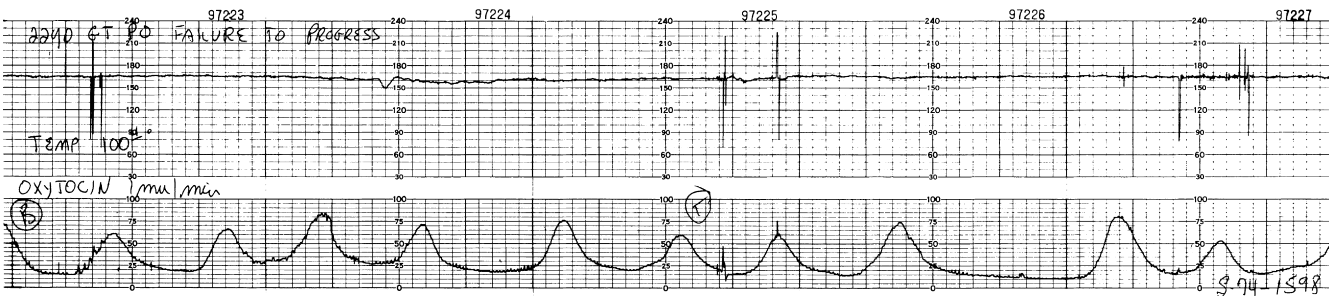
As described later, events that can be associated with hypoxemia or the later development of hypoxemia, such as umbilical cord compression, produce decelerations of the fetal heart rate. However, it is worth noting that the primary response to hypoxemia is not bradycardia but tachycardia secondary to sympathetic discharges. A progressive increase in the heart rate baseline during labor can raise concern for hypoxemia if other FHR anomalies, such as decreasing variability, become progressively apparent over the same time period. Tachycardia may also be associated with conditions other than hypoxia, such as maternal fever, intra-amniotic infection, thyroid disease, the presence of medication, and cardiac arrhythmia.

Fetal Heart Rate Variability

The presence of baseline FHR variability is a useful indicator of fetal CNS integrity. Variability is defined as fluctuations in FHR baseline of two cycles per minute or greater, with irregular amplitude and inconstant frequency. Of note, although the fetus will normally have beat-to-beat heart rate variation, the actual PQRS complexes themselves are normal, differentiating this healthy phenomenon from atrial fibrillation or other pathologic arrhythmias. The variation represents alternating responses to sympathetic and parasympathetic inputs. If either the sympathetic or parasympathetic system instead predominates, such as would be the case of vagal nerve stimulation or increased sympathetic activity owing to hypoxia, this variability would be lost (Fig. 12.4). Thus, moderate FHR variability is strongly associated (98%) with an umbilical pH greater than 7.15, and in combination with a normal FHR baseline, generates a high degree of reassurance regardless of the presence or absence of accelerations or decelerations.

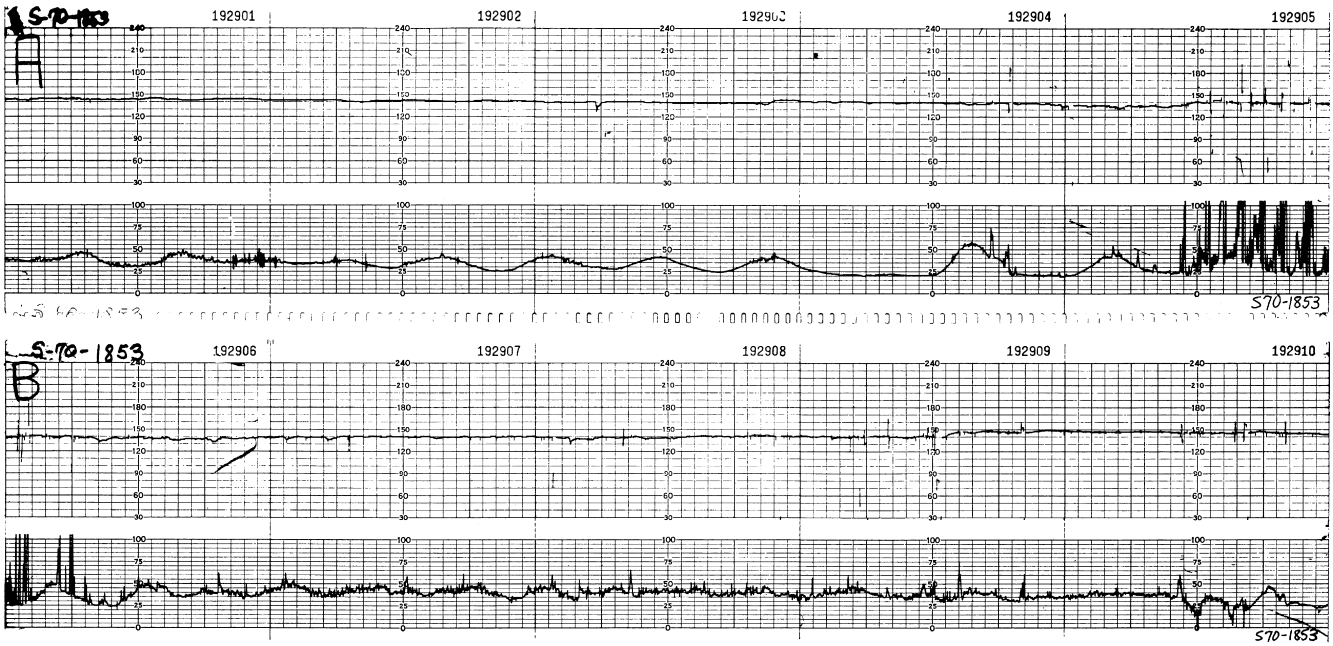
FHR variability is visually assessed as the amplitude of the peak to trough in beats per minute as follows:

Amplitude Range	Classification
Undetectable	Absent
1-5 beats/min	Minimal
6-25 beats/min	Moderate
>25 beats/min	Marked



• **Fig. 12.3** Fetal tachycardia, with a baseline fetal heart rate of 165 beats/min. This was in the setting of a maternal fever. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:70.)

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• **Fig. 12.4** Abnormal (absent) fetal heart rate (FHR) variability. Because there are no decelerations present, this would qualify as a category II FHR tracing. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:138.)

Accelerations

Accelerations in FHR are periodic elevations above the baseline, and they are usually associated with fetal movement. The presence of FHR accelerations during labor is always reassuring, as it is in a nonlaboring patient. Their absence during labor, however, is not necessarily concerning if other aspects of the FHR pattern are reassuring (see subsection Category I). Unlike a non-stress test in an antepartum patient, a "reactive" FHR tracing with "15 × 15" accelerations is not required for reassurance in the laboring patient.

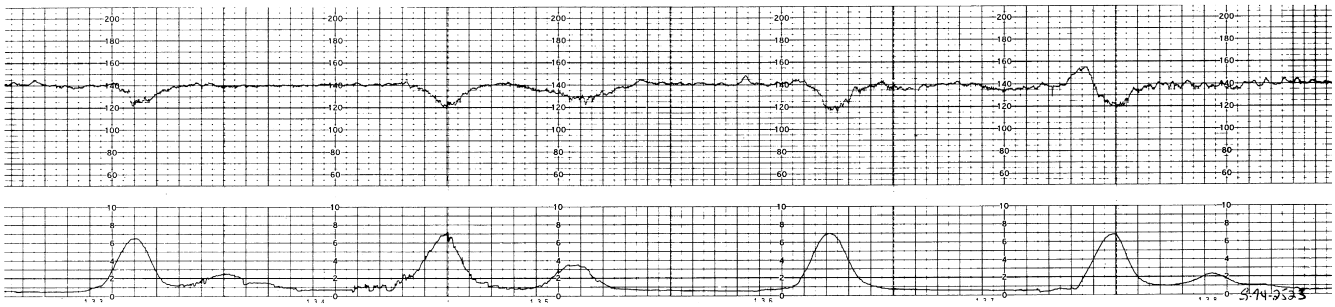
Decelerations

Decelerations in FHR are episodic decreases below the baseline. Most decelerations are mediated through parasympathetic stimulation from the vagal nerve. These, in turn, are triggered by a variety of stimuli, including transient increases in intracranial pressure ("early" decelerations), increased systemic vascular resistance ("variable" decelerations), and hypoxemia (some "late" decelerations). Thus, most decelerations do not specifically signify the presence of fetal acidosis, and in fact many are simply interesting demonstrations of human physiologic reflexes. A portion of "late" decelerations, however, occurs secondary to the suppression of myocardial function by tissue-level hypoxia, which is clinically concerning. Clinically differentiating these from other deceleration patterns, however, is often imprecise.

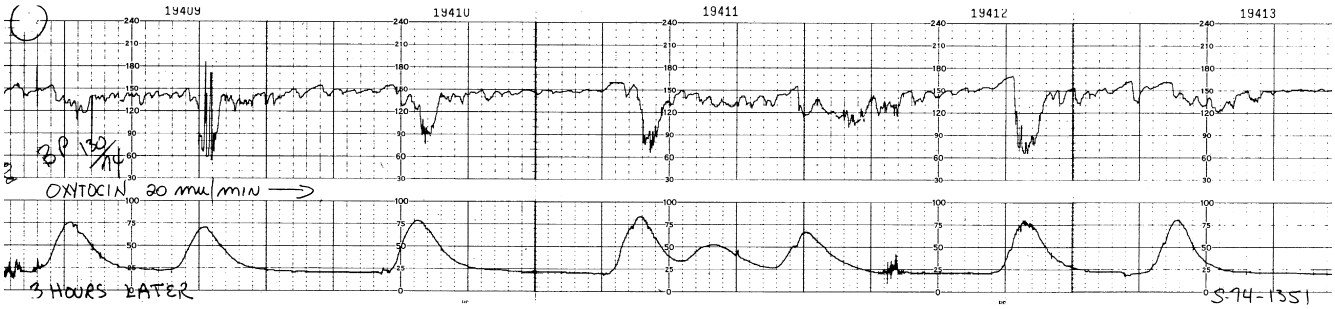
Decelerations are classified by their morphology and then by whether they are recurrent or prolonged. Decelerations are defined as "recurrent" if they occur with at least 50% of the contractions. A "prolonged" deceleration is one that lasts for more than 2 minutes. Three types of decelerations are described: early, variable, and late. Early decelerations are shallow and symmetric, gradual in onset and recovery, and associated with a contraction such that the nadir of the deceleration occurs at the same time as the peak of the contraction (Fig. 12.5). Physiologically, early decelerations are a demonstration of Cushing reflex, in which increased intracranial pressure generates bradycardia through stimulation of the vagal nerve. Because of the unfused cranial fontanelles, pressure applied to the fetal cranium, such as when the head is pressed against maternal tissue during a contraction, is translated into increased intracranial pressure and can trigger activation of the vagal nerve. Like most reflexes, the response is virtually instantaneous and the magnitude of vagal nerve stimulation correlates with the magnitude of pressure applied against the fetal head. This is why "early" decelerations appear as mirror images of the contractions. This entire process is unrelated to fetal oxygenation and acid-base balance, which is why early decelerations, although conceptually interesting, are not of clinical importance.

Variable decelerations are typically associated with an abrupt onset and abrupt return to baseline. They vary in shape, depth, and duration and in the occurrence of contractions. They are also frequently preceded and followed by small accelerations in FHR (Fig. 12.6 and Fig. 12.7). Variable decelerations are usually associated with compression of the umbilical cord and represent physiologic changes in response to alterations in vascular resistance and preload. The umbilical cord contains a single large, thin-walled vein and two smaller, muscular arteries. When the umbilical cord is initially compressed, the umbilical vein is thus occluded first. This causes a decrease in venous blood returning to

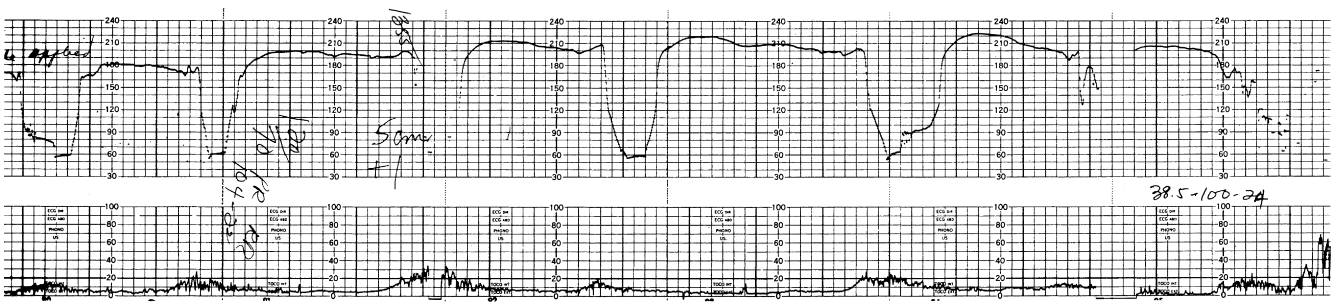
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• **Fig. 12.5** Early decelerations. Note the way in which the decelerations appear to "mirror" the uterine contractions. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:74.)



• **Fig. 12.6** Variable decelerations. Note the normal fetal heart rate baseline and variability between the decelerations. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:78.)

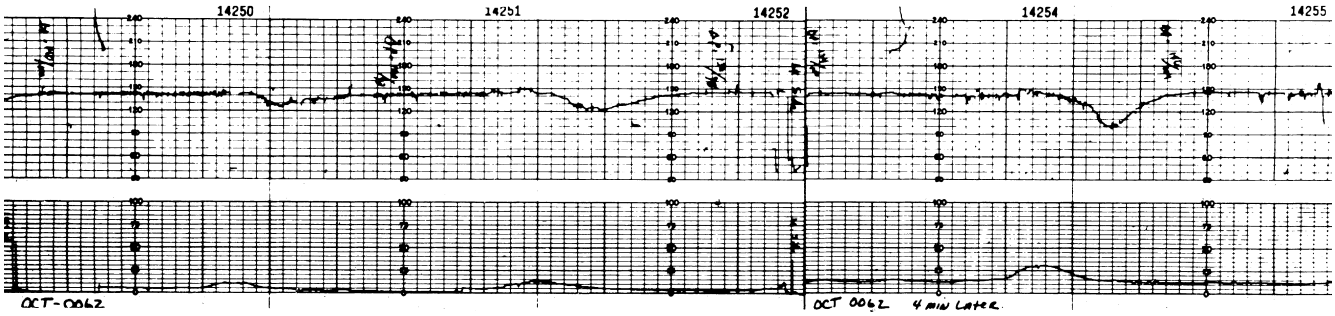


• **Fig. 12.7** Variable decelerations. In contrast to Fig. 12.8, note the tachycardic fetal heart rate (FHR) baseline and absent variability between the decelerations. Also note the prolonged FHR "overshoot" in the middle portion of the panel. This FHR tracing is more concerning for the presence of fetal hypoxia and acidosis and would be considered category III.

the fetal heart and, thus, a decrease in preload, which in turn triggers tachycardia. This is why variable decelerations are often preceded and followed by small increases in FHR, referred to colloquially as "shoulders." As increasing compressive force is applied to the umbilical cord, the muscular arteries are eventually compressed as well. This then leads to a significant increase in vascular resistance, which in turn generates bradycardia via vagal nerve stimulation via baroreceptors. Although variable decelerations can sometimes occur normally during the labor process or even antenatal testing, their presence should alert the practitioner to the potential presence of umbilical cord compression, causes for which could include low amniotic fluid (oligohydramnios) or prolapse of the umbilical cord through the cervix. Overall, variable decelerations represent anticipated physiologic reflexes to umbilical cord compression and not the presence of hypoxemia or acidemia per se. However, severe and repetitive compression will eventually compromise oxygenation and overall health, and thus interventions (which can be as simple as maternal positional changes) would be warranted in this circumstance. Additionally, some fetuses can develop hypoxemia during periods of umbilical cord compression, which then normalizes after the compression is released. This can present as a period of tachycardia that follows resolution of the variable deceleration, owing to a sympathetic response to the hypoxemia. These are referred to as "overshoots" (see Fig. 12.7).

Late decelerations, by contrast, have a more gradual onset and return to baseline—typically 30 seconds or more from onset to nadir. The onset, nadir, and recovery of the

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• **Fig. 12.8** Late decelerations. Note the timing of the onset, nadir, and recovery of the deceleration, which occur after the onset, peak, and end of the contraction. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:201.)

deceleration occur after the onset, peak, and end of the contraction (Fig. 12.8). During a uterine contraction, placental perfusion is temporarily impaired secondary to myometrial compression of the spiral arteries, which lose their muscularis in early pregnancy and are thus compressible. In a fetus that is undergoing the labor process normally, however, this transient event is well tolerated without clinically meaningful hypoxemia. For fetuses that are experiencing a decreasing oxygen reserve, however, the perfusion reduction during a contraction can have more significant effects, albeit not always tissue acidosis or multiorgan dysfunction. These effects and their resolution will always be delayed relative to the contraction itself, because the impact of decreased perfusion will be progressive and then require time to resolve once the contraction is complete. This is why "late" decelerations have their characteristic appearance relative to uterine contractions.

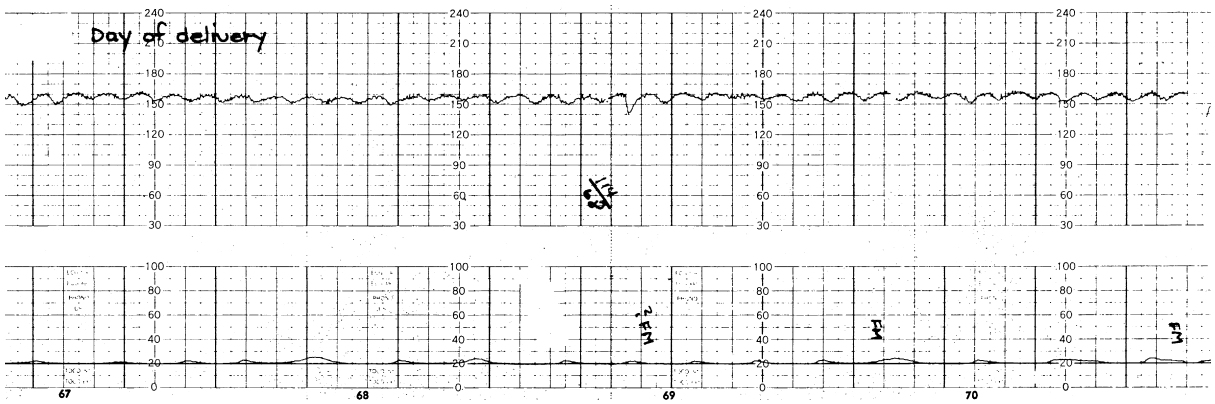
The actual mechanism of late decelerations occurs secondary to two separate although interrelated processes, one of which is related to hypoxemia and the other to tissue-level hypoxia. Although hypoxemia generates a sympathetic response that leads to tachycardia and thus an increasing FHR baseline, it can also generate bradycardia through a more indirect pathway: the decrease in peripheral oxygen concentration triggers a sympathetic output, which in turn transiently increases the blood pressure, which in turn triggers baroreceptors, which in turn stimulate the vagal nerve, which then decreases the heart rate. Thus, the presence of late decelerations can signify transient hypoxemia during and resolving after uterine contractions. In this situation, it would be optimal to resolve the transient hypoxemia, and interventional measures such as positional changes and supplemental oxygenation are usually undertaken. The fetus in this scenario, however, is not necessarily acidotic (or even has tissue-level hypoxia) and, presuming it can recover appropriately between contractions, can still possibly proceed with a normal labor course and uncomplicated vaginal delivery. The other potential mechanism for late decelerations, however, involves direct suppression of myocardial activity secondary to tissue-level changes in which the bradycardia reflects the inability of the myocardium to function properly in the setting of hypoxia. Secondary to differences between respiratory and metabolic acidosis and all of the other complex variables involved in organ function, many of the fetuses in this scenario will still have normal long-term outcomes, although this is the scenario of greatest clinical concern and the one in which consideration could be given to expedition through operative delivery. For the patient experiencing late decelerations, however, it can be difficult to determine if they are occurring secondary to which of these two underlying pathways. Context is important in this regard, such that in the case of a persistently hypoxic fetus, other FHR changes, such as progressive tachycardia and loss of variability, should accompany the late decelerations. The fetus who is experiencing late decelerations, but for whom the FHR has a normal rate and variability between contractions, is more likely to be experiencing only transient hypoxemia.

A sinusoidal heart rate pattern consists of a regular oscillation of the baseline variability in a smooth undulating pattern. This pattern typically lasts at least 10 minutes, has a relatively fixed period of three to five cycles per minute, and an amplitude of 5-15 beats/min above and below the baseline (Fig. 12.9). This pattern is quite rare but can be associated with severe chronic anemia or severe hypoxia and acidosis, although rarely can also be an incidental finding.

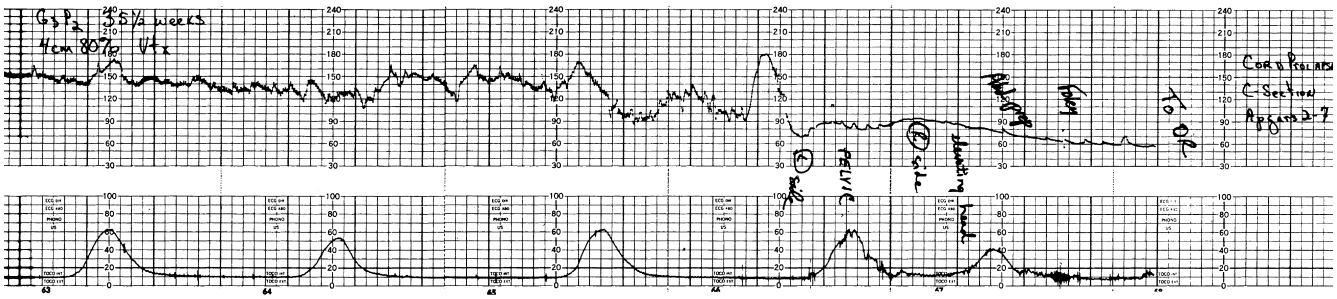
Interpretative Systems for Classification of Fetal Heart Rate Patterns

Since its introduction, the utility of electronic fetal monitoring has been limited by the subjective nature of its interpretation. Despite continual efforts at standardization, interpretation of FHR tracing is subjective and prone to significant interobserver and intraobserver variation.[3] Although many interpretative systems exist for FHR tracings, the 2008 National Institutes of Child Health and Human Development (NICHD) workshop dealing with Standardization of Nomenclature for Intrapartum Electronic Fetal Monitoring, jointly sponsored by NICHD, the American College of Obstetricians and Gynecologists, and the Society for Maternal Fetal Medicine, has been an important step toward standardization.[12] In this system, fetal tracings are divided into three categories.

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• **Fig. 12.9** Sinusoidal fetal heart rate pattern. This fetus was severely anemic and hydropic because of maternal Rh isoimmunization. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:166.)



• **Fig. 12.10** Prolonged deceleration associated with acute prolapse of the umbilical cord. Note the reassuring fetal heart rate tracing leading up to the deceleration, indicating an acute event. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:83.)

Category I

These are "normal" tracings, which are strongly predictive of normal fetal acid-base status at the time of observation and can be followed in a routine manner without any specific action required. They necessitate all of the following:

- Baseline rate of 110-160 beats/min
- Moderate variability
- Absence of any late or variable decelerations
- Early decelerations may or may not be present.
- Accelerations may or may not be present.

Of note, an FHR pattern during labor does not have to have accelerations that would meet the "reactivity" criteria of an antepartum non-stress test to still be a category I tracing.

Category II

These are indeterminate tracings that, although not predictive of abnormal fetal acid-base status, cannot be classified as category I or III and require evaluation and continued surveillance and reevaluation. These tracings are frequently encountered in clinical care and include any tracing that does not meet the more specified criteria for category I or III. Except for patterns that are sinusoidal, category III tracings require the combination of absent variability plus one more additional finding as described below. Thus, a tracing that has appropriate variability but has other findings, such as late or variable decelerations that would exclude it from category I, would fall into category II.

Category III

These are abnormal tracings that are potentially predictive of an abnormal fetal acid-base status at the time of observation. As such, they require prompt evaluation and initiation of attempts at correction. These tracings include *either*:

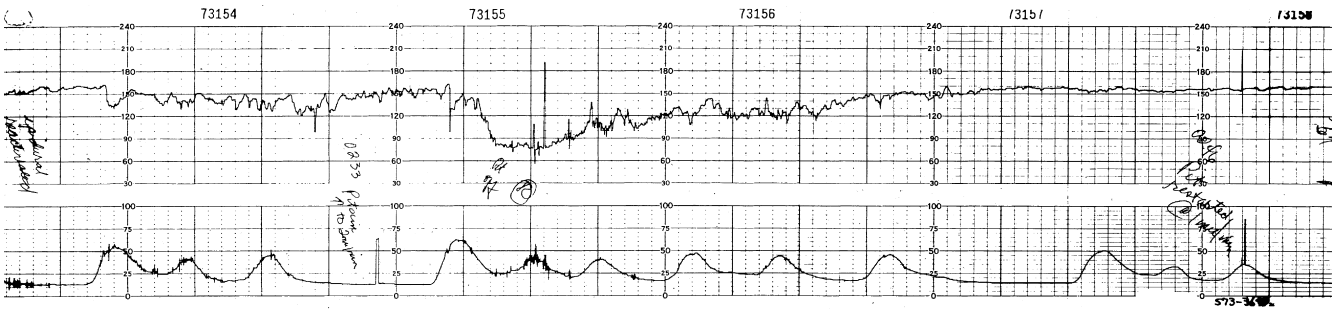
1. Absent baseline FHR variability along with *any* of the following:
   a. Recurrent late decelerations
   b. Recurrent variable decelerations
   c. Bradycardia
2. Sinusoidal pattern

"Recurrent" decelerations would be those that occur with greater than 50% of contractions.

Management of Non–Category I FHR Patterns During Labor

The evaluation of a category II or III pattern begins with a search for an underlying etiology that would itself require immediate delivery. For example, an acute change in the FHR pattern with prolonged deceleration (Fig. 12.10) could have occurred secondary to umbilical cord prolapse,

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• **Fig. 12.11** Prolonged deceleration associated with uterine hyperstimulation. Note the recovery of the deceleration after discontinuation of the oxytocin infusion. (From Freeman R, Garite T. *Fetal heart rate monitoring*. Baltimore: Williams & Wilkins; 1981:85.)

placental abruption, or uterine rupture. In the absence of such events, one should search for a remediable cause of the concerning FHR tracing. Uterine perfusion is very sensitive to maternal blood pressure, and even relative redistributions of maternal blood flow, such as can occur after the initiation of regional anesthesia, can impact the FHR pattern. Abnormal FHR patterns may also result from contractions that are too frequent in timing to allow for recovery between them. The occurrence of uterine contractions more frequently than 5 in 10 minutes, averaged over 30 minutes, is generally referred to as tachysystole (Fig. 12.11) and can occur as a consequence of labor induction agents. When the tachysystole is resolved, either by discontinuing or decreasing an oxytocin infusion or administering a tocolytic, the fetal status typically improves. Maternal position in labor can affect the FHR tracing, because the supine position decreases uterine blood flow and placental perfusion. Repositioning a patient to the lateral recumbent position can improve a concerning FHR pattern with no other intervention. Supplemental oxygen therapy for the mother should also be administered. When recurrent variable decelerations are present, amnioinfusion, in which fluid is infused into the uterine cavity, has been shown to decrease the rate of variable decelerations and cesarean delivery for nonreassuring fetal status.[10] When faced with a concerning FHR tracing with no clear secondary cause and which persists despite attempts at conservative management, some options do exist for additional reassurance, because many of these fetuses will still have a normal acid-base status secondary to the imprecision of continuous FHR monitoring. An acceleration in FHR after vibroacoustic stimulation or fetal scalp stimulation with a digital examination provides reliable reassurance of a normal fetal pH and allows labor to continue. Blood sampling from the fetal scalp can be used to assess the fetal pH or lactate directly, although this is invasive and uncommonly performed in contemporary practice.

Many FHR tracings will remain indeterminate without either a reversible cause or additional reassurance from scalp stimulation or pH measurement. Management of these cases is complicated and depends upon the exact clinical circumstances, including the stage and progress of labor. Because of this common scenario there has been longstanding interest in technological advancements to provide additional information regarding the fetal status. The two areas of greatest promise had been the fetal pulse oximetry and ST segment analysis. Unfortunately, neither of these technologies has demonstrated a reduction in cesarean delivery or neonatal outcomes in large clinical trials. Specifically, a randomized trial of ST segment analysis in 11,108 subjects was published in 2015 and demonstrated no differences in either composite neonatal morbidity or cesarean delivery between open and masked monitoring.[2]

Although research in this important area is continuing, at this time there are no technologies available for additional fetal reassurance that are either evidence-based or standard of care. In lieu of current or future technological advancements, there has been increased focus on optimizing our available fetal monitoring protocols through the increased use of guidelines and practice standardization. In particular, there is interest in increasing the uniformity of management for category II tracings, since these are both common and of indeterminate significance. For example, the occurrence of any late deceleration would exclude a designation of category I, and thus a tracing that was otherwise entirely reassuring with the exception of a single late deceleration would be category II. On the other end of the spectrum would be a tracing with absent variability and four late decelerations out of 10 contractions in a 30-minute period, since category III requires "recurrent" late decelerations, which would be greater than half of contractions. In addition to the wide range of severity, the overall clinical context needs to come under consideration as well, including the course of labor and degree to which longitudinal changes may be occurring within category II.[21] It would be more reasonable to continue with a category II tracing in a patient with normal labor progress who is nearing delivery than it may be for the same tracing for a patient who is either early in the latent phase or experiencing abnormal labor progress. Thus, attempts have been made at guideline development for category II management, including the publication of collaborative exert opinion.[6] These provide useful guidance although have not been formally adopted as national standards of care.

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Key Points

- Antepartum testing can decrease the risk of stillbirth in many pregnancies at risk of fetal compromise secondary to uteroplacental dysfunction.
- The most common strategy for antepartum testing is the weekly non-stress test performed after 32 weeks. A non-stress test is reassuring if the fetal heart rate demonstrates two accelerations that are 15 seconds in duration and 15 beats per minute above the baseline.
- The biophysical profile is an alternate antenatal testing modality that uses ultrasound to track fetal activity using a scoring system from 0-10. Values of 8 and 10 are reassuring and values of 6 are indeterminate.
- Low-risk fetuses during labor can be monitored with either intermittent or continuous monitoring.
- Continuous electronic fetal monitoring has not clearly resulted in a decreased incidence of cerebral palsy and may increase the risk of cesarean and operative delivery.
- A three-category scoring system is utilized for the interpretation of fetal monitoring during labor.

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13

Surgical Treatment of the Fetus

JARRETT MOYER, COREY W. IQBAL, SHINJIRO HIROSE, AND HANMIN LEE

Summary

Over the past half-century, implementation of high-resolution screening prenatal imaging, coupled with increasingly nuanced understanding of embryology and human fetal development, have created a new surgical patient: the fetus. Through decades of rigorous scientific investigation and technical innovation, congenital anomalies that previously carried a grim prognosis are now candidates for fetal intervention. As experience has grown with fetal surgical intervention, we have been able to quantify survival benefit and reduction in morbidity to the fetus for many conditions, while also coming to understand the specific risks for the fetus and the mother.

In fact, the potential impact of fetal surgery on the mother presents difficult ethical decisions. By undergoing general anesthesia, a surgical operation, postoperative recovery, and the remainder of pregnancy, the mother is subject to significant risk but can expect no direct health benefit from fetal surgical intervention. Specifically, short-term morbidity after fetal surgery includes preterm labor, the potential risk of anesthesia, the potential need for blood transfusion, premature rupture of membranes, chorioamniotic separation, chorioamnionitis, and placental abruption. Long-term morbidity related to the hysterotomy used in open fetal cases includes infertility, uterine rupture during future pregnancies, and mandatory cesarean section with future pregnancies. Therefore, it is crucial that the obstetric, medical, and surgical teams consider the protection of the pregnant woman as the utmost priority when making treatment decisions. Additionally, comprehensive discussion of the potential benefit to the fetus and the unique risks to the mother is required while obtaining informed consent. Specifically, women should be informed of and provided access to alternative treatment modalities, including postnatal therapy, palliative delivery, or pregnancy termination.[8,19]

Fetal Access

Access to the fetus can be considered in three general categories: percutaneous, fetoscopic, and open hysterotomy. Preoperative and intraoperative ultrasound are critical for defining the anomaly (or anomalies), delineating the placental anatomy, determining the position of the fetus, detecting the location of the maternal blood vessels, and monitoring the fetal heart rate during the procedure. Ultrasonography is particularly vital in percutaneous and fetoscopic procedures owing to limited direct visualization of the fetus, placenta, and uterus during the procedure.

Percutaneous Interventions

Needle-based interventions were first reported in 1963, when Liley performed the first fetal transfusion by inserting a 16-gauge needle into the fetal peritoneal space.[64] Since then, advances in imaging and instrumentation have broadened the application of percutaneous techniques in the treatment of the fetus. Percutaneous procedures are performed through small skin incisions on the mother's abdominal wall, utilizing real-time ultrasound to visualize the fetal and maternal anatomy and guide the intervention.[109] Cystic masses, ascites, pleural fluid, or other fluid collections can be aspirated as a diagnostic or therapeutic maneuver. Shunts can be inserted for more definitive drainage of fluid into the amniotic space. Other devices such as radio frequency ablation (RFA) probes can be deployed to treat complications of twin gestation. The needles used to place these catheters, as well as the RFA device, are approximately 1.5 to 2 mm in diameter, minimizing morbidity to the mother and irritation of the uterus.

Fetoscopic Surgery

Fetoscopic procedures are performed using a 1.2- to 3.0-mm fetoscope with or without a working channel, inserted through a 2.3- to 4.0-mm cannula placed into the uterus.[103] For procedures performed through a single port with a fetoscope containing a working port, the uterus can be accessed through a small incision on the mother's abdomen. Procedures requiring multiple instruments and ports may proceed either via multiple small abdominal incisions or a maternal laparotomy allowing port placement directly into the uterus. Fetoscopy permits direct visualization of the lesion at the time of intervention but is still facilitated by the use of fetal ultrasound. Additionally, access to the uterus is performed under ultrasonographic guidance to locate a

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Abstract

Fetal surgery is a developing field, with scientific, clinical, and ethical questions still under investigation, and innovation forging new paths forward. In all cases, the well-being of the expectant mother must be considered the top priority when making treatment decisions. Informed consent is especially vital, as any fetal intervention carries substantial risk of obstetric complications, including preterm labor, PPROM, membrane separation, and chorioamnionitis, and open hysterotomy necessitates eventual delivery by cesarean section. Fortunately, innovation in surgical instrumentation and technique has led to effective percutaneous and fetoscopic minimally invasive therapies for most conditions amenable to prenatal intervention. Given the risk of obstetric morbidity, fetal interventions are usually reserved for the fetus at risk of intrauterine or early neonatal demise, as is the case in congenital diaphragmatic hernia, congenital pulmonary airway malformations (CPAM), hydrothorax, sacrococcygeal teratoma, fetal neck mass, urinary tract obstruction, abnormalities of twin gestation, and congenital heart defects. Fetal repair of myelomeningocele is unique in that fetal intervention aims to minimize postnatal morbidity rather than mortality. In this chapter, the authors describe the indications, techniques, and outcomes of fetal interventions for the conditions listed above, as well as other congenital lesions that threaten the fetus.

Keywords

fetal surgery
fetoscopic
hysterotomy
congenital diaphragmatic hernia
myelomeningocele
sacrococcygeal teratoma

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"window" in the uterus that is devoid of the placenta in hopes of reducing the risk of maternal bleeding, placental abruption, and fetal morbidity. Occasionally, the amniotic fluid is not clear enough for adequate direct visualization with the fetoscope. In such cases, an amnio-exchange may be performed with warmed isotonic crystalloid solution to optimize visualization.

Open Hysterotomy

The early experience in surgically correctable fetal anomalies in utero was conducted through an open hysterotomy. Fortunately, continuing advancements in imaging and minimally invasive techniques have reduced the need for open fetal procedures. Open fetal procedures are usually performed through a low, transverse maternal skin incision. The fascia can be opened in a vertical or transverse fashion, depending on the exposure needed. Preoperative and intraoperative ultrasound is crucial to map out the placenta and determine the ideal placement of the uterine incision to optimize fetal exposure and avoid injury to the placenta. Uterine staplers with absorbable staples were developed specifically for fetal surgery to allow a hemostatic hysterotomy yet avoid infertility from permanent staples functioning as an intrauterine device. Typically, fetal exposure is limited to the site specific to the intervention to avoid hypothermia and unnecessary manipulation of the umbilical cord, which is prone to spasm that can result in fatal fetal ischemia. A fetal extremity may also be exposed for placement of an intravenous cannula if indicated. The uterus should be stabilized within the maternal abdomen to minimize tension on the uterine blood vessels that could impede placental flow. Amniotic fluid volume is maintained using warm, isotonic crystalloid solution. At the conclusion of the procedure, the amniotic fluid is completely restored, and the uterus is closed in multiple layers using absorbable sutures. Postoperatively, the mother and fetus are monitored continuously for uterine contractions and heart rate, respectively. Patients are often discharged with oral nifedipine as a tocolytic.

Open fetal surgery requires cesarean section for the current pregnancy and all future pregnancies owing to the potential for uterine rupture during labor. Although vaginal delivery after cesarean section (VBAC) may be considered for routine, lower uterine segment hysterotomy, VBAC is not an option after hysterotomy for fetal surgery owing to the increased risk of uterine rupture.

Exit Procedure

Ex-utero intrapartum therapy (EXIT) allows for a fetal intervention to be conducted while maintaining uteroplacental circulation, followed by immediate delivery. EXIT procedures are most commonly indicated for airway issues but have been described for extracorporeal membranous oxygenation, separation of conjoined twins, and resection of fetal neoplasms.[50] An EXIT procedure is performed similarly to the open fetal procedure described above. However, at the conclusion of the case, with an established fetal airway, the fetus is delivered. Since uterine relaxation is critical during any fetal intervention, the EXIT procedure carries a significant risk for maternal hemorrhage at the time of delivery, and coordination between the anesthesiologist and the surgeon is critical, as discussed below.

Anesthetic Considerations

In addition to providing amnesia, analgesia, and patient monitoring that are central to all anesthetic encounters, successful maternal-fetal anesthesia must maintain uteroplacental relaxation and circulation. The only exception to this is the EXIT procedure, in which uterine contraction after delivery of the fetus is necessary to prevent bleeding secondary to uterine atony.

In all cases, the mother is positioned supine with her left side down to minimize compression of the inferior vena cava by the gravid uterus. Commonly administered preoperative medications include indomethacin for tocolysis and an antibiotic, such as cefazolin, for infection prophylaxis. The maternal bladder is decompressed by either straight catheterization for short procedures or an indwelling bladder catheter for longer or open procedures.

For minimally invasive percutaneous interventions and fetoscopic procedures, locoregional anesthesia can be administered via epidural, spinal, or local injection, depending on the mother's preference and anticipated length of the procedure. Spinal and epidural anesthesia are especially useful for complex fetoscopic procedures requiring multiple ports or in cases when emergency cesarean section may become necessary.[107] Regional anesthesia can produce maternal hypotension and negatively impact uteroplacental blood flow; therefore, with spinal anesthesia normotension is maintained with a phenylephrine infusion. Both phenylephrine and ephedrine are effective vasopressors that maintain maternal blood pressure while minimizing the effect on umbilical cord blood flow.[53,100] Additional conscious sedation can be provided intravenously using propofol or inhaled nitrous oxide. Nitrous oxide has the added benefit of enhanced uterine relaxation.

For open fetal procedures, including EXIT, deep maternal general anesthesia is required to ensure adequate uterine relaxation. Volatile inhaled anesthetics are used at high concentrations (usually 2.0 minimal alveolar concentration), but the subsequent relaxation of the myometrium can lead to a drop in placental blood flow.[27] Therefore, maternal blood pressure is augmented in these cases with either ephedrine or phenylephrine. The surgeon should be vigilant about repeated assessment of uterine tone. When the uterus is open, amniotic fluid volume is maintained with warm, isotonic crystalloid solution to prevent compression of the umbilical cord.

For open fetal cases, as the hysterotomy is being closed, the inhaled anesthetic is reduced or turned off and tocolysis with magnesium sulfate is initiated. Amniotic fluid volume

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is restored. Alternatively, after delivery during an EXIT procedure, the inhaled anesthetic is reduced, and oxytocin is administered to enhance uterine contraction prior to closure of the hysterotomy.

For procedures performed directly on the fetus, additional fetal anesthesia and analgesia is required. In the fetus experiencing pain, systemic vascular resistance can increase, which may decrease umbilical cord blood flow and fetal perfusion. While transplacental passage of the volatile anesthetics does occur, the time needed for fetal levels to reach a therapeutic dose precludes maternal anesthesia from being an adequate source of fetal anesthesia. Furthermore, inhaled anesthetics do not provide analgesia. Thus, additional fetal anesthesia is administered intramuscularly and typically consists of opioid analgesics and non-depolarizing paralytic agents such as rocuronium or pancuronium.[65,107] Rocuronium and pancuronium have the added benefit of vagal inhibition that can abate bradycardia, which may result from opioid administration; however, atropine is often administered for additional protection against bradycardia.[102]

Transplacental passage of anesthetic from mother to fetus places the fetus at risk for demise. Inhaled anesthetics produce myocardial depression, which can augment the fetal bradycardic response to stress and contribute to malperfusion, as fetal cardiac output and end organ perfusion are primarily determined by heart rate.[13] Other environmental factors such as hypothermia and umbilical cord compression increase the risk for fetal demise. Accordingly, continuous fetal monitoring should be undertaken via transcutaneous pulse oximetry, intraoperative fetal echocardiography, and monitoring of amniotic fluid temperature.

Finally, in light of in vitro and animal data demonstrating lasting neurotoxic effects associated with exposure to all general anesthetics tested,[94] the Food and Drug Administration (FDA) issued a Safety Communication in 2016 acknowledging the potential for adverse effects on fetal brain development and postnatal learning with anesthetic exposure to the pregnant woman.[87] Clinical studies have not demonstrated worsened neurodevelopmental outcomes with brief anesthetic exposure,[26,101] but data suggest the effect may be dose-dependent, with prolonged and repeated anesthetic exposure placing the developing brain at higher risk. Further clinical studies characterizing the effects of anesthesia on developing brains are necessary and ongoing.[84]

Anomalies Amenable to Fetal Surgery

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a defect in the fetal diaphragm allowing herniation of abdominal contents into the thoracic cavity. This occurs in roughly 1 in 2500 live births[91] and leads to abnormal development of the lung parenchyma and pulmonary vasculature. The resultant pulmonary hypoplasia and associated pulmonary hypertension can lead to persistent fetal circulation (also known as persistent pulmonary hypertension, PPHN), cardiorespiratory failure, and neonatal death. Despite significant advances in neonatal cardiac and respiratory support, children born with CDH in the United States have a mortality rate of 20%-30%.[31,99] Prenatal diagnosis and poor prognosis have made CDH a primary target for effective fetal intervention, and this entity was one of the primary driving forces in the genesis of fetal surgery at the University of California, San Francisco.

Prenatal imaging with ultrasonography and MRI allows both diagnosis and risk-stratification of fetuses with CDH. The most reliable predictor of poor prognosis on ultrasound or MRI is the presence of liver herniation. A systematic review of 710 cases of CDH demonstrated 75% survival without liver herniation, compared to 45% with liver herniation.[79] An additional predictor of poor prognosis is a low lung-to-head ratio (LHR), which is calculated as the area of the contralateral lung at the level of the cardiac atria divided by the head circumference. In a retrospective case series, LHR correlated with survival: 100% survival with an LHR greater than 1.35, 61% survival with an LHR between 0.6 and 1.35, and 0% survival with an LHR less than 0.6.[72] This finding was corroborated in multiple subsequent trials.[59,66] As an adjunct to LHR, in order to account for discrepant growth rates between the head and lung throughout gestation, some centers use the observed-to-expected LHR (O:E LHR), represented as a percentage of the expected LHR based on a normal fetus of the same gestational age.[55] For left-sided defects, an O:E LHR less than 25% is associated with an 18% survival, whereas an O:E LHR greater than 45% correlates with 89% survival.[54]

Finally, MRI allows calculation of total lung volume and percent-predicted lung volume (PPLV) in CDH as an additional method of risk-stratification.[9,21] Different centers have described different outcome thresholds for PPLV in CDH, but generally a PPLV greater than 20%-35% offers an improved prognosis.[111]

Fetal repair of CDH was first conceptualized after reversal of CDH in the fetal lamb model resulted in increased lung growth and development, allowing survival of the lamb neonate.[4] Based on these results, open fetal surgery was investigated in human fetuses diagnosed with CDH. The first successful case was reported by investigators at the University of California, San Francisco, in 1990 using a two-step approach that involved creation of an abdominal silo to accommodate the reduced viscera and prevent compression of the umbilical vessels.[45] However, a prospective trial comparing open fetal repair to medical management followed by postnatal repair found that fetuses with poor prognosis (liver herniation) suffered from high mortality rates despite in utero correction, and fetuses with good prognoses (no liver herniation) had no difference in survival or need for extracorporeal membrane oxygenation (ECMO).[42,43]

These disappointing results were tempered by the subsequent observation that pulmonary hyperplasia developed in fetuses with congenital high airway obstruction syndrome (CHAOS).[48] This observation was applied to treatment of

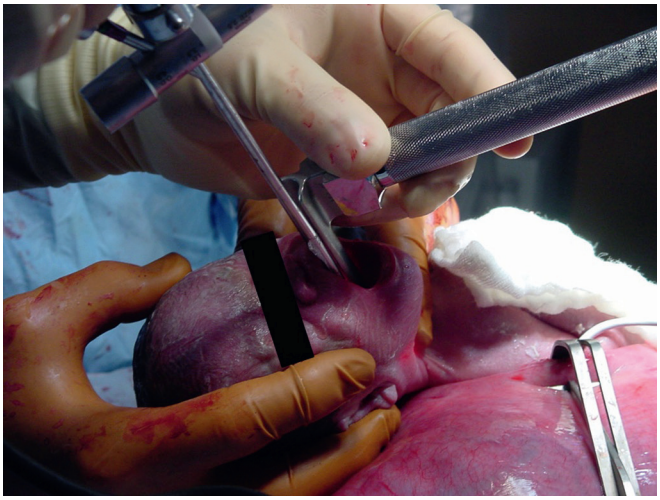
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CDH first in the fetal lamb model, where tracheal occlusion was achieved by suture ligation, foam-cuffed endotracheal tubes, or expandable foam inserts, and led to increased lung volume, decreased herniation of abdominal contents, and improved postnatal cardiopulmonary function.[10,30,47]

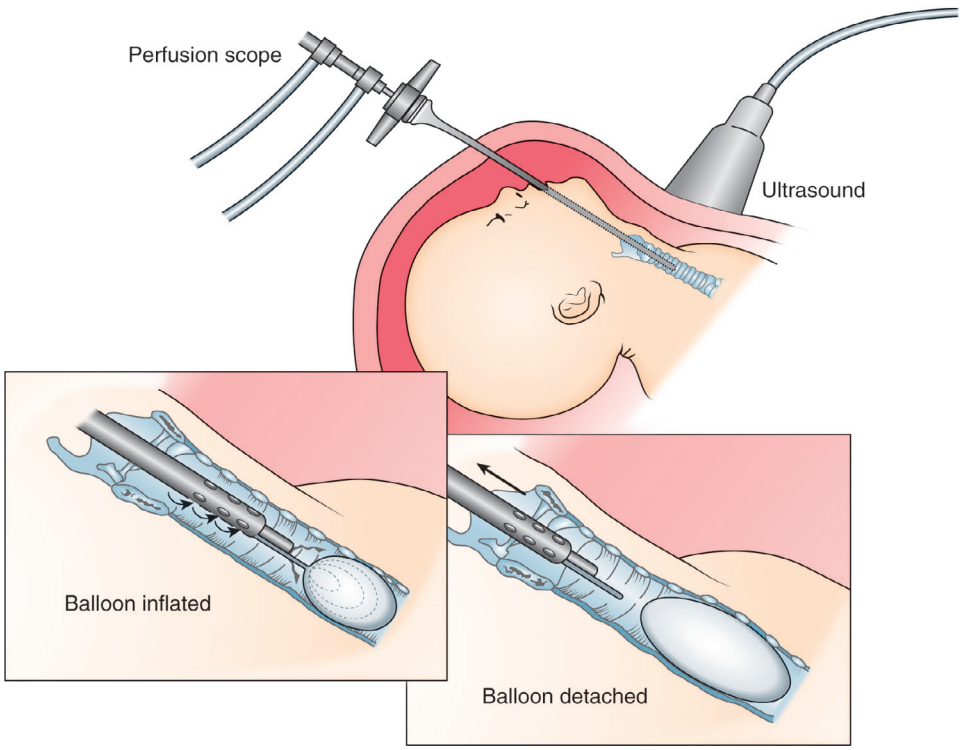
Based on these findings, in utero tracheal occlusion was applied in humans first in 1996, with placement of a metallic tracheal clip via maternal laparotomy and open hysterotomy.[44] The clip was then removed during EXIT procedure (Fig. 13.1). This approach suffered from a high rate of mortality and morbidity related to hysterotomy and preterm labor, as well as tracheal stenosis. To reduce morbidity related to open hysterotomy, fetal surgeons developed a minimally invasive technique for tracheal clipping, first performed in 1997.[110] However, clipping still suffered from frequent airway complications, including stenosis and vocal cord paralysis.

Despite these initially disappointing results, investigators remained optimistic that tracheal occlusion could improve outcomes for high-risk CDH lesions. Ongoing advancements in fetal surgery led to less invasive means for fetal tracheal occlusion, namely fetal endoscopic tracheal occlusion (FETO) via deployment of an obstructing tracheal balloon (Fig. 13.2).[46] FETO offers the benefits of being achieved through a single maternal fetoscopic port, as well as the avoidance of fetal neck dissection. FETO is performed between 26 and 30 weeks' gestation, and, when initially described, the balloon remained in place until delivery, with removal during EXIT procedure. However, relief of tracheal occlusion in utero via a second procedure in utero demonstrated increased type II pneumocyte differentiation, leading to increased surfactant production in the fetal lamb model,[14] and enables vaginal delivery, obviating the need for EXIT procedure. Currently, FETO is relieved at 34-36 weeks' gestation via a second fetoscopic procedure.[91]

The multicenter FETO consortium has reported an overall 48% survival rate among 210 cases of severe CDH (liver herniation, LHR ≤1.0) treated with temporary fetal tracheal occlusion compared to an 11% survival in historical



• **Fig. 13.1** The airway is established during an ex-utero intrapartum therapy (EXIT) procedure after relief of fetal tracheal occlusion in the treatment of congenital diaphragmatic hernia. (From Fetal therapy. In: Holcomb GW III, Murphy JP, eds. *Ashcraft's Pediatric Surgery*. 5th ed. St Louis: Elsevier; 2010:125-132.)



• **Fig. 13.2** Technique for fetoscopic tracheal occlusion using a balloon. (Modified from Fetal therapy. In: Holcomb GW III, Murphy JP, eds. *Ashcraft's Pediatric Surgery*. 5th ed. St Louis: Elsevier; 2010:125-132.)

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controls, based on CDH registry data.[56] A meta-analysis compiled series compared survival after FETO to contemporary control groups, demonstrating markedly improved survival after FETO in fetuses with isolated severe CDH (LHR <1.0).[7] Specifically, 46.3% of the cases undergoing FETO survived to discharge, compared to 5.9% in controls, translating to a survival odds ratio of 13.3 with FETO. While these results are promising, the true benefit of FETO is difficult to assess from retrospective case series and meta-analyses due to differences in assessment of CDH severity as well as postnatal care. Currently, international prospective randomized trials comparing FETO to expectant management in both moderate and severe lung hypoplasia secondary to CDH are ongoing (TOTAL trial, www.totaltrial.eu).[28]

Congenital Pulmonary Airway Malformations

Congenital pulmonary airway malformations (CPAM) are benign cystic pulmonary lesions with widely variable clinical presentations. Most CPAM are diagnosed in utero on screening ultrasound, and the majority of fetuses proceed to live birth with the absence of neonatal respiratory symptoms.[3,92] However, 5%-30% of prenatally diagnosed CPAM produce mediastinal shift, polyhydramnios, and nonimmune hydrops,[3,18] leading to certain fetal demise without prenatal intervention. The risk for development of nonimmune hydrops increases with lesion size. The cyst volume ratio (CVR) is a sonographic marker normalizing lesion volume to head circumference and is a widely used risk-stratification tool for the eventual development of nonimmune hydrops. Fetuses diagnosed with CPAM with CVR greater than 1.6 have an 80% risk for the development of hydrops.[22,118] Fetuses with CVR >1.6 should be monitored with weekly ultrasound exams, as hydrops is associated with near 100% fetal mortality if left untreated.[1,18]

The morphology of the lesion is also an important consideration in determining risk. Microcystic lesions have a more predictable course, with steady growth that tends to plateau at 26-28 weeks' gestation, at which point fetal growth exceeds that of the CPAM. For this reason, patients with microcystic or solid CPAMs should be followed closely up to 26-28 weeks' gestation, at which point the interval between ultrasound examinations can be lengthened if the pregnancy has been otherwise uncomplicated. In contrast, macrocystic CPAMs can undergo abrupt enlargement caused by rapid fluid accumulation in a dominant cyst regardless of the CVR. Therefore, macrocystic CPAMs require close follow-up with serial ultrasound throughout the duration of the pregnancy.[74]

The development of hydrops necessitates fetal intervention. Maternal betamethasone administration is especially effective in treating microcystic lesions producing nonimmune hydrops, with survival rates to delivery as high as 92%.[25,67,105] Current practice is to initiate maternal betamethasone for nonimmune hydrops or a CVR greater than 1.6 whether or not hydrops is present for microcystic lesions. Predominantly macrocystic lesions are not routinely treated with steroids, as they are less likely to respond. Maternal steroids can be re-dosed, but care should be taken because repeated courses of maternal steroids beyond three to five courses can result in untoward effects such as reduced birth weight.[37]

Given the effectiveness of prenatal steroids in the treatment of hydrops, there are few clinical scenarios in which invasive fetal intervention is indicated. However, in CPAM with a predominant macrocyst or large pleural effusion at less than 32 weeks' gestation, in utero drainage can relieve mass effect, leading to resolution of hydrops and improved surrounding lung development.[114] In a series of 75 cases of thoracoamniotic shunt placement, shunts produced a 55% decrease in CPAM volume.[83] This led to resolution of hydrops in 83% of cases, survival to birth of 93%, and long-term survival of 68%. Thoracoamniotic shunting is not without complications, which can include shunt migration, development of chest wall abnormalities, shunt occlusion, hemorrhage, membrane separation, placental abruption, and/or preterm labor.[71] Furthermore, the majority of neonates born after in utero thoracoamniotic shunting experience respiratory distress requiring intubation for >24 hours[83] and thus should be delivered at a tertiary referral center.

Open fetal thoracotomy for resection of the CPAM is no longer routinely performed due to the success of maternal betamethasone administration and thoracoamniotic shunting. Historically, the procedure was performed through an open hysterotomy and a thoracotomy through the fifth intercostal space, followed by resection of the lobe containing the CPAM (Fig. 13.3).[2]

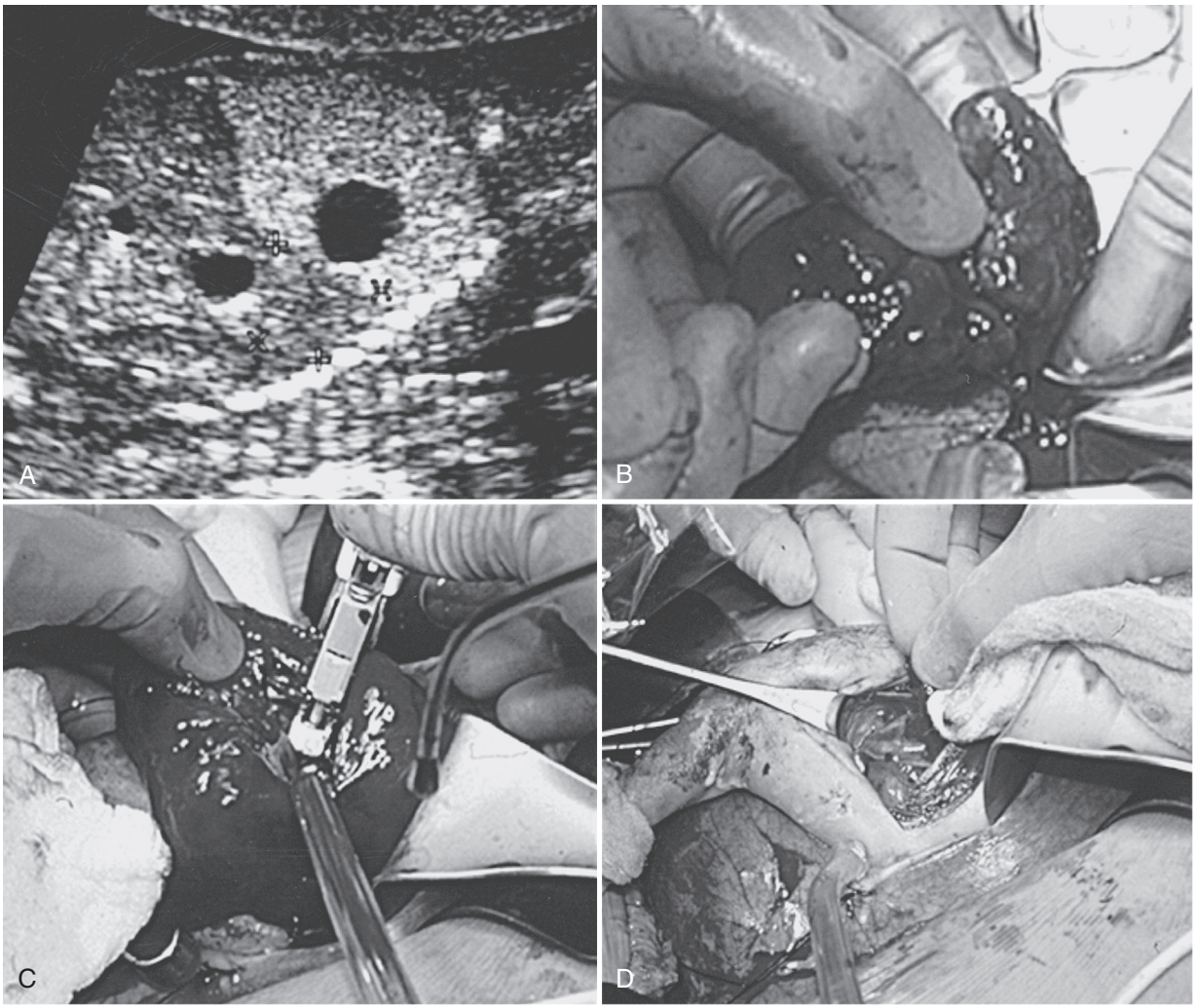
Fetal Hydrothorax

Fetal hydrothorax can be classified as either primary or secondary. Primary fetal hydrothorax occurs because of a lymphatic malformation, predominantly of the thoracic duct, that results in a chylous effusion. Secondary hydrothorax can be caused by immune or non-immune hydrops, chromosomal anomalies, or infections. Overall survival for fetal hydrothorax has been reported to be between 45% and 78%; therefore, close surveillance of these pregnancies is required, with the possible need for diagnostic and therapeutic fetal interventions that include thoracentesis and thoracoamniotic shunting.[68]

Percutaneous thoracentesis is both a diagnostic and therapeutic maneuver in the setting of fetal hydrothorax. Roughly one-quarter of fetuses undergoing an initial percutaneous thoracentesis for primary fetal hydrothorax will not require further intervention. The pleural fluid that is obtained can be sent for differential cell count and culture to determine the etiology of the effusion. Typically a lymphocyte count ≥85% is consistent with a chylothorax.

The majority of fetal hydrothoraces will reaccumulate after aspiration, with ongoing compression of the lung placing the fetus at risk for progression to hydrops and/or lung hypoplasia. In these cases, placement of a thoracoamniotic

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• **Fig. 13.3** **A,** Fetal sonogram demonstrating an echogenic congenital pulmonary airway malformation of the lung (CPAM), with a single large cyst and compressed normal lung outlined by cursors posteriorly. **B,** Exposure of CPAM through fetal thoracotomy. **C,** Resection of CPAM from adjacent normal lung and hilum using surgical stapler. **D,** Fetal pleural cavity after resection of the CPAM. (From Shaaban AF, et al. The role of ultrasonography in fetal surgery and invasive fetal procedures. *Semin Roetgenol.* 1999;34:62.)

shunt for definitive decompression of the hemithorax is indicated. Currently, two devices are available for shunt placement. The Harrison catheter was developed at the University of California, San Francisco, and is a polyurethane double coil stent deployed through a trocar, allowing the distal coil to be deployed within the fluid-filled cavity and the proximal coil to be deployed within the amniotic cavity. The alternative shunt is the Rocket catheter, which is larger than the Harrison catheter.

In a retrospective cohort of 88 pregnancies complicated by primary fetal hydrothorax, 74 (80.7%) neonates were born alive, with 52 (70.3%) surviving the neonatal period.[117] Fifty-nine fetuses had developed hydrops prior to shunt insertion, with these cases exhibiting survival of 52.5%. In fetuses in which hydrops resolved, 71% survived past the neonatal period. These results compare favorably to historical data from noninvasive management of hydropic fetuses. Although decompression of the hydrothorax via shunt placement is minimally invasive and may offer improved perinatal outcomes, complications related to fetal intervention persist. In the series described above, 11.4% of pregnancies experienced complications related to shunt insertion, including emergency cesarean for fetal distress, fetal demise due to cord laceration, PPROM within 7 days of shunting, and preterm delivery.[117]

Amniotic Bands

Amniotic bands are difficult to identify with standard prenatal imaging, including ultrasound and MRI. Often, the diagnosis is made by deformities that are consistent with amniotic bands (such as limb deformities) in the absence of visible bands. Although many believe that the bands result from membrane disruption, a recent single-institution review found that only 40% of cases have associated membrane separation.[52] The clinical manifestations of amniotic bands are determined by the anatomic location affected. Simple bands involving the extremities can cause

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TABLE 13.1 Distribution of Amniotic Bands From the University of California, San Francisco, Single-Center Experience

Anatomic Location	N (%)
Extremity	20 (71)
Single extremity	16 (57)
Multiple extremities	4 (14)
Umbilical cord	7 (26)
Abdomen	5 (19)
Limb-body-wall-complex	5 (19)
Head	1 (4)
Chest	1 (4)

deformity or amputation of the affected limb, whereas more complex bands involving the abdominal wall can lead to large abdominal wall defects mimicking gastroschisis or omphalocele.

Extremity involvement can account for more than 70% of cases, but any other anatomic region of the fetus can be involved (Table 13.1). Fetoscopic release of amniotic bands affecting one or more extremities can prevent limb loss and preserve limb function when distal flow is still identifiable on preoperative ultrasound.[29] In fact, amniotic bands isolated to the extremities remain the primary indication for fetoscopic band release. The procedure is performed using a 10 French cannula, similar to fetoscopy for laser ablation in TTTS. A 3-mm fetoscope is introduced, and the amniotic bands are then visualized. Through the side channel of the fetoscope, endoscopic instruments can be used to release constricting bands.

Bands involving other anatomic regions have usually resulted in irreversible defects at the time of diagnoses, and currently there does not appear to be any indication for fetal intervention in those cases. One exception is umbilical cord involvement, which may be an evolving indication for fetoscopic amniotic band release. A mortality rate of 67% with umbilical cord involvement compared with only 19% when the cord is not involved has been observed. In two patients, amniotic band release was performed for umbilical cord involvement identified at the time of fetoscopy for release of extremity bands, with both patients doing well and delivering at 40 weeks' gestation.[29]

Neoplastic Mass Lesions

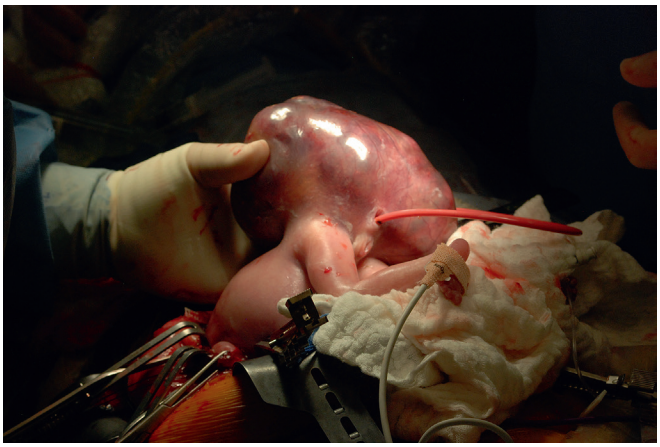
Sacrococcygeal Teratoma

Sacrococcygeal teratoma (SCT) is a rare germ cell tumor that can grow to a large size in utero. Its rapid and disproportionate growth leads to high risk for perinatal complications and fetal demise secondary to nonimmune fetal hydrops as a result of high-output cardiac failure, hemorrhage, and obstetric complications, including preterm labor and polyhydramnios. Delivery can be particularly dangerous when the diagnosis has not been made prenatally, resulting in traumatic delivery causing tumor rupture and/or life-threatening hemorrhage. A nationwide Japanese survey of 97 cases of SCT from 2000–2009 found an overall fetal mortality of 26%, reduced to 16% when elective terminations were excluded.[106] However, 21% of fetuses with SCT were delivered before 32 weeks' gestation, with mortality of 44% in this cohort. Previous case series have shown perinatal mortality as high as 43%.[115] Surgical intervention is centered upon providing temporizing measures to relieve cardiovascular compromise through debulking, ablation, or devascularization, usually followed by definitive resection in the neonatal period.

To guide prenatal surveillance and potential intervention, investigators discovered the tumor volume to fetal weight ratio (TFR) as an important prognostic indicator for fetuses with SCT.[89] Tumor volume is assessed by ultrasound or MRI, and fetal weight is calculated by ultrasound using the Hadlock formula. Originally, TFR was applied to 10 fetuses with SCT, and a TFR greater than 0.12 was associated with an 80% incidence of fetal hydrops and 60% mortality. However, a TFR less than 0.12 was associated with 100% survival.[89] Subsequent multi-institutional case reviews validated TFR >0.12 as a poor prognostic sign.[6,98] In addition to TFR, case series have shown cystic SCT to have better perinatal outcomes than solid SCT.[98]

Despite the development of TFR and tumor characterization (solid vs. cystic) as an overall prognostic indicator, there is not a universally accepted indication for fetal surgical intervention. Most commonly, fetal surgery is considered in the presence of nonimmune hydrops or evidence of impending cardiac failure at a gestational age too young for delivery and neonatal care.[60] This is best assessed via fetal echocardiography to measure the combined cardiac output, which increases dramatically prior to the development of hydrops, with a value of 550 mL/kg/min associated with poor outcome in SCT.[17,95] As mentioned above, the goal of surgical intervention is to relieve the hemodynamic impact of the large mass on the fetal cardiovascular system. The most frequently utilized approach is a debulking resection via maternal laparotomy and open hysterotomy (Fig. 13.4). Minimally invasive techniques are also described and include both interstitial ablation and vascular interruption techniques with radiofrequency or laser energy sources. A recent systematic review of case reports of both open and minimally invasive interventions for SCT in the setting of nonimmune hydrops found a survival of 55% (6/11) after open hysterotomy and SCT debulking, compared to 30% (6/20) after minimally invasive interventions, including radiofrequency and laser ablation.[108] However, given reporting bias, survival is likely to be over-represented in these series, making a true comparison of open and minimally invasive techniques difficult. Additionally, while survival rates were poor in both cohorts, these interventions were performed in fetuses in the presence of hydrops, which confers a very high risk for fetal demise without intervention.[41] Finally, in both open and minimally invasive cohorts,

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• **Fig. 13.4** Open fetal debulking of sacrococcygeal teratoma.

mean gestational age at delivery was less than 30 weeks, emphasizing the risk for preterm birth after surgical intervention and the need for intensive neonatal care after birth.

Additional experience is needed with minimally invasive techniques before they are abandoned in favor of open resection. Typically, lumped together as "minimally invasive," there is some suggestion that not all techniques employed are equal. A recent review sought to compare interstitial ablative procedures and vascular disruption procedures.[93] Eleven fetuses underwent devascularization procedures, with a survival of 63.6%. This compared favorably to a survival of 40.9% in 22 fetuses who had interstitial ablation. The authors hypothesized that the sudden tumor necrosis and subsequent risk for hemorrhage contributed to decreased survival with interstitial ablation.

Cystic SCTs are usually amenable to percutaneous drainage or shunt placement, which may not be indicated given the favorable prognosis for cystic SCTs and the lower incidence of fetal hydrops with cystic SCTs.[98] However, immediate decompression of an SCT may be indicated just prior to delivery to prevent dystocia, to facilitate cesarean delivery, and to prevent rupture with spillage of neoplastic cells.

Fetal Neck Mass

The fetal neck mass poses a significant risk to the fetus with a nearly 20% risk of intrauterine fetal demise (IUFD) and a 35% risk of death due to airway obstruction immediately after delivery.[11] Obstruction of the trachea and esophagus can result in polyhydramnios and preterm labor; local compression can lead to craniofacial defects and cranial nerve injury. Highly vascular lesions can result in high-output cardiac failure with nonimmune fetal hydrops and subsequent IUFD.[51] The primary histologic lesions encountered are cervical teratoma, cystic hygroma, or other vascular malformations. Rarely, neck masses can include thymic cysts or congenital neuroblastoma.[40]

Fetal neck masses are readily identified on prenatal ultrasound, and upon diagnosis, fetal MRI should be obtained to better characterize the mass—specifically to distinguish between a cystic hygroma and teratoma based on the presence of fat. Fetal MRI can also aid in the identification of the fetal trachea. Ultrasound imaging can help in diagnosis and prognosis by demonstrating polyhydramnios, the lack of a fluid-filled stomach indicating esophageal compression, and a dilated hypopharynx. The tracheoesophageal displacement index (TEDI) is a useful prognostic measurement described by the group at Texas Children's Hospital.[62] This measurement is defined as the sum of the lateral and ventral displacement of the trachea and esophagus from the ventral most aspect of the cervical spine. In their series of 24 prenatally diagnosed neck masses, all patients with a TEDI of greater than 12 mm had a complicated airway, whereas only 46% of those with a TEDI less than 12 mm had a complicated airway. Furthermore, the authors found that the presence of a cervical teratoma or polyhydramnios also increased the risk for a complicated airway.

Pregnancies complicated by a fetal neck mass require very close surveillance. Large masses that cause significant extension of the neck require delivery via cesarean section due to the risk of dystocia. In the presence of fetal hydrops prior to 30 weeks' gestation, successful open fetal resection has been reported.[51] In all cases, at the time of delivery, immediately securing the airway is paramount, as 35% of cases in which the neonate dies immediately are a result of airway compromise.[11] For this reason, the EXIT-to-airway procedure should be considered to permit safe establishment of the airway prior to delivery. However, it is important to keep in mind that most cystic neck masses do not cause airway obstruction, and judicious use of EXIT procedures for these patients is required.

If delivery is pursued via EXIT-to-airway procedure, strict adherence to anesthetic principles are required. Deep maternal anesthesia is required to maintain complete uterine relaxation and preserve uteroplacental circulation so that the fetus does not undergo premature transition from fetal to neonatal circulation. During an EXIT-to-airway procedure, the uterus is exposed and a hysterotomy is made to deliver the fetus's head and neck.[50] Direct laryngoscopy can be attempted for endotracheal intubation. Airway management can be escalated using bronchoscopy or tracheostomy if laryngoscopy is not successful. In the presence of a large neck mass, the trachea is often deviated, and this displacement must be recognized prior to tracheostomy. In cases of large cystic lesions, decompression of the cyst may facilitate establishing an airway by relieving any airway compression. When an airway still cannot be obtained, resection of the mass while still on uteroplacental circulation may be necessary, converting the procedure to an EXIT-to-resection. Once an airway has been established and confirmed (usually by flexible bronchoscopy), the umbilical cord can be divided and the baby completely delivered.

Post-delivery and post-resection hypothyroidism and hypoparathyroidism are the most common non-airway complications. Therefore, an endocrine evaluation should be initiated with specialist consultation as indicated. Given the small malignant potential for cervical teratomas, screening for recurrence should also be implemented by following alpha-fetoprotein levels and obtaining surveillance imaging.

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Cystic hygromas and other vascular malformations presenting as fetal neck masses can be difficult to manage postnatally given that these lesions have a propensity for significant cervical, oral, and intrathoracic extension, making complete resection difficult, recurrence rates high, and disfigurement likely.

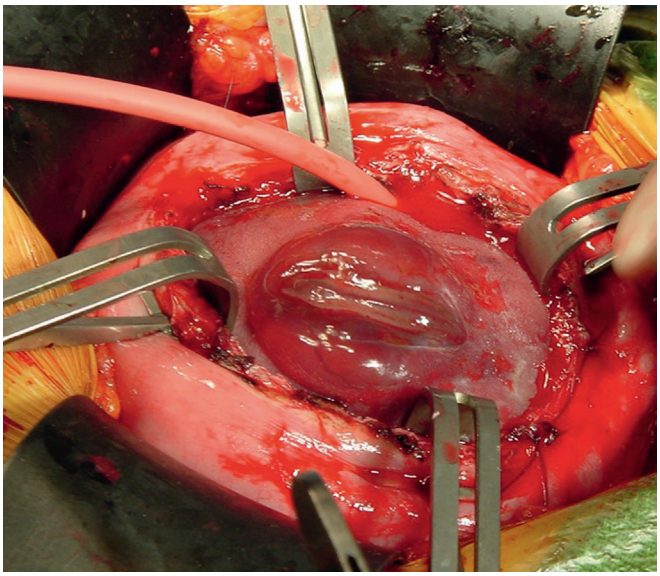
Myelomeningocele

Myelomeningocele (MMC), or spina bifida, is characterized by incomplete closure of the neural tube resulting in exposure of the spinal canal elements. This can occur anywhere along the spine but most commonly occurs at the lumbar or cervical vertebral levels. The primary manifestations include neurologic deficits with motor and somatosensory abnormalities that correspond to the level of the spinal defect, autonomic nervous system injury resulting in impaired bowel and bladder function, and the Chiari II malformation of the hindbrain leading to hydrocephalus and the need for ventriculoperitoneal (VP) shunting. Contrary to most targets for fetal surgical intervention, fetuses with MMC do not have high risk for perinatal mortality. However, MMC confers severe long-term morbidity to the child, and up to 30% of patients with MMC die before reaching adulthood, owing to respiratory, urinary, or central nervous system complications.[49]

The rationale for fetal intervention in MMC is centered on a "two-hit" hypothesis for development of morbidity, in which the first hit is the original neural tube defect that results in an open spinal canal, and the second hit is postulated to be trauma to the exposed neural elements while the fetus is in utero.[73] By minimizing secondary trauma to the exposed neural elements through fetal repair, it was hypothesized that neurologic outcomes for MMC could be improved.[113] Indeed, early results from animal studies showed improved neurologic outcomes with prenatal closure, which was confirmed in the first human studies along with a decreased need for VP shunting.[16,34]

Initial attempts at minimally invasive techniques of MMC repair resulted in high rates of fetal death,[15] leading to further development and refinement of open surgical techniques. Thus, fetal repair of MMC is performed most often through a maternal laparotomy and open hysterotomy (Fig. 13.5) with either primary repair of the defect or coverage of larger defects using allografts.[5] Recently, two minimally invasive approaches have been described,[61,81] but outcomes are not extensively studied.

Initial success with open surgical repair prompted a multi-institutional prospective randomized trial, known as the Management of Myelomeningocele Study (MOMS), comparing open fetal repair at 19-26 weeks' gestation to postnatal repair.[5] For the MOMS trial, a power analysis based on the initial, nonrandomized human studies indicated 200 patients were required to adequately study the primary outcome, which was the need for a VP shunt within the first 12 months of life. However, the study was terminated early after demonstrating superiority of prenatal repair. Patients undergoing fetal repair had decreased need for VP shunt placement (40% compared to 82% in the postnatal repair group) and improved motor function, as 42% of the fetal repair group could walk by 30 months of age, compared to 21% in the postnatal repair group.



• **Fig. 13.5** Open fetal myelomeningocele repair. (From Fetal therapy. In: Holcomb GW III, Murphy JP, eds. *Ashcraft's Pediatric Surgery*. 5th ed. St Louis: Elsevier; 2010:125-132.)

Despite demonstrating a convincing benefit to the fetus in terms of neurologic outcomes, the excitement for fetal repair of MMC has been tempered by the incidence of obstetric morbidity demonstrated in the MOMS trial. Complications included a 38% incidence of preterm labor, with a mean gestational age in the prenatal repair group of 34 weeks compared to 37 weeks in the postnatal group. Furthermore, premature rupture of membranes occurred in 46%, chorioamniotic membrane separation in 26%, and placental abruption in 6%. Additionally, fetal demise occurred in 3% of the prenatal repair group. For these reasons, extensive counseling should be provided to families to ensure that they fully understand the risks and benefits of prenatal MMC repair.

Urinary Tract Abnormalities

Hydronephrosis

Hydronephrosis is a common prenatal diagnosis. In most cases, especially when the extent of hydronephrosis is mild, there is complete resolution. However, 10% will have persistent or progressive disease and require postnatal evaluation.[77] In the setting of minimal hydronephrosis, an ultrasound should be obtained in the third trimester to determine if there has been resolution or progression, which will help determine the need for postnatal evaluation.

In more severe cases of hydronephrosis, ureteropelvic junction (UPJ) obstruction, ureterovesical junction obstruction, or an obstructing ureterocele should be suspected. If the obstruction is unilateral, there is no indication for fetal

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intervention, because the unaffected contralateral collecting system functions normally, maintaining adequate amniotic fluid volume. However, bilateral obstruction leading to hydronephrosis can produce severe oligohydramnios, placing the fetus at risk for developing pulmonary hypoplasia leading to neonatal death. Improved survival with urinary tract decompression and restoration of amniotic fluid volume via shunting has been demonstrated.[23] Yet, further postnatal care is still complicated by dysplastic change of the kidneys from chronically elevated hydrostatic pressure in the collecting system. The first fetal intervention for hydronephrosis was for bilateral UPJ obstruction in 1982[39]; fortunately, UPJ leading to oligohydramnios is uncommon and the need for fetal intervention with shunting is rare.

Lower Urinary Tract Obstruction

Lower urinary tract obstruction (LUTO) is most commonly caused by posterior urethral valves (PUV) but can also result from urethral atresia and Eagle-Barrett syndrome (prune belly).[35] LUTO is most commonly diagnosed on screening prenatal ultrasound at 20 weeks' gestation, with observance of the classic triad of a dilated keyhole-shaped bladder, bilateral megaureters, and bilateral hydronephrosis.[69] The fetus with LUTO is at high risk for the development of oligohydramnios as a result of mechanical obstruction of urinary flow and dysplastic changes in the kidneys. Resultant development of pulmonary hypoplasia is associated with a perinatal mortality around 50%, with surviving neonates placed at a 20% to 30% risk of developing end-stage renal disease in their lifetime.[12,85] Additionally, chronic distention of the bladder is associated with a 45% incidence of neurogenic bladder, with most babies developing at least a mild degree of permanent bladder dysfunction.

Oligohydramnios in the setting of LUTO is considered an indication for fetal intervention, with the aims of preventing pulmonary hypoplasia by restoring the amniotic fluid volume and preventing further kidney injury, as animal models of LUTO suggest renal dysplasia is more severe the earlier it occurs and the longer it is sustained.[36]

Fetal interventions employed in the treatment of LUTO include vesicoamniotic shunting (VAS), fetoscopic cystoscopy with PUV ablation, and open fetal vesicostomy. VAS is the most common modality in use today. A meta-analysis of early case reports found improved perinatal survival, especially in fetuses with poor prognoses.[20] However, the Percutaneous Vesicoamniotic Shunting versus Conservative Management for Fetal Lower Urinary Tract Obstruction (PLUTO) trial, an international prospective randomized trial aimed at characterizing benefit in renal function over long-term follow-up, showed that patients in both the VAS and control groups had poor renal function at 1 and 2 years of age.[78] The study ended early due to poor enrollment, and survival to 28 days showed a trend toward improvement in the VAS group in intention to treat analysis. These results suggest irreversible damage to the renal parenchyma occurs prior to diagnosis, and that surgical intervention may only provide a small benefit, if any, to long-term outcome.

TABLE 13.2 Normal* Values for Fetal Urine Electrolytes

Measurement	Normal Values
Osm	<210 mEq/L
Na	<100 mEq/L
Cl	<90 mEq/L
Ca	<2 mmol/L
PO_4	<2 mmol/L
β_2-microglobulin	<2 mg/L

*Validated after 20 weeks' gestational age.

Furthermore, vesicoamniotic shunting can be complicated by shunt dislodgment, shunt occlusion, iatrogenic gastroschisis, and obstetric complications.

Imaging and fetal urine electrolyte studies are well-described but are not definitive in identifying those fetuses with LUTO that do not have oligohydramnios and have not yet developed irreversible renal injury, making them optimal candidates for intervention. Fetal urine electrolytes are only interpretable after 20 weeks' gestation,[80] and the initial bladder needle aspiration may be a misrepresentation of renal function because that urine may have been in the bladder for some time. Thus, serial taps are usually more helpful in determining the presence of renal dysplasia, especially if the β_2-microglobulin is elevated. Established normal values for other fetal urine electrolytes are outlined in Table 13.2; these values are representative of fetal urine electrolyte composition after 20 weeks' gestation. On ultrasound, findings of echogenic calyces and loss of corticomedullary differentiation may be early indicators of renal dysplasia. Cystic changes or the presence of a perinephric urinoma are late findings.[69] Further investigation to identify at-risk patients and more effective therapies is needed. Whether intervention is undertaken or not, these pregnancies require close monitoring, especially regarding the amniotic fluid volumes. Delivery should occur in a tertiary center.

Abnormalities of Twin Gestations

Monochorionic twin gestations carry up to a 50% incidence of developing a complication (see Chapter 21). This is predominantly because of the unpredictable nature in which the two umbilical cords are implanted in the uterus and how the placental circulation is shared. Of the multiple complications that arise from the shared placenta, twin–twin transfusion syndrome (TTTS) is the most common complication, occurring in 10% of all monochorionic twin pregnancies.[96]

Twin–Twin Transfusion Syndrome

TTTS occurs when vascular connections (which can be arterial-to-venous, venous-to-arterial, or arterial-arterial)

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form between the umbilical cord vessels of both fetuses, resulting in a bypass of maternal circulation and an imbalance of umbilical flow. If the net blood flow from one twin (the donor) exceeds flow from the other twin (the recipient), then TTTS ensues. The donor twin develops hypovolemia, manifesting in oliguria and oligohydramnios secondary to decreased renal perfusion, while the recipient twin suffers from volume overload leading to polyuria and polyhydramnios.[58] These physiologic alterations place the donor twin at risk for hypoxic-ischemic injury and restricted growth while the recipient can suffer from nonimmune hydrops. The pathognomonic diagnostic finding in TTTS is oligohydramnios, defined as a deepest vertical pocket (DVP) less than 2 cm in the donor twin, with concurrent polyhydramnios, defined as a DVP greater than 8 cm in the recipient twin. It is also common to see growth discordance between the twins, with the donor being smaller than the recipient. Growth discordance becomes worrisome in any twin pregnancy when the estimated weights are greater than 20% discordant. Quintero et al. developed sonographic criteria widely utilized as a staging system for TTTS (Table 13.3).[86] If severe TTTS is left untreated, mortality for both twins is greater than 90%.

Two primary modes of therapy have been offered for TTTS: amnioreduction and fetoscopic laser ablation. Amnioreduction of the polyhydramniotic sac was initially used to reduce the amniotic volume and decrease the risk of preterm labor. Based on survival outcomes for TTTS treated with amnioreduction reported through the International Amnioreduction Registry, high-volume amnioreduction was associated with a 60% single twin survival rate.[88] However, fetoscopic laser ablation for TTTS has largely replaced amnioreduction as the primary therapy for TTTS. Fetoscopic laser ablation is performed through a 10 French cannula using a 3-mm fetoscope that is equipped with a side channel for deployment of a laser fiber. Under direct fetoscopic visualization, intertwin vascular connections are readily identified on the surface of the placenta and are all ablated.

The use of amnioreduction versus laser ablation in the treatment of TTTS has been comparatively studied in multiple retrospective studies that prompted prospective trials. Initial studies varied in whether or not laser ablation was associated with a survival benefit, but overall neurologic outcomes favored those twins undergoing laser ablation.[112] Two large prospective trials comparing amnioreduction to laser ablation have been conducted, primarily favoring laser ablation. The first trial, conducted by the Eurofetus group, enrolled 70 women for treatment with amnioreduction and 72 women for treatment with laser ablation.[97] Early interim analysis showed a clear survival advantage for laser therapy—76% versus 51% single survivor and 36% versus 26% for dual survivors—and the study was closed prior to full enrollment. A North American trial sponsored by the NIH was also closed early after 42 mothers were randomized: 20 in the amnioreduction arm and 22 in the laser ablation cohort.[24] There was no demonstrable survival benefit in this underpowered study, but it was stopped early due to poor recruitment. The data obtained in these two trials was pooled in a 2014 Cochrane review, which showed a nonsignificant trend toward improved survival with laser ablation (overall survival of 66% for laser ablation compared with 48% for amnioreduction).[88] Additionally, a higher percentage of children alive at 6 years had no neurologic abnormality in the laser group. Given these findings, laser ablation has to become the treatment of choice for advanced TTTS; however, when laser ablation is not available or not possible for technical reasons, amnioreduction is an appropriate alternative.

At what stage to intervene for TTTS is highly controversial. There is wide agreement that cases of stage II or greater require intervention; however, there is no consensus regarding the management of stage I TTTS. Favorable outcomes with expectant management for stage I TTTS are possible, with laser ablation reserved for those cases with stage II or more advanced disease; this strategy has been supported in multiple observational studies.[90] However, a multicenter retrospective review demonstrated improved outcomes with prenatal intervention (amnioreduction or laser) over observation.[33]

TABLE 13.3 Quintero Stages of Twin–Twin Transfusion Syndrome

Stage	Description
I	Polyhydramnios (DVP >8 cm) with oligohydramnios (DVP <2 cm) with bladders present in both twins
II	Bladder not visible in the donor twin
III	Changes in umbilical cord or ductus venosus end-diastolic flow; tricuspid regurgitation in the recipient twin
IV	Evidence of hydrops in either twin
V	Fetal death

Selective Fetal Reduction

In addition to TTTS, monochorionic twin pregnancies are subject to complications, including selective intrauterine growth restriction, structural anomalies, twin anemia polycythemia sequence, and twin reversed arterial perfusion sequence (TRAP).[104] In complicated monochorionic pregnancies at high risk for hemodynamic compromise or intrauterine fetal death, fetal reduction may prevent secondary neurologic injury or demise of the co-twin.[82] Selective termination can be achieved via umbilical cord ligation, fetoscopic laser coagulation, ultrasound-guided bipolar cord coagulation, or radiofrequency ablation (RFA).[116]

Selective reduction is especially beneficial in TRAP sequence, a rare complication occurring in 1% of monochorionic pregnancies. In TRAP sequence, one twin has an absent or nonfunctional heart, and receives blood flow from arterial-arterial anastomoses between the twins, resulting in

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one twin acting as a "pump," providing blood flow to the acardiac twin.

Because the normal twin is maintaining blood flow for itself as well as the acardiac twin, TRAP sequence can lead to high-output heart failure with progression to hydrops and fetal demise. Untreated, there is a 50% to 75% mortality rate in the pump twin, owing to cardiac failure and nonimmune hydrops.[76] Generally, intervention is indicated when there is evidence of high-output cardiac failure or hydrops in the pump twin, or when the estimated fetal weight of the acardiac twin is 50% or more relative to the pump twin.[57]

Selective reduction occurs most commonly via RFA of the acardiac twin's umbilical cord. A 2013 review of 98 cases of RFA for TRAP across 12 centers in the North American Fetal Therapy Network found survival of the pump twin in 80% of cases to 30 days of life.[63]

Congenital Heart Disease

Advancements in the prenatal care of congenital heart disease include fetal interventions in cardiac bradyarrhythmias and valvular stenosis resulting in evolving hypoplasia of the right or left ventricle. Bradyarrhythmias occur in 9% of cases, and the outcome is best determined by the etiology of the bradyarrhythmia. In nearly half of the patients, the heart is structurally normal, but transplacental antibodies from mothers with collagen vascular disease affect the fetal heart. These patients may benefit from maternal steroid administration to lower maternal antibody titers; however, if that is not successful, the only alternative that has been explored is fetal pacemaking. Unfortunately, the best reported outcome to date was 5 days post-implantation with no survivors to delivery.[32]

Critical outflow stenosis of the fetal aortic or pulmonary valves can progress to complex congenital heart defects, namely, hypoplastic right and left heart, respectively. Hypoplastic congenital heart defects require multiple, staged procedures to achieve double ventricular physiology, and even then, the outcomes are poor. Therefore, attempts at correction in utero have been made and focus solely on early relief of the obstructive lesion to prevent hypoplasia of the affected ventricle. In 1991, Maxwell described the first percutaneous balloon fetal aortic valvuloplasty (FAV) in a fetus with evolving hypoplastic left heart syndrome (HLHS).[70] In this procedure, ultrasound guidance was used to advance a guidewire through the apex of the heart and across the stenotic aortic valve. Using a Seldinger technique, a balloon catheter was deployed across the valve and inflated to relieve the obstruction.

In a recent retrospective review of 100 cases of FAV between 2000 and 2013, 88 fetuses survived to birth, and 38 had biventricular circulation.[38] Fetuses who progressed to birth with biventricular cardiac physiology had an 84% cardiac death-free survival to 10 years. However, even in patients who developed biventricular physiology, 37 of 38 required postnatal interventional procedures. While these results are promising, multiple complications have been reported with percutaneous balloon valvuloplasty. These include IUFD, pericardial effusions requiring aspiration, fragmentation of the device in the heart, significant valvular regurgitation, need for pressor support intraprocedurally for hemodynamic instability, and all of the other risks associated with percutaneous procedures.[75]

Conclusion

The application of in utero correction for fatal fetal anomalies has existed for more than three decades, and over that time the indications and techniques have evolved dramatically, showing great promise to improve outcomes for anomalies that historically have been poor and increasing our understanding of the natural history of most congenital anomalies. Traditionally, fetal surgery had been reserved for the fetus in distress, but the improved outcomes for myelomeningocele with open fetal repair have challenged this paradigm and beg the question: what other anomalies might benefit from prenatal therapy? Despite this growing optimism and interest in the utility of fetal interventions, maternal and fetal risk should not be underestimated. We should remain critical of our progress by inclusion of multiple areas of discipline, and we should approach innovation in the field of fetal surgery responsibly to minimize unintended harm to our patients, both born and unborn.

Key Points

- Fetal surgery is a developing field, with scientific, clinical, and ethical questions still under investigation, and innovation forging new paths forward.
- The well-being of the expectant mother must be considered the top priority when treatment decisions are made.
- Any fetal intervention carries substantial risk of obstetric complications, including preterm labor, PPROM, membrane separation, and chorioamnionitis; open hysterotomy necessitates eventual delivery by cesarean section.
- Fetal interventions are usually reserved for the fetus at risk of intrauterine or early neonatal demise, as is the case in congenital diaphragmatic hernia, CPAM, hydrothorax, SCT, fetal neck mass, urinary tract obstruction, abnormalities of twin gestation, and congenital heart defects.
- Fetal repair of myelomeningocele is unique in that fetal intervention aims to minimize postnatal morbidity rather than mortality.
- Innovation in surgical instrumentation and technique has led to effective percutaneous and fetoscopic minimally invasive therapies for most conditions amenable to prenatal intervention.

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14

Adverse Exposures to the Fetus and Neonate

ALISON J. FALCK, SANDRA MOONEY, AND CYNTHIA F. BEARER

Exposure to environmental toxicants during pregnancy may have a significant impact on the developing fetus. Fetal adverse exposures are growing in importance as our population expands and the number of women participating in the workforce continues to rise. In 2015, women comprised 47% of the workforce in the United States, and 73.5 million women aged 16 and over were employed. Approximately 75% worked full time.[115] In addition, more pregnant women are staying in the workforce and continuing to work until later into pregnancy. According to the U.S. Census Bureau (2011), 66% percent of women worked during their first pregnancy in 2008, and 88% percent continued into the third trimester.[74]

Environmental exposures increase as the world's population and economic needs expand. In 1900, there were 1.25 billion people on Earth. This number doubled by 1950 and doubled again in 1987 to 5 billion. The world population was estimated at 7.6 billion in 2017; it is projected to increase to 9.8 billion by 2050, and 11.2 billion by 2100.[109] Pressures of population growth are reflected in increasing need for land, water, food, and fuel. With population expansion, economic growth, and technologic advances comes increasing interaction with chemicals in our environment that are developed to support our society. The growth of industry, commerce, and agriculture brings overuse of land; changes to the environment such as global warming; and contamination of air, water, food, and soil. It is inevitable that all humans are exposed to environmental toxicants, including the developing fetus.

The Developmental Origins of Health and Disease (DOHaD) is a field of study that explores the relationship between exposure to environmental stressors during critical periods of fetal development and adverse health outcomes that occur across a lifetime (see also chapter 16). This paradigm suggests that the developing fetus exhibits significant genetic plasticity that may be impacted by the intrauterine environment. Thus, genetic "reprogramming" that occurs prenatally can alter phenotypic expression, both following birth and in generations to come.[4,78,121] The DOHaD is based on work originally published in 1990 by a British epidemiologist, Dr. David Barker. The Barker hypothesis (or fetal origins hypothesis) describes fetal nutritional and metabolic programming as the mechanism linking intrauterine growth restriction to the development of coronary artery disease as an adult.[73,121] Fetal exposure to toxicants is a stressor that has also been implicated in the DOHaD and is the subject of this chapter.[55,121] Toxic environmental exposures may be non-concurrent or concurrent with pregnancy. This chapter describes the role of epigenetics and developmental plasticity, pathways of fetal exposure to environmental toxicants, unique pharmacokinetics of the fetus, and the spectrum of adverse outcomes associated with fetal exposure to specific environmental toxicants (Fig. 14.1).

Exposures Not Concurrent With Pregnancy

Environmental exposures that affect the fetus may occur long before conception and possibly in an earlier generation than the parents. Commonly, the exposure impacts the ovum or sperm. In addition, there are chemicals that bioaccumulate prior to pregnancy and impact the fetus by enhanced elimination during pregnancy. Lipid-soluble toxins and heavy metals such as lead are stored in adipose and bone and mobilized during pregnancy. Some chemicals, such as organohalogens, can affect the fetus by both non-concurrent and concurrent exposure.[4]

Preconceptual Effects

The Epigenome

Epigenetics is the study of phenotypic changes occurring in the absence of modification of DNA sequence. Environmental epigenetics describes the relationship between endogenous and exogenous factors (such as chemical exposure) and the epigenome.[90] Changes to the epigenome are stable, heritable, and a target for environmental toxicants. The term *epimutation* refers to a heritable change in gene expression that does not affect DNA base pair structure.[35,90]

The epigenome is susceptible to dysregulation at any time but is highly vulnerable during fetal life when the

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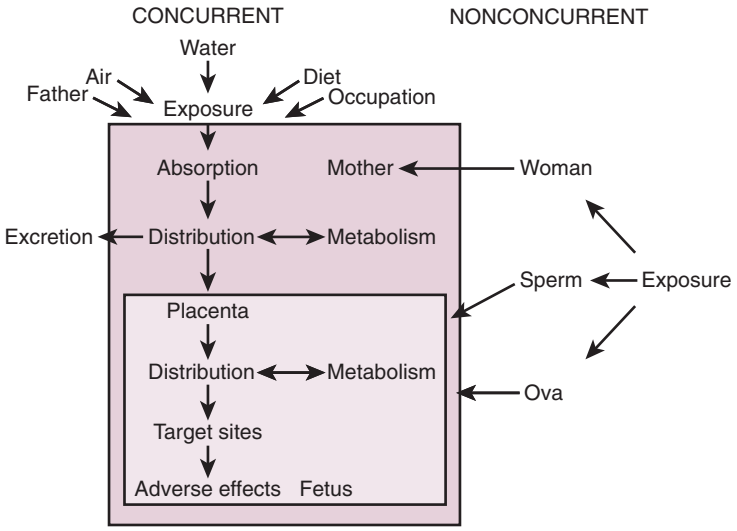
Abstract

Environmental exposures during pregnancy may significantly affect the fetus during critical stages of development. Toxicants can adversely influence phenotypic expression following birth and impact health across a lifetime. In addition, genetic and epigenetic modifications may be transferred to future generations. Both maternal and paternal toxicant exposure that occurs prior to pregnancy and during the periconceptual period may impact fertility and contribute to development of congenital malformations. Other exposures that are non-concurrent with pregnancy include maternal body burden with chemicals such as lead and polychlorinated biphenyls that are mobilized from stores in bone and adipose tissue during pregnancy. Histone modification, expression of microRNA, and DNA methylation are examples of epigenetic mechanisms that alter the fetal phenotype without changing DNA sequence; the epigenome is highly susceptible to environmental toxicants during fetal development. Air pollution, heat, drinking water, and diet represent examples of sources of toxic exposure that occur during pregnancy. Toxicants primarily reach the fetal compartment via passive diffusion across the placenta; lipid solubility, molecular weight, protein binding, and ionization impact placental transport. Other placenta-independent pathways that may be harmful to the developing fetus include heat, noise, and ionizing radiation. The complex physiologic environment during pregnancy impacts absorption and distribution of chemicals to the fetal compartment. Both ontogeny of fetal hepatic metabolic enzymes and genetic polymorphisms are important factors in determining susceptibility of the fetus to toxic effects. Throughout this chapter, specific examples of environmental toxicants, their known effects on pregnancy and the fetus, and preventive strategies are explored.

Keywords

environmental toxicants
epigenome
DNA methylation
developmental origins of health and disease
maternal body burden
fetal pharmacokinetics

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• **Fig. 14.1** Maternal concurrent and nonconcurrent exposures and fetal exposure.

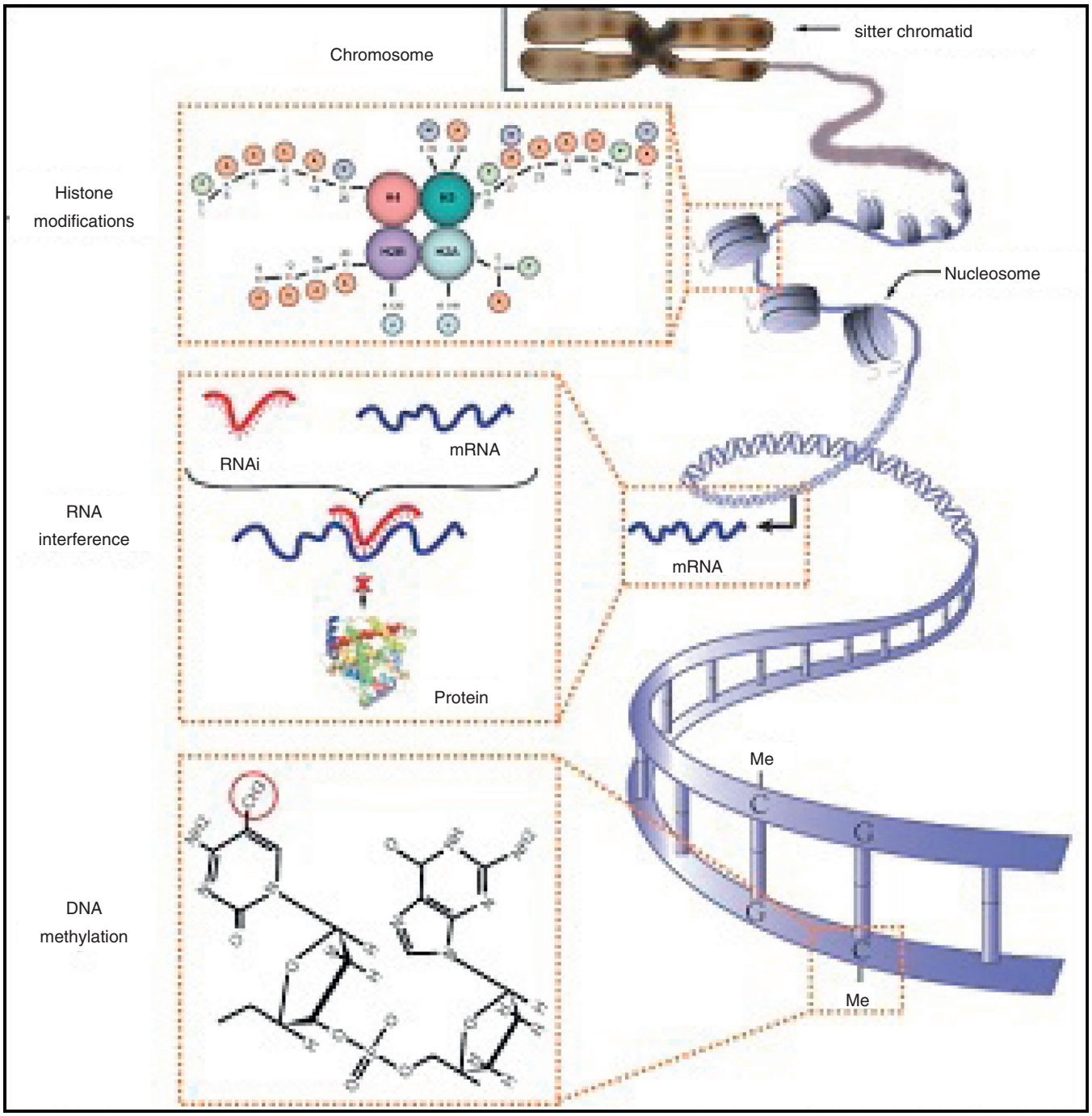
rate of DNA synthesis is high. Epigenetic mechanisms include alterations in expression patterns of microRNAs, modifications of histone proteins, and DNA methylation. These epigenetic mechanisms are described in Fig. 14.2.[102] MicroRNAs are small segments of noncoding RNA that regulate post-transcriptional expression of mRNA.[35,78,90,95,102,129] Histones are a group of eight nuclear proteins that package and tightly compact DNA chromatin into smaller, coiled segments called nucleosomes containing 146 base pairs. Histone modifications such as acetylation and phosphorylation alter the histone protein at the N-terminal tail, changing nucleosome structure, and activating or repressing transcription.[95,102] DNA methylation is a well-described epigenetic modification involving addition of a methyl group to the nucleotide cytosine when it precedes guanine, frequently at the promoter region. Methylated segments of DNA are more tightly coiled, hiding the promoter region and limiting gene expression. In less methylated areas, the promoter is open, allowing for DNA transcription.[4,35,49,95] DNA methylation is the mechanism of X-chromosome inactivation during embryogenesis in females. Aberrant DNA methylation of the X-chromosome is implicated in fragile X syndrome.[90] While DNA methylation is not entirely static across a lifetime, much of the epigenome is established during fetal development.[49]

One of the best-described epigenetic processes is genomic imprinting. Genomic imprinting occurs during early development and involves silencing of one parental allele leading to monoallelic gene expression. Dysregulation of genomic imprinting, potentially due to aberrant methylation of DNA, leads to disorders such as Angelman syndrome, Prader-Willi syndrome, and Beckwith-Wiedemann syndrome, and has been linked to autism and cancer later in life.[90] Imprinted genes are ideal models to study epigenetic modifications. As imprinting occurs early in fetal development, epigenetic adaptations are likely to have a significant effect. For example, adults who were conceived during the Dutch famine of World War II (1944–1945) demonstrate widespread and persistent changes in DNA methylation of imprinted insulin-like growth factor-2 (IGF-2) loci, with diverse biologic functions. These genes are known to be important modulators of growth, and epigenetic modifications are implicated in the development of metabolic and cardiovascular disease in adults.[78] Offspring conceived during the famine have developed these metabolic and cardiovascular conditions more frequently as adults.[129]

Fig. 14.3 illustrates potential periods of fetal development in which environmental toxins may impact the phenotype of the developing fetus.[90] Environmental toxicants have been shown to alter the epigenome during fetal life via modifications in DNA methylation. Measures of global DNA methylation can quantify the methylation state of the epigenome and have been utilized to investigate the relationship between toxicant exposure and epigenetic modifications. Global DNA hypomethylation is correlated with instability of the genome and cancer risk.[58]

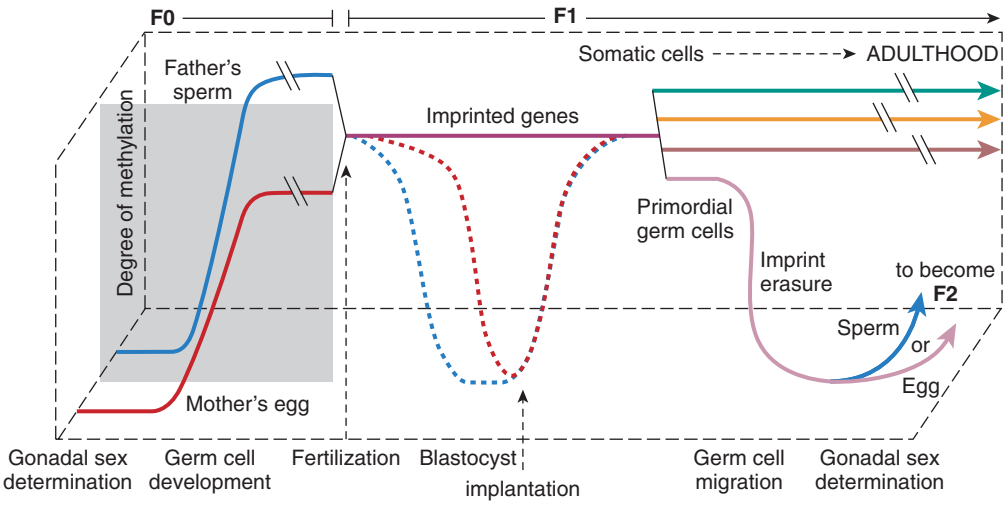
An association between prenatal exposure to metals such as arsenic, cadmium, and lead and DNA methylation has been documented in the literature.[4,35,49,78] Buccal samples from children prenatally exposed to maternal cigarette smoking show both global hypomethylation and in specific loci important in modulating cellular proliferation.[49] Polycyclic aromatic hydrocarbons (PAHs) are neurotoxic and carcinogenic chemicals found in fumes from vehicle exhaust, coal, charbroiled foods, and cigarette smoke. PAHs are lipophilic and cross the placenta and fetal blood-brain barrier. Byproducts of PAH metabolism have the capacity to bind DNA, forming PAH-DNA adducts. The fetus is highly susceptible to formation of PAH-DNA adducts and associated genetic mutations, a known cancer risk. In a cohort of 159 children, prenatal airborne PAH exposure was associated with global hypomethylation of umbilical cord WBC DNA, which persisted at 3 years of age. In addition, increased global methylation was associated with the presence of BPH-DNA adducts in cord blood, two independent findings associated with increased cancer risk.[58,90]

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• **Fig. 14.2** Examples of epigenetic mechanisms: Histone modification, RNA interference (micro RNA), and DNA methylation. These mechanisms interact with DNA or mRNA to control gene expression. A nucleosome is the building block of chromatin, consisting of 146 base pairs wrapped tightly around nuclear proteins called histones. Histones are modified at the N-terminal tail, altering nucleosome structure and regulating transcription. RNA interference involves regulation of post-transcriptional expression of mRNA by noncoding segments of RNA called microRNAs. DNA methylation is characterized by addition of a methyl group to cytosine when it precedes guanine, frequently at the DNA promoter region. Regions in which methylation occurs are more tightly coiled, hiding the promoter region and limiting gene expression. In less methylated areas, the promoter is open, allowing for DNA transcription. (Reprinted from Sawan C, et al. Epigenetic drivers and genetic passengers on the road to cancer. In: *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 2008*. Vol. 642., New York: Elsevier, 2008:2. Reprinted with permission from Elsevier.)

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• **Fig. 14.3** Potential periods in which environmental toxicants may impact the phenotype of the developing fetus by epigenetic modifications such as DNA methylation. F0 = parental germ cell development; F1 = the developing fetus; F2 = future generation(s). (From Perera F, Herbstein J. Prenatal environmental exposures, epigenetics, and disease. *Reprod Toxicol*. 2011;31:364.)

Maternal Exposures

In early fetal life, oogonia are formed by meiotic division. Before birth, oogonia develop into primary oocytes and complete prophase of the first meiotic division.[94] Oocytes remain in this state until puberty. As cells are highly susceptible to environmental toxicants while in active phases of division, fetal life represents a critical period of vulnerability. This hypothesis is supported by the increasing incidence of nondisjunction events with advancing maternal age and prolonged environmental exposures. Exposures impacting regulatory and endocrine functions of the ovum can influence ovarian competence throughout life. Fig. 14.4 represents critical windows of exposures that may impact the male and female reproductive system.[94]

Active smoking during pregnancy is associated with loss of ova in the fetus, which may reduce fertility in women born to mothers who smoke. In animal models, fetal exposure to nicotine results in granulosa cell proliferation, impaired ovarian steroidogenesis and angiogenesis, increased ovarian cell apoptosis, and reduced fertility.[12] Endocrine disrupting chemicals (EDCs) are compounds that act as agonists or antagonists to the endocrine system. Epidemiologic studies demonstrate an association between developmental exposure to EDCs and infertility. Bisphenol A (BPA) is an EDC found in plastic products. An inverse relationship has been found between the number of eggs recovered during in-vitro fertilization and urinary BPA levels.[129]

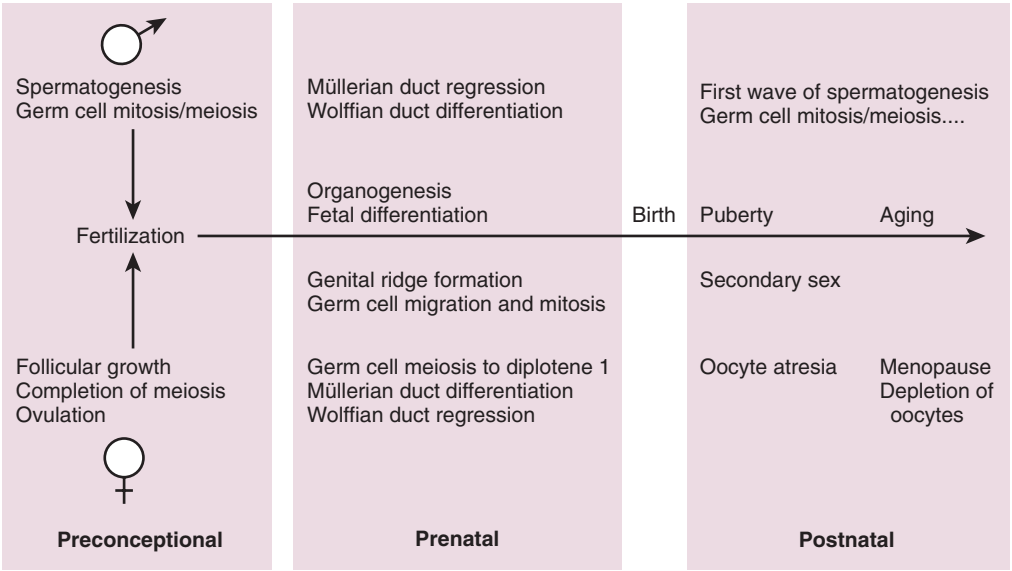
Developmental exposure to environmental toxicants can have an impact on fertility that may be transmitted to future generations. Inheritance of epigenetic information between generations that leads to phenotypic variation in the absence of direct environmental influence is termed *epigenetic transgenerational inheritance*. Epigenetic transgenerational inheritance requires epimutations to be present in the germline, as it is only sperm and eggs that pass this information to the next generation.[82] Epigenetic transgenerational inheritance has been proposed as a mechanism for phenotypic aberrations that have occurred following fetal exposure to the EDC diethylstilbestrol (DES). DES is an estrogenic drug that was prescribed to 5–10 million women worldwide from the 1940s to the 1970s to prevent miscarriage. Although vaginal clear cell adenocarcinoma has occurred infrequently in daughters of women exposed to DES, infertility and poor pregnancy outcomes are extremely prevalent. In addition, other disorders of the reproductive, cardiovascular, and immune systems have been reported in both male and female offspring and these effects have persisted in the grandchildren of DES-treated women.[55,68,129] The incidence of breast cancer is at least twofold higher in the daughters of DES-exposed mothers.[60]

Paternal Exposures

Environmental toxicants that impact spermatogenesis have been identified. Spermatogonia are highly sensitive to apoptosis after exposure to cytotoxic agents. Toxicants may also impact male fertility by limiting sperm production. Unlike the female, cell divisions in the male that produce mature spermatozoa occur after puberty. However, mature spermatozoa have no DNA repair mechanisms and are vulnerable to the effects of mutagens. Transient aneuploidy of autosomal and sex chromosomes has been reported in sperm of men treated for Hodgkin disease with chemotherapy in the preceding 3 months.[94]

A gradual decline in sperm concentration has been reported in reproductive-age males, and human male infertility is currently approaching 10%. Increased exposure to environmental toxicants has been postulated as a contributing factor. For many of these exposures, findings have been reproduced for several generations, and epigenetic transgenerational inheritance is a proposed mechanism.[77,82] Chronic occupational exposure to the pesticide 1,2-Dibromo-3-chloropropane (DBCP) is associated with cessation or

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• **Fig. 14.4** Critical windows of exposure of the reproductive system to environmental toxicants during preconception, prenatal, and postnatal period. (From Pryor JL, et al. Critical windows of exposure for children's health: the reproductive system in animals and humans. *Environ Health Perspect*. 2000;108(3):492.)

reduction in spermatogenesis.[94] In the rat model, exposure of the pregnant female to two EDCs (vinclozolin, a fungicide used in the wine industry, and the pesticide methoxychlor) led to impaired spermatogenesis and infertility in males in four subsequent generations.[77,82,94] Phthalates are plasticizers and known EDCs that are now ubiquitous in our environment. Bis (2-ethylhexyl) phthalate (DEHP) is found in polyvinyl compounds, while dibutyl phthalate (DBP) is used primarily to add flexibility to plastics. Both compounds can adversely affect male reproductive function. In animal studies, prenatal exposure has been linked to spermatogenic cell apoptosis, seminiferous tubule atrophy, and testicular dysfunction. Phenotypic alterations following exposure prenatally included cryptorchidism, hypospadias, ambiguous genitalia, reduced sperm production, and decreased anogenital distance.[77]

The relationship between paternal occupation and cancer in offspring has been extensively studied.[40,99] One study reported increased risk of central nervous system (CNS) tumors with paternal occupational exposure to pesticides (relative risk [RR] 2.36; 95% CI 1.27-4.39) and work as a painter (RR 2.18; 95% CI 1.26-3.78). Increased incidence of childhood leukemia has been associated with paternal periconceptual occupational exposure to woodworking, solvents, paints, pesticides, and motor vehicles (driving, exhaust fumes, and inhaled particulate hydrocarbons).[40] A case control study evaluating paternal exposure to pesticides reported increased risk of astrocytoma in offspring; combining occupational and home exposures significantly elevated this risk (OR = 1.8, 95% CI 1.1–3.1).[99]

Approximately 60% of congenital malformations of unknown etiology are estimated to be secondary to environmental toxicants.[37] Increased prevalence of birth defects in offspring of fathers employed as janitors, painters, printers, agricultural workers, groundskeepers, welders, electrical industry workers, and firefighters have been reported.[23,32,37] In addition, paternal exposure to organic solvents and pesticides was a significant risk factor for congenital anomalies in offspring.[23]

Male fertility diminishes and sperm DNA mutations increase with advancing paternal age. Advanced paternal age is associated with pregnancy loss, birth defects, and autosomal dominant genetic disorders such as Marfan syndrome and achondroplasia. Congenital malformations seen more frequently in fetuses of older fathers include cleft lip and palate, hydrocephalus, neural tube defects, limb reduction defects, tracheoesophageal fistula, congenital cataracts, and congenital heart disease.[50] A possible mechanism for paternally mediated effects is the impairment of a paternal gene necessary for the normal growth and development of the fetus. Replacement of the father's genetic material with a second copy of the mother's genetic material (uniparental disomy), or vice versa, results in a nonviable conceptus.[53] In Prader-Willi syndrome, there is a functional mutation in paternal 15q, resulting in inactivation of the genes in that region of the chromosome. Environmental factors may play a role in uniparental disomy and lead to paternally mediated effects on the fetus. Studies have shown association between paternal exposure to hydrocarbons and Prader-Willi syndrome. In one study, approximately 50% of fathers of children with Prader-Willi syndrome were occupationally exposed to hydrocarbons.[15]

Secondary Fetal Exposure: Maternal Body Burden

The developing fetus may be exposed to xenobiotics (chemicals not naturally produced by the organism) after increased mobilization from maternal storage compartments during pregnancy. Adipose tissue is a storage site for

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hydrophobic chemicals, while both lead and fluoride are stored in bone.

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are endocrine disruptors (EDCs) that are mobilized from adipose tissue during pregnancy and readily cross the placenta. They are lipophilic organochlorine chemicals that bioaccumulate in the environment, enter the food chain, and are stored in adipose tissue.[4,28,76] Exposure occurs primarily through ingestion of dairy, animal fat, and fish. PCBs were used as liquid insulators for transformers and capacitors in the 1970s. Because PCBs remain stable in the environment and are resistant to biologic breakdown, they are classified as persistent organic pollutants (POPs).[76] Although use has been banned or limited in many countries, exposure remains a public health concern. Two recent studies (2011, 2014) document the presence of PCBs in blood samples from pregnant women and in breast milk.[76]

Prenatal exposure to PCBs has been correlated with neurodevelopmental impairment and autism.[76] Maternal occupational exposure is linked to low birth weight and prematurity.[28] Human poisonings have occurred through dietary consumption of PCBs. In 1979, an epidemic of PCB poisoning from contaminated rice oil occurred in Taiwan termed *yu-cheng disease*. Adults who were exposed developed hyperpigmentation, acne, and peripheral neuropathy. Of the first 39 hyperpigmented children born to poisoned women, 8 died. Children born up to 6 years after the outbreak of yu-cheng disease had ectodermal defects and developmental delay. Children born 6 years after maternal exposure were as developmentally impaired as those born within 1 year of the epidemic, indicating significant maternal body burden.[21] Cognitive defects seen in Taiwanese children with yu-cheng disease are comparable to those observed in American children prenatally exposed to PCBs. Studies in Michigan and North Carolina showed neurodevelopmental impairment in children prenatally exposed to PCBs through maternal body burden. In Michigan, cognitive deficits were seen in children who had elevated cord blood levels of PCBs and whose mothers had regularly consumed contaminated sport fish.[28]

Lead

The major repository for lead is bone, and chronic exposure results in significant accumulation of lead in the skeleton. Lead stores are mobilized from bone during pregnancy, potentially exposing the fetus during critical stages of brain development. It is postulated that enhanced calcium turnover during pregnancy increases lead mobilization. Maternal tibial and patellar bone lead levels are correlated with low birth weight and decreased head circumference. One study established maternal trabecular bone lead level as an independent risk factor for cognitive delay at 24 months of age. Lead is readily transported across the placenta and blood-brain barrier. Lead is a potent neurotoxin. Developmental exposure is linked to learning disability, cognitive and language deficits, and attention deficit hyperactivity disorder (ADHD). Treatment of pregnant women with calcium supplementation may limit lead mobilization from bone and could decrease circulating maternal lead levels and placental transfer to the fetus.[45]

Maternal Exposures Concurrent With Pregnancy

Biomarkers of fetal exposure have been developed using cord blood and meconium.[27,86] In 2007, The Environmental Working Group measured cord blood levels of 413 chemicals from 10 US newborns. They found 287 toxicants, with an average of 200 chemicals in cord blood of each infant. Chemicals included pesticides, PCBs, and heavy metals such as mercury.[27] Meconium analysis is a sensitive tool utilized to determine antenatal exposure to environmental toxicants. In a study of 426 infants born in the Philippines, exposure rate was 26.5% for lead, 83.9% for mercury, and 53% for the organophosphate pesticide malathion.[86]

Occupation and Paraoccupation

The strongest associations between maternal exposures and adverse pregnancy outcome (spontaneous abortion, miscarriage, and congenital anomalies) have been found for lead, mercury, pesticides, organic solvents, and ionizing radiation. Occupations linked with adverse pregnancy outcome secondary to exposures include anesthesiologists, hair dressers, laboratory technicians, dry cleaners, agricultural workers, and those working in chemical, electronic, or shoe factories.[41]

Specific congenital anomalies have been linked to maternal occupations. For example, cleft lip and palate occurs more frequently in offspring of leather workers, hairdressers, housekeepers, and transport and communication workers. Limb anomalies have been reported in children of agricultural workers, and neural tube defects in children of cleaners and health care providers working with anesthesia and radiation.[59] In a large population-based case control study that examined the relationship between various maternal occupations and 45 birth defects, jobs with the highest number of associated anomalies were janitors/cleaners, scientists, and electronic equipment operators. Teachers and health care workers had the lowest risk of delivering a child with congenital anomalies.[59] However, in health care providers, adverse pregnancy outcomes (miscarriage and congenital anomalies) have been reported with chronic occupational exposure to antineoplastic medications, especially when this exposure occurs during the first trimester.[24]

Paraoccupational exposures occur when others living in the home come in contact with an occupationally exposed individual, or occupational chemicals are brought into the home on clothing or other materials. Paraoccupational exposure to pesticides remains an occupational hazard today. An important route of exposure to neurotoxic organophosphate

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pesticides (OPs) occurs in families of farm workers. A systematic review of 10 studies assessing prenatal exposure to OPs reported neurocognitive impairment involving working memory and attention in toddlers and children at school age.[80]

Air Pollution

Many chemicals found in outdoor air pollution are neurotoxic. Exposure is associated with disruption of the blood-brain barrier, chronic CNS inflammation, microglia activation, and white matter injury.[51] The United States Environmental Protection Agency (EPA) established air quality standards in 1971. Although some progress has been achieved, outdoor air pollution continues to carry significant health risks. Particulate matter, ground-level ozone, sulfur dioxide, nitrogen dioxide, carbon monoxide, and airborne lead are examples of outdoor air pollutants with known adverse health outcomes. These air pollutants are the focus of air quality standards, such as the EPA's Clean Air Act. The air quality index (AQI) is an indicator of daily air quality calculated by the EPA for these six major air pollutants that are regulated by the Clean Air Act. Both carbon monoxide and airborne lead are typically meeting safety standards.[112]

Particulate matter pollution consists of fine inhalable particles comprised of many different chemicals found in outdoor air ($PM_{2.5}$ and PM_{10}, 2.5 micrometers and 10 micrometers in diameter, respectively). Particles less than 10 micrometers are readily inhaled into the lungs, interact with the immune system, and are absorbed systemically. Ground-level ozone (the primary component of smog) is formed in the atmosphere by photochemical reactions between sunlight, nitrogen oxide species, and volatile organic compounds (VOCs), which are photochemically reactive hydrocarbons. Sulfur dioxide and nitrogen dioxide are also components of smog. Emissions from industrial facilities, motor vehicle exhaust, gasoline vapors, and chemical solvents are common sources of these toxicants.[112]

Exposure to outdoor air pollution is difficult to avoid during pregnancy, especially in highly polluted areas. There is strong evidence concerning exposure to air pollution to both increased infant mortality and respiratory morbidities such as asthma in early childhood. In addition, there is evidence from epidemiologic studies linking prenatal exposure to air pollution and prematurity, low birth weight, impaired lung and immune function, autism spectrum disorders, and neuromotor impairment in early childhood.[51,93,98]

Drinking Water

The drinking water supply is obtained from a variety of sources that include ground water and surface water from rivers, lakes, reservoirs, and aquifers. Environmental toxicants that contaminate drinking water are associated with adverse health outcomes. Common drinking water contaminants include the heavy metals lead and arsenic, inorganic compounds such as nitrates and nitrites found in fertilizers and livestock manure, pesticides such as atrazine and glyphosate, disinfection byproducts such as chloroform, and organic solvents such as trichloroethylene. Congenital anomalies, specifically cardiac defects, and low birth weight were found in studies evaluating trichloroethylene-contaminated drinking water. The EPA and the Food and Drug Administration (FDA) monitor the safety of drinking water; the EPA is responsible for drinking water standards for public water systems.[113]

Arsenic enters the water supply naturally and is also found in agricultural and industrial chemicals. Arsenic readily crosses the placenta; prenatal exposure is associated with fetal growth restriction and increased infant mortality in animal models. Population studies of health outcomes associated with arsenic exposure have been conducted primarily in countries such as Bangladesh, Taiwan, and Chile, where naturally occurring arsenic levels in groundwater are elevated. A systematic review and meta-analysis of these studies notes an association between prenatal arsenic exposure and spontaneous abortion, stillbirth, low birth weight, and neonatal mortality. While studies on dose response were limited, the strongest correlation was between prenatal arsenic exposure and spontaneous abortion.[96]

Diet

Maternal diet during pregnancy appears to impact the fetal epigenome. In animal models, fetal growth restriction has been linked to cardiovascular disease, including adult-onset hypertension and central adiposity. Diets low in protein or iron and high in saturated fat appear to have the greatest impact on blood pressure. Conversely, several studies have documented the relationship between maternal obesity, gestational diabetes mellitus, and altered epigenome methylation in the placenta and cord blood; findings that may potentially correlate with risk for metabolic conditions in offspring.[73]

The effects of nutritional modification can be selective. Genetically identical agouti mice contain a coat color gene controlled by DNA methylation. If pregnant mice are fed normal rat chow, offspring have either a yellow coat or brown coat. Those with a brown coat have normal weight, while those with a yellow coat are prone to obesity, diabetes, and cancer. Mice fed a diet supplemented with methyl donors such as folic acid tend to develop brown color coat and are not obese.[49,73,90] Maternal exposure to bisphenol A (BPA), an endocrine disruptor, shifts distribution of offspring's coat color to yellow. This effect can be reversed by dietary supplementation with methyl donors such as choline or folate.[35]

Similarly, B12 and folate deficiency during pregnancy have been proposed to impact the fetal methionine-homocysteine cycle via epigenetic alterations in DNA methylation. The methionine-homocysteine pathway is an important regulator of methylation and is dependent on Vitamin B12 and folate as cofactors. Deficiency in

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B12 or folate leads to high levels of homocysteine, a well-established risk factor for adult cardiovascular disease. Pregnant sheep exposed to diets restricted in B12, folate, and methionine deliver offspring who develop increased body mass, impaired immune function, insulin resistance, and hypertension as adults.[73]

Inorganic mercury (methylmercury) is an example of a xenobiotic that contaminates our food supply. Methylmercury is a lipid-soluble and potent neurotoxin found in fish and seafood. Methylmercury readily crosses both the placenta and blood-brain barrier.[69] The US EPA has set an oral reference dose of mercury at 0.1 μg/kg/day. Approximately 8% of women have body burdens exceeding this reference dose. The fetus is very susceptible to the neurotoxic effects of methylmercury. Prenatal exposure has been associated with microcephaly, seizures, and cognitive and sensory impairment.[27,69] In 1956, methylmercury contaminated the food chain in Minamata Bay, Japan. Offspring of pregnant women from a local fishing village exposed to methylmercury developed severe neurodevelopmental impairment.[55]

Pathways of Fetal Exposure

Placenta-Dependent Pathways

Two routes of fetal exposure to environmental toxins are placenta-dependent pathways and placenta-independent pathways. Placenta-dependent pathways require chemicals to enter the mother's bloodstream and cross the placenta in significant amounts. Not all environmental toxins meet these criteria; asbestos and radon gas do not, unless they have been ingested. Most xenobiotics cross the placenta by passive diffusion. Therefore, the concentration gradient between maternal and fetal circulation and placental blood flow are the primary determinants of exposure.[3]

Properties enabling chemicals to cross the placenta more readily are low molecular weight, protein binding, lipid solubility, ionization, and resemblance to nutrients with specific transport mechanisms. An example of a low-molecular-weight compound is carbon monoxide, a constituent of environmental tobacco smoke (ETS). Carbon monoxide has a very high affinity for hemoglobin and displaces oxygen. Accumulation of carboxyhemoglobin leads to hypoxia and impaired cellular metabolism.[34] Examples of lipid-soluble chemicals that readily cross the placenta are PCBs, ethanol, and polycyclic hydrocarbons such as benzo[a]pyrene, a carcinogen in ETS. Lead is actively transported across the placenta via calcium-specific channels; calcium supplementation may reduce the transfer of lead to the fetus.[45]

Placenta-Independent Pathways

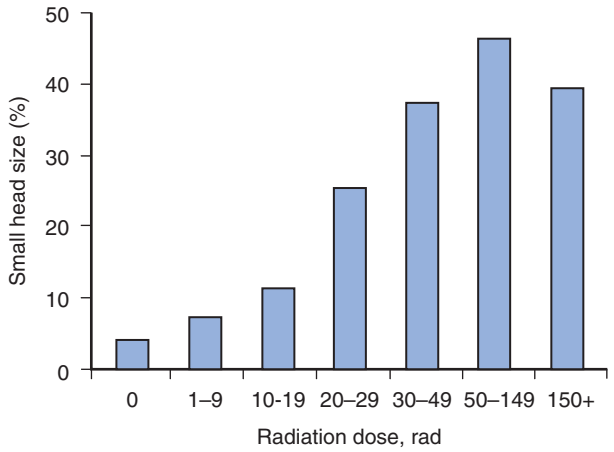
Radiation

Ionizing radiation is a well-characterized teratogen that is most harmful to the fetus in the first trimester during organogenesis. Prenatal exposure is associated with infertility, microcephaly, and increased incidence of childhood cancer in offspring.[4] Children of survivors of the atomic bombs in Hiroshima and Nagasaki exposed in utero at <18 weeks' gestation developed microcephaly, with the lowest observable effect at a dose of 1-9 rad (Fig. 14.5).[8]

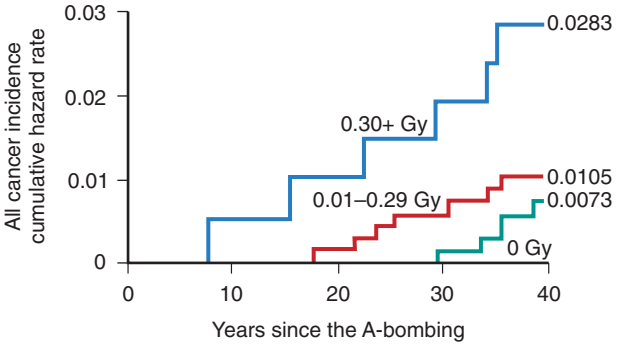
The brain of a neonate undergoing cranial computed tomography (CT) with settings of 400 mA, 125 kV (peak), and a standard slice thickness of 4 mm receives a dose of 10.5 rad.[125] Therefore, it has been recommended that CT be used sparingly for infants, particularly when other imaging techniques are available. An excess of cancer among Japanese individuals exposed in utero has also been reported (Fig. 14.6).[128] Not all forms of radiation are hazardous to the fetus. Ultraviolet light does not penetrate to the fetus and does not constitute a future cancer risk.[4]

Heat

Heat may directly penetrate to the fetus and cause birth defects. Animal studies demonstrate that both maternal core temperature 2°C above baseline and duration of



• **Fig. 14.5** Percentage of Hiroshima children with head circumference 2 or more standard deviations below average, by fetal dose. Exposure occurred before 18 weeks of gestation. (From Blot WJ. Growth and development following prenatal and childhood exposure to atomic radiation. *J Radiat Res [Tokyo]*. 1975;16[suppl]:82.)



• **Fig. 14.6** Cumulative hazard rate for cancer among survivors of intrauterine radiation in Hiroshima and Nagasaki, for three exposure groups through 1984. Gy, Gray (a measure of an absorbed dose of ionizing radiation). (From Yoshimoto Y, et al. Risk of cancer among children exposed in utero to A-bomb radiations, 1954. *Lancet*. 1988;2:667.)

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hyperthermia are important risk factors. One study showed association between hot tub use after conception and twofold increased risk of miscarriage. In a study of the effects of heat on the outcome of pregnancy, 22,491 women undergoing α-fetoprotein screening were asked about their use of hot tubs, saunas, and electric blankets, and whether they had experienced a fever during the first trimester. The adjusted relative risk for neural tube defects with hot tub use was 2.8 (95% CI 1.2–6.5). With exposure to two of these heat sources, the relative risk increased to 6.5.[20]

Noise

Sound exposure is an important form of sensory stimulation in the developing fetus. At 23-25 weeks, sound begins to produce physiologic changes in fetal state; by 25-29 weeks' gestation the auditory system is functional.[47,48] At 27 weeks, the fetus primarily hears low frequency sounds below 500 Hz; frequencies above 500 Hz are not perceived until closer to 29 weeks due to filtering by the maternal tissues and uterus.[47,72]

Both low- and high-frequency noise can be detrimental and produce physiologic changes in the fetus. Applying vibroacoustic stimulation directly to the maternal abdomen leads to increase in fetal heart rate and movement.[72] Intense and sustained noise exposure during the prenatal period is associated with congenital anomalies, prematurity, and low birth weight.[47] In addition, noise-induced hearing loss may be evident after in utero exposure. The cochlear hair cells are sensitive to low frequency sound. Animal studies show that intense low frequency sound can damage the cochlear hair cells; effects are determined by gestational age and the intensity and duration of sound exposure.[48,72] The Sound Study Group recommends that pregnant women should avoid extended exposure to low frequency sound levels (<250 Hz) greater than 65 dB, and that sources of sound applied directly to the mother's abdomen (headphones) should be avoided because of no clear benefit and potential risks to fetal hearing.[48,72]

Fetal Pharmacokinetics

Absorption and Distribution

Physiologic changes during pregnancy influence maternal absorption and distribution of toxicants to the fetus. Increases in maternal progesterone concentration prolong gastric emptying time and slow intestinal motility, impacting enterohepatic circulation and absorption of xenobiotics. This results in reduced peak maternal levels of xenobiotics but increased overall exposure.[3] Another maternal physiologic change that affects absorption of xenobiotics occurs in the lungs. Both hyperventilation and increased pulmonary blood flow associated with pregnancy favor uptake of toxicants such as air pollutants into the lungs, where they can be absorbed systemically.[64,88]

Distribution of xenobiotics in the maternal compartment are impacted by increases in fat stores, extracellular fluid volume, and plasma volume during pregnancy. In addition, amniotic fluid represents a third potential compartment for distribution of water-soluble chemicals. This amniotic fluid compartment is characterized by low protein concentration and delayed elimination, resulting in a potential source for prolonged exposure to unbound chemicals that may be harmful to both mother and fetus. As the fetal kidney matures, higher concentrations of xenobiotics may be stored in this compartment.[3,88]

During pregnancy, plasma volume increases by 50%. Dilutional hypoalbuminemia is a result of plasma volume expansion that surpasses albumin production. Dilutional hypoalbuminemia alters the ratio of protein-bound chemicals and the volume of distribution in maternal blood, facilitating both clearance of free fractions of xenobiotics in the liver and placental transport to the fetal compartment.[3,88] Changes in maternal plasma volume also impact excretion of toxicants. Increased renal blood flow, glomerular filtration rate, and tubular transport result in maternal excretion of toxicants before reaching the fetus.[3]

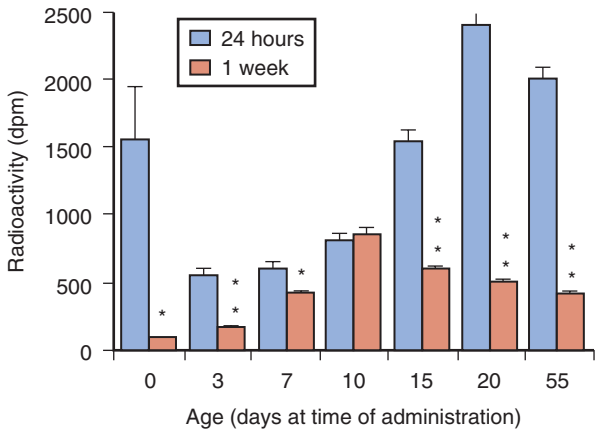
Distribution of xenobiotics in the fetal compartment is also influenced by acid-base status and protein binding. As fetal pH is more acidic than maternal pH, weak bases that are non-ionized in the maternal compartment are readily transported across the placenta. In the fetal compartment, weak bases become ionized, resulting in higher concentration and "ion trapping." While maternal serum albumin gradually declines during pregnancy relative to plasma volume, fetal albumin concentration progressively increases. Thus, unbound xenobiotics that easily cross the placenta become protein-bound in the fetus and can accumulate in the fetal compartment.[88]

While maternal fat stores serve as a reservoir for lipophilic compounds, there is minimal fetal adipose development until after 29 weeks' gestation. Before that time, lipid soluble toxicants accumulate in tissues containing adipose, such as the developing brain. An example is shown in Fig. 14.7. The pesticide DDT (dichlorodiphenyltrichloroethane) was administered orally to mice at ages that correspond to the human brain growth spurt. Radioactivity was measured in brain tissue after 24 hours and 7 days. At 24 hours, 20-day-old mice accumulated more DDT in their brains than at other ages. DDT persisted longest in the animals given DDT at 10 days. Mice treated at 10 days had more behavioral abnormalities than those treated on other days, suggesting that the persistence was more important than initial accumulation. These results reflect the complexities of chemical distribution in the developing fetus.[39]

Metabolism

Maternal basal metabolic rate increases during pregnancy, facilitating hepatic metabolism of xenobiotics. The most widely described hepatic metabolizing enzyme systems are phase I (cytochrome P450 enzymatic oxidation, dehydrogenation, reduction, and hydrolysis) and phase II (enzymatic glucuronidation, sulfation, methylation, and glutathione

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• **Fig. 14.7** Radioactivity levels (in disintegrations per minute [dpm]) in mouse brain 24 hours and 1 week after oral administration of 1.48 MBq [^{14}C]DDT (dichlorodiphenyltrichloroethane) per kg of body weight. Height of bars represents mean ± standard deviation; statistical difference between 24 hours and 1 week is indicated by $P = .01$ (*) and $P = .001$ (**). (From Eriksson P. Age-dependent retention of [^{14}C]DDT in the brain of the postnatal mouse. *Toxicol Lett*. 1984;22:326.)

conjugation) processes. Approximately 75% of chemicals are toxic in their original state, and the remaining 25% are metabolized to toxic intermediates in the liver. Certain phase I and phase II enzymatic processes have been shown to be activated as a direct response to pregnancy-induced circulating estrogen levels, impacting metabolism and excretion of xenobiotics. Maternal metabolism and clearance of xenobiotics may additionally be reduced by estrogen-induced cholestasis that occurs physiologically during pregnancy.[3,64,85]

Prior to reaching the fetal compartment, some degree of first pass metabolism by phase I and phase II processes occurs in the placenta. In the fetus, expression of metabolic enzymes in the liver matures with advancing gestational age. Metabolism can lead to detoxification and facilitate excretion or activation of a xenobiotic to a more potent toxin.[3,91] The fetus may be protected if the active form of a toxin is its metabolite. An example is acetaminophen, a common drug used in suicide attempts during pregnancy. Acetaminophen is metabolized by phase I enzymes to hepatotoxic and nontoxic intermediates. Expression of the phase I enzymes is developmentally regulated. Because many of these enzymes are poorly expressed in fetal tissues, the fetus may be protected.[104]

Polymorphisms in human drug-metabolizing enzymes have been described that impact the susceptibility of the fetus to environmental toxicants. For example, risk of fetal alcohol spectrum disorder is impacted by genetic polymorphisms in the expression of the enzyme alcohol dehydrogenase (ADH). If the high-activity variant of ADH is inherited, ethanol oxidation and elimination is enhanced, decreasing the teratogenic effects of alcohol on the developing fetus.[91] A second example involves deactivation of organophosphate pesticides by the antioxidant enzyme paraoxonase 1 (PON1). In the liver, certain organophosphates are converted to a biologically active toxic form by cytochrome P450 enzymes. PON1 is responsible for hydrolyzing this toxic intermediate to an inactive metabolite that can be excreted. Genetic polymorphisms in PON1 have been described that impact both expression and catalytic capability of PON1, thus providing enhanced protection or greater susceptibility to toxic effects of these pesticides. When four birth cohorts were pooled (n = 936), negative associations were found between organophosphate metabolites in maternal urine and the Bayley MDI at 24 months in carriers of a particular PON1 allele.[38]

Specific Exposures

Cigarette Smoke

Despite the known consequences of smoking, 15%-20% of women in the United States smoke, and many are of childbearing age.[31] Both active maternal smoking during pregnancy and passive exposure to environmental tobacco smoke (ETS) are harmful to the fetus. ETS consists of smoke coming from the end of a burning cigarette (sidestream smoke) and from smoker's exhalation (mainstream smoke); it is also known as secondhand smoke. ETS contains over 250 harmful chemicals, including carbon monoxide, cyanide, benzene, ethylene oxide, nitrogen oxides, arsenic, formaldehyde, vinyl chloride, toluene, and polycyclic aromatic hydrocarbons such as benzo(α)pyrene. At least 69 are known carcinogens; the amount of each chemical varies with each cigarette.[81] Cotinine is a metabolite of nicotine that has a long half-life (~20 hours) and is the biologic marker used to measure exposure to ETS. There is no safe level of exposure to ETS.[34,81,84]

E-cigarettes are a diverse class of inhaled aerosol devices that have recently increased in popularity. They are battery powered and typically contain nicotine and other flavoring such as mint, fruit, or chocolate. Toxic additives may include particulate matter, solvents such as benzene and toluene, and heavy metals (lead, nickel, and tin). According to the US Department of Health and Human Services, e-cigarettes are the most commonly used tobacco product among adolescents. In 2015, one of every six high school students reported use of e-cigarettes within the past month.[114]

Sources of Exposure

Since smoking in public and the workplace has been restricted, the most common source of ETS exposure is at home. Paternal smoking is the most frequently reported source of environmental exposure.[84]

Toxic Effects

Active smoking is associated with infertility, reduction in successful in-vitro fertilization, and early onset of menopause.[31] Impaired female fertility may be secondary to hormonal imbalance, direct impact on follicular growth and ovulation, or reduced motility in the female reproductive tract.[31,84] Cotinine and benzo(a)pyrene (carcinogen, endocrine disruptor) have been found in follicular fluid and

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ovarian granulosa cells; levels correlate with the degree of active and passive exposure.[31,84] Active paternal smoking is linked to decreased production, impaired motility, and altered sperm morphology.[84] Active smoking also impacts the developing fetus. Nicotine leads to vasoconstriction of the uteroplacental blood vessels, reducing delivery of oxygen and nutrients. Additionally, carboxyhemoglobin production from carbon monoxide contributes to fetal hypoxia and chronic hypoxic stress.[34,62] Fetal exposure to active maternal smoking is associated with placental dysfunction, spontaneous abortion, intrauterine growth restriction, preterm delivery, and congenital anomalies such as cleft lip and palate. Active maternal smoking during pregnancy is an important risk factor for sudden infant death syndrome (SIDS).[4,34,84,114] A direct dose-response relationship has been noted between maternal smoking and intrauterine growth restriction; one study suggested a 5% reduction in relative fetal weight per pack of cigarettes smoked daily.[34] Nicotine is toxic to the developing nervous system, impacting neuronal proliferation and differentiation. Maternal active smoking during pregnancy is associated with impaired cognitive functioning, auditory processing deficits, impulsivity, anxiety, depression, ADHD, obesity, and conduct disorders in offspring.[34,49,62] Maternal smoking also appears to impact infant stress response via epigenetic mechanisms. DNA hypomethylation of the placental glucocorticoid receptor promotor region was found in one study to correlate with infant salivary cortisol levels over the first month of life.[49] Epidemiologic studies show a relationship between prenatal maternal active smoking and both reduced lung function and asthma in offspring.[12,34] At present, there is insufficient evidence to decisively link ETS with infertility, spontaneous abortion, or congenital anomalies. However, prenatal exposure to ETS has been associated with increased incidence of both SIDS and low birth weight.[34,84] Evidence is suggestive of a relationship between ETS and preterm delivery. The literature also suggests a relationship between prenatal exposure to both active maternal smoking and ETS and the incidence of childhood cancers; further evidence is necessary to support this relationship.[84]

Prevention Strategies

Smoking prevention programs should focus on education and treatment of preteens, adolescents, and women of childbearing age. As nicotine is a neurotoxin, nicotine replacement should be avoided as a means to quit smoking during pregnancy. Smoking during pregnancy and common sequelae such as preterm birth and low birth weight have been diminished using behavioral therapy programs.

Ethanol

Effects of alcohol on the fetus are extensive, devastating, and often permanent. Approximately 8%-30% of women report drinking alcohol at some time during their pregnancy (CDC MMWR).[16] The incidence of fetal alcohol syndrome (FAS) in the United States is estimated as 0.3 per 1000 live births, and 2%-5% of preschoolers may have a fetal alcohol spectrum disorder (FASD).[79]

Sources of Exposure

While most ethanol exposure is the result of deliberate ingestion, measurable levels of ethanol in the blood after use of hand sanitizers has been documented. There are sporadic reports of people ingesting hand sanitizers.[46,66] Recent data show measurable levels of ethanol in air in NICU incubators following the use of hand sanitizers.[61] Patients are also exposed to ethanol as an excipient in medications; studies in the United States, the Netherlands, and New Zealand report that ethanol is present in 47 pediatric medications with concentrations ranging from 0.6% v/v to 76% v/v ethanol.[1,25,105,119] Measurement of blood ethanol concentrations in samples from 289 neonates show that these mostly remain relatively low (typically 10 mg/dL or lower), although 11 of the 289 blood samples had ethanol concentrations at or above 20 mg/dL.[25]

Toxic Effects

FAS was identified more than 40 years ago. It is defined by craniofacial abnormalities (including smooth philtrum, thin upper lip, and short palpebral fissures), growth deficiency (at or below the 10th percentile), and central nervous system dysfunction (structural, neurologic, and/or functional). FAS is generally considered to be the extreme end of the spectrum of negative outcomes that result from alcohol exposure during pregnancy.[65,75]

Fetal alcohol spectrum disorder (FASD) is an umbrella term that covers all diagnoses that pertain to children who were exposed to alcohol in utero. This includes FAS, as well as partial FAS, alcohol-related neurodevelopmental disorder, and alcohol-related birth defects. Children exposed to alcohol in utero tend to have poor outcomes. They can have lower IQ scores; poor reasoning skills; hyperactivity; poor memory; learning difficulties; speech and language delay; intellectual disability; and/or problems with attention, sleep, vision, or hearing, or with heart, kidney, or bone. Prenatal exposure to ethanol is still the leading known cause of intellectual delay.[65,75] A recent meta-analysis identified 428 comorbid conditions in people with FASD across all organ systems.[92] The top five were: "abnormal results of function studies of peripheral nervous system and special senses, conduct disorder, receptive language disorder, chronic serous otitis media, and expressive language disorder." People prenatally exposed to alcohol are also at risk for epilepsy; a recent study showed that 17.7% of a prenatally alcohol-exposed population have at least one documented seizure[7] and depression and anxiety disorders.[56]

While much of the work examining outcomes after exposure to ethanol is focused on brain development and behavior, other organ systems are also at risk. For example, prenatal alcohol exposure results in smaller, immature lungs as well as disruption of both innate and adaptive immunity in the lung, which increases risk of infection.[44] There is an

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increased risk of congenital heart disease.[13] The growth deficiency is part of the diagnosis of FAS points to skeletal abnormalities; this deficiency continues at least through early adolescence[30] and is associated with abnormal bone growth.[52] There are also reports of abnormalities in other systems including kidney, liver, and gastrointestinal.[14] However, such associations may not hold up under closer examination. This is partly due to a paucity of case reports and may also reflect the lack of information about alcohol exposure in the child's medical record.

Heavy alcohol consumption increases the risk of miscarriage from ~15% to 45%[54] and increases stillbirths sixfold.[26] It is possible that prenatal alcohol exposure increases the risk for preterm birth, however this is not definitive and the risk may depend on the amount of alcohol consumed.[83,87]

Typically, FAS and FASD are associated with moderate to high levels of alcohol consumption. While there are some reports that low to moderate alcohol consumption is not harmful,[70] these same authors later found deficits in graphomotor skills in 5-year-old children exposed to ~9 drinks per week[63] and participated in a meta-analysis that identified behavior deficits in children exposed to <6 drinks.[42] In both studies that described deficits, these were more pronounced if the alcohol was consumed in a binge.

Prevention Strategies

Certainly, the cause of FAS and FASD is known and has been for many years; however, the rate of alcohol consumption by pregnant women is remarkably stable over time.[16] Although the human literature can be inconsistent regarding outcomes following exposure to alcohol, the best advice remains to abstain from alcohol exposure during pregnancy. Women planning to become pregnant should also consider abstaining as the effects of preconception exposure are not well understood at this time, although the animal literature suggests that preconception exposure can alter gene expression and epigenetic regulation of genes.[97] Intriguingly, work from the preclinical field suggests that some protection against alcohol effects may be provided by omega-3 polyunsaturated fatty acids[122,123] or choline[6]; in humans, choline appears to provide some therapeutic benefit to children with FASD.[127]

Pesticides

Pesticides are applied in agriculture and both in and around our homes. More than one billion pounds of pesticides are applied annually in the United States, and 5.6 billion pounds are used worldwide.[2] Pesticides are defined as any chemical utilized to eradicate insects (insecticides), plants and weeds (herbicides), rodents (rodenticides), and microorganisms (disinfectants, bactericides, fungicides, and algaecides).[2,99,124] Pesticides are classified by the function of their active ingredient and the intended target organism. Some of the more common classifications of pesticides, mechanisms of action, and examples are shown in Table 14.1. In addition to their active ingredient, pesticides contain other chemicals that are not required to be readily available for consumers.[2]

Organochlorines (DDT, methoxychlor, chlordane, aldrin, dieldrin, and lindane) and organophosphates (chloropyrifos, diazinon, and parathion) are neurotoxic insecticides that were historically applied commercially in agriculture. Both classes of insecticides have been restricted because of toxic effects in animals and humans.[17,38,99] Organochlorines are lipid-soluble and bioaccumulate in the environment.

TABLE 14.1 Common Pesticide Classifications and Their Characteristics

Classification	Mechanism of Action	Toxicity	Use and Characteristics	Examples
Organochlorine	GABA antagonist	High	Insecticides Residential and agriculture Many banned in U.S. EPA due to health risk, bioaccumulation Lipid soluble Lindane for lice, scabies	DDT Chlordane Lindane Aldrin
Organophosphates	Acetylcholinesterase inhibitors	High	Insecticides Used in agriculture, residential use banned Water-soluble	Chlorpyrifos Malathion Parathion Phosmet
Pyrethrins and Pyrethroids	Sodium channel antagonist	Low to moderate	Insecticides Residential and agriculture	Permethrin Deltamethrin
Carbamates	Acetylcholinesterase inhibitors	Variable	Insecticides Agriculture and residential	Aldicarb Carbaryl Primicarb
Neonicotinoids	Selective for insect acetylcholine receptors	Lower	Flea control for domestic animals Agriculture	Imidacloprid

DDT, dichlorodiphenyltrichloroethane; GAGA, gamma-aminobutyric acid.

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Although the organochlorine DDT was banned by the US EPA in 1972, use continues in some parts of the world for control of diseases such as malaria and for agriculture. Organophosphates are water-soluble and exert their neurotoxic effects via irreversible inhibition of acetylcholinesterase. Residential application of most organophosphates has been restricted or banned due to toxicities in humans.[38,99,110] Pyrethoids, pyrethrins, and piperonyls are insecticides primarily marketed for residential use. Generally, they are less toxic, but health effects have been reported.[17] The CDC conducts a biomonitoring program for many common pesticides. In 2005, 29 of 45 pesticides were identified in samples from random subjects; the most prevalent were organochlorine and organophosphate insecticides.[99]

Sources of Exposure

Important sources of exposure include direct inhalation after application and ingestion of contaminated food. Organochlorine pesticides have a long half-life and bioaccumulate in our food supply.[17] Frequent sources of the organochlorine DDT include meat, dairy products, and fish. DDT and its metabolites have been found in breast milk. The organochlorines aldrin and dieldrin are found in fish, shellfish, root crops, dairy products, and meats. Plants absorb these chemicals directly from the soil; even organic vegetables may contain high levels if grown in contaminated areas.[99] The EPA sets acceptable standards for pesticide residue, which are regulated by the FDA. In 2014, pesticide residues were found in 29% of 1458 domestic and 47% of 4814 imported samples, with violations of EPA standards (residue for which there is no tolerance or residues above the tolerance level) in 1.4% of domestic and 12% of imported samples. The violation rate was greatest for imported grains. Boscalid (fungicide used on food crops), chloropyrifos (organophosphate insecticide), and imidacloprid (neonicotinoid insecticide used in agriculture) were the most frequently reported pesticide residues.[116]

Pregnant women may be exposed in the home environment via indoor use of disinfectants, insecticides, and rodenticides, and outdoor application of herbicides, insecticides, and fungicides. Certain products such as sprays and foggers may lead to prolonged exposure in the home. Another potential source of exposure in the home is drinking water. Herbicides are a frequent contaminant of drinking water in agricultural areas; in urban areas both insecticides and herbicides are known contaminants.[99] Occupational or paraoccupational exposure to pesticides and living in close proximity to pesticide-treated agricultural areas represent other important sources for pregnant women or women of childbearing age.[38,124]

Biomarkers have been identified to evaluate fetal pesticide exposure. In 2004, the Environmental Working Group found 21/28 organochlorine pesticides in cord blood of 10 babies. Amniotic fluid from amniocentesis samples has been used to characterize early fetal exposure; meconium samples have been utilized to determine exposure during the second and third trimester. While organophosphates have been identified in amniotic fluid, both organophosphates and pyrethroid pesticides have been found in meconium samples.[27]

Toxic Effects

While most pesticides are neurotoxins, the degree of toxicity varies between classes. Pesticides also can function as endocrine disruptors, immunotoxicants, and carcinogens in animals and humans.[2,38,124] Epidemiologic data suggest a link between parental pesticide exposure and infertility, spontaneous abortion, fetal demise, preterm birth, intrauterine growth restriction, and congenital anomalies.[99,124] One study demonstrated a relationship between exposure to chloropyrifos and DDE (a metabolite of DDT) and both low birth weight and microcephaly.[27] Additionally, biomarkers for organophosphates found in maternal urine, blood, or umbilical cord samples are associated with low birth weight and preterm birth.[124] A relationship between exposure to organochlorines such as DDT and both cryptorchidism and hypospadias has been reported, suggesting endocrine disruption as a mechanism of toxicity.[99]

The developing fetal nervous system appears to be especially vulnerable to the neurotoxic effects of pesticides. Four case reports have linked exposure to chloropyrifos to multiple congenital anomalies and severe cognitive delay.[110] Evidence supports a relationship between prenatal exposure to organochlorine and organophosphate pesticides and adverse neurodevelopmental and behavioral outcomes that persist into childhood. Findings include increased incidence of cognitive delays and intellectual disability that persist into childhood, and increased incidence of both ADHD and autism spectrum disorders.[9,27,38,76,99]

There is increasing epidemiologic evidence correlating parental pesticide exposure and childhood cancers. Multiple studies report correlation between maternal pesticide use (both occupational and household) before and during pregnancy and childhood acute lymphoblastic leukemia. There is stronger evidence linking maternal exposure to pesticides and leukemia than paternal exposure. Similarly, more than 25 studies have described a relationship between prenatal pesticide exposure and brain tumors. The most consistent risk factors identified are maternal and paternal prenatal exposure to pesticides at home or at work. Two case-control studies specifically report an association between parental pesticide exposure and childhood astrocytoma.[99,108,120]

Prevention Strategies

Dietary changes may decrease contact, and exposure to pesticide residues may be limited by ingestion of organic foods. One study showed that urinary excretion of organophosphate metabolites significantly decreased when children were placed on an organic diet for 5 days.[4,99]

Washing produce may remove pesticide residue, and avoiding animal fat and certain fish can limit exposure to lipid-soluble pesticides such as organochlorines. The EPA recommends integrated pest management (IPM) as a strategy to avoid environmental exposure to pesticides. Maternal

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occupational and household exposures should be avoided during pregnancy.[4]

Bisphenol A, S, and F

Bisphenol A (BPA) is a chemical plasticizer that is added to plastic resins to enhance rigidity. It has been used since the 1960s in the production of polycarbonate plastic bottles and in epoxy resins utilized as protective coating inside metal food and beverage cans. It is also used in water supply pipes, medical devices, dental sealants and composites, and many other products that are part of our daily lives.[4,10,11,36,101] BPA is in widespread use worldwide and is pervasive in our environment, with more than six billion pounds manufactured annually.[101,118]

As concerns for the health effects of BPA have been identified and have become widely recognized by the public, alternative products that are "BPA-free" are sought by both consumers and industry. Two BPA analogs, Bisphenol S (BPS) and Bisphenol F (BPF), are utilized as alternatives to BPA with similar physical properties. BPS is used as a coating for thermal paper that allows for inkless printing. Rolled thermal paper with BPS ("BPA-free" paper) is found in cash register and ATM terminal receipts and paper products such as boarding passes and currency. BPF is used in epoxy resins and coating of industrial and consumer materials to increase thickness and durability. Use of BPS and BPF is currently not regulated.[100]

Sources of Exposure

Human exposure to BPA is significant. BPA leaches from plastic bottles and the epoxy resin coating metallic cans and other products; contamination of the food supply and routine ingestion by humans is presumed. Leaching also occurs from dental sealants. Heat and both acidic and basic conditions lead to hydrolysis of BPA polymers and leaching into the food supply.[10,101,117,118] Transdermal absorption and inhalation have been shown to be less common routes of exposure. Studies demonstrate serum concentrations of unconjugated (biologically active) BPA between 0.2 and 20 ng/mL.[117,118] BPA was detected in the urine of 90% of over 2,489 participants ≥6 years of age in the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control (CDC) between 2011 and 2012.[18] BPA has been measured in urine and blood during pregnancy, amniotic fluid, ovarian follicular fluid, placental tissue, fetal blood, and umbilical cord blood.[101,117,118] In one study, there was a fivefold difference in mean amniotic fluid BPA concentration at 15-18 weeks' gestation (8.3 ng/mL), as compared to mean concentration in maternal blood in early pregnancy (1.4 ng/mL). Immature fetal liver function and phase II enzyme activity may explain high levels of BPA documented in amniotic fluid.[117]

Like BPA, BPS and BPF can leach from plastic bottles, epoxy resins, and thermal paper. Both of these BPA analogs have been identified in paper products (commonly store receipts) and personal care products (body wash, hair products, makeup, and toothpaste). Like BPA, BPS and BPF are found in indoor dust particles and can also be inhaled.[100]

Toxic Effects

BPA is a known estrogenic endocrine disruptor. BPA binds to estrogen receptors; recent *in vitro* studies of molecular mechanisms demonstrate a similar potency to estradiol. BPA is primarily unbound to plasma proteins; in this active form BPA may exert estrogenic effects during critical stages of fetal development. In an animal model, hepatic glucuronidation of BPA to its inactive form in pregnant rats was reduced by 40% during pregnancy, suggesting increased susceptibility to endocrine disruption for both the mother and fetus.[49] BPA may significantly impact fetal neurodevelopment, as estrogen plays an important role in the developing brain. Specifically, estrogen is important for sexual differentiation in the brain.[101]

More than 150 studies have documented adverse effects in vivo, many at doses below acceptable reference levels for human daily intake (50 μg/kg). Animals exposed to BPA during gestation develop a wide range of endocrine pathology. In the rodent, low-dose perinatal effects of BPA include urogenital anomalies, accelerated pubertal development, and predisposition to prostate cancer in the male and breast cancer in the female.[101,117,118] Additionally, animal studies have shown that prenatal exposure impacts neurodevelopment and increases behaviors such as aggression and anxiety.[11] In the mouse model, perinatal BPA exposure modifies estrogen sensitivity later in life.[101,117]

The body of epidemiologic literature documenting BPA exposure in humans is increasing. In women, BPA exposure has been associated with recurrent miscarriages, preterm delivery, polycystic ovarian syndrome, breast cancer, and chromosomal anomalies in offspring.[5,101,117] In men, elevated urinary BPA levels have been correlated with low sperm count, poor motility and quality, and increased sperm DNA breakage.[36,101] Decreased anogenital distance has been documented in male infants whose fathers were occupationally exposed to BPA.[36]

Prenatal and childhood exposure is associated with hypospadias, precocious puberty, neurodevelopmental and behavioral impairment, increased adipokine levels, and obesity. Adipokines are a diverse group of secretory proteins that modulate lipid and glucose metabolism.[5,10,36] In one study of 244 mothers and their 3-year-old children, a 10-fold increase in urinary BPA levels during pregnancy was associated with higher scores for anxiety, depression, hyperactivity, and poor emotional regulation in offspring.[11]

BPS and BPF are also estrogenic endocrine disruptors. While the literature documenting the estrogenic effects of these BPA analogs in vivo is limited, in vitro studies indicate similar toxicity and potency to BPA.[36,100] In one study, BPF and BPS administration decreased basal secretion of testosterone in cultured human fetal testis.[36] Another study in which BPF was administered to pregnant rats via a feeding

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TABLE 14.2 Phthalates and Their Characteristics

Phthalate	Source	Fetal Effects (Animal Models)
Di(2-ethylhexyl) phthalate (DEHP)	Medical tubing and intravenous fluid bags Food packaging Plastic toys Wall coverings, floor tiles, shower curtains Rainwear, shoes Furniture and auto upholstery	Skeletal malformations, cleft palate, cryptorchidism, hypospadias, testosterone synthesis, sexual differentiation, anogenital distance, neural tube defects, growth restriction
Dibutyl phthalate (DBP)	Nail polish, makeup, perfume Coatings on pharmaceuticals/herbal products	Skeletal malformations, cleft palate, cryptorchidism, hypospadias, testosterone synthesis, delayed puberty, neural tube defects, growth restriction
Dimethyl phthalate (DMP)	Insecticides Adhesives Hair styling products, shampoo, aftershave	
Butyl benzyl phthalate (BBP)	Vinyl flooring and tile, carpet, artificial leather Adhesives and sealants Food packaging Furniture upholstery	Skeletal malformations, cleft palate, cryptorchidism, hypospadias, delayed puberty
Diethyl phthalate (DEP)	Cosmetics, nail polish, deodorant, perfume, lotion Insecticide Pharmaceuticals, herbal products	Skeletal anomalies, decreased testosterone

tube, the active form was found in the placenta, amniotic fluid, and fetal tissue.[100]

Prevention Strategies

To avoid exposure to BPA and its structural analogs, pregnant women can refrain from using plastic materials that contain BPA. Reducing contact with thermal paper receipts can also limit exposure to these chemicals. Resin identification codes are identified by symbols appearing on plastic products that identify the plastic resin out of which the product is made. Many products that contain BPA contain the resin identification code 7. As heat may lead to release of BPA, plastic materials containing BPA should not be boiled, washed in the dishwasher, or placed in the microwave.[4,5]

Phthalates

Phthalates are a class of chemical plasticizers that provide flexibility to plastics such as polyvinyl chloride (PVC). Phthalates are also used as solvents, lubricants, and insect repellants. They are utilized to manufacture toys, vinyl products, plastic bags, plastic food packaging products, and detergents. They are found in medical gloves, blood and intravenous fluid and bags, tubing, the coating of pharmaceuticals, and in cosmetics. Eighteen billion pounds of phthalates are produced annually worldwide. Like BPA, phthalates are ubiquitous in our environment and have become significant environmental pollutants. Certain phthalates are considered toxic chemicals, and their release into the environment is monitored by the EPA's Toxic Release Inventory (TRI) database available at www.epa.gov/tri. Table 14.2 lists some of the more common phthalates used as plasticizers, and products that contain them.[5,29,111]

Sources of Exposure

Like BPA, exposure to phthalates is substantial. Diet is the main source of exposure; phthalates leach from plastic containers and plastic wrap, particularly after heating, and can be ingested. Transdermal absorption from cosmetics, fragrances, lotions, and insect repellents has been reported. In particular, usage of fragrance, nail polish, and eye shadow has been correlated with concentration of phthalate metabolites in the urine of pregnant women. Dibutyl phthalate (DBP) is commonly used in deodorant, cosmetics, and nail polish. DBP levels are significantly higher in women of reproductive age than in men.[5,29] Inhalation is another potential route of exposure. Phthalates have been found in ambient air, household dust, and fumes from new paint or vinyl flooring.[29,111] There is potential for direct intravascular exposure via IV tubing and blood product or IV bags.[111] The National Health and Nutrition Examination Survey (NHANES) conducted by the CDC in 2013–2014 measured 13 phthalate metabolites in the urine of 2685 participants. Of the 13 phthalate metabolites measured, 10 were present in greater than 90% of participant urine samples.[19] Several studies have documented phthalate metabolites in amniotic fluid and cord blood, suggesting that phthalates cross the placenta and may impact the developing fetus.[126] Silva et al. found three phthalate metabolites in samples from amniocentesis during the second trimester.[103] Wittassek et al. measured phthalate metabolites in amniotic

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fluid sampled at the time of cesarean section; phthalate metabolites were found in 11/11 samples.[126]

Toxic Effects

Phthalates are anti-androgenic endocrine disruptors. Phthalate exposure during pregnancy has been associated with pregnancy loss, preterm delivery, and adverse neurodevelopmental outcomes.[5] It appears that the most sensitive tissue to phthalates is the male reproductive tract.[29,111] In rats, phthalates and their metabolites cross the placenta. Prenatal exposure to di(2-ethylhexyl) phthalate (DEHP), butyl benzyl phthalate (BBP), and dibutyl phthalate (DBP) results in increased incidence of cleft palate, skeletal malformations, and fetal death in offspring of exposed pregnant rats. Male offspring developed hypospadias and cryptorchidism, low sperm production, and testicular Leydig adenomas as adults.[111] Findings seen in animal studies are similar to testicular dysgenesis syndrome described in humans.[111,126] Data documenting similar anti-androgenic effects of phthalates on the human fetus are increasing. Studies have shown a relationship between phthalate concentration in maternal urine and fetal amniotic fluid and decreased anogenital distance (AGD) in offspring, a marker that has been utilized in vivo to evaluate anti-androgenic endocrine disruptors and male reproductive development.[106] Swan et al. demonstrated that decreased AGD is significantly correlated with small scrotum, reduced penile length, and testicular maldescent. The effect on AGD was noted at levels well below the US EPA reference dose.[106] Similar to animal models, studies have correlated maternal phthalate exposure and hypospadias in male newborns.[29]

Prevention Strategies

Food and products made from PVC plastics represent the most common sources of exposure. PVC plastics are labeled with the resin identification code 3.[5] Processed foods and those individually wrapped in plastic tend to contain the highest concentrations. The FDA recommends careful use of plastic containers, avoidance of reheating plastic containers in the microwave, and only using plastics in the microwave labeled for microwave oven use. One-time-use containers (such as carry out containers) should not be used in microwave ovens. Plastic wrap should not touch foods during microwaving. Avoidance of long-term storage of foods in plastic, heating plastic containers, and consumption of processed foods may decrease exposure.[4] Until more information is available, limiting exposure to phthalates during pregnancy is a reasonable approach.

Organic Solvents

Organic solvents are a large, diverse group of volatile carbon-based chemicals used to dissolve lipids and other high molecular weight compounds in solution. Organic solvents are found in volatile anesthetics, paint and paint thinners, cleaning supplies, dry cleaning solutions, dyes, office supplies such as copier fluid and printer ink, cosmetics, nail polish remover, glues, adhesives, spot removers, and detergents.[32] They can be classified into three families of chemicals: oxygenated solvents, petroleum solvents, and chlorinated solvents.[89] Glycol ethers are oxygenated solvents. Ethylene glycol is found in sunscreen and cosmetics and propylene glycol is a component of antifreeze. Prenatal exposure to glycol ethers is associated with male infertility.[22] Benzene, toluene, and xylene are petroleum solvents. Benzene is a known human carcinogen, and prenatal exposure is linked to neural tube defects in offspring. Chlorinated solvents include perchloroethylene used in the dry cleaning industry, a carcinogen in animals. Many are neurotoxins, as demonstrated by reports of neurotoxicity in adults after acute poisoning and chronic occupational exposure.[67,89]

Sources of Exposure

Organic solvents are ubiquitous in our environment, and concentrations are much greater indoors than outdoors. Many of these chemicals persist in ambient air long after their use. Organic solvents are commonly found in household products such as cleaning supplies, and occupational exposure is significant.[89] As many women continue to work throughout pregnancy, exposure to organic solvents poses a risk to the fetus. Since organic solvents are volatile, inhalation represents the most common route of exposure. Recreational inhalation of toluene found in spray paint and glue has resulted in multiple congenital anomalies and neurodevelopmental delay. Oral ingestion and transdermal exposure also occurs.[43]

Toxic Effects

Organic solvents cross the placenta and, as with other lipophilic chemicals, concentrate in organs with higher lipid content such as the brain.[67] In animals, organic solvents are teratogenic. Spontaneous abortion and congenital anomalies are seen in animals prenatally exposed. Exposure of both chick embryos and fetal rats to chlorinated solvents such as trichloroethylene leads to increased incidence of congenital heart disease.[22,43] Epidemiologic studies in humans link maternal occupational exposure to organic solvents with risk of spontaneous abortion and congenital anomalies. Congenital malformations include cleft lip and palate, neural tube defects, and congenital heart disease (CHD).[22,32,43] The National Birth Defects Prevention Study 1997–2002 was a case control study that enrolled 2951 control mothers and 2047 mothers of infants with CHD. The study demonstrated an association between occupational organic solvent exposure during the month prior to conception through the first trimester and CHD; specifically left ventricular and right ventricular outflow tract obstruction, conotruncal defects, and septal defects.[43] Toluene (methyl benzene) is an aromatic hydrocarbon utilized in industry in paint, glue, and other organic compounds. Toluene embryopathy has been described after maternal abuse of these organic solvents as inhalants, termed "solvent sniffing." Findings include intrauterine growth restriction, microcephaly, facial

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features similar to fetal alcohol syndrome, and neurodevelopmental impairment.[75] Several studies have investigated maternal prenatal occupational solvent exposure and neurodevelopmental outcome linked exposure to delays in motor skills verbal skills; visual-motor and memory function; and behaviors such as aggression, hyperactivity, and impulsivity.[67,89] The visual system appears to be sensitive to developmental exposure. Till evaluated visual function of 21 infants born to mothers with occupational exposure to organic solvents and found both reduced contrast sensitivity and deficits in color vision in exposed infants, as compared to 27 age-matched controls.[107]

Prevention Strategies

Organic solvents should be used in a well-ventilated area, and partially used containers should be discarded after use. Pregnant women should avoid paint fumes to reduce exposure in both home and occupational settings. Cleaning supplies should be used in well-ventilated areas while wearing protective gloves. There are specific recommendations for nail salon workers and hairdressers that include limiting work hours, wearing gloves and masks when appropriate, ensuring optimal ventilation, covering containers and garbage, and separating areas to handle food and to eat.[4]

Conclusions

In 2014, the leading causes of infant death were congenital malformations and chromosomal abnormalities, short gestation and low birth weight, newborns affected by maternal complications of pregnancy, and sudden infant death syndrome.[71] All have been associated with environmental exposures discussed in this chapter. This chapter has described the many different sources of exposure and the timing of exposure to occupational and environmental chemicals. The complexity of maternal-fetal pharmacokinetics has been outlined, and many of the various types of outcomes have been discussed. The science of environmental medicine continues to evolve. More recently, literature has begun to focus on the impact of co-exposure to environmental toxicants; a growing body of evidence supports the deleterious effect of simultaneous exposure at concentrations lower than known to cause toxicity individually.[57] Genome-wide association studies (GWAS) and epigenome-wide association studies (EWAS) are novel methodologies being utilized to better understand the molecular basis for exposure risk.[55]

When caring for a patient with a diagnosis that may be secondary to an environmental exposure, it can be difficult to demonstrate a causal relationship. Hotlines for teratology information are part of the Organization of Teratology Information Services and are listed online at www.otispregnancy.org. Case Studies in Environmental Health can be obtained from the ATSDR at www.atsdr.cdc.gov/atsdrhome.html.

Key Points

- The fetus is highly vulnerable to environmental toxicant exposures that can alter phenotypic expression, both following birth and in future generations.
- Fetal exposure becomes a growing concern as our population expands and the number of women participating in the workforce during pregnancy increases.
- *Epigenetics* is the study of phenotypic changes occurring without modification of DNA base pair sequence. Epimutations are stable, heritable, and a target for environmental toxicants. Mechanisms include histone modifications, altered DNA methylation, and expression of microRNA.
- *Epigenetic transgenerational inheritance* refers to epimutations in the germline (egg or sperm) that are passed to future generations and leads to variation in phenotypic expression.
- Exposure to environmental toxicants that impacts the developing fetus may be concurrent or nonconcurrent with pregnancy. Certain toxicants, such as lead and polychlorinated biphenyls, are stored in maternal compartments and mobilized during pregnancy. Air pollution and diet (food and water) represent common sources of exposure during pregnancy.
- Toxicants reach the fetus via placenta-dependent and placenta-independent pathways. Certain chemical properties promote transport across the placenta, such as low molecular weight, lipid solubility, protein binding, and ability to utilize nutrient transport mechanisms. Examples of placenta-independent environmental exposures that are potentially hazardous to the fetus include ionizing radiation, heat, and noise.
- Maternal and fetal absorption, distribution, and metabolism of toxicants are influenced by the maternal physiologic environment during pregnancy, ontogeny of fetal phase I and phase II metabolism in the liver, and genetic polymorphisms in drug-metabolizing enzymes.
- Active cigarette smoking during pregnancy is associated with reduced male and female fertility, placental dysfunction, spontaneous abortion, intrauterine growth restriction, preterm delivery, and congenital anomalies. Smoking during pregnancy is a known risk factor for SIDS.
- Fetal alcohol spectrum disorder (FASD) encompasses the entire range of sequelae of prenatal exposure to alcohol; fetal alcohol syndrome (FAS) describes the extreme end of the spectrum with characteristic facial features and neurodevelopmental impairment.

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- While most pesticides are neurotoxins, some also exhibit toxic effects as endocrine disruptors, immunotoxicants, and carcinogens. Evidence supports a relationship between prenatal exposure to pesticides and both cognitive impairment and cancer in offspring.
- Bisphenol A (BPA) and phthalates are plasticizers that are ubiquitous in our environment. Both BPA and phthalates leach from plastic containers into our food supply. They are known endocrine disrupting chemicals (EDCs); BPA is an estrogenic EDC, while phthalates are anti-androgenic.
- Organic solvents are a large and diverse group of volatile lipid-soluble chemicals commonly found in household products such as cleaning supplies. These chemicals, many of which are teratogens, readily cross the placenta and concentrate in organs with high lipid content such as the brain.

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15

Intrauterine Growth Restriction

ALISON CHU AND SHERIN U. DEVASKAR

Summary

Intrauterine growth restriction (IUGR) broadly encompasses pregnancies complicated by poor fetal growth, where the fetus's growth is less than its genetic potential. IUGR is an important condition to recognize, as it is a common complication of pregnancy that has both short- and long-term sequelae for offspring. This is a particularly difficult diagnosis to manage in both the prenatal and postnatal periods for a number of reasons. Firstly, definitions and terminology lack consensus among practitioners, researchers, as well as organizations that inform clinical practice. Secondly, the etiologies are multiple, and the pathophysiology remains incompletely understood. Given these challenges, diagnostic criteria and prenatal practice guidelines remain uncertain, no definitive prevention strategy or treatment has been identified, and postnatal management and surveillance guidelines are scant, variable, and ill defined. Despite the major global burden of IUGR, it remains a condition that is difficult to diagnose, prevent, or treat, and further research is essential in this field.

Definitions and Terminology

In clinical practice and in research studies, IUGR can be defined in multiple ways and there remains a lack of consensus regarding terminology. Commonly, "normal" fetal growth results in a neonate whose birth weight falls between the 10th and 90th percentile for gestational age (deemed "appropriate for gestational age" or AGA). Therefore, a birth weight less than the 10th percentile is categorized as "small for gestational age" (SGA) and correlates with a birth weight that is two standard deviations or more below population norms. In contrast, IUGR encompasses all fetuses with evidence of malnutrition or in utero growth restriction, which can still include an infant born with a birth weight above the 10th percentile.[4] Therefore, close communication between the obstetric and newborn medical teams is imperative to accurately identify which neonates exhibited true in utero growth deceleration and not base the label of "IUGR" on birth weight alone. Clinically, this is an essential distinction to make as infants with IUGR are at risk for both short-term and long-term complications, whereas constitutionally small infants that fall into the SGA category but had consistent growth patterns in utero are at much lower risk for long-term adverse outcomes.

The Health Burden of IUGR

Given the difficulties and inconsistencies in defining IUGR, the true prevalence of IUGR is not known. However, it has been estimated that up to 10 percent of live-born infants are characterized as IUGR, and that this percentage is likely higher among stillborn neonates.[70] Globally, IUGR is the second leading cause of perinatal morbidity and mortality after prematurity.[71] The risk of fetal death increases with severity of growth restriction, such that a fetus with a weight less than the 10th percentile for gestational age has a 1.5% risk of fetal death (twice the risk of stillbirth in normally grown fetuses), whereas risk for a fetus with a weight less than the 5th percentile increases to 2.5%.[30]

Not only does fetal growth restriction increase overall mortality by increasing risk of intrauterine demise, stillbirth, and neonatal death,[4] it also carries significant comorbidities for the surviving neonate. After birth, IUGR neonates are at increased risk for admission to the intensive care unit, requiring monitoring and treatment for complications of IUGR, which include but are not limited to hypoglycemia, hyperbilirubinemia, hypothermia, and respiratory distress syndrome. These issues will be discussed more in the management section of this chapter. In the long term, infants born IUGR are at risk for neurodevelopmental delay and cardiometabolic diseases in adulthood, including obesity, type 2 diabetes mellitus, and cardiovascular disease.[7]

Classification of IUGR

Historically, IUGR has been classified into two types: asymmetric versus symmetric (Table 15.1). In asymmetric IUGR, it is believed that decreased fetal growth occurs in response to suboptimal intrauterine provision of nutrients and oxygen. The fetus adapts to this environment by conserving energy and focusing nutrient delivery to vital organs such as the brain and the heart. Therefore, asymmetric IUGR typically manifests as a fetus with a disproportionately high

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Abstract

Intrauterine growth restriction (IUGR) broadly encompasses pregnancies complicated by poor fetal growth, where the fetus's growth is less than its genetic potential. IUGR is an important condition to recognize, as it is a common complication of pregnancy that has both short- and long-term sequelae for offspring. This is a particularly difficult diagnosis to manage in both the prenatal and postnatal periods for a number of reasons. Firstly, definitions and terminology lack consensus among practitioners and researchers, as well as organizations that inform clinical practice. Secondly, the etiologies are multiple, and the pathophysiology remains incompletely understood. Given these challenges, diagnostic criteria and prenatal practice guidelines remain uncertain, no definitive prevention strategy or treatment has been identified, and postnatal management and surveillance guidelines are likewise variable and ill defined. Despite the major global burden of IUGR, it remains a condition that is difficult to diagnose, prevent, or treat, and further research is essential in this field.

Keywords

intrauterine growth restriction
placental insufficiency
small for gestational age
fetal growth

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TABLE 15.1 Characteristics of Symmetric Versus Asymmetric IUGR

Characteristics	Symmetric IUGR	Asymmetric IUGR
Typical period of insult and presentation	Earlier gestation (often second trimester)	Later gestation (often detected in the third trimester)
Percentage of all IUGR cases	20%-30%	70%-80%
Etiology	Genetic disorders Congenital infections	Placental insufficiency
Antenatal scan	Proportionately decreased head circumference (HC), abdominal circumference (AC), biparietal diameter, and femur length	Only abdominal circumference decreased
Cell number	Decreased	Normal
Cell size	Normal	Decreased
Postnatal anthropometry	All parameters (HC, length, and weight) reduced	Reduced weight, HC normal, length low to normal
Features of malnutrition	Less pronounced	More pronounced

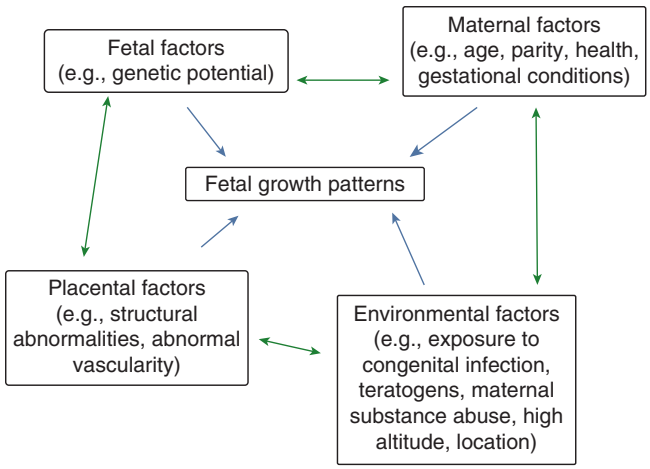
IUGR, Intrauterine growth restriction.
Adapted from Sharma D, Shastri S, Sharma P. Intrauterine growth restricion: antenatal and postnatal aspects. *Clin Med Insights Pediatr.* 2016;10:67-83.

head circumference percentile compared to percentile for weight. Height can be normal to low normal. Prenatally, fetal growth deceleration in asymmetric IUGR tends to manifest in the third trimester (notably, the period of most rapid fetal growth), when prenatal measurements on growth scans demonstrate a low abdominal circumference, whereas head circumference, biparietal diameter, and femur length often remain within normal ranges. This pattern of growth has also been coined as "head-sparing" IUGR. Asymmetric IUGR is more common than symmetric, accounting for 70%-80% of all IUGR fetuses,[54] and more often than not can be due to maternal, environmental, and/or placental factors that result in placental insufficiency.

Symmetric IUGR, on the other hand, results in a fetus or neonate with proportionately low anthropometric measurements of head circumference, weight, and length. This pattern is less common than asymmetric IUGR, representing 20%-30% of all IUGR cases, and the poor growth rate is often detectable earlier in pregnancy. Often, asymmetric IUGR is seen in association with fetal etiologies such as genetic or chromosomal disorders, and prognosis is generally worse in these cases.[21] It can also be seen with early pregnancy infections resulting in congenital syndromes, such as congenital rubella or congenital cytomegalovirus (i.e., "TORCH" infections). At times, severe maternal malnutrition extending from the first trimester throughout pregnancy can result in symmetrical IUGR, which is also seen with maternal malarial infection.[58,68]

Etiology of IUGR

There are four broad etiologic categories for IUGR: maternal, fetal, placental, and environmental factors. IUGR can also result from a combination of these factors, as inherent genetic potential and the "environment" both determine fetal growth (Fig. 15.1). Although the underlying pathophysiologic mechanisms may differ among and within these categories, the majority of IUGR cases share the same common pathway that results in suboptimal nutrient and oxygen provision to the fetus, oftentimes secondary to poor placental perfusion (Table 15.2). The exception to this common pathway is oftentimes due to "fetal" etiologies, which largely are due to genetic or structural disorders and thought to result from a decreased number and growth of fetal cells.



• **Fig. 15.1** A schematic illustrating the complex interactions between the fetus, mother, environment, and placenta that affect fetal growth patterns.

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TABLE 15.2 Etiologies of Asymmetric and Symmetric IUGR

	Asymmetric IUGR	Symmetric IUGR
Fetal	• Genetics	• Chromosomal disorders (e.g., trisomy 13, trisomy 18, trisomy 21) • Structural disorders (specific forms of congenital heart disease, gastroschisis)
Maternal	• Age • Parity • Ethnicity/race • Height • Poor weight gain • Short pregnancy intervals • Medical conditions: pregestational diabetes mellitus, renal insufficiency, autoimmune disease, cyanotic cardiac disease • Diseases related to pregnancy (gestational hypertension, preeclampsia, gestational diabetes) • Thrombophilia (antiphospholipid antibody syndrome)	• Advanced maternal diseases (e.g., severe hypertension, hemoglobinopathies)
Placental	• Multiple gestation • Placental insufficiency • Placental disorders and umbilical cord abnormalities	
Environmental	• Teratogen exposure (e.g., cyclophosphamide, valproic acid, antithrombotic drugs) • Substance use (alcohol, tobacco, cocaine, narcotics) • Altitude • Assisted reproductive technology	• Infectious diseases during early pregnancy (e.g., malaria, cytomegalovirus, rubella, toxoplasmosis, syphilis)

IUGR, intrauterine growth restriction.

Fetal Etiologies

IUGR can be associated with chromosomal abnormalities of the fetus; classically, trisomies 13, 18, and 21 are among the more common chromosomal disorders seen in IUGR, accounting for up to 20% of IUGR cases. Fifty percent of fetuses with trisomy 13 or 18 have evidence of fetal growth restriction.[27] Other chromosomal abnormalities associated with IUGR include placental mosaicism.[74]

Fetuses with certain congenital birth defects (even without chromosomal or genetic underlying abnormalities) may be at increased risk of IUGR,[39] such as those with gastroschisis.

Maternal Etiologies

The overall health and "reproductive potential" of the mother are obviously critical in determining fetal health and outcome. Demographic factors that may affect this potential include maternal age, parity, or last pregnancy interval. In addition to baseline demographics, maternal health conditions prior to pregnancy affect risk for IUGR. In the past, certain health conditions may have precluded the woman's ability to conceive or to carry a viable pregnancy to term. However, with medical advancements, many of these conditions can be managed to the extent that pregnancy can be maintained but may still affect the fetus's growth potential. For example, hypertension and diabetes, either pre-existing or gestational, put the fetus at risk for IUGR. Other maternal diseases that may affect the mother's overall ability to provide optimal nutrition, oxygen, or blood flow to the infant include pulmonary and renal disease, autoimmune disease, thrombophilic disorders (specifically antiphospholipid syndrome but not factor V Leiden or prothrombin mutations),[19,56] and/or congenital heart disease.

In addition, the mother's own diet and access to nutrition affects the fetus's risk for IUGR. Historically, there are numerous large epidemiologic studies that link low birth weight with maternal malnutrition during famine periods.[6,60] In these cohorts, low birth weight was specifically linked to poor protein intake in the first two trimesters and with severe caloric restriction (<600-900 kcal daily). However, it is important to note that in cases of suspected fetal growth restriction in the absence of true maternal malnutrition, additional nutritional supplementation does not increase fetal weight or improve outcomes.[57] In the current era, maternal malnutrition (largely in developing nations) still can lead to IUGR, and conversely, especially in developed nations, maternal obesity can also lead to IUGR. It is also of note that an adolescent mother's own metabolic demands compete for the nutrient supply to the growing fetus, resulting in IUGR. In Western societies, disorders

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related to image distortion, such as bulimia, anorexia, or hyperemesis gravidarum, at times can cause IUGR.[68]

Environmental Etiologies

Exposure of the fetus to environmental stressors at various points during gestation may result in IUGR as well.

In early pregnancy, exposure to infectious agents such as *plasmodium* (resulting in malaria), rubella, cytomegalovirus, *Toxoplasma gondii*, and syphilis can result in congenital syndromes with multiple birth abnormalities, including IUGR. Of these, malaria represents the largest portion of global burden of IUGR secondary to infectious etiologies.[24] These infectious etiologies represent approximately 5%-10% of all IUGR cases.

Exposure to teratogens, maternal medications, or maternal substance abuse can also lead to IUGR. The effect of teratogen exposure on fetal growth depends on a number of factors, such as the inherent teratogenicity of the drug, the timing/duration/dosage of exposure during gestation, as well as the mother's particular ability (or inability) to metabolize the drug (whether from genetic disposition or health conditions such as hepatic or renal disease that affect drug metabolism). Teratogens classically associated with IUGR include antiepileptic medications (e.g., valproic acid), antithrombotic agents (e.g., warfarin), and chemotherapeutic/antineoplastic agents (e.g., cyclophosphamide). Heavy substance abuse can also result in IUGR, with alcohol and tobacco use being the most common etiologic agents.[46] It should be noted that tobacco use is associated with a 3.5-fold increased risk of SGA, and that the risk of SGA with alcohol use is increased even with the intake of 1-2 drinks daily. Cocaine, heroin, and narcotic use during pregnancy are also associated with IUGR.[29]

It can also be argued that where the neonate is born affects their risk for IUGR. For example, it is well documented that fetuses gestating at higher altitudes are less likely to reach their growth potential, compared to their counterparts at sea level.[73] Another example of the birth location effect is when comparing developed versus developing nations. The resources available to the low-income populations in developing nations may predispose mothers to poor food availability, air pollution, infectious agents, and poor/limited health care. Poorly resourced nations, such as in the Indian subcontinent and in South Africa, have much higher rates (estimated at six times higher) of IUGR compared to developed nations.[36]

Placental Etiologies

Placental insufficiency resulting from abnormal placentation is the most common pathology associated with IUGR. However, placental insufficiency may have myriad causes, multifactorial etiology, and results in a broad spectrum of severity. Pregnancy disorders such as preeclampsia and preterm birth, as well as IUGR, generally exhibit some degree of placental insufficiency or malperfusion. These placentas are often small in size and are histopathologically characterized by hypovascular villi, fibrin deposition, and/or trophoblast degeneration, which taken together lead to poor nutrient and oxygen provision to the fetus on a physiologic level.[43]

Specific placental disorders such as chronic placental abruption, infarction, circumvallate shape, chorioangioma, and umbilical cord abnormalities such as velamentous or marginal cord insertion have been associated with IUGR.[47] Placenta accreta and previa have not been consistently associated with IUGR, nor is the presence of a single umbilical artery consistently associated with IUGR.

Twin or multiple gestation also is an important consideration in IUGR, as multiple gestation is on the rise secondary to rapidly advancing artificial reproductive technology.[22] It is debated whether or not IUGR in multiple gestation should be considered physiologic or not. In general, growth deceleration is evident and expected to some degree in the third trimester in multiple gestation, as the physical and functional capacity of both the uterus and/or placenta may be exceeded in this period of rapid fetal growth. However, it should be noted that twin gestation disproportionately accounts for adverse neonatal outcomes (10%-15%), while only accounting for 2%-3% of live births in the United States. Multiple gestation is associated with both SGA and prematurity, with the risk of SGA as high as 25% in twin pregnancies and up to 60% for triplet and quadruplet pregnancies.[52] Moreover, monochorionic twin pregnancies are at higher risk of SGA and IUGR because of unequal placental sharing and increased risk of twin-to-twin transfusion syndrome (with the donor born IUGR).

Pathophysiology

The pathophysiology of intrauterine growth restriction remains poorly understood. In the case of chromosomal abnormalities, it is surmised that poor fetal growth is due to decreased numbers of fetal cells and poor cellular growth. Beyond this, little data is available on the pathophysiology of growth restriction in fetal chromosomal disorders.

It should be noted that fetal growth also depends on a number of hormones, including insulin, thyroid hormones, adrenal hormones, and pituitary hormones. Insulin has a number of roles in growth; it has been described to: (1) control cell number via direct mitogenic effects on cellular development, (2) regulate glucose uptake and consumption in somatic tissues, and (3) regulate other metabolic pathways, such as protein breakdown. Hormones such as insulin-like growth factor 1 (IGF-1), insulin-like growth factor-II (IGF-2), insulin-like growth factor binding protein-2 and -3 (IGFBP-2 and -3) have all been implicated in the pathophysiology of IUGR in experimental models. A number of other genes involved in these various hormonal and metabolic pathways have been implicated in IUGR in human genomic studies as well.[58]

The knowledge of pathophysiology underlying placental insufficiency, which is present in the majority of IUGR

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neonates, especially those with idiopathic IUGR (i.e., not due to chromosomal abnormalities, teratogen exposure, or congenital infection), is limited. Given the difficulty and risks of obtaining human placental samples during an ongoing pregnancy, and that IUGR is often detected late, studies investigating the pathophysiology of IUGR have been largely limited to animal models, tissue explants, or cell culture work. Animal models of IUGR include various stressors to reduce blood flow or nutrient provision to the developing fetus, such as maternal food restriction, gestational hypoxia, or uterine artery ligation. Each of these models have distinct advantages and disadvantages, and the animal chosen also is important in considering the extrapolation of findings in these studies to the human condition of IUGR. Placentation is a unique biological process that varies significantly among different species, and in combination with different stressors, the resulting phenotype can differ greatly between models. The limitation of tissue explant and cell culture work is that in true pregnancy, these tissues and cells do not exist in isolation, as multiple inputs in pregnancy affect cellular biological behavior and function. For cell culture results (such as is utilized in trophoblast or human umbilical vein endothelial cell studies), it is important to consider the characteristics of the cell line utilized (e.g., in what trimester the cells were originally obtained, immortalized versus not, etc.).

Taken together, studies using these various models suggest that placental insufficiency oftentimes results from a disruption in normal early vascularization of the placenta. Specifically, incomplete spiral artery remodeling results in shallow invasion of the placental vasculature. This poor invasion contributes to failure of these vessels to appropriately become low-resistance vessels, thus limiting blood flow to the fetus and nutrient/oxygen provision to the fetus and placenta itself. However, insults during mid to late pregnancy may affect the exchange tissue barrier and the vascular surface area as well.

Antenatal Screening and Prenatal Management

Given the inherent differences and difficulties in how IUGR is defined, in combination with its poorly understood pathophysiology, guidelines for how to screen for IUGR generally lack strong evidence to back them.[31] Subsequently, the outcomes in this high-risk population have improved very little despite advances in obstetric and neonatal care. However, identification of the fetus at risk is essential to providing close prenatal surveillance and to heighten the awareness of the postnatal neonatal care team for complications. Based upon what is known at this time, the components that should be included in antenatal screening for IUGR are (Table 15.3):

1. **A detailed maternal and family history**: Standard diagnostic tools include a thorough maternal and familial history to identify the presence of etiologic risk factors as outlined above. Accurate gestational dating, either by last menstrual period (LMP) or first-trimester ultrasound results, is an essential component in the detection and prenatal management of IUGR. Previous history of an SGA newborn should be sought out, as risk of recurrence is reported as ~20%,[5] and risk of recurrent IUGR is estimated at ~20%-50%.[11]
2. **A detailed maternal physical exam, including fundal height measurements**: Maternal physical examination with close attention to maternal nutritional status as well as fundal height should be performed. Fundal height as measured between 24 and 38 weeks of gestation may be a useful screen for fetal growth less than the 10th percentile.[62] However, the accuracy of fundal height measurement is limited by factors such as maternal obesity, multiple gestation, or uterine leiomyomas.

Once a pregnancy or fetus is identified as at risk for IUGR, evaluation should include:

1. **Fetal ultrasound**: Serial ultrasound evaluation for growth assessment is key in the evaluation of the growth-restricted fetus. Four biometric measures are commonly used to assess fetal growth: (1) biparietal diameter, (2) head circumference, (3) abdominal circumference, and (4) femur length. In combination, an estimated fetal weight can be calculated from these measurements.[32] It should be noted that there is the possibility of significant error in these measurements—estimates of fetal weight may deviate from actual weight up to 20% in the majority of cases.[26] However, used as a screening tool and used serially, prenatal ultrasound is the most powerful screening tool available for identification of fetuses at risk for IUGR. It is recommended that if the estimated fetal weight falls below the 10th percentile for gestational age, a more detailed evaluation including amniotic fluid measurement and Doppler flow studies be performed. In addition, evaluation of fetal anatomy should be completed given the high incidence of structural and genetic abnormalities presenting with fetal growth restriction.[4] Additional testing for chromosomal disorders or infections can also be performed, as indicated (especially in the presence of structural abnormalities identified on imaging, or for growth restriction detected early in gestation). Of the biometric measurements, abdominal circumference appears to have the best "stand-alone" specificity and a negative predictive value of almost 90% for diagnosing IUGR.[10] Decreased abdominal circumference is thought to represent a small liver, which reflects decreased hepatic glycogen stores and subcutaneous fat. The other biometric measurements can help to distinguish symmetric from asymmetric fetal growth restriction, and taken in combination, may improve the sensitivity, specificity, and positive and negative predictive value for IUGR.[10] The optimal interval frequency of growth scans (optimal surveillance regimen) has not been established, although the American College of Obstetricians and Gynecologists (ACOG) suggest every 3-4 weeks to minimize false-positive rates.[4]

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TABLE 15.3 Prenatal Management and Testing in Cases of Suspected IUGR

Prenatal Test	Clinical and Diagnostic Utility	Other Recommendations and Specifics
A detailed maternal and family history	Previous history of SGA of IUGR, as recurrence risk is ~20% and ~20%-50%, respectively	Accurate gestational dating is essential
Maternal physical exam	Fundal height measured during the second half of pregnancy may be a useful screen for fetal weight <10% (specificity ~92%-93% and negative predictive value ~92%-98%)[62]	Assess maternal nutritional status Assess fundal height
Fetal ultrasound	An estimated fetal weight based upon biparietal diameter, head circumference, abdominal circumference, and femur length should be obtained, and serial measurements of growth (every 3-4 weeks) are key in the management of IUGR.[32] If estimated fetal weight <10%, include amniotic fluid measurements, full anatomy evaluation, and Doppler studies. Abdominal circumference has the best "stand-alone" specificity, and negative predictive value of almost 90%, for diagnosing IUGR.[10]	
Umbilical artery (UA) Doppler velocimetry	UA Doppler measurements can be helpful in prognosticating severity of IUGR and in guiding clinical management. Absent or revered end-diastolic flow is associated with increased perinatal mortality. When used in cases of suspected fetal growth restriction, the rate of perinatal death decreases by almost 30%.[37]	UA Doppler is less sensitive in mild disease and cannot be used as a screening tool for IUGR.
Doppler studies of fetal circulation	Doppler studies of fetal circulation, such as the ductus venosus, middle cerebral artery, or aortic isthmus may be reasonable predictors of short-term risk of fetal death, neonatal acidosis, and/or increased mortality and neurologic morbidity in the setting of fetal growth restriction.[61]	There can be technical difficulties in obtaining these measurements, and available studies are small, limiting the ability to make conclusive recommendations.
Genetic testing or infectious disease testing	Prenatal genetic testing should be offered in the presence of suspected structural abnormalities seen on fetal ultrasound or for growth restriction detected early in pregnancy.	

IUGR, Intrauterine growth restriction; SGA, small for gestational age.

2. **Doppler velocimetry, especially of the umbilical artery**: Doppler velocimetry, especially of the umbilical artery, is a well-studied measurement in the setting of IUGR and can specifically be a powerful tool in prognosticating severity of fetal growth restriction, potentially dictating prenatal management of IUGR fetuses.[61] Flow in the umbilical artery is a reflection of maternal circulation; normally, the resistance in the umbilical artery should decrease with increasing gestational age. However, with placental insufficiency, resistance will increase and subsequently, diastolic flow will decrease. Based upon data extrapolated from animal models, absent or reversed end-diastolic flow in the umbilical artery is thought to occur when two-thirds of the placental villous tree is damaged.[48] Clinically, absent or reversed end-diastolic flow in the umbilical artery is well documented as a poor prognostic factor, associated with increased perinatal mortality.[40] When included in prenatal testing in cases of suspected fetal growth restriction, the rate of perinatal death is decreased by almost 30%,[2] indicating it is a powerful tool in the management of IUGR. However, umbilical artery Doppler is less sensitive in mild placental disease. Other studies have suggested that measures of fetal circulation such as Doppler of the ductus venosus, middle cerebral artery, and aortic isthmus may be useful predictors of short-term risk of fetal death or increased mortality/neurologic morbidity in early-onset fetal growth restriction.[61] However, not enough evidence is available to routinely recommend that abnormalities noted on these studies dictate clinical care.
3. **Other standard fetal surveillance**: Some studies suggest that the use of Doppler velocimetry in combination

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with nonstress tests, biophysical profiles (BPP), or both may improve outcomes in IUGR fetuses,[3] although a Cochrane meta-analysis did not find sufficient evidence that the BPP is an adequate measure of fetal well-being upon which clinical decisions should be based in high risk pregnancies.[42]

The timing of delivery for growth-restricted fetuses remains debated but in general is dependent upon the underlying etiology of growth restriction as well as the estimated gestational age. Early delivery of an IUGR fetus with known aneuploidy or congenital infection is not associated with improved outcomes and may in fact portend worse outcomes. In such cases, nonintervention may be a reasonable option while respecting parental desires. In other instances, such as in IUGR due to placental insufficiency, multidisciplinary input should be considered and each case considered individually. When intervention is preferred, antenatal surveillance may be helpful in guiding the timing of delivery, taking into account risk–benefit ratios. Decisions about the mode of delivery should be based upon other factors, as IUGR in itself does not require cesarean delivery. The overall goal is to balance delivery of the IUGR fetus prior to severe fetal compromise, with early delivery leading to increased incidence of prematurity and its comorbidities. Only two randomized clinical trials to assess timing of delivery of the growth-restricted fetus (in one study, in IUGR fetuses less than 34 weeks' gestation, and in the other, IUGR fetuses greater than 36 weeks' gestation) have been published, and both suggested that earlier delivery versus expectant management did not improve rates of perinatal survival or longer-term outcomes.[12,72] Between 34 and 36 weeks of gestation, no adequately powered randomized trials exist. Based upon these studies, the ACOG recommends delivery at 38 0/7 to 39 6/7 weeks in cases of isolated fetal growth restriction, and delivery at 34 0/7 to 37 0/7 weeks for IUGR fetuses with additional risk factors for poor prognosis (e.g., oligohydramnios, abnormal umbilical artery Doppler velocimetry).[64] For preterm deliveries, delivery ideally should be coordinated and performed at a center with both high-risk maternal fetal medicine teams and a neonatal intensive care unit. Antenatal corticosteroids should be given, and magnesium sulfate administration should be considered when appropriate.[4]

Prevention

There are no to very few "preventative" strategies for IUGR. Counseling regarding modifiable risk factors, for example, cigarette smoking during pregnancy, diet during pregnancy, and malarial prophylaxis in high-risk areas, may be somewhat effective in preventing or mitigating IUGR. Outside of these interventions, no effective preventive strategy has been identified. Nutritional and dietary supplementation regimens such as increased consumption of specific food groups, a low-salt diet, iron, zinc, calcium, protein, or vitamin D[23,35,51,53] supplementation have not been effective. Bed rest is not recommended for suspected fetal growth restriction.[4] The preliminary evidence behind the use of aspirin suggests potential efficacy in mitigating more severe IUGR (with evidence of abnormal umbilical artery Doppler studies), with aspirin-treated groups showing increased birth weight at delivery, prolonged gestation, and decreased need for admission of the newborn to the neonatal ICU, but is not routinely indicated at this time given that existing studies are small.[14]

Postnatal Diagnosis of IUGR

The diagnosis of IUGR postnatally is problematic because of the lack of consensus in how to define IUGR and the unclear and myriad pathophysiologic mechanisms that may be involved. Anthropometric measurements should be taken at birth and considered in combination with the prenatal history. The birth weight "cut-off" that should be used to delineate IUGR is variable, with some clinicians recommending below the 10th and some recommending below the 3rd percentile. However, the percentiles, as defined upon growth curves, are only as good as the population upon which the data is based. Extrapolation from these growth curves may be limited by the specific demographic and genetic make-up of the population measured. As noted earlier, it is imperative to take into consideration the prenatal pattern of growth as well as other prenatal findings (e.g., other placental and fetal structural abnormalities, abnormal genetic testing, family and previous maternal pregnancy history, and pregnancy infections). For example, a neonate with a significant history of poor fetal growth in the third trimester, even if above the 10th percentile in birth weight for gestational age, should be monitored for complications related to IUGR. Histopathologic evaluation of the placenta may be helpful in identifying overall size, shape, presence of structural abnormalities, and large infarctions.

Examination of the infant may also be helpful. Stigmata of "malnourished" fetuses may include: a large and wide anterior fontanelle, absent buccal fat, small and scaphoid abdomen, thin umbilical cord, decreased skeletal muscle mass and subcutaneous fat, disproportionately large hands and feet, and/or loose and dry skin (especially at the nape of the neck, axilla, and gluteal regions) (Fig. 15.2). These physical examination findings may be more consistent with asymmetric, or "brain-sparing," IUGR. In symmetric IUGR, other features may be present, depending upon the underlying etiology. For example, in aneuploidies, dysmorphic facies or other congenital anomalies may be present, or in certain congenital infections, classic stigmata such as microcephaly, petechiae and "blueberry muffin" rashes, cardiac murmurs secondary to congenital heart defects, and/or hepatosplenomegaly may be seen. Historically, there are a number of indices that can be calculated, such as Ponderal index, mid-arm to head circumference ratio (McLaren's index), the clinical assessment of nutrition score, and cephalization index. Cut-off values for each of these measures have been defined as suggestive of fetal malnutrition.

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• **Fig. 15.2** This is a 36-week male neonate with a birth weight of 1600 grams who was born to a mother with severe pre-eclampsia. This baby was noted to have asymmetrical intrauterine growth restriction (IUGR). Note the loss of fat over the body, visible rib cage, excessive skin folds noted over the whole body, and relatively large head compared to the body. (From Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. *Clin Med Insights Pediatr.* 2016;10:67-83.)

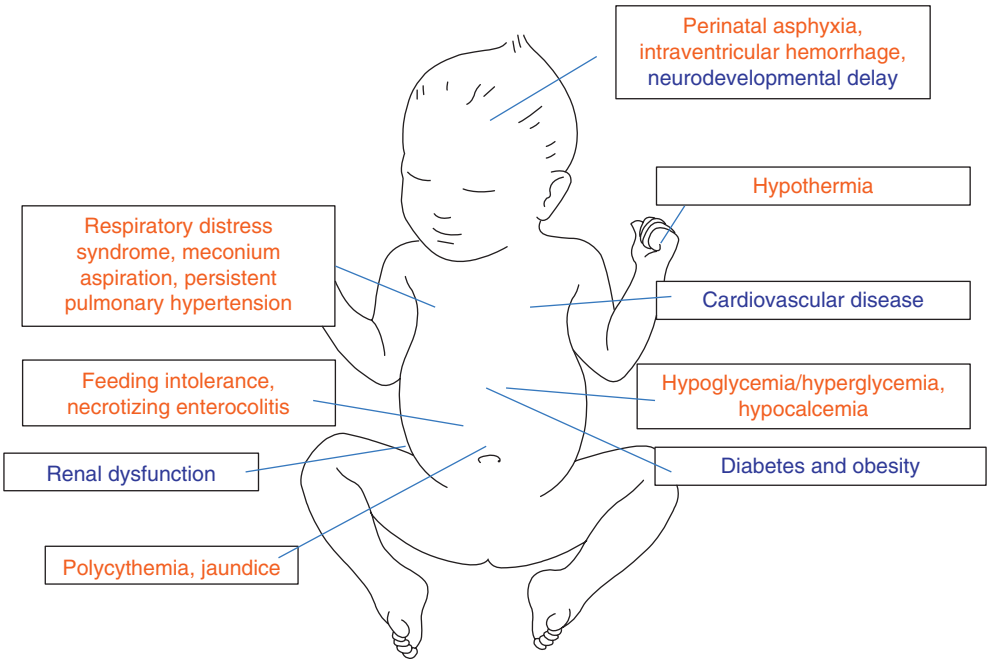
Postnatal Management

Clinically, the IUGR infant is at increased risk of stillbirth, neonatal death, and prematurity: estimates are that approximately half of unexplained stillbirths are IUGR; IUGR infants suffer a 5- to 30-fold increase in morbidity and mortality even when born at term; and IUGR infants are 2.5 times more likely to be born premature than their AGA counterparts.[41] These infants also are at increased risk for needing more perinatal intervention, such as cesarean delivery, exposure to antenatal steroids, and admission to the neonatal intensive care unit.[69] A skilled team that is able to resuscitate the newborn should be present at delivery, given that IUGR newborns oftentimes do not tolerate labor well given the acute stress of laboring superimposed upon chronic poor blood flow and hypoxia. Once delivered, the IUGR neonate is at increased risk for a number of neonatal complications (Fig. 15.3), which should be monitored for and managed appropriately (Table 15.4). The problems that these IUGR infants encounter are often due to the fetal adaptations that occur in utero in the setting of poor nutrient and oxygen provision, which are poorly tolerated ex utero. In general, the fetus responds to hypoglycemia and/or hypoxemia by increasing catecholamine concentration, adjusting glucose transport and insulin receptor expression in a tissue-specific manner,[75] decreasing fetal pancreatic insulin secretion,[45] and increasing hepatic glucose production.[25,67] The overall metabolic and hormonal adaptations promote fetal survival and brain development at the expense of other somatic tissues,[67] especially in asymmetric IUGR. The management of the issues that arise postnatally as a result of IUGR results in prolonged hospital stays and increased health care costs for these infants in the short-term.

Hypoglycemia

Postnatal hypoglycemia is common in IUGR neonates, given that they are born with suboptimal glycogen stores, impaired

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• **Fig. 15.3** A schematic of complications of IUGR. Orange labels indicate short-term complications, and blue labels indicate long-term complications.

gluconeogenesis, decreased fat, and increased sensitivity to insulin. The hormonal and metabolic predispositions in IUGR neonates may be further exacerbated by polycythemia and hypothermia. Clinically, close glucose concentration monitoring of IUGR neonates is warranted, given that over half of infants born SGA have some episode of hypoglycemia (defined as <2.6 mmol/L [46 mg/dL]) postnatally, and that about a third of these infants have severe, prolonged and/or recurrent hypoglycemia.[33] These infants may require formula or oral glucose supplementation shortly after birth, tube feedings, and/or supplementation with dextrose-containing intravenous fluids (IVF) in combination with continued frequent monitoring until hypoglycemia is resolved without supplemental feeding or IVF.

Hypothermia

Hypothermia occurs in IUGR neonates because of decreased brown fat deposition in utero. Thermal regulation should be monitored closely soon after delivery of the IUGR neonate. Although hypothermia can sometimes be managed in a general care nursery with close monitoring and may self-resolve over a matter of hours or minutes, some IUGR neonates require an exogenous heat source or incubator for management of hypothermia, particularly those born premature.

Respiratory Complications

IUGR neonates are at increased risk for both respiratory distress syndrome in the short term and bronchopulmonary dysplasia/chronic lung disease in the long term, which is due in part to both poor in utero growth and concomitant risk for prematurity.[13] Although some believe that fetal growth restriction may accelerate lung maturity (perhaps via catecholamine hormonal adaptations), this effect may be countered by the cellular growth restriction in IUGR that may manifest in the lung as decreased alveolar number and dysfunction, in combination with vascular remodeling (perhaps secondary to altered fetal circulation in IUGR). This pulmonary vascular remodeling also may lead to increased risk of pulmonary hypertension, in combination with chronic lung disease. In later childhood, these infants exhibit lung dysfunction.[49] Supportive care and respiratory support should be provided as needed.

Necrotizing Enterocolitis

Whether or not IUGR predisposes infants, especially those born preterm, to increased risk for necrotizing enterocolitis (NEC) is debated. However, severe cases of IUGR (those with evidence of absent or reversed end diastolic flow on prenatal ultrasound) seem particularly susceptible to necrotizing enterocolitis, although the underlying mechanisms are unclear. Formula feeding seems to increase this risk in preterm IUGR infants,[44] but early initiation of trophic or small-volume feedings is associated with better weight gain and decreased parenteral nutrition exposure and associated cholestasis[55] in these infants. Interestingly, SGA infants seem particularly susceptible to parenteral nutrition-associated liver disease.[55] Taken together, prompt initiation of feeding when possible is prudent, and provision of breast milk instead of formula should be encouraged.

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TABLE 15.4 Postnatal Issues in IUGR

Postnatal Concern	Overall Risk and Etiology	Management Recommendations
Perinatal distress/asphyxia	IUGR infants, compared to AGA, have a 5-30x increase in morbidity and mortality, even when born at term, and are 2.5x more likely to be born premature. Overall increased risk for stillbirth and prematurity makes the delivery of an IUGR neonate high risk. Increased risk of perinatal distress given the stress of labor in the setting of chronic poor blood flow and hypoxia.	Attendance at delivery by a skilled team that can resuscitate a low birth weight or premature infant, ideally at a center with a neonatal intensive care unit.
Hypoglycemia	Half of infants with a birth weight <10th percentile have some episode of hypoglycemia, and 1/3 of infants with a birth weight <10% have severe, recurrent, and/or prolonged hypoglycemia. Due to suboptimal glycogen stores, impaired gluconeogenesis. Decreased fat, increased sensitivity to insulin. May be exacerbated by polycythemia or hypothermia.	Serial monitoring for hypoglycemia, initiated soon after birth. If persistent, prolonged, or severe: Formula supplementation, gavage feeding, provision of dextrose-containing intravenous fluids.
Hypothermia	Decreased brown fat deposition in utero.	Temperature monitoring, initiated soon after birth. Provision of an exogenous heat source or incubator may be required.
Respiratory complications	Poor in utero growth and concomitant risk for prematurity put IUGR infants at risk for respiratory distress syndrome in the short term and chronic lung disease in the long term. Some IUGR infants exhibit evidence of pulmonary vascular remodeling, which may result in increased risk of pulmonary hypertension.	Supportive care and respiratory support, as necessary.
Necrotizing enterocolitis/ feeding intolerance	Severe cases of IUGR (those with absent or reversed end-diastolic flow on UA Dopplers), especially with concomitant prematurity, may have increased susceptibility to NEC and/or feeding intolerance.	Breastmilk provision and avoidance of formula. Early initiation of trophic or small volume feeding.
Intraventricular hemorrhage	Increased risk may be due to cerebral vascular remodeling, cerebral autoregulatory mechanisms, and overall hemodynamic instability in IUGR.	Surveillance with head ultrasound. Avoiding fluctuations in cerebral oxygenation using continuous monitoring such as near infrared spectroscopy.
Electrolyte abnormalities	Hyperglycemia and hypocalcemia	Monitor for and correct abnormalities.
Polycythemia/jaundice	May occur as a response to long-standing hypoxia in utero.	Check for underlying hematologic abnormalities, and treat when clinically indicated.
Abnormal innate and humoral immunity	Unclear etiology, although speculated to occur due to bone marrow suppression secondary to chronic hypoxia.	Check for underlying abnormalities with a complete blood count and differential. Low threshold for infectious work-up and aggressive management of infection.

AGA, Appropriate for gestational age; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; UA, umbilical artery.

Seizures, Intraventricular Hemorrhage

IUGR neonates, especially those born premature, may be at increased risk for intracranial hemorrhage (ICH). Some studies have demonstrated an increased association of ICH with IUGR neonates with abnormal cerebral blood flow patterns (as measured by prenatal middle cerebral artery measurements),[20] while others have not demonstrated the same association after correcting for gestational age and other confounding factors.[65] The mechanisms underlying

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intracranial hemorrhage in IUGR neonates are also debated, as there is evidence to suggest that cerebral vascular remodeling, cerebral autoregulatory mechanisms, and overall hemodynamic instability in IUGR infants may contribute to predisposition toward IUGR. Given the unknowns, recent research into the utility of cerebral oxygenation (via near-infrared spectroscopy) as a marker of brain perfusion suggests that serial measurement may be helpful in predicting neurodevelopmental outcome. When available, avoiding fluctuations in cerebral oxygenation may be helpful in avoiding intracranial hemorrhage,[50] and thus, continuous monitoring of cerebral oxygenation may be a much better marker than the use of blood pressure values alone, which do not extrapolate to adequate tissue perfusion, particularly in the brain.[1]

Other

Other reported complications of IUGR in the immediate postnatal period include perinatal asphyxia, electrolyte abnormalities (e.g., hyperglycemia, hypocalcemia), hematologic issues (e.g., polycythemia, jaundice), feeding difficulties and intolerance, and abnormal innate and humoral immunity.[59] These issues should be closely monitored for, and addressed, as possible.

Long-Term Consequences of IUGR

There is a wealth of evidence that the in utero environment contributes greatly to the fetus's development in a manner that can have long-lasting implications. For IUGR infants, there are long-term neurodevelopmental, as well as cardiometabolic consequences, of poor growth in utero (see Fig. 15.3). This phenomenon is known as developmental programming,[15] a concept that has a foundation built in large epidemiologic studies showing that maternal gestation during periods of famine results in IUGR offspring that are at increased risk for cardiometabolic disease during adulthood.[8]

The neurodevelopmental outcomes of IUGR offspring are known to be worse than those of their AGA counterparts, but the mechanisms by which this occurs remain controversial. IUGR neonates are at increased risk for cerebral palsy and for lower scores across multiple neurocognitive domains including cognition, attention, mood, and social skills,[38] even after correcting for confounders such as socioeconomic status, prematurity, and its co-morbidities. In placental insufficiency underlying asymmetric IUGR, vasoconstriction of the peripheral vascular bed and raised placental vascular resistance in combination with vasodilation of the cerebral arteries preferentially shifts cardiac output toward the brain.[63] It is important to note that brain-sparing appears to be regional, not global, and that patterns of increasing and decreasing blood flow in specific portions of the brain change during the course and chronicity of hypoxia, implying a hierarchical order to blood flow response even within a single organ.[34] It was previously believed that this phenomenon was a brain-protective response in the face of chronic hypoxia; however, other studies suggest that neurodevelopmental outcomes are worse in IUGR subjects with evidence of "brain-sparing"[28] (as measured by blood flow patterns in cranial blood vessels). It has been proposed that increased cerebral blood flow may actually suggest advanced stages of brain injury and that the persistently increased cerebral blood flow seen after birth in IUGR infants despite no longer being in an hypoxic environment[37] may be a maladaptive change resulting from long-standing blood flow changes that alter structure and function of the cerebral vasculature (e.g., loss of cerebral vasoreactivity), leading to hyperoxic and reperfusion injury postnatally.[18] In addition, the contribution of elevated cortisol exposure in utero, as is seen in IUGR,[17] is unknown, although the link between synthetic steroid exposure and altered brain structure and cognitive function is well-established.[66] Studies on human infants born IUGR demonstrate that they have decreased brain volume, gray matter, and hippocampal volumes, and these changes persist into childhood and are associated with neurodevelopmental impairments.[9]

The concern about neurodevelopmental impairment shapes, in large part, the discussion about the benefits and risks of postnatal "catch-up" growth. Although optimized postnatal growth seems to portend better neurocognitive outcomes,[16] it has been associated with increased risk for cardiometabolic syndromes such as obesity, cardiovascular disease, and diabetes.[7] In general, it is believed that the fetal adaptations that allow the IUGR fetus to reallocate energy sources during starvation/undernourishment toward survival in utero manifest a propensity for insulin resistance, the development of diabetes, and obesity when as an adult, the offspring is exposed to abundance in the nutritional environment. The same adaptations occur in the vascular system and the hormonal axis. Fetal development is believed to be a critical window, during which the "programming" of disease is particularly susceptible to environmental influences. It is believed in part that these fetal adaptations occur via epigenetic mechanisms.[15]

There are a number of other long-term sequelae that are being reported in association with IUGR, such as propensity toward cancer, schizophrenia, Alzheimer's disease, polycystic ovarian syndrome, shorter life span, and immune dysfunction.

Conclusions

Given the huge burden of disease, both to an individual and to public health worldwide, intrauterine growth restriction remains a devastating problem for obstetricians and perinatologists alike. There remain many unknowns in how to best define the disease, identify pregnancies at risk, manage these pregnancies antenatally, and minimize complications postnatally. Furthermore, IUGR offspring may contribute significantly toward adult diseases that compromise the majority of adult mortality, including cardiovascular disease,

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obesity, diabetes, and cancer predisposition. Monitoring for these long-term morbidities is important as these children enter adulthood. There is a need for improved modalities in detecting IUGR and predicting some of the morbidities. It behooves us to closely monitor these infants not just in the neonatal intensive care unit but throughout childhood to ensure better societal assimilation and care toward prevention of non-communicable chronic disorders.

Key Points

- Intrauterine growth restriction occurs when fetal growth is less than its genetic potential.
- There are many definitions of IUGR and etiologies leading to IUGR, which contribute to difficulties in how to diagnose, prevent, and develop therapies for intrauterine growth restriction.
- The general categories of etiologies causing IUGR are: fetal, maternal, environmental, and placental.
- Prenatal screening for IUGR is largely dependent on serial ultrasound and Doppler velocimetry, although there is still debate as to how these indicators should be used to dictate prenatal care and delivery planning.
- IUGR has significant short- and long-term consequences for the neonate.

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16

Developmental Origins of Adult Health and Disease

JOSEPHINE M. ENCISO AND SHERIN U. DEVASKAR

Fetal Origins of Adult Disease Concept

The concept of fetal origins of adult disease popularized by Barker arose from a robust association between small size at birth and the risk of chronic adult diseases, such as coronary artery disease, hypertension, stroke, type 2 diabetes mellitus, and osteoporosis.[4,9,20,29] These original epidemiologic observations have been extensively replicated by multiple groups in varying populations of different ethnicities employing birth weight as a surrogate for the intrauterine state.[9,20,36] During the 1944-1945 Dutch famine, women who were previously adequately nourished were subjected to low caloric intake and the associated environmental stressors. The offspring that were conceived or were gestating in their mothers' wombs during the famine, as adult survivors at age 50-60 years, showed a higher incidence of hypertension, cardiovascular-related mortality and morbidity, and glucose intolerance/insulin resistance. The culmination of all these epidemiologic associations is referred to as the "Barker hypothesis" or "developmental origins of health and disease (DOHaD)."[4,9]

Although fetal growth and birth weight have served as surrogate markers of fetal nutrition and health, it is clear that fetuses subjected to nutritional perturbations with no resultant change in size or growth also develop adult chronic diseases.[9] Moreover, although in utero calorie restriction serves as a classic example of the far-reaching implications of the "Barker hypothesis," other triggers, including a deficiency or excess of specific nutrients, stress, inflammation, toxins, and drugs, can perturb the fetal hormonal-metabolic milieu and set the stage for the subsequent onset of chronic diseases.[9,20,23,36] These observations support that adaptations in an adverse in utero environment occur to ensure immediate survival, which may or may not interfere with fetal growth depending on the type, timing, and severity of adversity. Although nutritional deficiency is considered to exist only in poorly resourced countries, differential socioeconomic status with varying access to health care and sociocultural and ethnic differences resulting in disparities are rampant in the Western world, including the United States. These situations can lead to malnutrition, overnutrition, and other forms of maternal-fetal stress, which translate into an altered phenotype of this subpopulation.

As more investigations in human and animal models are accumulating, various mechanisms responsible for this fetal-adult association are being unraveled.[9] These adaptive mechanisms, or "thrifty phenotype," combat an adverse nutritional and/or metabolic intrauterine environment by developing safeguards for the energy supply sometimes at the expense of growth, ensuring a reduced fetal demand. After birth, these same adaptive systems can remain masked, however, without much contribution to short-term health or disease. Over time, with or without additional nutritional or metabolic stressors, the finely crafted phenotype may tip toward a disease state. The conventional belief is that these phenotypic features are expressed mainly in aging adults. Given lifestyle changes toward an increased caloric intake and relative inactivity, however, some of these features are seen in childhood or during late teenage years (Box 16.1).[59]

Influences on the Early Embryo

The use of artificial reproductive technology continues to increase worldwide; 1%-3% of live births are secondary to artificial technology.[18] Different culture media and techniques used in artificial reproductive technology can alter the environment of the developing embryo and subsequent phenotype of the offspring.[18,23,41] Even after accounting for confounding factors such as infertility and advanced maternal or paternal age, there is evidence that artificial reproductive technology is linked to an increased incidence of prematurity, growth restriction, congenital malformations, and imprinting disorders.[10,18,23,41] Imprinting refers to the differential expression of specific genes according to parental origin. Genes are "silenced" by epigenetic modifications. In pregnancy, imprinted genes play a critical role in determining placental size and fetal growth. Most paternally expressed genes enhance placental and fetal growth, whereas

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Abstract

The "Barker hypothesis" or concept of the developmental origins of health and disease (DOHaD) connects maternal health status and exposure to stress or environmental toxins during pregnancy with later development of disease in the offspring. In this chapter we will review the studies, both animal and human, that provide support for the concept of fetal origins of adult health and disease. We will describe the effects of maternal overnutrition, undernutrition, diabetes mellitus, obesity, and maternal exposure to stress and environmental toxins, as well as how the existence of these adverse conditions during pregnancy can affect fetal growth, organ, and vascular development and predict health problems and chronic diseases later in life, including obesity, metabolic disease, diabetes mellitus, hypertension, coronary artery disease, and cancer. The epigenetic mechanisms that are associated with the fetal programming of disease from one generation to the next will also be discussed.

Keywords

Barker hypothesis
developmental origins of health and disease (DOHaD)
epigenetics
mismatch concept
fetal programming

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• BOX 16.1 Chronic Diseases Attributed to Developmental Origins

- Diabetes mellitus
- Obesity
- Dyslipidemia
- Hypertension
- Coronary artery disease
- Stroke
- Kidney disease
- Liver disease
- Lung abnormalities—reactive airways disease
- Immune dysfunction
- Polycystic ovarian syndrome, premature pubarche
- Osteoporosis
- Alzheimer disease
- Depression, anxiety, bipolar disorder, schizophrenia
- Cancer
- Social problems
- Poor cognitive performance
- Shortened life span

most maternally expressed genes reduce placental and fetal size. Imprinting disorders, such as Beckwith-Wiedemann, Angelman, Prader-Willi syndromes, and hypomethylation syndrome, appear to be increased in children who are a product of artificial reproductive technology.[41] The incidence of Angelman syndrome is estimated to increase from 1 in 400,000 births to 1 in 20,000 births with artificial reproductive technology.[41] Moreover, artificial reproductive technology may alter the growth patterns of children.[19] Children conceived by in vitro fertilization also have decreased growth early in infancy and then experience "catch-up growth" after about 6 months of age, resulting in higher blood pressures and altered body composition.[10] These alterations in growth patterns and risk for disease illustrate that reprogramming at an early stage can increase the risk for adult disease later on.

Postnatal Growth and Nutrition

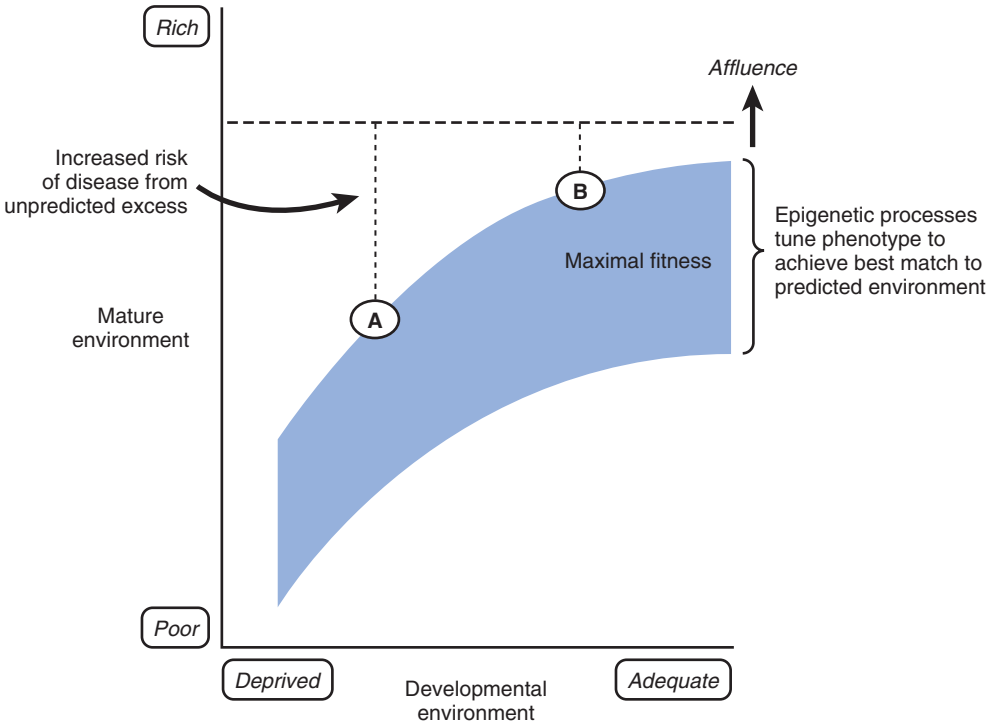
The first indication that postnatal stages of development can influence the long-term outcome related to perturbed fetal nutrition came from observations during the Leningrad siege.[9] Exposure in utero and postnatally to nutritional deprivation failed to produce signs of chronic diseases in adults. These findings suggested that postnatal manipulation of nutrition may have a protective effect on the trajectory of fetal origins of adult disease. Investigations have revealed that in girls and boys, low birth weight with a slow growth pattern followed by exponential growth during childhood increases the risk for metabolic syndrome, which is characterized by obesity, insulin resistance, hypertension, and dyslipidemia.[3,59,68] These studies established that postnatal growth patterns were important in modulating the fetal trajectory toward predetermining the adult phenotype. These findings are of particular interest to neonatology, where there continues to be an ongoing dilemma as to what is ideal postnatal growth and whether this growth rate should be the same for infants of varying birth weights, gestations, sexes, ethnicities, and races.

The phenomenon of postnatal catch-up growth seems to reflect intrauterine or early postnatal nutritional deprivation. It is a normal tendency by the body to compensate after a nutritionally restricted period, showing rapid growth. This rapid growth targets short-term benefits, which include survival and protecting the reproductive capacity.[6] It is evident, however, that catch-up growth tends to favor nutrient deposition in white adipose tissue, resulting in adiposity, particularly visceral adiposity; a rearrangement of skeletal muscle mitochondria; and increased oxidative injury.[6] These changes set the stage for metabolic syndrome, diabetes mellitus, and coronary artery disease as the child matures into an adult.[59] This catch-up growth results in a shortened life span with changes in the telomeric length.[19] For "short-term gain," catch-up growth results in "long-term pain" (Fig. 16.1).

The question arises, should postnatal catch-up growth not be fostered? If postnatal nutrition matches intrauterine nutrition, can adult chronic diseases be curbed and result in longevity? Although animal and human studies lend credence to this concept, the absence of catch-up growth, although resulting in glucose tolerance, lean body composition, and reduced coronary artery disease with longevity, may negatively affect cognition and reproductive capacity. Rapid postnatal growth, whether superimposed on low birth weight (LBW) or normal birth weight, seems to have a similar effect in producing adult chronic diseases.[4,6,9] Avoidance of rapid postnatal catch-up growth within a short period may be beneficial if replaced with moderate long-term growth and may be influenced not only by the amount of calories ingested but also by the quality and composition of the nutrition. In a study of small-for-gestational-age (SGA) infants exposed to either maternal breast milk or formula, babies who received breast milk exhibited decreased adiposity and normal serum adiponectin concentrations, while those who received either standard or protein-enriched formula had increased fat mass and lower adiponectin concentrations.[15] Other studies have revealed an association between fortified formulas and elevated blood pressures and insulin resistance during the childhood years.[65]

At the other end of the spectrum, infants born with a heavier birth weight, resulting from either maternal diabetes or obesity, are also prone to adult chronic diseases. These infants are obese during childhood and develop insulin resistance with the associated phenotypic presentations.[68] One can speculate that these infants experience catch-up growth during fetal life after experiencing slow growth during the early embryonic phase. Further postnatal escalated growth leads to earlier acquisition of adult chronic diseases and the associated complications. The weight status in the first 6 months of life predicts obesity at 3 years of age and future mortality (Fig. 16.2).[68]

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• **Fig. 16.1** Schematic representation of the mismatch concept that emphasizes the degree of disparity between the environment experienced during development and that experienced later (*hatched line on top*), on the risk of disease. During the period of developmental plasticity in prenatal and early postnatal life, epigenetic processes are thought to alter gene expression to produce phenotypic attributes best suited to the environment and based on environmental cues transmitted via the mother (*shaded area*). Greater mismatch gives greater risk of disease from unpredicted excessive richness (high-calorie-density food, sedentary lifestyle) in the environment. Risk is greater with poorer developmental environment (**A** versus **B**) and with socioeconomic transitions to an affluent Western lifestyle. (From Godfrey KM, et al. Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. *Pediatr Res*. 2007;61:5R.)

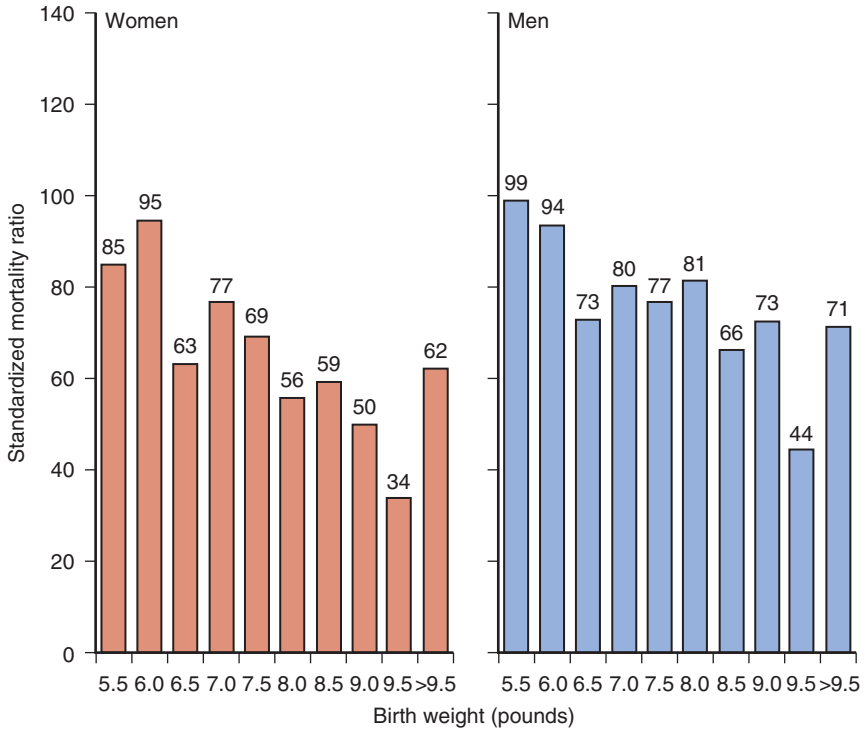
Mismatch Concept

Investigations have solidified the concept of profound effects resulting from a "mismatch" between the early developmental environment and the subsequent environment after birth into childhood and adult life. The degree of mismatch can be increased by deprived environmental conditions during a critical phase of development (prenatal or postnatal) or an excess later or both (see Fig. 16.1). Compromised maternal health, nutrition, toxins, stressors, infections, and inflammation can contribute to the former, whereas energy-dense foods and television watching with reduced physical activity can contribute via the latter pathway, exaggerating the mismatch further. Such a phenomenon has considerable significance to developing societies that are undergoing rapid socioeconomic transitions or to immigrant families in Western countries that came from poorly resourced countries.[36]

Most important to neonatal intensive care units are the neonatal health concerns of nutrition, toxins, stressors, hypoxia, infections, and inflammation during the early phase of life that can have similar effects on the life course of a particular individual. Thought should be exercised before introducing interventions during this period of development that have the potential of altering the life course. The concept of catch-up growth should be reevaluated to determine what is optimal for every subset of the population. At both ends of the spectrum—infants who are large for gestational age (LGA) and intrauterine growth restriction (IUGR)—there is a period of deprivation followed by exposure to excess. In the case of the former, this deprivation usually occurs during the first trimester, with rapid catch-up growth observed during the third trimester, resulting in an infant who is LGA, whereas in the latter category, the deprivation is generally in the third trimester, with rapid catch-up growth postnatally. In premature infants who have very low birth weight (VLBW), the deprivation is in early postnatal life followed by catch-up growth during the post-neonatal stage of development. Very low birth weight children may also be faced with superimposed fetal growth restriction, further increasing their disease risk. Thus, it appears that the earlier the deprivation phase is followed by catch-up growth, the more significant the consequences as an adult.[6]

Although considerable emphasis in most studies has rested on the prenatal or postnatal growth pattern and size at birth or infancy, a perturbation in growth and size is evidence that adaptations are in place to conserve energy at

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• **Fig. 16.2** Standardized mortality ratio based on birth weight in pounds in women and men from studies of Barker and Sultan. (From Barker DJ, Sultan HY. Fetal programming of human disease. In: Hanson M, et al., eds. *Fetus and neonate physiology and clinical applications: growth*. Vol 3. Cambridge, UK: Cambridge University Press; 1995.)

the expense of growth. Situations of deprivation or exposure to stressors can occur, however, in the absence of any effect on the growth potential or size. This makes it difficult sometimes to understand the mismatch concept and its role in the growing incidence of chronic adult diseases. The developmental origins of adult health and diseases are now recognized to have major public health implications worldwide. The World Health Organization states, "The global burden of death, disability, and loss of human capital as a result of impaired fetal development is huge and affects both developed and developing countries." (http://www.who.int/nutrition/publications/fetal_dev_report_EN.pdf, accessed December 18, 2017). This statement advocates for a broader concept of maternal well-being and achieving an optimal environment for the fetus (and newborn) to maximize the potential for a full and healthy life. This concept has widened to include plasticity during childhood, which is being presently investigated in prospective studies consisting of large populations (Fig. 16.3).

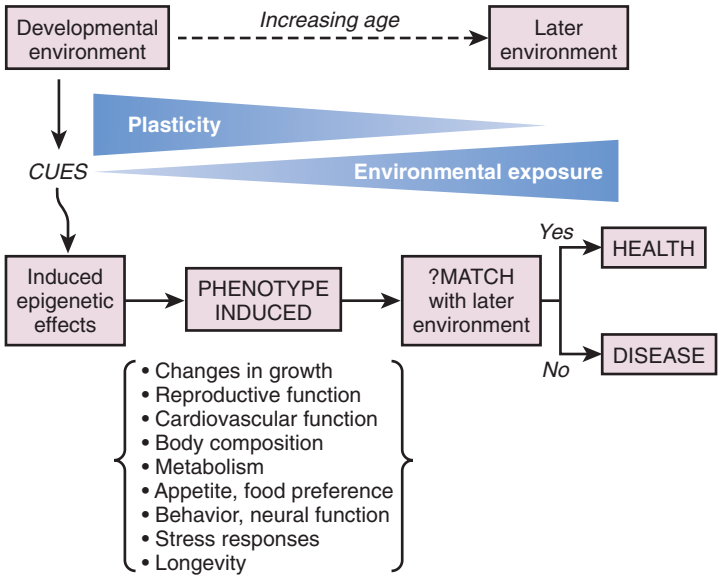
Fetal Origins of Vascular Structural Abnormalities and Dysfunction in Adult Cardiometabolic Disease

The Barker hypothesis established a connection between maternal nutrition during pregnancy, low birth weight in the offspring, and development of cardiovascular disease in offspring in adulthood, such as hypertension, coronary heart disease, stroke and metabolic syndrome including insulin-resistance, type 2 diabetes, and obesity. Maternal undernutrition as well as nutritional excess during pregnancy can predispose offspring to later cardiovascular disease. Specifically, maternal caloric intake has been shown to influence vasculogenesis, angiogenesis, barrier integrity, and vascular maturation in the fetus.[38] On the other extreme, maternal obesity and excessive maternal weight gain in pregnancy can predispose offspring to elevated blood pressure and increased adiposity and risk of also becoming obese.[39,52] There is building evidence that maternal nutrition and cardiovascular and metabolic disease such as hypertension, type 2 diabetes, and obesity can have adverse effects on fetal vascular development and function that predispose the fetus to future adult cardiovascular and metabolic disease (Fig. 16.4).[14] Most of the evidence has been based on animal studies and less on human studies.

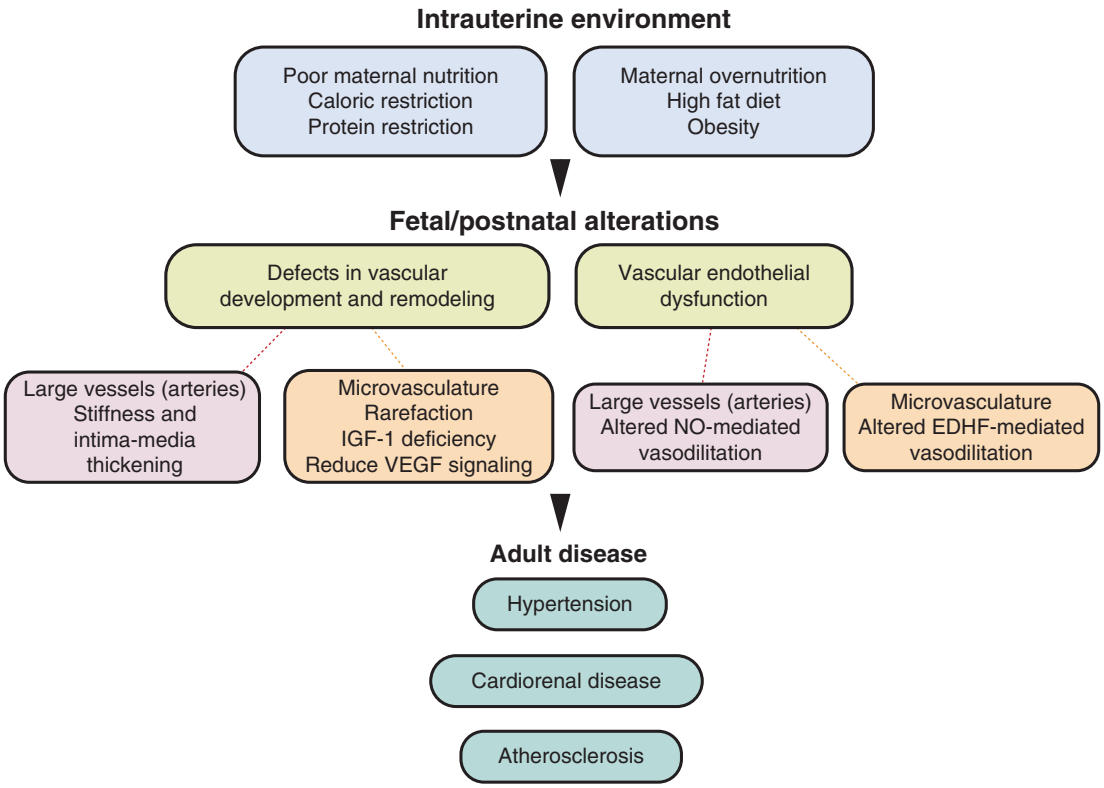
In regard to larger vessels, arterial stiffness and increased coronary artery intima-media thickness has been described in low birth weight and small for gestational infants.[50,51] Infants with excessive gestational weight gain had correlating postnatal obesity with higher body mass index (BMI) and systolic blood pressures.[39] Animal studies, rodent and nonhuman primate models, also provide evidence that undernutrition as well as a high fat diet prenatally can lead to vascular remodeling in offspring, specifically increased arterial stiffness, and increased arterial wall thickness that can lead to atherosclerosis.[21,27]

Endothelial dysfunction, or loss of normal control of vasodilation by the endothelium, is also seen in hypertension

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• **Fig. 16.3** Developmental plasticity declines and exposure to environmental challenges increases with age. Epigenetic processes are induced by cues from the developmental environment. They play a role in determining the phenotype of the offspring as part of a life course strategy to match the environment. If not appropriately matched, the risk of later disease is increased. (From Godfrey KM, et al. Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. *Pediatr Res*. 2007;61:5R.)



• **Fig. 16.4** Impact of maternal nutritional status during pregnancy on vascular development, structure, and function and implications for programming of adult cardiovascular disease in offspring. EDHF, endothelium-derived hyperpolarizing factor; IGF-1, insulin-like growth factor 1; NO, nitric oxide; VEGF, vascular endothelial growth factor.

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and metabolic syndrome. The vascular endothelium, the inner lining of blood vessels, has multiple roles including the regulation of vascular tone, trafficking of inflammatory cells, and an antithrombotic role. Vascular tone is regulated by local, neural, humoral, and myogenic factors. Vasoactive endothelium-derived mediators that activate their corresponding receptors on nearby smooth muscle cells include vasoconstrictors such as thromboxane A2, endothelin-1 (ET), and prostaglandin H2 and vasodilators such as nitric oxide (NO), prostacyclin (PGI2), and endothelium-derived hyperpolarizing factor (EDHF).[11,28] In addition to structural remodeling abnormalities, low birth weight infants and infants with poor fetal nutrition have evidence of endothelial dysfunction characterized by impaired vasodilation.[22,66] In human studies, utilization of the noninvasive techniques of flow-mediated dilatation and pulse wave velocity has allowed for the measurement of vascular function in large conductance and resistance arteries.[62] A cohort study showed that abnormal flow-mediated dilatation and findings of early atherosclerosis mediated by elevated blood pressure, triglyceride levels, and inflammation were associated with impaired fetal growth.[66] Endothelial dysfunction in animal models has been studied by measuring endothelium-dependent acetylcholine-induced relaxation of vascular smooth muscle cells by wire myography or measurement of shear mediated dilatation using pressure myography.[72] Multiple animal studies have shown that maternal diet can lead to abnormal acetylcholine-mediated arterial dilatation in adult offspring.[27,64,69] IUGR induced early in pregnancy resulted in adult offspring with abnormal endothelium-dependent and endothelium-independent dilatation and hypertension. Nitric oxide (NO) has a central role in mediating vascular dilatation and is dependent on NO bioavailability. Increased oxidative stress and the presence of reactive oxygen species (ROS) reduce NO bioavailability.[11] The increased oxidative stress and increased ROS production in conditions such as obesity and type 2 diabetes are associated with endothelial dysfunction.[71] Increased oxidative stress and low levels of antioxidant enzymes are associated with SGA and LGA infants.[63] Maternal overnutrition resulted in increased placental expression of ROS and was associated with neonatal insulin resistance and obesity.[57]

The microvasculature, or small resistance arteries, arterioles, capillaries, and venules with diameter less than 200 μm located within tissue parenchyma, has a primary role in regulating tissue perfusion and optimal exchange of gases, nutrients, water, and solutes between the blood and surrounding tissues. The microvasculature has an important regulatory role in maintaining adequate tissue perfusion and controlling blood pressure.[56] Microvascular rarefaction, or decreased vascular density, and dysfunction leading to the development of cardiovascular and metabolic disease in adulthood may be primed by the maternal environment, thus stressing the importance of the pre- and perinatal environment in the development of vascular disease such as hypertension, coronary heart disease, and stroke. Rarefaction has been observed in obesity and hypertension and is thought to contribute to insulin resistance. Rarefaction results in restricted tissue perfusion and longer capillary diffusion distances for metabolic exchange. Studying microvascular structure and function in humans is, however, challenging and limited to accessible vascular beds including skin and retinal microvasculature. Low birth weight has been shown to be associated with rarefaction and impaired endothelium-dependent vasodilatation of skin microvasculature. SGA babies have evidence of decreased retinal vascularization that is known to be mediated by downregulation of vascular endothelial growth factor (VEGF) and associated with insulin-like growth factor 1 (IGF-1) deficiency in preterm and IUGR infants.[33] Although the findings of rarefaction in the skin and retinal vasculature of low birth weight and SGA infants may not be reflective of the microvascular environment in major organs such as the kidney, heart, and skeletal muscle, the data suggests that impaired vasculogenesis and angiogenesis also occur at these sites and may contribute to the microvascular dysfunction and the development of cardiometabolic disease in this risk group. The effect of maternal or intrapartum factors, including high fat diet, calorie restriction, hypertension, and fetal oxygen stress on microvascular structure in animal studies have been demonstrated.[42,48] Reduced microvascular development, specifically in the renal and intestinal microvasculature, in the offspring of mothers with these conditions during pregnancy has been associated with the development of hypertension and cardiometabolic disease in these offspring.[35,54,74,75] Offspring born to dams on a low protein diet had evidence of microvascular rarefaction of arterioles and capillaries at age 7–28 days and later were associated with the development of elevated blood pressure.[54] The reduction in VEGF and VEGF receptor expression has been demonstrated in some of these studies, indicating that the absence of angiogenic signaling from the VEGF pathway may be the mechanism inhibiting microvascular development.

Endothelial dysfunction in the microvasculature can alter normal vasoconstrictor and dilator responses and adversely affect blood flow, perfusion, and glucose uptake and oxygenation. Overall, few studies, particularly human studies, have demonstrated the effects of maternal nutritional status on endothelial function specifically in the microvasculature. In animal models, a reduction in acetylcholine-induced vasodilation in cremaster arterioles has been observed in offspring of mothers fed a high-fat diet.[47] Further, endothelium-derived hyperpolarization (EDH)-mediated vasodilation in the microvasculature can be impaired in the setting of fetal growth restriction and in offspring exposed to both excessive and restrictive calories in utero.[46,69] Data is yet lacking on the effects of excessive nutrition during pregnancy on the microvascular function of the offspring exposed to an adverse in utero environment.[55]

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Placental Abnormalities and Association With Adult Disease

The placenta has an essential role in promoting normal fetal development and maintaining pregnancy. Its major functions include providing oxygen and gas exchange; transfer of macro- and micronutrients, vitamins, hormones, and antibodies; elimination of waste products; metabolism of glycogen, cholesterol, and fatty acids; and endocrine secretion of hormones that sustain pregnancy. Fetal growth and infant birth weight not only depend on maternal nutrition but are also dependent on placental function and transport of nutrients from the mother to the fetus.[8] Nutrient transfer by the placenta is reflected in the weight, size, and shape of the placenta, and these placental characteristics have been found to be a marker for later disease in adulthood, including hypertension and coronary heart disease.[5,25] Epidemiologic studies have demonstrated associations between placental size and shape and adult chronic disease.[61] The Helsinki Birth Cohort of 13,345 men and women born between 1943 and 1944 showed the association between low placental weight and surface area with hypertension in adulthood.[5] In this same birth cohort, small placentas, small placental surface area, and placental inefficiency was a powerful predictor of coronary heart disease in the men followed in this study. There is also data to suggest that a large placenta with increased surface area and increased number of lobes can also result in elevated blood pressure. Children in a study from Bristol, United Kingdom (ALSPAC study), had higher birth weights and were found to have elevated blood pressure at age 9.[2] In all, these studies demonstrated that both large and small placentas can limit the flow of nutrients to the fetus and ultimately have long-term effects on cardiovascular health into adulthood.

Gestational Diabetes and Long-Term Metabolic Effects on Offspring

Gestational diabetes is increasingly prevalent in industrialized countries wherein overnutrition leading to obesity and type 2 diabetes is a health concern. Investigations have uncovered an association of type 2 diabetic risk alleles in infants born with a reduced size, linking the genetics of type 2 diabetes with low birth weight.[45] There is evidence from epidemiologic studies that intrauterine exposure to maternal diabetes can lead to adverse metabolic outcomes in offspring, including obesity, insulin resistance, and type 2 diabetes.[3,16,17,73] Data from a population of Pima Indians in Arizona with high rates of obesity and type 2 diabetes revealed that offspring of women who had gestational diabetes were obese and had a higher prevalence of type 2 diabetes.[17] To address the confounding factor that genetics contributes to the development of type 2 diabetes in offspring of diabetic mothers in the same population of Pima Indians, a sibship study was done to compare body mass index (BMI) and the prevalence of type 2 diabetes in siblings born before and after their mother was diagnosed with type 2 diabetes. Among a population of mothers genetically predisposed to type 2 diabetes, it was demonstrated that offspring born to mothers after they had developed diabetes had a significantly higher risk of type 2 diabetes and a higher body mass index (BMI) than their siblings born prior to development of diabetes in the mother.[16] Other studies have provided evidence that intrauterine exposure to hyperglycemia can result in offspring with either type 2 diabetes or type 1 diabetes, obesity, and metabolic syndrome.[73]

Cancer

Although most cancers are diagnosed later in life, the pathogenesis of cancer is multifactorial, and prenatal events may bear some contribution to the disease. Birth weight has been speculated to be associated with the development of breast, ovarian, colon, lung, and some blood cancers.[9,26,60] Although numerous oncogenes have been identified, genetics and environmental triggers cannot completely explain the pathogenesis of many cancers.

Increased or decreased maternal concentrations of estrogen and testosterone may play roles in a tissue's potential for cellular dysplasia. Trichopoulos first proposed that elevated estrogen concentrations during pregnancy increase the risk of breast cancer in female offspring.[70] Estrogen concentrations peak during pregnancy, being 10 times higher in pregnant women. Higher maternal estrogen concentrations are noted with advanced maternal age, twin gestations, and LGA status. Conversely, estrogen is inversely associated with pregnancy-induced hypertension. Fetal mammary gland cells are undifferentiated and particularly vulnerable to the carcinogenic effects of estrogens and other growth hormones such as IGF. As a result, in utero exposure to high estrogen levels increases the risk of mitogenic activity and adult-onset cancer.

Preeclampsia and eclampsia have shown to be protective against breast cancer.[43,70] A clear positive association between breast cancer and higher birth weight, birth length, and placental weight was reported. Further epidemiologic studies have confirmed these findings. In a meta-analysis of 18 studies consisting of 16,424 breast cancer cases, the risk for breast cancer increases 7% for each 1 kg increase in birth weight.[43]

Psychosocial Aspects

When examining psychosocial consequences of low birth weight, the question is raised why suboptimal fetal and neonatal growth are risk factors for a less successful adult life. Low birth weight is associated with poor cognition, increased risk for behavioral disorders such as autism and attention deficit hyperactivity disorder, and adult-onset psychiatric disorders such as depression and schizophrenia.[1,53,58] The fetal programming model provides some answers. Adults who were SGA or VLBW have had remodeling of their hormones and metabolism in early neonatal life from heightened stress responses.[34] Chronic stress, either antenatal

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or postnatal, can permanently alter the hypothalamic-pituitary-adrenal axis, resulting in high concentrations of glucocorticoids.[34] Compounding the neonate's hyperactive state, fetuses and premature and critically ill neonates are often prescribed varying doses and types of synthetic glucocorticoids, which may further alter brain development. This hormonal and central nervous system remodeling leads not only to neurodevelopmental impairments and an increased risk for cardiovascular disease but also maladaptive behaviors such as anxiety and depression.[1,34] Malnutrition during a critical time in prenatal and postnatal development may also play a vital etiologic role. In summary, fetal origins of adult disease not only help explain why fetal reprogramming can affect systemic adult disease processes but also explain the difference seen in academic performance, professional attainment, sexuality and reproduction, emotionality, personality, and overall quality of life.[1,34,58]

Improvements in technology and the practice of neonatology have allowed clinicians to adequately resuscitate preterm infants at younger and younger gestational ages. The generations of preterm infants who have survived are now being followed into adulthood, and they provide information on the types of problems facing infants who are SGA and have a VLBW.[58] The particular medical problems these infants experience are well described in the literature. The social implications of being born premature have not been studied that well, however, and are only now beginning to emerge. Countries in Europe and the United States that maintain national databases are reporting their findings on adult outcomes for premature and low birth weight neonates. In a Helsinki cohort, fast postnatal growth superimposed on restricted prenatal growth was also shown to influence development of the anxiety trait in men and women at 63 years of age. This pattern resembled the pattern seen with the development of cardiovascular events, supporting a shared common developmental origin.[37]

Toxins, Endocrine Disrupters, and Micronutrient Metabolism

(See Also Chapter 14)

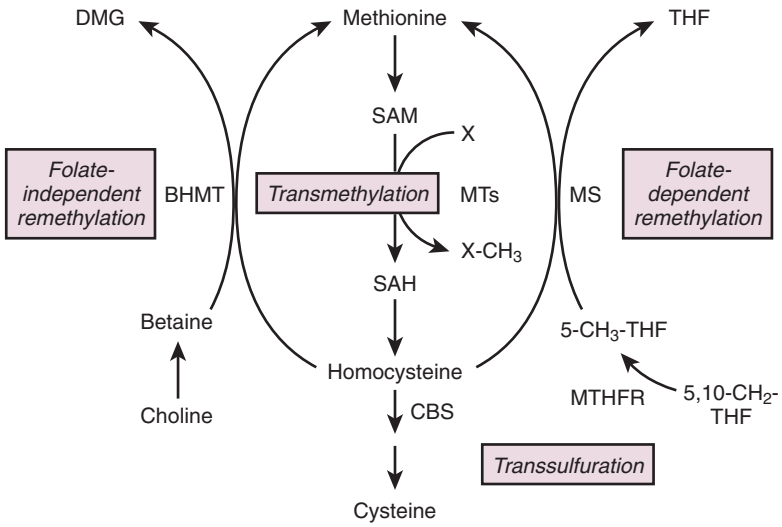
Although considerable focus has been on prenatal and postnatal nutrition as the inciting factor, other factors, such as maternal stress, prenatal glucocorticoids, infections associated with inflammation, and hypoxic-ischemic insults secondary to a diminution of fetal blood flow, seem to affect fetal development, resulting in subsequent cardiovascular and metabolic abnormalities.[9,20] Certain endocrine disrupters, such as pesticides, estrogens, antiandrogenic compounds (bisphenol A and phthalates), can affect endocrine function and have far-reaching effects on the phenotype of animals and children.[40,44,49] These changes, which are considered epigenetic in nature, persist into future generations when a pregnant animal is exposed. The fetus (second generation) and the gametes of the fetus (which give rise to the third generation) face the same exposure. Increases in pubertal abnormalities, ovarian and testis disease, and obesity have been observed.[40] The classic example of how an endocrine disruptor can be responsible for tissue and hormonal reprogramming is diethylstilbestrol (DES), a synthetic estrogen. In animal studies, offspring of mothers exposed to low-dose DES exhibit low birth weights, catch-up growth, adult-onset obesity, decreased activity, and abnormal glucose metabolism.[49] Bisphenol A, a chemical used in plastics and an environmental estrogen, is also linked to obesity and insulin resistance.[49] These changes may be sex-specific depending on the time of exposure. Moreover, other airborne toxins can also have a long-term effect on the adult offspring.

Epigenetics

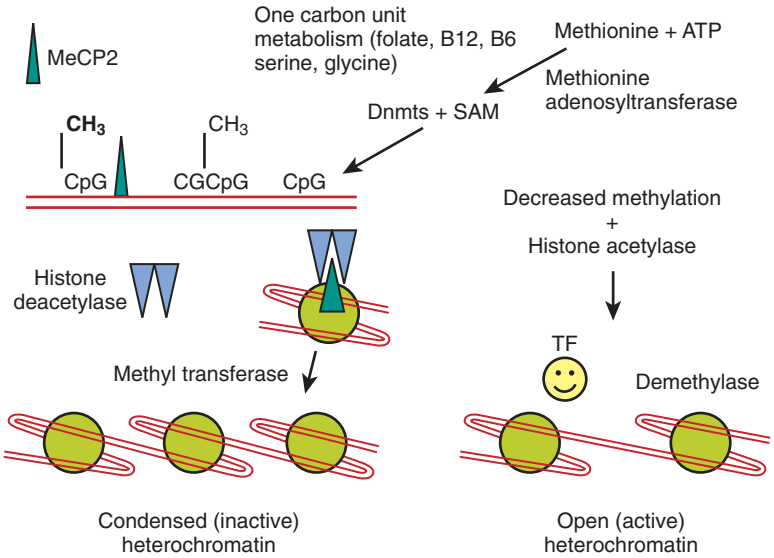
Waddington coined the term *epigenetics* and defined it as a branch of biology that studies the causal interactions between genes and the phenotype. Epigenetics consists of heritable covalent modifications of DNA and histones that affect gene expression without alterations in DNA nucleotide sequence. Epigenetic changes in gene expression form the important link between environment and genome. Environmentally induced epigenetic modifications, in the form of DNA methylation, histone acetylation, or microRNA, can result in permanent changes in gene regulation and expression that are transmitted from parental cells to daughter cells through rounds of somatic cell division and are inherited across multiple generations.

Subtle changes in DNA methylation occur through the rest of fetal development and subsequently during extrauterine life, explaining the phenotypic differences with age in monozygotic twins. Although DNA methylation relies on the one-carbon metabolism involving methyl donors (folic acid, methionine, betaine) (Fig. 16.5), DNA is methylated in specific noncoding regions and at DNA repeats of transposable elements. In particular, CpG islands, DNA regions where a cytosine (C) nucleotide is followed by a guanine (G) nucleotide and linked together by a phosphate (p) group, of a gene promoter are unmethylated in tissues of expression but can undergo methylation in tissues in which that particular gene is not expressed (Fig. 16.6). Hypomethylation of the imprinted locus *IGF2*, a gene that regulates growth and development, was observed six decades later in individuals born during the Dutch hunger winter of 1944 who had developed obesity later in life after periconceptual exposure to famine.[32] Of more relevance today is the transgenerational epidemic of obesity in industrialized countries wherein overnutrition is prevalent. More recent epidemiologic studies have demonstrated epigenetic changes in offspring born to mothers with overnutrition, obesity, metabolic disease, and diabetes mellitus during pregnancy that predispose these offspring to similar conditions. A study using a mass spectrometry–based approach assessing blood methylation in offspring from mothers before and after bariatric gastrointestinal bypass surgery to reduce obesity demonstrated differences in DNA methylation of glucoregulatory, immunologic, and cardiovascular

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• **Fig. 16.5** Scheme of the one carbon metabolism showing the folate-dependent and -independent pathways related to transmethylation that provide methyl groups to the CpG islands of DNA. In addition, methionine is a methyl donor. BHMT, Betaine homocysteine methyltransferase; CBS, cystathionine β-synthase; DMG, dimethyl-glycine; MS, methionine synthetase; MTs, methyltransferases; MTHFR, methylene tetrahydrofolate reductase; SAH, *S*-adenosyl-L-homocysteine; SAM, *S*-adenosyl-L-methionine; THF, tetrahydrofolate.



• **Fig. 16.6** Simplistic scheme showing methylation (CH_3) of CpG islands achieved by DNA methyltransferases (Dnmts) and *S*-adenosyl-L-methionine. Methylated DNA attracts methylated CpG binding protein 2 (MeCP2), which recruits histone deacetylases and histone methylases, resulting in histone deacetylation and methylation. When this occurs in a gene promoter, it causes heterochromatin formation, repressing gene expression. This is facilitated further by heterochromatin protein (HP1) binding. In contrast, hypomethylation of DNA attracts histone acetylases and demethylases, which have the opposite effect, resulting in euchromatin formation, transcription factor (TF) binding, and activation of gene transcription. ATP, Adenosine triphosphate. (From Devaskar SU, Thamotharan M. Metabolic programming in the pathogenesis of insulin resistance. *Rev Endocr Metab Disord*. 2007;8:105.)

disease genes.[31] Gene candidate studies have demonstrated hypomethylation of specific genes such as mesoderm-specific transcript (MEST) isolated from fetal cord blood and placenta in offspring born to mothers with either diet-treated or insulin-dependent diabetes mellitus compared to controls without diabetes mellitus.[24] These studies show that epigenetic changes involving DNA methylation can result from prenatal exposure to hyperglycemia and predispose to later increased risk of obesity, metabolic disease, and diabetes mellitus in offspring.

A more recently recognized epigenetic mechanism resulting in altered gene expression is the post-transcriptional

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regulation of RNA by short single-stranded, noncoding microRNAs.[12] MicroRNAs indirectly affect translation of key factors or enzymes required for epigenetic processes in the nucleus. MicroRNAs bind to specific complementary sequences in the 3′-untranslated region of a gene suppressing translation. By suppressing DNA methyltransferase enzyme translation, microRNAs indirectly can regulate DNA methylation. In a study of monozygotic twin pairs discordant for type 2 diabetes, 20 microRNAs isolated from skeletal muscle were identified that were downregulated in the twins with diabetes compared to their nondiabetic twin.[7] The downregulation of two microRNAs, miR-15b and miR 16, were found to be the most statistically significant and were shown to target the expression of key proteins in the insulin signaling pathway, including insulin receptor (INSR), IRS1, and PIK3R1.

A few studies have started to identify epigenetic biomarkers that could predict the risk for obesity and developing metabolic disease later in life. Promoter methylation of the retinoid X receptor, alpha (RXRA), a nonimprinted gene, in umbilical cord tissue of healthy neonates was associated with increased adiposity during later childhood.[30] RXRA promoter methylation had a stronger effect in predicting later childhood adiposity than other factors such as birth weight or maternal body composition, supporting the usefulness of this epigenetic biomarker in predicting obesity. Promoter methylation of another gene, peroxisomal proliferator-activated receptor- gamma-co-activator-1 alpha (PPARG-C1A) in blood from children as early as 5-7 years old was found to be stable over time from childhood to puberty, and when detected, was able to predict risk for increased adiposity several years later up to age 14.[13]

Overall, an aberrant environment during a critical phase of development imposes permanent adaptive changes as a mode of survival. These adaptations are mediated by epigenetic alterations of the genome, which change gene expression. Changes in gene expression affect the cell cycle and phenotype and are carried transgenerationally. This phenomenon underlies the concept of developmental origins of adult health and disease.

Translation to Neonatology

How do these epidemiologic associations in humans and mechanistic paradigms discovered in animal models affect neonatology? Epidemiologic associations and human and animal studies continue to demonstrate that a reduction or an increase in birth weight is associated with an array of adult-onset chronic diseases.

In practice, changes of 1 kg in birth weight can be seen in infants with growth restriction and LGA compared with appropriate-for-gestational-age neonates. However, although weight serves as an overall indicator for a fetus's and child's well-being, in utero and extrauterine stressors can trigger later disease without any change in growth. It has become apparent that intrauterine and postnatal nutrition and growth trajectories have far-reaching implications for an individual. Further postnatal interventions (nutritional or otherwise) can cause lifelong perturbations requiring close long-term follow-up. Particularly, postnatal nutrition walks a fine line between guarding against "nutritional excess" while ensuring adequate energy for the developing brain.

The recognition of variability in a given population based on ethnicity, prenatal nutrition, stressors, maternal disease, placental health, infections, and toxin exposure is important. An example is growth rate and nutritional practices that vary based on ethnicity and the country/region of origin. An ideal growth pattern for the West may not be reflected or achieved in certain South Asian countries. Although infants may be smaller in size, their body composition may be entirely different. More evidence is emerging that body mass index measurements may not reflect the whole picture. Fat distribution plays a major role in whether an infant is prone to developing obesity and insulin resistance with time. Individuals who have subcutaneous fat accumulation may be relatively more protected than individuals with visceral adiposity. Further signs of lipotoxicity seen with fat redistribution and accumulation in tissues such as the liver, beta-islet cells of the pancreas, skeletal muscle, and bone marrow are detrimental to metabolic homeostasis. Various biomarkers, such as circulating insulin (C-peptide), leptin, adiponectin, and cytokine concentrations are considered to preempt childhood and adolescent disorders secondary to insulin resistance.

Similar approaches are emerging with respect to the development of other chronic disorders, such as hypertension and neuropsychoses. Although the search for an ideal battery of biomarkers that can predict the adult phenotype of an infant is ongoing, the prenatal and postnatal periods of life form the critical window of developmental plasticity that contributes to the entire life cycle of the individual, including the phenotype of future generations.

Key Points

- The Barker hypothesis identified a link between cardiovascular disease and birth weight.
- Maternal nutrition, diabetes mellitus, obesity, and exposure to stress and environmental toxins during pregnancy can affect fetal growth, organ, and vascular development, and predispose the fetus to cardiovascular and metabolic disease, psychiatric disorders, and cancer in adulthood.
- Epigenetic mechanisms drive fetal programming of adult disease and can have generational effects.

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17

Hypertensive Disorders of Pregnancy

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Hypertensive disorders of pregnancy consist of a broad spectrum of medical complications, including gestational hypertension, preeclampsia, eclampsia, and pregestational hypertension. The incidence is estimated to be between 3% and 10% of all pregnancies.[4,26,74] Worldwide, preeclampsia and related conditions are among the leading causes of maternal mortality.[26] Although maternal death caused by preeclampsia is less common in developed countries, maternal morbidity remains high. Hypertensive disorders of pregnancy are also the leading cause of fetal growth restriction and indicated preterm deliveries, with the associated complications of prematurity such as neonatal deaths and serious long-term morbidity being substantial.[26]

Preeclampsia is a pregnancy-specific syndrome that is clinically recognized by new onset hypertension and proteinuria after 20 weeks' gestation. Vascular dysfunction is central to the systemic maternal manifestations of preeclampsia, including increased peripheral vascular resistance, heightened sensitivity to vasopressors, endothelial dysfunction, vasospasm, ischemia, inflammation, activation of the coagulation cascade, and platelet aggregation leading to multiorgan damage.[69] The term *eclampsia* is derived from the Greek, meaning "sudden flashing" or "lightning," and refers to the seizures that can accompany this syndrome. Although the Egyptians and Indians described this disorder more than 2000 years BCE, the only known cure for preeclampsia remains delivery of the fetus and placenta.

Classification of Hypertensive Disorders of Pregnancy

Precise classification of the hypertensive disorders of pregnancy has remained challenging because of the changing nomenclature over time, with terms such as *toxemia* and *pregnancy-induced hypertension* now considered outdated. Furthermore, varying diagnostic criteria are used in different regions of the world.[4,70] The classification system most commonly used in the United States is based on the Working Group Report on High Blood Pressure in Pregnancy published in 2000 and revised in 2013 by the American College of Obstetricians and Gynecologists (ACOG) Task Force for Hypertensive Disorders of Pregnancy.[4,30] The goals of the Task Force were to evaluate the existing evidence and update the classification system as well as the management of hypertensive disorders of pregnancy.[4] Four major categories are described: gestational hypertension, preeclampsia-eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension (Table 17.1).

Gestational Hypertension

Gestational hypertension is defined by elevated blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic) in a previously normotensive woman. High blood pressure should be sustained with documented elevations on at least two occasions 4 hours apart. Blood pressure should be measured in the semi-Fowler or seated position with an appropriately sized cuff. Disappearance of sounds (Korotkoff phase V) is used to determine diastolic pressure. Gestational hypertension is a provisional diagnosis during pregnancy and includes women in three categories: (1) women who will progress to develop preeclampsia, (2) women with "transient hypertension of pregnancy" who do not develop preeclampsia and revert to normal blood pressures by 12 weeks' postdelivery, and (3) women who may have previously unrecognized chronic hypertension. Definitive diagnosis is possible only after reassessment at 6-12 weeks' postpartum.

Preeclampsia

Preeclampsia (see Table 17.1) is defined as new onset of elevated blood pressure and new onset of proteinuria after 20 weeks of gestation; or in the absence of proteinuria, hypertension with any of the following: thrombocytopenia (platelet count of less than 100,000/μL), impaired liver function blood (elevated blood concentrations of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine of greater than 1.1 mg/dL or doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new onset of cerebral or visual disturbances. The term "mild" preeclampsia has been replaced by "preeclampsia without severe features" to emphasize the need for ongoing vigilance

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Abstract

Hypertensive disorders of pregnancy, including preeclampsia, are common complications of pregnancy and associated with significant maternal and fetal/neonatal morbidity and mortality.

Keywords

preeclampsia
hypertensive disorders
pregnancy-induced hypertension
HELLP syndrome

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TABLE 17.1 Classification of Hypertensive Disorders of Pregnancy

Preeclampsia	• Blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least two occasions at least 4 hours apart after 20 weeks' gestation in a woman with a previously normal blood pressure OR • Blood pressure ≥160 mm Hg systolic or ≥110 mm Hg diastolic; hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy AND • Proteinuria ≥300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection) OR protein/creatinine ratio of ≥0.3 OR dipstick reading of 1+ (used only if other quantitative methods not available) OR in the absence of proteinuria, new-onset hypertension with the new onset of any of the following: • Thrombocytopenia with platelet count <100,000/μL • Renal insufficiency with serum creatinine of >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease • Impaired liver function with elevated blood concentration of liver transaminases to twice the normal concentration • Pulmonary edema • Persistent cerebral or visual symptoms
Severe features of preeclampsia (any of these findings)	• Systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥110 mm Hg on two occasions at least 4 hours apart while a patient is on bed rest (unless antihypertensive therapy is initiated before this time) • Thrombocytopenia (platelet count <100,000/μL) • Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both • Progressive renal insufficiency (serum creatinine concentration of >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease) • Pulmonary edema • Persistent cerebral or visual disturbances
Eclampsia	• Generalized seizures that occur in a preeclamptic woman that cannot be attributed to other causes
Superimposed preeclampsia (likely when any of these are present)	• A sudden increase in blood pressure that was previously well-controlled or an escalation of antihypertensive therapy to control blood pressure • New onset of proteinuria or sudden increase in proteinuria in a woman with known proteinuria before or early in pregnancy Severe features: • Severe range blood pressure despite escalation of antihypertensive therapy • Thrombocytopenia (platelet count <100,000/μL) • Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both • New onset or worsening renal insufficiency • Pulmonary edema • Persistent cerebral or visual disturbances
HELLP syndrome	• Presence of *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets; may or may not occur in the presence of hypertension and is often considered a variant of preeclampsia
Gestational hypertension	• New onset of sustained elevated blood pressure after 20 weeks' gestation in a previously normotensive woman (≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least two occasions 6 hours apart) • No proteinuria

*Precise diagnosis is often challenging, and high clinical suspicion is warranted given the increase in maternal and fetal-neonatal risks associated with superimposed preeclampsia.

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as well as the progressive and systemic nature of this syndrome. Severe features of preeclampsia include:

- Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while a patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count <100,000/μL)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration of >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- Persistent cerebral or visual disturbances

Eliminating the dependence on proteinuria from the diagnosis of preeclampsia is a major revision from the previous diagnostic criteria, with the intent to recognize the systemic and progressive nature of preeclampsia. This is more consistent with other diagnostic criteria used internationally. Fetal growth restriction was also removed from the diagnosis but remains an important aspect in the evaluation and management of women with preeclampsia. As in the 2000 Working Group Recommendations, an increase of 30 mm Hg systolic or 15 mm Hg diastolic blood pressure from baseline in early pregnancy measurements is not included in the diagnostic criteria, because women with these changes alone are not at increased risk for adverse outcomes. Although edema may raise clinical suspicion for preeclampsia, it is not a diagnostic criterion for preeclampsia, because nondependent edema occurs in 10%-15% of women who remain normotensive throughout pregnancy and is neither a sensitive nor specific sign of preeclampsia.

Eclampsia

Eclampsia refers to generalized seizures occurring in a woman with preeclampsia that cannot be attributed to other causes.

Chronic Hypertension

Chronic hypertension is defined as hypertension present prior to pregnancy or that is newly diagnosed before 20 weeks of gestation. Persistent blood pressure of greater than 140/90 mm Hg is considered hypertension. High blood pressure that persists 6-12 weeks postpartum is also classified as chronic hypertension.

Superimposed Preeclampsia

Preeclampsia superimposed on chronic hypertension is characterized by a sudden and sustained increase in blood pressure with or without substantial increase in proteinuria. Diagnosis is often challenging because both blood pressure and urinary protein excretion increase toward the end of pregnancy. High clinical suspicion is warranted given the increase in maternal and fetal-neonatal risks. End-organ involvement such as thrombocytopenia, elevated liver transaminase enzymes, or a rapid decline of renal function are also diagnostic of superimposed preeclampsia.

HELLP Syndrome

HELLP syndrome is defined by the presence of *h*emolysis, *e*levated *l*iver transaminases, and *l*ow *p*latelets. This may or may not occur in the presence of hypertension or proteinuria. It is generally considered a variant of preeclampsia.

A major criticism of the various classification systems is that none have been independently evaluated for the ability to identify the subgroup of women who are at increased risk of adverse pregnancy outcomes. Furthermore, there is disagreement regarding the degree of hypertension, presence or absence of proteinuria, and criteria for disease severity among the different classification systems used internationally.[70] These inconsistencies have led to challenges in comparing and generalizing epidemiologic and other research findings. Studies have sought to develop clinically relevant definitions guided by the evidence and based on predictors of adverse outcomes.[71] The most recent ACOG Task Force recommendations address many of these issues.

Epidemiology of Preeclampsia

The incidence of preeclampsia is increasing in the United States and is likely related to the higher prevalence of predisposing disorders, such as hypertension, diabetes, and obesity, and to delay in child-bearing, as well as to the use of assisted reproductive technologies with their associated increase in multifetal gestation.[22,74] The global impact of preeclampsia is profound, with short- and long-term effects on both mother and baby.

Maternal Effects

Short Term

In a systematic review by the World Health Organization, hypertensive disorders of pregnancy account for 16% of all maternal deaths in developed countries and as high as 26% in Latin America and the Caribbean.[40] In areas in which maternal deaths are high, mortality is largely attributable to eclampsia rather than preeclampsia.[26] Based on data from the United States National Hospital Discharge Survey, the rate of preeclampsia increased by 25% between 1987 and 2004; however, there was a trend toward a decrease in eclampsia by 22%.[74] Although maternal mortality owing to hypertensive disorders is less common in high-income countries, rates of severe morbidity—including renal failure, stroke and permanent neurologic impairment, cardiac dysfunction or arrest, respiratory compromise, coagulopathy, and liver failure—are high. In a study of hospitals managed

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by the Health Care America Corporation, preeclampsia was the second leading cause of pregnancy-related admission to intensive care units after obstetric hemorrhage.[54]

Recurrence in Subsequent Pregnancies

Recurrence of preeclampsia varies between 7% and 20%. This wide variation in the estimates is based on the quality of the diagnostic criteria used. The risk of recurrent preeclampsia is even higher with two prior preeclamptic pregnancies or with earlier gestational age of preeclampsia onset.[33,47]

Long-Term Cardiovascular Risks

A landmark study published in 1976 demonstrated that women who had eclampsia in any pregnancy after their first had a mortality risk that was two- to fivefold higher over the next 35 years compared with controls.[13] Since that time, several large epidemiologic studies have confirmed that women with preeclampsia in any pregnancy have an increased risk of cardiovascular diseases later in life and related mortality.[48] This risk is higher among women with preeclampsia that was recurrent, that necessitated a preterm delivery, or that was associated with fetal growth restriction. Hypertension, dyslipidemia, insulin resistance, endothelial dysfunction, and vascular impairment have all been observed months to years after the preeclamptic pregnancy, further supporting the link between preeclampsia and cardiovascular disease.[48] In 2011, the American Heart Association added preeclampsia to its list of recognized risk factors for cardiovascular disease. Based on these data, women with a history of preeclampsia should have ongoing, close surveillance to prevent or detect cardiovascular disease. Further investigation is needed to resolve whether common risk factors lead to the development of both preeclampsia and subsequent cardiovascular disease or whether preeclampsia itself contributes to this future risk.

Fetal and Neonatal Effects

Fetal and neonatal outcomes related to hypertensive disorders vary widely around the world and are associated with resource availability, presence of neonatal intensive care facilities, and limits of viability as defined by gestational age and birth weight. In developing countries, one-quarter of stillbirths and neonatal deaths are associated with preeclampsia-eclampsia. Infant mortality is three times higher in low-resource settings compared to high-income countries, largely due to the lack of neonatal intensive care facilities.[26]

It is estimated that 12%-25% of fetal growth restriction and small-for-gestational-age (SGA) infants, as well as 15%-20% of all preterm births, are attributable to preeclampsia.[4] These preterm births are generally indicated, because the only known cure for preeclampsia is delivery of the fetus and placenta. The associated complications of prematurity are substantial, including neonatal deaths and serious long-term morbidity. The risk of complications is inversely associated with gestational age at delivery. Extremely premature infants (<25 weeks) have the highest mortality rate, and if they survive, they are at substantial risk for long-term issues. These include neurodevelopmental impairment such as impaired cognitive skills, motor deficits with fine and/or gross motor delay, cerebral palsy, vision problems, hearing loss, and behavioral and psychological problems, as well as recurrent hospitalization and chronic lung problems and other health problems.[35]

Prematurity also impacts adult health and has been associated with increased insulin resistance, hypertension, and cardiovascular disease.[17,39] There is growing evidence suggesting that the in utero environment affects later life health and disease (termed the *Barker hypothesis*) with particular focus on fetal growth restriction and later life cardiovascular disease (see also Chapter 16). A systematic review of 18 studies that included 45,249 individuals demonstrated that cardiovascular risk factors, specifically blood pressure and body mass index (BMI), were increased in children and young adults born to preeclamptic pregnancies.[17] Thus, preeclampsia and related complications may be associated with long-term sequelae in both the mother and infant.

Risk Factors

Risk factors for preeclampsia reflect the heterogeneous nature of the syndrome and can be broadly classified into pregnancy-specific characteristics and maternal pre-existing features (Box 17.1).

Pregnancy-Specific Characteristics

Nulliparity is a strong risk factor, almost tripling the risk of preeclampsia.[22] It is estimated that two-thirds of cases occur in first pregnancies. New paternity also increases the risk of preeclampsia in a subsequent pregnancy. Excess placental volume, as with multifetal gestations and hydatidiform moles, is also associated with the development of

• BOX 17.1 Risk Factors for Preeclampsia

Pregnancy-Specific Factors

- Nulliparity
- Partner-related factors: new paternity, limited sperm exposure (e.g., barrier contraception)
- Multifetal gestation
- Hydatidiform mole

Maternal Pre-Existing Conditions

- Older age
- Higher body mass index
- Pregestational diabetes
- Chronic hypertension
- Renal disease
- Antiphospholipid antibody syndrome
- Connective tissue disorder (e.g., systemic lupus erythematosus)
- Family history of preeclampsia
- Prior preeclampsia
- Lack of smoking

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preeclampsia.[18,22] The disease process may occur earlier and have more severe manifestations in these cases. The risk progressively increases with each additional fetus.

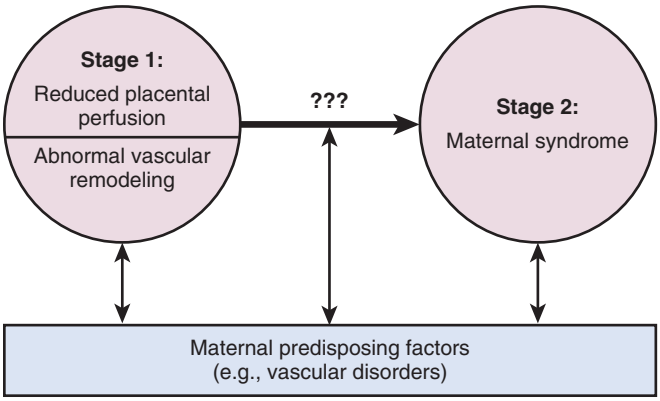
Maternal Characteristics

Extremes of childbearing age have been associated with preeclampsia.[74] However, when adjustments for parity are made in the younger age group (because most first pregnancies occur at a younger age), the association between younger age and preeclampsia is lost.[22] Women who were 40 years of age or older had almost twice the risk of developing preeclampsia after controlling for baseline differences such as chronic medical conditions.[22] The association between race and preeclampsia has been confounded by the higher prevalence of chronic hypertension among African-American women, which is often undiagnosed. Whereas some studies demonstrate a higher risk of preeclampsia among African-American women,[29,42] larger prospective studies that controlled for other risk factors and rigorously defined preeclampsia did not find a significant association between preeclampsia and African-American race.[64,65] More severe forms of preeclampsia may be associated with maternal nonwhite race.

A family history of preeclampsia nearly triples the risk of preeclampsia, whereas a personal history of preeclampsia in a previous pregnancy increases the risk of recurrence by sevenfold.[22,33,47] Cardiovascular risk factors such as pre-existing hypertension, diabetes, obesity, and vascular disorders (renal disease, systemic lupus erythematosus, antiphospholipid antibody syndrome) also increase the risk of preeclampsia.[22] This risk correlates with the severity of the underlying disorder. Obesity increases the overall risk of preeclampsia by approximately two- to threefold.[11] The risk of preeclampsia progressively increases with increasing body mass index (BMI), even within the normal range. Importantly, it is not only the late or mild forms that are increased but also early-onset and severe preeclampsia, which are associated with greater perinatal morbidity and mortality.[10] Given the obesity epidemic in the United States and around the world, this is one of the largest attributable and potentially modifiable risk factors for preeclampsia. Paradoxically, cigarette smoking during pregnancy is associated with a reduced risk of preeclampsia.[28]

Pathophysiology

Although research in this area is extensive and ongoing, the precise pathophysiology remains incompletely understood. Preeclampsia has been described as occurring in two stages.[58] The first stage consists of inadequate remodeling of the maternal spiral arteries by the invasive placental trophoblasts, which results in reduced placental perfusion. The second stage describes the maternal systemic vascular dysfunction, which leads to clinical features, including multiorgan involvement (Fig. 17.1). Some women enter pregnancy with vascular disease (e.g., chronic hypertension, diabetes, renal disease, lupus), which may result in poor placental implantation (stage I) and/or a susceptibility to the vascular damage associated with preeclampsia (stage II), thereby increasing the risk of developing preeclampsia.



• **Fig. 17.1** Two-stage concept describing the pathophysiology of preeclampsia.

The placenta plays a critical role in the pathophysiology of preeclampsia. The placenta, but not necessarily the fetus (as with hydatidiform moles), is requisite for the development of preeclampsia. Greater placental volume, as with multifetal gestation, hydatidiform moles, and hydropic placentas, is associated with a higher risk of preeclampsia.[22] Importantly, delivery of the placenta is the cure for preeclampsia. In normal pregnancy, the cytotrophoblast cells of the developing placenta invade the uterine spiral arteries within the decidua and myometrium of the uterus and remodel the small-caliber, high-resistance arteries into large-caliber, low-resistance vessels. Persistence of the uterine artery smooth muscle renders these vessels susceptible to local and circulating vasoconstrictors as well as poor perfusion, which can result in placental ischemia-hypoxia and generation of potentially harmful reactive oxygen species.[69]

The precise factor(s) linking stage I and stage II has been the focus of numerous studies in this field. There is evidence to support the role of angiogenic factors, inflammatory cytokines, circulating placental microparticles, and oxidative stress, to name a few.[69] Preeclampsia has been called the "disease of theories"—and it is likely that this syndrome is heterogeneous with multiple different pathways, either individually or in combination, that converge to result in vascular dysfunction and clinical features of the syndrome. Classifying preeclampsia into subtypes may facilitate research and a better understanding of pathophysiology. For example, experts have proposed a "placental preeclampsia" in which placental dysfunction and fetal growth restriction are major features.[68]

Angiogenic Factors

Pro-angiogenic factors, placental growth factor (PlGF), and vascular endothelial growth factor (VEGF), as well as the anti-angiogenic factors, soluble VEGF receptor 1 (soluble fms-like tyrosine kinase-1 [sFlt-1]), and soluble endoglin (coreceptor for transforming growth factor [TGF-β]) have

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gained increasing attention for their role in the pathogenesis of preeclampsia. It is proposed that circulating sFlt-1 from the placenta binds and inactivates VEGF and PlGF, thus competing with receptors located on the endothelium and resulting in impaired vascular function.[46] Soluble endoglin inhibits TGF-β1 signaling in endothelial cells, disrupting nitric oxide–induced vasodilation. Compared with normotensive women, circulating sFlt-1 and soluble endoglin levels are higher and PlGF levels lower in preeclampsia, even weeks prior to the recognition of the clinical condition, and also correlate with disease severity.[44,45] Soluble Flt-1 administered to pregnant rats induces preeclampsia-like features (hypertension, proteinuria, glomerular endotheliosis).[46] Soluble endoglin potentiates these effects in pregnant rats, resulting in features of severe preeclampsia, HELLP syndrome, and fetal growth restriction.[72] Placental ischemia and hypoxia is hypothesized to trigger sFlt-1 release from the placenta.[31]

Immunologic/Inflammatory Factors

Prior exposure to paternal antigens appears to be protective against preeclampsia, whereas less exposure to paternal antigens is associated with a higher risk of preeclampsia, such as with nulliparous women, new paternity, longer interpregnancy interval, barrier contraceptive use, and pregnancies achieved by intracytoplasmic sperm injection.[60] These epidemiologic observations support the role of immunologic factors in stage I of preeclampsia. The immunologic abnormalities observed with preeclampsia have been compared to transplant organ rejection.[49] The only known polymorphic histocompatibility antigens on the fetal trophoblast are HLA-C molecules. Maternal decidual natural killer (NK) cells express killer immunoglobulin receptors (KIRs) that recognize specific HLA-C molecules and interact with the invasive trophoblast cells to regulate placental implantation. The conflict between maternal and paternal genes observed in preeclampsia may lead to increased NK activity and abnormal placental implantation. Some HLA-C and KIR isoforms predispose to preeclampsia.[49] Placental bed biopsies from women with preeclampsia also demonstrate increased numbers of dendritic cells (antigen-presenting cells) in the decidua, which may also affect placental implantation and/or maternal immunologic responses.[56] Compared with the nonpregnant state, normal pregnancy is an inflammatory state; this is even more exaggerated in women with preeclampsia, which likely contributes to stage II and generalized endothelial dysfunction. Circulating inflammatory markers, C-reactive protein, tumor necrosis factor-α, and interleukin-6 are all elevated in preeclampsia compared with uncomplicated, normotensive pregnancy.[56] Placenta hypoxia and reperfusion can result in oxidative stress, with subsequent apoptosis and necrosis of the syncytiotrophoblast with release of these materials into the maternal circulation, which can stimulate inflammation.[56] These circulating placental microparticles and trophoblastic debris have been shown to be bioactive and even contain antiangiogenic factors.[55,56]

Renin Angiotensin System

Normal pregnancy is characterized by vasodilation and resistance to vasopressors. Despite the decrease in systemic vascular resistance, levels of renin, angiotensin, and aldosterone are increased with normal pregnancy. With preeclampsia, there is increased sensitivity to angiotensin II and other vasoconstrictors. Circulating autoantibodies to the angiotensin II type 1 receptor have been demonstrated in women with preeclampsia.[19] This autoantibody is an agonistic antibody similar to angiotensin II that is able to activate the receptor and result in hypertension and vascular injury, which are characteristic of preeclampsia. In a rodent model, injection of these antibodies results in some of the clinical features of preeclampsia, further supporting the pathogenic nature of these autoantibodies.[19]

Genetics

Epidemiologic associations of preeclampsia with positive family history, preeclampsia in a prior pregnancy (see "Risk Factors"), or a male partner who has fathered a preeclamptic pregnancy indicate a genetic basis for preeclampsia. A number of candidate genes have been studied with positive findings in small cohorts, but subsequent larger studies have not confirmed their association with preeclampsia. Genome-wide association studies have been performed and have shown modest associations, but the findings are not consistent across different populations.[75] Genetic studies are likely confounded by the heterogeneity of preeclampsia, inconsistent definitions, and population variation. Recent investigations are turning toward evaluating environmental influences such as hypoxia and epigenetic modifications that may be associated with preeclampsia.[75]

Endothelial Dysfunction

The endothelium, an important modulator of vascular tone, is dysfunctional in preeclampsia and contributes to the increased peripheral vascular resistance.[16] Endothelial dysfunction is central to the systemic maternal manifestations of preeclampsia, including increased blood pressure, increased response to vasoconstrictors, vasospasm/ischemia, activation of the coagulation cascade, proteinuria, and reduced perfusion leading to multiorgan damage, including renal, hepatic, cerebral, and placental injury.[16] In vivo assessments in women have demonstrated reduced vasodilatory responses during and even prior to the onset of clinically evident preeclampsia. Ex vivo investigations using subcutaneous resistance arteries have demonstrated reduced to absent flow-mediated and endothelium-dependent vasodilatory responses in women with preeclampsia relative to normal pregnancy. Markers of endothelial dysfunction such as cellular fibronectin, von Willebrand factor, and thrombomodulin are also increased in blood or urine of women with preeclampsia, with some of these changes manifested weeks before the clinically recognized syndrome. In addition, there appears to be increased production of vasoconstrictors such as endothelin-1 and thromboxane, as

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well as a decrease in vasodilators such as prostacyclin and nitric oxide.[16] Markers of oxidative stress are also increased in preeclampsia; the imbalance of potentially damaging reactive oxygen species and the ability to scavenge these harmful products are postulated to be a point of convergence leading to endothelial damage. Immunologic, inflammatory, and angiogenic components are also important contributors.

Pathophysiology by Organ System

Cardiovascular

Preeclampsia is characterized by high systemic vascular resistance, which manifests clinically as hypertension. This is in contrast to marked lowering of vascular resistance during normal pregnancy. Preeclampsia does not appear to directly affect the myocardium. However, the heart responds to the hemodynamic changes. In an untreated group of preeclamptic women, the systemic hemodynamics were characterized as a low output–high resistance state.[73] Others have suggested that a high output–low resistance state precedes the clinical onset of preeclampsia, with subsequent crossover to a low output–high resistance state.[12,27] Many of the studies are confounded by the treatments used for preeclampsia, such as antihypertensive medications and intravenous magnesium sulfate.

Renal

Marked renal alterations occur with preeclampsia.[36] Glomerular filtration rate and renal plasma are reduced, on average, by 32% and 24%, respectively, from normal late-pregnancy levels. Handling of proteins and other substances such as uric acid and calcium are altered. Urinary protein excretion is increased owing to the impaired integrity of the glomerular barrier as well as altered tubular handling of filtered proteins. Both size and charge selectivity of the glomerular barrier are affected. Glomerular endotheliosis is considered a renal pathologic lesion characteristic of preeclampsia. Features include endothelial swelling, loss of fenestrations, and occlusion of the capillary lumina. This is believed to resolve after delivery.

Brain

Headaches, visual symptoms, and seizures are thought to be related to pathophysiologic changes in the brain.[14] Histopathologic findings based on autopsy specimens include hemorrhage, petechiae, cerebral edema, vasculopathy, ischemic brain damage, microinfarcts, and fibrinoid necrosis. Retinal arteriolar narrowing has been noted on funduscopic examination. Cerebral edema and ischemia with or without hemorrhagic changes in the posterior hemispheres are often observed on computed tomography and magnetic resonance imaging.[14] These findings are posited to be related to vasospasm associated with severe hypertension or the loss of cerebrovascular autoregulation leading to areas of vasoconstriction and forced vasodilation, which has been termed *posterior reversible leukoencephalopathy syndrome*.

Hepatic

Periportal hemorrhage and intraparenchymal hepatic infarction associated with intense vasospasm are the major hepatic histopathologic lesions associated with preeclampsia.[38] Pain in the epigastrium and/or right upper quadrant associated with preeclampsia is thought to be secondary to stretching of the Glisson capsule owing to liver swelling and/or subcapsular hemorrhage.

Placenta

A common finding in the preeclamptic placenta is acute atherosis, which refers to fibrinoid necrosis of the vessel wall and accumulation of lipid-laden macrophages, and a mononuclear perivascular infiltrate.[41] This can also occur in the maternal decidual vessels. The syncytiotrophoblast contains areas of apoptosis and necrosis, whereas the cytotrophoblast cells are increased in number and have higher mitotic activity; these changes are thought to be associated with hypoxia.[37] Chronic underperfusion of the placenta may also lead to small placenta (weight less than the tenth percentile) and areas of ischemia and infarction.

Clinical Presentation of Preeclampsia

The clinical presentation and course of disease progression can be quite variable. In most cases, the diagnosis of preeclampsia with hypertension and proteinuria is made after 34 weeks' gestation. Approximately 10% of preeclamptic women develop early-onset preeclampsia prior to 34 weeks. Approximately 25% of women will present with, or develop features of, severe preeclampsia; however, the degree of hypertension and proteinuria and presence/absence of severe features are highly variable (see Table 17.1).[4] *Importantly, the progression of preeclampsia to severe disease and/or worsening clinical status is unpredictable and potentially rapid within hours to days, highlighting the critical need for close surveillance even if there are no severe features of preeclampsia at the time of presentation.* Preeclampsia may also be first recognized postpartum in 5% of women, usually within the first 48 hours after delivery.[2]

Initial Evaluation

A high degree of clinical suspicion for preeclampsia is warranted, given its unpredictable nature and serious consequences. Frequent visits in the third trimester, a routine part of prenatal care, are intended to facilitate timely detection and avoid adverse pregnancy outcomes. Each visit should include assessment of blood pressure and urine dipstick for proteinuria, as well as a careful history regarding symptoms and signs of maternal end-organ involvement (see Table 17.1). Women should be questioned about neurologic symptoms (headache, visual changes, scotomata), epigastric or right upper quadrant abdominal pain, nausea and/or vomiting, difficulty breathing, decreased urine output, decrease in fetal movement, and vaginal bleeding. Initial

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evaluation of preeclampsia should generally occur in a triage or hospital setting. Serial blood pressures should be measured to confirm sustained elevations. Physical examination should be performed with attention to signs of preeclampsia and associated complications. Proteinuria should be assessed by urine dipstick, protein-to-creatinine ratio, or a 24-hour urine collection. Although the urine protein-to-creatinine ratio has the advantage of being convenient, rapid, and not subject to the errors of 24-hour urine collection, the 24-hour urine total protein excretion remains the standard for preeclampsia diagnosis. Laboratory evaluation should include a complete blood count with platelets, liver transaminases, and serum creatinine to evaluate for possible end-organ involvement. Uric acid may be useful in identifying a subgroup of hypertensive women who are at increased risk for premature delivery and infants small for gestational age.[59] Peripheral blood smear, lactate dehydrogenase, haptoglobin, and/or indirect bilirubin may be ordered if there is concern for hemolysis and possible HELLP syndrome. Fetal well-being should be assessed with ultrasound to evaluate estimated fetal weight, growth, and amniotic fluid index. Nonstress testing and/or fetal biophysical profiles should also be performed. In the setting of fetal growth restriction, umbilical artery Doppler measurement is a useful tool to assess resistance within the placental and umbilical vasculature. Use of these assessments has been shown to reduce perinatal death as well as unnecessary delivery of the preterm growth-restricted fetuses.[9]

Principles of Management

Definitive treatment for preeclampsia is delivery. Delivery is always beneficial for the mother to prevent disease progression and organ damage; however, preterm delivery may be hazardous to the fetus/neonate. Thus, the decision to deliver is based on gestational age, severity of the disease, and maternal and fetal well-being. Other management considerations include administration of antenatal glucocorticoids, magnesium sulfate for seizure prophylaxis, antihypertensive therapy, and fetal surveillance (Fig. 17.2).

Administration of Corticosteroids

Women with preeclampsia diagnosed prior to 37 weeks' gestation are at risk of preterm delivery. Antenatal glucocorticoids have been demonstrated to decrease the risk of neonatal respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis, as well as mortality. As per the National Institutes of Health consensus guidelines, antenatal glucocorticoids should be administered to women at less than 34 weeks' gestation who are at risk for preterm delivery to decrease neonatal morbidity and mortality.[5] The dosing regimen consists of two doses of betamethasone 12 mg intramuscular injection 24 hours apart. Intravenous dexamethasone may be considered if there is concern for a coagulopathy and complications associated with a deep muscular injection. More recent data indicate potential benefit of betamethasone administration between 34 0/7 weeks and 36 6/7 weeks if late preterm delivery is anticipated.[32]

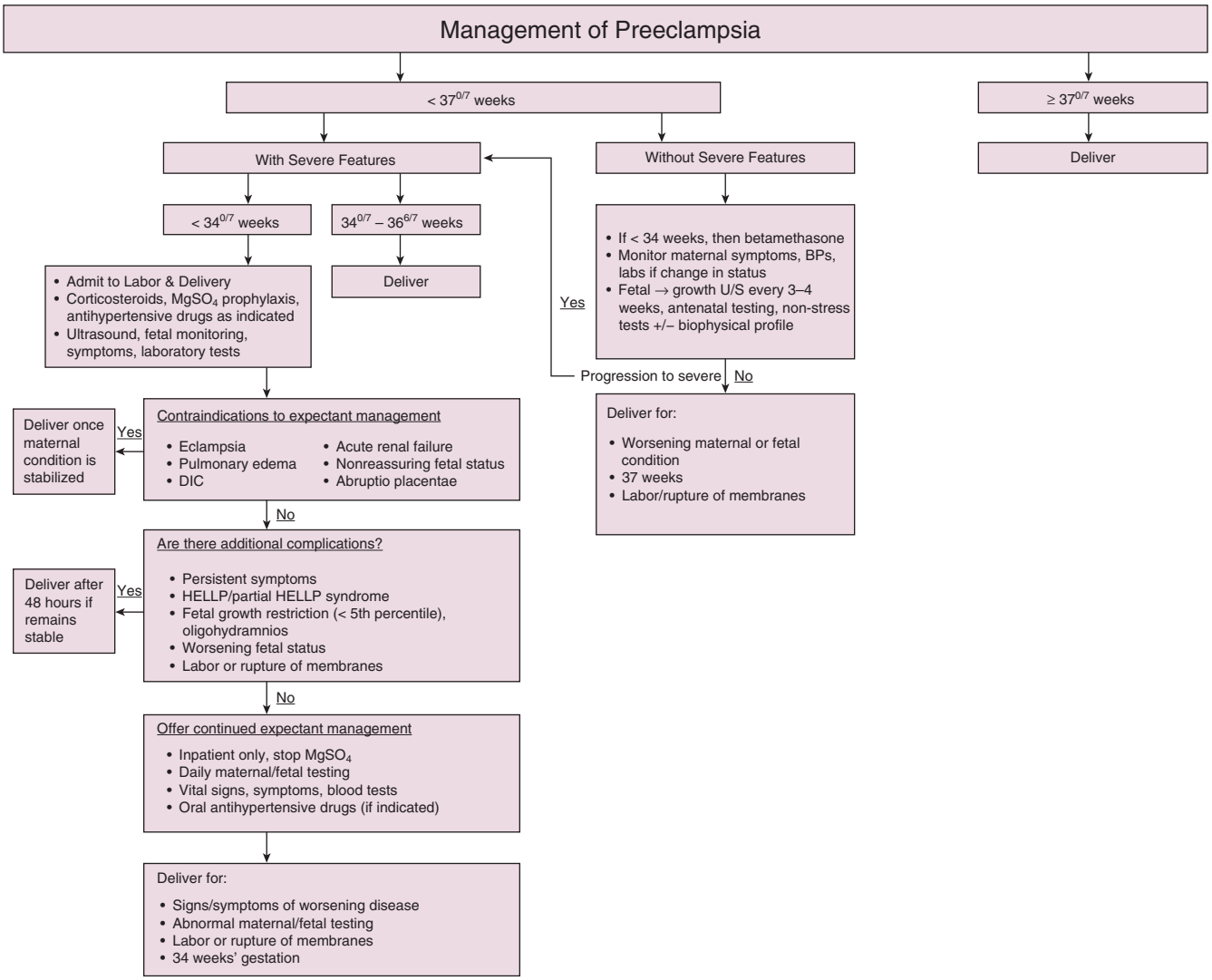
Seizure Prophylaxis

Eclampsia is associated with maternal mortality in the range of 0.3%-1% and is associated with serious morbidity, including renal failure, pulmonary edema, aspiration pneumonia, stroke, and cardiopulmonary arrest.[4] Most women recover without permanent neurologic injury; however, there is evidence of long-term maternal sequelae such as persistence of white matter lesions and impaired cognitive function.[7,8] Most eclamptic seizures occur during the intrapartum and postpartum period (within 48 hours of delivery) or with the initial presentation of severe preeclampsia. A Cochrane systematic review included six trials with 11,444 women comparing magnesium sulfate to placebo for seizure prophylaxis with a risk reduction of 0.41 (95% confidence interval 0.29-0.58).[23] Magnesium sulfate is also superior to a number of other agents (phenytoin, diazepam, lytic cocktail) for the prevention of seizures in women with preeclampsia. Intrapartum and postpartum magnesium sulfate is recommended for women with severe preeclampsia. There remains disagreement about its routine use in mild preeclampsia. Signs and symptoms that are traditionally considered premonitory to eclampsia (e.g., neurologic symptoms, clonus, right upper quadrant pain) as well as worsening clinical course should be included in the decision to initiate magnesium sulfate during labor and delivery. The usual dose is a 4-gram intravenous loading dose followed by constant infusion of 1-2 g/hour. The infusion dose may need to be reduced in the setting of renal failure. Duration of therapy is generally during labor and then 24-48 hours postpartum. Patients should be monitored closely for evidence of toxicity, including loss of reflexes and respiratory depression. Magnesium crosses the placenta with cord blood concentrations approximating maternal serum levels. Neonatology presence should be considered if there are concerns for neonatal effects, including respiratory depression related to magnesium toxicity. Results from numerous large studies indicate that magnesium sulfate given before an anticipated early preterm birth has neuroprotective effects and reduces the risk of cerebral palsy in surviving infants.[21]

Antihypertensive Therapy

Antihypertensive medications are not routinely given to women with preeclampsia. The primary reason for using antihypertensive drugs is for the treatment of severe maternal blood pressure elevations with the goal of reducing cerebrovascular accidents such as strokes and intracranial hemorrhage as well as acute coronary events. This is in contrast to the principles of blood pressure control in nonpregnant adults whereby tight control is advocated to decrease the risk of end-organ damage. There is no evidence that lowering blood pressure reduces fetal morbidity or prevents maternal seizures. Acute therapy is reserved for systolic blood pressures of greater than 160 mm Hg and/

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• **Fig. 17.2** Management scheme for preeclampsia.

or diastolic blood pressures of greater than 105 mm Hg.[1,24] Treatment should occur in a hospital setting. Rapid and marked lowering of blood pressure may compromise uterine perfusion and lead to iatrogenic fetal distress. Intravenous labetalol and hydralazine are considered first-line agents for acute lowering of blood pressure in pregnant women.[24] Table 17.2 summarizes the mechanism of action, dosing, and frequency of commonly used medications for the acute lowering of blood pressure. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. These medications have teratogenic potential and are associated with central nervous system and cardiac anomalies with first-trimester use.[15,51] Second- and third-trimester use is associated with fetal renal failure and oligohydramnios, which can lead to pulmonary hypoplasia. Fetal skull ossification defects have also been reported.

Ongoing Maternal and Fetal Surveillance

Timing of Delivery

Delivery is recommended for preeclampsia diagnosed at term (≥37 0/7 weeks). Neonatal outcomes are favorable, and continuation of pregnancy incurs risks to both the mother and fetus.[67] Preeclampsia without severe features diagnosed prior to term (<37 0/7 weeks) should be managed expectantly, with delivery if there is progression to severe disease or nonreassuring maternal or fetal status. Preeclampsia is generally managed as an inpatient, at least initially, to ensure that the disease is not rapidly progressing. Outpatient management may be considered in a subset of preeclamptic women without severe features who have remained stable, are able to comply with frequent maternal and fetal monitoring, and have ready access to medical facilities (e.g., distance to the hospital, transportation). No major differences in clinical outcomes were observed with outpatient management with monitoring in antenatal day facilities compared to hospital admission.[20] Recommendations include close monitoring of symptoms, home blood pressures, strict fetal kick counts, at least twice weekly nonstress tests and/or biophysical profile, and monthly growth ultrasounds, as well as weekly laboratory evaluation and physician office visits. As previously noted, umbilical artery Doppler velocimetry is useful in the setting of fetal growth

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TABLE 17.2 Drugs for the Acute Management of Hypertension†

Drug	Mechanism of Action	Dose	Onset of Action	Comments†
Labetalol	α- and β-Adrenergic antagonist	10-20 mg IV, then 20-80 mg every 20-30 minutes to a maximum dose of 300 mg OR continuous infusion 1-2 mg/min IV*	5-10 min	Considered a first-line agent. Less tachycardia and fewer side effects. Avoid in patients with asthma or congestive heart failure.
Hydralazine	Arteriolar vasodilator, smooth muscle relaxant	5 mg IV or IM, then 5-10 mg IV every 20-40 minutes OR continuous infusion 0.5-10 mg/hour	10-20 min	Higher or frequent dosing associated with maternal hypotension, headaches and fetal distress—may be more common than other agents.
Nifedipine	Calcium channel blocker	10-20 mg orally, repeat in 30 minutes if needed, then 10-20 mg every 2-6 hours	10-20 min	May observe reflex tachycardia, headaches.
Sodium nitroprusside		0.25-20 mcg/kg/min IV*	Within seconds	Relatively contraindicated and agent of last resort; longer use associated with cyanide toxicity.

*Continuous IV infusions should be used only in an ICU setting.
†All agents are associated with headache, flushing, nausea, and tachycardia (likely due to hypotension and reflex sympathetic activation); these side effects are less with labetalol.

restriction. This management strategy should be modified if there is any change in maternal and/or fetal status. In addition to the above, inpatient surveillance includes frequent monitoring of maternal symptoms and blood pressure as well as daily fetal assessment.

For women with preeclampsia with severe features diagnosed at or after 34 0/7 weeks, delivery is recommended. With severe preeclampsia prior to 34 0/7 weeks, timing of delivery is based on maternal and fetal status as well as the risk-benefit balance of expectant management. Options include: (1) immediate delivery after maternal stabilization, (2) short-term pregnancy prolongation to achieve steroid benefit for the fetus, and (3) pregnancy prolongation for greater than 48 hours (expectant management) with the goal of improving gestational age and neonatal outcomes. Because of the significant maternal and fetal/neonatal morbidity, immediate delivery after maternal stabilization is recommended if any of the following are present: uncontrollable severe hypertension, eclampsia, pulmonary edema, disseminated intravascular coagulation, new and/or worsening renal dysfunction, placental abruption, or nonreassuring fetal status. Unfortunately, many studies do not clearly differentiate between immediate delivery and an attempt to achieve some degree of steroid benefit.[62,63] Women with neurologic or epigastric pain symptoms, HELLP syndrome or partial HELLP syndrome, thrombocytopenia, elevated liver transaminases, or fetal growth restriction are potential candidates for short-term (48-hour) pregnancy prolongation to achieve steroid benefit with close inpatient monitoring and with readily available tertiary obstetric, intensive care unit, and neonatal and anesthesia services.[62,63] Delivery is recommended for worsening of maternal or fetal status. Multidisciplinary care is essential with close communication between maternal-fetal medicine, neonatology, critical care medicine, and obstetric anesthesiology teams.

In two randomized trials comparing expectant management of severe preeclampsia at less than 34 0/7 weeks of gestation with planned delivery at 48 hours after steroid administration, expectant management was associated with significant prolongation of pregnancy, reduction in neonatal respiratory distress syndrome, fewer days in the neonatal intensive care unit, and higher birth weight with reasonable maternal safety in the expectantly managed group.[50,63,66] Women with severe preeclampsia were candidates for expectant management if blood pressures were controlled, there was no evidence of severe end-organ involvement, and fetal status was reassuring without growth restriction. Based on these and other supporting data from observational studies, expectant management of severe preeclampsia is acceptable in a well-selected population with close inpatient management in a tertiary center until 34 weeks or worsening disease, whichever comes first.

Mode of Delivery

Vaginal delivery is generally recommended for women with preeclampsia; cesarean section is reserved for the usual obstetric indications. The rate of vaginal delivery decreases to approximately 33% at less than 28-32 weeks owing to the higher rate of nonreassuring fetal tracing and failure of

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induction, which may influence counseling on mode of delivery at these early gestational ages.[3]

Other Hypertensive Disorders of Pregnancy

Gestational Hypertension

The risk of gestational hypertension progressing to preeclampsia is estimated to be 15%-25%. Pregnancy outcomes with nonsevere gestational hypertension are generally favorable. Initial evaluation is similar to that of women with preeclampsia. Close monitoring for worsening blood pressure, progression to preeclampsia, and fetal status is recommended. Severe gestational hypertension is associated with higher rates of preterm delivery, small for gestational age infants, and placental abruption comparable to rates reported with severe preeclampsia.[4] Therefore, management approach is similar to that described for severe preeclampsia. Timing of delivery is recommended between 37 and 39 weeks.[4,43,67] In most cases, blood pressures normalize within the first few weeks postpartum. Approximately 15% of women with gestational hypertension will have persistent hypertension 12 weeks postdelivery, which represents either previously undiagnosed or a new diagnosis of chronic hypertension.

HELLP Syndrome

HELLP syndrome develops in approximately 10%-20% of women with severe preeclampsia-eclampsia. Although HELLP is considered a variant of preeclampsia, as many as 15%-20% of women with HELLP do not have antecedent hypertension or proteinuria.[62] This syndrome is often characterized by sudden and progressive deterioration in maternal and fetal status as well as increased rates of morbidity and mortality. Clinical presentation is variable, with common symptoms including abdominal pain in the epigastric area and/or right upper quadrant. In addition to symptoms of preeclampsia, nausea, vomiting, and malaise may be presenting complaints. Diagnosis is based on symptoms and laboratory abnormalities indicating hemolysis, elevated liver transaminases, and low platelets. HELLP syndrome may be associated with serious hepatic manifestations including liver infarction, hemorrhage, and rupture. Prompt delivery is recommended. Delaying delivery to achieve steroid benefit may be reasonable in select cases with close monitoring in a tertiary setting with experienced personnel.[4] Several observational and retrospective studies have suggested that corticosteroid use for HELLP syndrome improves maternal morbidity. A recent Cochrane meta-analysis demonstrated improved maternal platelet count but no evidence of improvement in maternal mortality or severe morbidities.[4] Additional well-conducted studies are needed to clarify whether steroids or other therapies improve maternal morbidity with HELLP syndrome.

Differentiating HELLP syndrome from acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura (TTP), or hemolytic uremic syndrome (HUS) may be challenging.[36] Acute fatty liver is characterized by progressive hepatic failure in pregnancy and is associated with nausea, vomiting, malaise, abdominal pain, jaundice, and (less commonly) mental status changes. Laboratory abnormalities include elevated liver transaminase enzymes, hyperbilirubinemia, elevated ammonia levels, clotting abnormalities, and hypoglycemia. Treatment is delivery and supportive care. Thrombocytopenic purpura is associated with a pentad of findings, including thrombocytopenia, hemolytic anemia, fever, neurologic abnormalities, and renal dysfunction. There are similar features with HUS except that renal involvement is more profound, and neurologic involvement is less frequent. As previously mentioned, it is often difficult to differentiate these conditions from the preeclampsia spectrum of disorders (Table 17.3). Proper diagnosis is important because the treatments are different. Delivery is the primary treatment for preeclampsia, HELLP, and acute fatty liver, whereas plasmapheresis is the mainstay of therapy with TTP/HUS. Often the diagnosis can only be made by following the disease progression after delivery. Supportive therapy and a multidisciplinary medical team are critical in the acute phase, particularly until the diagnosis is clear.

Chronic Hypertension

Chronic hypertension complicates approximately 0.5%-5% of all pregnancies. The prevalence of chronic hypertension increases with age and is higher in African-American women. Perinatal complications are increased with chronic hypertension, primarily related to superimposed preeclampsia, fetal growth restriction, and perinatal death. In a large cohort study the perinatal death frequency was 29/1000, and fetal growth restriction was 10.5% among uncomplicated chronic hypertensive women, which was significantly higher than among normotensive pregnant women.[57] Superimposed preeclampsia has a prevalence of 20%-25% in women with mild chronic hypertension but can be as high as 50% in women with severe pre-pregnancy hypertension.[4] Rey and colleagues also reported a relative risk for perinatal death of 3.6 in women with superimposed preeclampsia compared with uncomplicated chronic hypertensive controls. The incidence of fetal growth restriction was 35% among superimposed preeclamptic women.[57]

Clinical care for pregnant women with chronic hypertension is focused on blood pressure management, close monitoring for superimposed preeclampsia, and careful fetal surveillance. In contrast to the guidelines for tight blood pressure control and associated benefits for nonpregnant hypertensive individuals, the guidelines for pregnant women with chronic hypertension are less clear. As discussed previously, the goal of antihypertensive therapy during pregnancy is to prevent maternal cerebrovascular and coronary events associated with severe blood pressure elevation. The controversy surrounding "tight control"

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TABLE 17.3 Other Conditions That Can Mimic Preeclampsia and HELLP Syndrome*

	Preeclampsia/ HELLP	Acute Fatty Liver of Pregnancy	Thrombotic Thrombocytopenic Purpura	Hemolytic Uremic Syndrome
Onset	Usually 3rd trimester	Close to term	Median 23 weeks	Often postpartum
Primary/unique clinical manifestation	Hypertension and proteinuria	Nausea, vomiting, malaise	Neurologic symptoms	Renal involvement
Purpura	Absent	Absent	Present	Absent
Fever	Absent	Absent	Present	Absent
Hemolysis	Mild	Mild	Severe	Severe
Coagulation studies	Variable	Prolonged abnormal	Normal	Normal
Hypoglycemia	Absent	Present	Absent	Absent
Other possible lab abnormalities	Absent	Absent	ADAMTS 13 deficiency and increase in von Willebrand factor multimers	May be complement-mediated or associated with Shiga toxin
Primary treatment	Delivery	Delivery	Plasmapheresis	Plasmapheresis

*Precise diagnosis can often be made only after delivery. Preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy resolve soon after delivery.

versus "less tight control" during pregnancy in this subgroup is not yet resolved. Issues include: (1) the concern for higher fetal exposure to antihypertensive drugs that have not been studied well in terms of long-term growth and development; (2) the theoretical concern that marked lowering of blood pressure could chronically reduce uterine blood flow resulting in reduced delivery of oxygen and nutrients to the fetoplacental unit, which may lead to fetal compromise; and (3) the lack of evidence to support the lowering of blood pressure to prevent superimposed preeclampsia.[4] Given these concerns, the focus in pregnancy has been on short-term outcomes and avoiding fetal harm rather than long-term prevention of cardiovascular risk and end-organ damage. Oral medication therapy is generally initiated when systolic pressures exceed 150 mm Hg and diastolic pressures exceed 95-100 mm Hg.[4] Exceptions include pre-existing renal disease or other evidence of end-organ compromise that may benefit from tighter blood pressure control, such as retinopathy and cardiac disease. Additional research is needed to determine the optimal level of blood pressure control in the chronic hypertensive woman during pregnancy.

Frequent outpatient visits and home blood pressure monitoring are helpful in detecting progressive blood pressure elevations, which may be the first sign of superimposed preeclampsia. Regular assessment of urinary protein excretion and educating the patient regarding symptoms of preeclampsia are helpful in early diagnosis of superimposed preeclampsia (see previous discussion on clinical management of preeclampsia). Baseline urine protein excretion, renal function, and laboratory testing obtained in early pregnancy can be helpful for comparison. Serial growth ultrasounds, approximately every 3-4 weeks, in the third trimester are recommended with nonstress tests and/or biophysical profiles after 32 weeks' gestation, particularly if there is any evidence of fetal growth restriction. Given the overall increased perinatal morbidity, delivery is recommended at 39 weeks or sooner if indicated.

Pharmacologic therapy is guided by safety and efficacy. Medications used for the treatment of chronic hypertension are outlined in Table 17.4. Oral labetalol, nifedipine, and methyldopa are most commonly used. These medications are considered safe in pregnancy and with breastfeeding.[4]

Superimposed Preeclampsia

Distinguishing superimposed preeclampsia from benign and expected third-trimester increases in blood pressure and proteinuria in women with underlying chronic hypertension can be quite challenging (see Table 17.1). Given the substantial risk of adverse pregnancy outcomes with superimposed preeclampsia, high clinical suspicion and overdiagnosis of preeclampsia may be preferable, with the goal of increasing vigilance and preventing catastrophic maternal and fetal outcomes. End-organ involvement such as thrombocytopenia, elevated liver transaminases, or a rapid decline of renal function are also diagnostic of superimposed preeclampsia. Initial evaluation should occur in a hospital setting to confirm the diagnosis, evaluate maternal and fetal status, and monitor for progressive worsening of the disease.

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TABLE 17.4 Oral Antihypertensive Drugs Used for the Management of Chronic Hypertension

Drug (FDA Category)	Mechanism of Action	Dose	Maximum Dose	Comments
Labetalol (C)	α- and β-Adrenergic antagonist	200-2400 mg/day orally in 2-3 divided doses	2400 mg/day	Well-tolerated. Potential bronchoconstrictive effects.
Nifedipine (C)	Calcium channel blocker	30-120 mg/day orally of a slow-release preparation	120 mg/day	Do not use sublingual form. Side effects include headache, flushing, tachycardia; once a day dosing may improve compliance.
Methyldopa (B)	Centrally acting α2-receptor agonist	0.5-3 g/day orally in 2-3 divided doses	3 g/day	Childhood safety data up to 7 years. May not be as effective in control of severe hypertension. Side effect profile includes lethargy.
Hydrochlorothiazide (C)	Thiazide diuretic	12.5-50 mg/day orally	50 mg/day	Not used as a primary agent in pregnancy and considered an adjunctive agent; theoretical concerns of reduced intravascular volume and decreased uterine blood flow in pregnancy; electrolytes should be monitored.
Hydralazine (C)	Vasodilation, smooth muscle relaxant	50-300 mg per day orally in 2-4 divided doses	300 mg/day	Not used as a primary agent in pregnancy and considered an adjunctive agent; may be used in combination with a sympatholytic agent (e.g., methyldopa or labetalol) to prevent tachycardia.
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers		Associated with anomalies		CONTRAINDICATED IN PREGNANCY AND PRECONCEPTION PERIOD

Principles of management are generally extrapolated from preeclampsia, including administration of antenatal glucocorticoids if less than 37 weeks' gestation, antihypertensive therapy for acute lowering of severely elevated blood pressures, and magnesium sulfate for seizure prophylaxis. Delivery is recommended if there is any evidence of end-organ involvement or concern for fetal well-being. In the absence of severe features and with reassuring fetal status, expectant management with ongoing close maternal and fetal surveillance is reasonable. Optimal timing of delivery between 34 and 37 weeks with superimposed preeclampsia without any evidence of severe features or worsening disease is unclear.

Prediction

The utility of any predictive test depends on the overall prevalence of the disease. Because the incidence of preeclampsia in the general obstetric population is low (3%-8%), screening tests with a positive test result require high likelihood ratios to predict the probability of disease in an individual patient. Likewise, tests with a negative result would require low likelihood ratios to confidently exclude the disorder. Importantly, for any predictive test for preeclampsia to be clinically useful, there needs to be evidence that interventions (e.g., instituting preventive care, specific treatments, more intensive surveillance) improve maternal and/or fetal outcomes.[4] As of 2017, there is no single predictive test for preeclampsia that is recommended for general obstetric use.

Using clinical risk factors to predict preeclampsia during early pregnancy, the detection rate was 37% for early-onset preeclampsia and 29% for late-onset preeclampsia, with a false positive rate of 5%.[52] Many different biomarkers and combinations of biomarkers have been proposed for the prediction of preeclampsia, including uterine artery Doppler, angiogenic factors, placental protein-13, and uric acid, to name a few.[4] When placental growth factor was combined with uterine artery pulsatility index, mean arterial pressure, pregnancy-associated plasma protein-A, BMI, parity, and previous preeclampsia, Poon and colleagues demonstrated a 93% detection rate for early-onset preeclampsia with a false positive rate of 5%.[53] While these biomarkers are promising, future studies are needed to validate these results in other populations and demonstrate clinical utility of preeclampsia prediction in improving maternal and fetal outcomes.

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Prevention

Numerous strategies have been tested for the prevention of preeclampsia, including protein or salt restriction, zinc, magnesium, fish oil, diuretics, antihypertensive medications, heparin, aspirin, calcium, and vitamins. Results from most of these trials showed little to no benefit for preeclampsia prevention.[4] Calcium, aspirin, and antioxidant vitamin therapy have been evaluated more recently. A common theme has been promising results from small, single-center studies followed by larger, appropriately powered, randomized trials that failed to show a significant benefit in preventing preeclampsia or other adverse pregnancy outcomes.

Aspirin, an antiplatelet agent with anti-inflammatory properties, has been tested extensively for the prevention of preeclampsia in both low- and high-risk women. Initial studies indicated a substantial benefit of aspirin therapy; however, subsequent large, randomized trials of high-risk and low-risk women failed to demonstrate a statistically significant benefit. A systematic review of aspirin therapy to prevent preeclampsia in high-risk women demonstrated a modest reduction of preeclampsia, perinatal death, and preterm birth.[25] A subsequent meta-analysis using individual patient data from 32,217 women in 31 randomized trials of antiplatelet therapy for the primary prevention of preeclampsia demonstrated a lower risk of preeclampsia (RR 0.90, 95% CI 0.84-0.97), delivery before 34 weeks (RR 0.90, 95% CI 0.83-0.98), and overall serious adverse pregnancy outcome (0.90, 95% CI 0.85-0.96).[6] No single identifiable subgroup preferentially benefitted from this prophylaxis. Importantly, there were no substantial risks of aspirin therapy. Although there is no consensus, low-dose aspirin may be considered in women at high risk for developing preeclampsia.

Oxidative stress has been posited as a pathogenic factor in preeclampsia; thus, antioxidant vitamins have been proposed for the primary prevention of preeclampsia. Despite initial, promising results from a small study in high-risk women, large, randomized, placebo-controlled trials of vitamins C and E did not reduce the risk of preeclampsia or improve maternal or fetal outcomes in various low- and high-risk populations. A Cochrane systematic review of vitamins C and E for the prevention of preeclampsia that included over 20,000 women enrolled in 15 randomized clinical trials found no benefit (relative risk 0.94, 95% CI 0.82-1.07).[61] Therefore, antioxidant therapies are not currently recommended for preeclampsia prevention.

Calcium supplementation for the prevention of preeclampsia has also been studied extensively.[4] In a multicenter, randomized, placebo-controlled trial of healthy, nulliparous women conducted in the United States, calcium supplementation of 2 g per day did not reduce the incidence or severity of preeclampsia or delay its onset. However, a Cochrane meta-analysis of 13 trials, which included 15,730 women, demonstrated a significant reduction in preeclampsia risk with calcium supplementation (RR 0.45, 95% CI 0.31-0.65), with the greatest effect among women with low calcium intake at baseline (RR 0.36, 95% CI 0.20-0.65).[34] In aggregate, the evidence suggests a beneficial effect of calcium supplementation of 1.5-2 g per day for preeclampsia prevention in populations with low calcium intake at baseline.

Lifestyle modifications such as activity level have also been considered in the prevention of preeclampsia. Evidence to support bed rest is limited to small studies that have not adequately addressed other important adverse pregnancy outcomes and side effects of bed rest such as venous thromboembolism.[4] Physical activity has been hypothesized to reduce the risk of preeclampsia by improving vascular function as well as promoting placental angiogenesis. Although several small studies have evaluated modest exercise in the prevention of preeclampsia, results are inconclusive, and larger, well-controlled studies are needed to fully evaluate the effect of exercise on adverse pregnancy outcomes.[4]

Further research is warranted to identify pathophysiologic subtypes of preeclampsia that may benefit from targeted preventive therapies.

Key Points

- Hypertensive disorders of pregnancy, including preeclampsia, affect up to 10% of all pregnancies and are associated with substantial maternal and fetal/neonatal morbidity and mortality.
- Appropriate diagnosis and classification are important for management.
- Preeclampsia is a multi-organ syndrome that can rapidly progress within hours to days. Proper recognition of maternal and fetal status with escalation of care may be indicated.
- Key principles of management include anti-hypertensive therapy, magnesium sulfate for seizure prophylaxis, antenatal glucocorticoids for fetal benefit, and appropriate timing of delivery.
- Ideal care for women with hypertensive disorders of pregnancy requires a multidisciplinary team approach often including specialists in maternal-fetal medicine, critical care medicine, obstetric anesthesia, and neonatologists.
- Low-dose aspirin therapy may have modest benefit in preeclampsia prevention in high-risk women.
- To date, there is no single test that accurately predicts preeclampsia.

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18

Pregnancy Complicated by Diabetes Mellitus

ISAAC BLICKSTEIN, SHARON PERLMAN, YENON HAZAN, AND ERIC S. SHINWELL

In the United States, depending on the applied diagnostic criteria, 135,000-200,000 women develop gestational diabetes mellitus (GDM) annually, adding to the number of pregnant women diagnosed with either type 1 or type 2 diabetes.[17] Of greater concern may be the fact that approximately 80% of these mothers will develop type 2 diabetes and metabolic syndrome, both of which are associated with high mortality and morbidity. Furthermore, not only the diabetic mothers are at risk for development of metabolic syndrome but also their neonates (see Chapter 16).

Diabetes mellitus (DM) that results from relative or absolute lack of insulin is encountered during pregnancy in two situations: pregestational (pre-GDM) and gestational diabetes mellitus (GDM). The former refers to women who had diabetes mellitus prior to conception, with the well-known microvascular diabetes-associated complications (renal, retinal, cardiac, and nervous system), and the latter refers to otherwise healthy women who developed glucose intolerance during pregnancy.

These two entities are entirely distinct from both obstetric and neonatal perspectives: Pre-GDM and its associated small vessel injury may affect placental function and fetal growth, while GDM is a transient pregnancy problem that affects the fetus in the opposite way (i.e., macrosomia and its obstetrical consequences—dystocia and increased incidence of operative delivery).

This chapter focuses mainly on GDM and its neonatal consequences.

Gestational Diabetes Mellitus

GDM is defined as glucose intolerance presenting or diagnosed for the first time during pregnancy.[2] GDM complicates approximately 7% of all pregnancies in the United States. Despite the great variations that exist between populations and ethnicities, the prevalence of GDM is increasing in the United States, probably secondary to increasing rates of maternal overweight and overt obesity.

Screening and Diagnosis

Screening and diagnosing GDM have a long history of controversy, related mainly to significant implications on health care costs, the effect on obstetric interventions, and whether diagnosis and treatment of GDM will improve maternal and perinatal outcomes. In 2001, the American College of Obstetricians and Gynecologists (ACOG) recommended that all pregnant women should be screened for GDM, whether by patient history, clinical risk factors, or a glucose challenge test.[2] The latter is comprised of a "two step" method consisting of a 50-g, 1-hour glucose challenge test (GCT) and a 100-g, 3-hour oral glucose tolerance test (OGTT) for a definitive diagnosis. However, in 2003, the US Preventive Services Task Force (USPSTF) and the Cochrane Collaboration found insufficient evidence to recommend for or against screening for GDM, similar to the conclusions reached in 2008; namely, that insufficient evidence exists to balance between the benefits and harms of screening for gestational diabetes.[26] In the same year, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Group published the results of a large, multicenter observational study designed to examine the relationship between maternal hyperglycemia less severe than overt GDM and adverse pregnancy outcome.[14,20] This study clearly demonstrated a relationship between increased maternal blood glucose and birth weight, cord blood C-peptide (a measure for intrauterine fetal hyperinsulinemia), neonatal hypoglycemia, and delivery by cesarean section.

The International Association of Diabetes in Pregnancy Study Group recommended in 2007 a simplified "one step" approach to the screening and diagnosis of GDM with a 75-g, 2-hour glucose tolerance test.[18] Although implementation of these guidelines would presumably double the number of patients diagnosed with GDM, no evidence exists that this will lead to clinically significant improvement in maternal and neonatal outcomes. Regardless of these reservations, universal screening for GDM was adopted by more than 90% of practices.[2]

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Abstract

Gestational diabetes mellitus (GDM) is defined as glucose intolerance beginning or diagnosed for the first time during pregnancy. The prevalence of GDM varies according to ethnicity, method of diagnosis, and incidence of overweight and obesity in a specific population. At present, two screening methods are available: the two-step approach (50 g glucose challenge test followed by 100 g oral glucose tolerance test) and the single oral 75 g test. Normoglycemia may be achieved with diet alone (GDMA1) or with insulin therapy (GDMA2).

GDM is mainly implicated in fetal macrosomia hence the risk of difficult birth, brachial plexus injury, and obstetrical interventions. GDM, as opposed to pregestational DM, is not associated with increased risk of malformations. It follows that management is aimed to control fetal growth. In addition, theory suggests that intrauterine exposure of the fetus to the diabetic environment may increase the risk of metabolic syndrome in the offspring. Pregestational DM is a disease state that might affect many target organs before pregnancy. Also, placental insufficiency may be present with consequential fetal growth restriction and potential fetal distress. The approach and management of these two types of diabetes during pregnancy are different.

Keywords

Gestational diabetes mellitus
pregestational diabetes mellitus
macrosomia
glucose challenge test
oral glucose tolerance test

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In the sequential "two step" testing, a 50-g GCT is performed in pregnant women between 24 and 28 weeks' gestation unless a high risk for developing GDM exists (glycosuria, diabetes in first-degree relative, history of glucose intolerance, previous GDM, marked obesity, and previous infant with macrosomia). At-risk women should be screened by the 50-g GCT at their first prenatal visit. Screening cutoff values are 130 mg/dL (7.20 mmol/L; 90% sensitivity) or 140 mg/dL (7.75 mmol/L; 80% sensitivity). Random or fasting glucose measurement is not recommended for screening because of poor specificity.

In women who screen positive, a 100-g, 3-hour OGTT is used to diagnose GDM. Gestational diabetes is diagnosed if two or more plasma glucose measurements are abnormal. The World Health Organization and the American Diabetes Association recommend simultaneous screening and diagnosis using a 75-g OGTT (Table 18.1).

The interested reader will find more information about the controversial diagnosis of GDM elsewhere.[19]

Antenatal Management

Despite uncertainty regarding the clinical value of treating GDM, data strongly suggest that treatment may reduce adverse maternal and neonatal outcomes. The Australian Carbohydrate Intolerance Study in Pregnant Women randomized patients to receive either routine care or treatment for GDM.[7] Primary fetal outcomes included death, shoulder dystocia and its consequences such as bone fracture, and nerve palsy. Primary maternal outcomes were induction of labor and cesarean delivery. Infants of women in the treatment group had significantly fewer perinatal complications (RR 0.33; 95% CI 0.14, 0.75). There were more labor inductions in the treatment group (RR 1.36; 95% CI 1.15, 1.62), but the number of cesarean deliveries was similar in both groups. Further evidence of possible adverse effects associated with even mild maternal hyperglycemia comes from the HAPO trial.[14,18] The results of this trial point to a linear correlation between increasing maternal glucose levels and increasing birth weight, primary cesarean delivery, fetal C-peptide levels, and neonatal hypoglycemia. Most clinicians use glucose targets as defined by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (Table 18.2).

Diabesity is a relatively new term denoting the combination of diabetes and obesity. In a recent large population based study, Blickstein et al. found that the ill-effect of pregravid obesity is greater than that of GDM.[4] Obesity, with and without GDM, increased the odds of having chronic hypertension, whereas preeclampsia appears to be influenced by obesity only, as were the risk of births at <33 weeks' gestation, of birth weight >4000 g, low 5-minute Apgar scores, and neonatal intensive care unit (NICU) admissions. They concluded that obesity (without diabetes) is more frequently associated with adverse perinatal outcomes than GDM in nonobese mothers. They argued that a campaign to decrease pregravid obesity should have at least the same priority as any campaign to control GDM.

TABLE 18.1 Diagnostic Glucose Values for Gestational Diabetes

Diagnostic Test	Fasting mg/L (mmol/L)	First Hour mg/L (mmol/L)	Second Hour mg/L (mmol/L)	Third Hour mg/L (mmol/L)
100-g OGTT Carpenter and Coustan*,6	95 (5.25)	180 (10.0)	155 (8.6)	140 (7.75)
75-g OGTT World Health Organization†	126 (7.0)	—	140 (7.75)	—
75-g OGTT American Diabetes Association*	95 (5.25)	180 (10.0)	155 (8.6)	—

OGTT, oral glucose tolerance test.
*Two or more abnormal values.
†One or more abnormal values.
From American College of Obstetricians and Gynecologists. Gestational diabetes: ACOG practice bulletin No. 30. *Obstet Gynecol*. 2001;98:525-538.

TABLE 18.2 Treatment Targets for Gestational Diabetes Mellitus

	Fasting mg/L (mmol/L)	First Hour Postprandial mg/L (mmol/L)	Second Hour Postprandial mg/L (mmol/L)
Glucose levels	<96 (5.35)	<140 (7.75)	120-127 (6.65–7.05)

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Interestingly, this effect of diabesity was not found in twin pregnancies.[25]

Treatment

First-line therapy for women with gestational diabetes (the so-called GDM-A1) is nutritional and lifestyle modification; however, the impact on patient outcome has not been conclusively demonstrated in large randomized controlled trials. Pharmacotherapy is indicated when nutritional control is inadequate (the so-called GDM-A2), especially in patients with elevated fasting glucose levels, since diet is largely ineffective in this metabolic presentation. The ACOG and the American Diabetes Association recommends insulin therapy for women in whom the fasting glucose level exceeds 95 mg/dL, 1-hour postprandial glucose level is greater than 130-140 mg/dL, or 2-hour postprandial glucose level is greater than 120 mg/dL (6.65 mmol/L). Intermediate- and short-acting insulins served as the first-line therapy for GDM for many years; however, long-acting insulin was approved for use during pregnancy with its clear advantages in measures of patient compliance.

A safe and effective oral agent for the treatment of gestational diabetes is highly desired. Research efforts have focused on the effectiveness, safety, and placental metabolism of sulfonylurea glyburide. Despite a large number of studies, the absolute number of patients is relatively small and currently glyburide is classified as FDA class C (i.e., animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Nevertheless, glyburide therapy is a viable alternative for women who are unable or unwilling to take insulin, and it is used in many practices as first-line therapy.

Metformin (Glucophage) may be another option for women with GDM. Although metformin clearly crosses the placenta, it is classified as FDA class B (i.e., animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women).

Further research is needed to establish the role of oral hypoglycemic medications in the treatment of GDM either as a first-line therapy or in addition to insulin.

Fetal Surveillance

Gestational diabetes mellitus is associated with increased perinatal morbidity and mortality. In an attempt to reduce the risk of adverse outcome, prenatal surveillance, including assessment of fetal well-being and growth as well as screening for congenital anomalies, is recommended.

Screening for Congenital Anomalies

The time frame for risk of congenital malformations is during organogenesis, which takes place between 5 and 8 weeks of gestation (3-6 weeks after conception). Therefore, prevention of anomalies via improvement of the glycemic profile requires prenatal counseling and adequate compliance during the preconception period, since in the well-controlled population, the anomaly rate is similar to that in the general population. However, in poorly controlled pregestational diabetic mothers, the risk is three to five times higher (4%-11%). Jensen compared adverse pregnancy outcome and glycosylated hemoglobin (HbA1C) levels and found a good correlation between levels of HbA1C and the risk for congenital anomalies[16] (Fig. 18.1).



• **Fig. 18.1** Three-dimensional ultrasound of a 36-week macrosomic fetus of a mother with poorly controlled gestational diabetes mellitus. The characteristic "chubby" face is apparent. (Courtesy of Dr. Y. Hazan.)

It is believed that GDM does not carry an increased risk of congenital anomalies, because the hyperglycemia develops after embryonic organogenesis and the fetus is not exposed to high levels of glucose, ketones, and other metabolites involved in the pathophysiology of malformations in pre-GDM. Nevertheless, women with a history of GDM in previous pregnancies, obesity, or those with a presumable diagnosis of pre-GDM (HbA1C levels greater than 9%, fasting glucose levels greater than 120 mg/dL, GDM diagnosis during the first trimester) may have an increased risk for congenital anomalies and should be offered a detailed sonographic anatomical scan for detection of fetal anatomical malformations.[29] Special attention should be focused on the cardiovascular, neural tube, gastrointestinal, urinary, and skeletal systems (Box 18.1) with the possibility of malformation sequences such as VATER or VACTERL (*v*ertebral defects, *a*nal atresia, *c*ardiac defects, *t*racheo-*e*sophageal fistula, *r*enal anomalies, and *l*imb abnormalities).

Although the detection rate of fetal malformations has its own limitations, the benefits of ultrasonography should be discussed with all patients with GDM, and appropriate multidisciplinary prenatal counseling should be given accordingly to the future parents.

The most common malformations in the fetus of the diabetic mother are cardiac. In addition to developmental

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• BOX 18.1 Major Congenital Malformations in Infants of Diabetic Mothers

Cardiac

Septal defect	Ventricular septal defect (VSD), atrial septal defect
Conotruncal anomalies	Transposition of the great arteries, truncus arteriosus, single ventricle, coarctation of aorta
Situs anomalies	Dextrocardia

Central Nervous System

Neural tube defects
Holoprosencephaly
Caudal regression syndrome
Sirenomelia

Gastrointestinal

Duodenal atresia
Imperforate anus
Small left colon syndrome
Esophageal atresia/tracheoesophageal fistula
Intestinal malrotation/atresia
Situs anomalies
Urorectal septum malformation sequence

Renal Anomalies

Renal agenesis
Hydronephrosis
Double collecting system
Horseshoe kidneys

Genitalia

Hypospadias
Megalourethra
Urogenital malformation sequence

Skeletal

Polydactyly
Syndactyly
Focal femoral hypoplasia
Rib defects
Spine defects—abnormal vertebral segmentation
Sacral defects
Limb deficiency

Others

Single umbilical artery

malformations, it should be noted that cardiomegaly, septal hypertrophy, and hypertrophic cardiomyopathy with left ventricle outflow tract obstruction may develop and, therefore, in cases of poor glycemic control, sequential fetal echocardiograms should be considered.

Caudal agenesis, seen predominantly (300- to 400-fold greater) in insulin-dependent diabetic pregnancies, is a specific malformation to the fetus of the diabetic mother. The exact etiology of this malformation or the correlation with abnormal glycemic control remains unknown.

Monitoring Fetal Well-Being

Frequency and timing of fetal well-being monitoring is based on the degree of metabolic control, pharmacological intervention, and co-existence of other complications such as hypertension. Generally, antenatal monitoring of women with GDM-A2, as well as those with poor glucose control, should be the same as for women with pre-GDM. A nonstress test and sonographic biophysical profile should be conducted at least weekly, beginning early in the third trimester.

Assessment of Fetal Weight

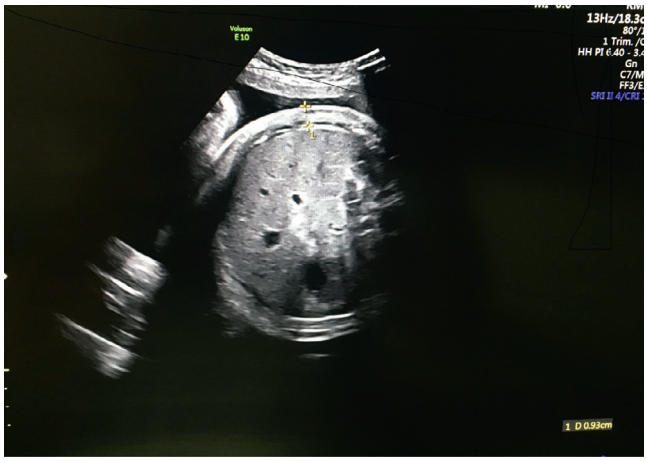
Virtually all fetuses of GDM mothers are growth promoted. Fetal macrosomia, which is frequently confused with large for gestational age (weight above the 90th percentile for gestational age), is defined as a birth weight greater than 4000-4500 grams. The incidence of macrosomia increases significantly when the mean maternal blood glucose values are greater than 130 mg/dL.

The accuracy of sonographic-estimated weight and characteristics of the fetus of the diabetic mother were studied quite extensively in the literature because of the increasing incidence of gestational and pregestational diabetes, wide implementation of prenatal diagnosis, and increased awareness to medicolegal issues. Several studies indicated that clinical estimation of fetal weight is as reliable as or even superior to those made by sonographic measurements.[24] A reliable, accurate, and predictive formula based on sonographic data is still lacking; therefore, routine sonographic fetal weight assessment to identify fetal macrosomia should be used cautiously in clinical management.

Since the estimated fetal weight is used for risk assessment for labor complications such as obstructed labor and shoulder dystocia, various studies assessed the predictive value of sonographic measures such as the difference between abdominal diameter and biparietal diameter and evaluation of fetal fat layer with quite disappointing results. None of the previously mentioned measures became a tool in the decision-making process regarding mode of delivery[5,9] (Fig. 18.2).

Polyhydramnios (i.e., increased amniotic fluid volume) is a frequent sonographic finding defined either by a single vertical pocket of 80 mm or according to nomograms of amniotic fluid index per gestational age. The etiologies for polyhydramnios in the context of the fetus of the diabetic mother are the large-for-gestational-age fetus and osmotic diuresis secondary to high glucose level. However, in cases of severe polyhydramnios and poor glycemic control, the presence of malformations such as tracheo-esophageal fistula, which are more common in the fetus of the diabetic mother, should be considered and investigated appropriately. It

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• **Fig. 18.2** Increased subcutaneous fat at the fetal abdominal level (0.93 cm) is an important sign of infants of diabetic mothers (IDMs).

should be noted that polyhydramnios itself serves as an adjunct sign for fetal macrosomia.

Timing and Mode of Delivery

Definite data to support the optimal timing or and mode of delivery in women with GDM is lacking. Although earlier deliveries reduce the risk for macrosomia, this policy did not reduce the rate of brachial plexus injuries, clavicular fractures, or neonatal hypoglycemia. Although the common belief is that brachial plexus injury is solely the result of vaginal delivery, the risk for such injury in the fetus of the diabetic mother is 4% in cesarean deliveries. Shoulder dystocia may indeed cause debilitating results, and its high frequency in macrosomic fetuses of diabetic mothers lead many clinicians to recommend cesarean upon vaginal delivery in such cases.

Since hundreds of elective cesarean deliveries will be performed to prevent one case of brachial plexus injury, and since the exact cut-off (either 4000 or 4500 g) is controversial, additional data combining maternal and fetal demographic and sonographic parameters are needed for better prediction and risk assessment of shoulder dystocia in the population of macrosomic fetuses of diabetic mothers.

Intrapartum Management

While patients with GDM-A1 (dietary control) do not require glucose monitoring during labor, women with GDM-A2 require frequent glucose measuring. Most patients are euglycemic during labor and do not require insulin. In case of hyperglycemia, dextrose solution with intravenous insulin should be administered. The patient should discontinue long-acting insulin treatment during labor and delivery, and regular insulin should be used to meet most or all of the insulin needs of the mother at this time.

Postpartum Maternal Management

Insulin requirements typically drop markedly after delivery, and most GDM patients do not require insulin postpartum. Women with gestational diabetes have an approximately 50% risk to develop type 2 diabetes within 5-10 years after birth in addition to being at risk of recurrent GDM in subsequent pregnancies. Therefore, an oral glucose tolerance test at 3-year intervals is a cost-effective strategy for screening these women. Continuous nutritional modifications to encourage prompt postpartum weight loss, breastfeeding, and moderate exercise are all recommended.

Pregestational Diabetes Mellitus

In the past, most patients presenting with pregestational diabetes were those affected by juvenile diabetes; however, during recent years, the proportion of maturity onset diabetes of the young (MODY) has increased in parallel to the increase in maternal age.

Pre-GDM is much more difficult to control, and insulin treatment with frequent dosing or by insulin pump is required. Potential risks are the development of life-threatening diabetic ketoacidosis (DKA) on one hand and profound hypoglycemia on the other. It is recommended that patients and their families should know how to respond quickly and appropriately to hypoglycemia.[1]

In contrast to GDM, uncontrolled pre-GDM carries increased risk for fetal malformations. However, the risk of malformations appears to be significantly reduced (to background levels) if the patient conceives when glucose levels are controlled. This can be estimated by the HbA1C. Adequate glucose control near physiologic levels before conception and during pregnancy may decrease the risk of abortion, macrosomia, fetal death, and neonatal morbidity.

Target organ diabetic effects (renal, retinal, cardiac, and nervous system) should be evaluated prior to conception and during pregnancy. The effect of DM on the microvasculature and placenta may cause growth restriction rather than growth promotion, which is the hallmark of GDM.

Pre-GDM pregnancies are at increased risk for fetal death, therefore, fetal movement counting, nonstress testing, and sonographic biophysical profiles performed at appropriate intervals might prove valuable to monitor these pregnancies. Timing and mode of delivery are usually tailored to the patient's condition, degree of vasculopathy, and fetal thriving, among other factors.

Implications for the Neonate

Infants of diabetic mothers are at risk for increased morbidity and even mortality in the neonatal period. Mortality is mostly secondary to malformations and the complications of prematurity. The recognition that there is a clear relationship between degree of control of maternal hyperglycemia and the risk for congenital anomalies and the

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occurrence and severity of birth trauma and neonatal morbidity and mortality has led to improved outcomes in recent years.[3] Long-term effects have been recognized in recent years. Interestingly, recent data indicate that in high-resource settings, maternal diabetes is not associated with an increased risk of in-hospital mortality or severe morbidity in very preterm infants with a birth weight <1500 g.[21a]

Maternal hyperglycemia causes intermittent and prolonged fetal hyperglycemia, leading to upregulation of insulin production by the fetal pancreas. Because fetal insulin mostly does not cross the placenta, a state of chronic hyperinsulinemia ensues, leading to increased fetal growth that results in macrosomia and visceromegaly, particularly in the liver, kidneys, skeletal muscle, and heart. Secondarily, insulin raises the metabolic rate, increasing oxygen demand leading to chronic mild hypoxemia that stimulates erythropoietin production. After birth, this will express itself as polycythemia and hyperviscosity and secondary hyperbilirubinemia. The hyperviscosity, together with low cardiac output secondary to cardiomyopathy and low maternal levels of protein C, protein S, and antithrombin, contribute to increased risk for thrombotic events, in particular renal vein thrombosis.

Hyperinsulinemia also retards the production and secretion of pulmonary surfactant, both phospholipids and surfactant-associated proteins, leading to significant increase in the risk for respiratory distress syndrome (RDS) up to 38 weeks' gestation.[8,10,22] Additional mechanisms have been identified that include reduced pulmonary vascular function and inhibition of angiogenesis that appear to be mediated via downregulation of hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF) secondary to changes in the insulin signal transduction pathway.[15] In addition, the tendency to deliver diabetic women by elective cesarean section without labor contributes to an increased risk for transient tachypnea of the newborn (TTN). Fortunately, tighter control of glucose levels in pregnancy has significantly reduced both of these respiratory risks for infants of diabetic mothers (IDMs).

After birth, the infant is suddenly removed from the source of excess glucose and other nutrients, namely, the mother, but continues to have upregulated insulin production, and despite increased glycogen stores, appears incapable of secreting glucagon and catecholamines to prevent the resultant hypoglycemia. Both the incidence and the severity of hypoglycemia are increased when the mother has received insulin and also when glycemic control has been inadequate. All IDMs require close monitoring of blood glucose, particularly during the hours and days shortly after birth. Hypoglycemic infants may be asymptomatic or may show clinical signs such as tremor, seizures, poor feeding, respiratory distress, and hypotonia. Debate continues around the definition of hypoglycemia, which is based mostly on statistical calculations and not on the relationship between specific values over specific periods of time and neurodevelopmental outcomes. Unfortunately, medical uncertainty over a condition that may have long-term adverse effects opens the door to litigation in which a judge or jury are left to decide on how low is too low.[13] Continuous subcutaneous monitoring of blood glucose is a technique that may help clarify this uncertainty.[11]

Congenital malformations in a number of organ systems are increased two- to threefold in IDMs whose mothers require insulin, but not so in patients with gestational diabetes that developed after the stage of embryogenesis (see Box 18.1). Poor diabetic control with raised HbA1C in the periconceptual period exposes the fetus to hyperglycemia during early embryogenesis and organogenesis, thereby exerting a significant teratogenic effect. Hyperinsulinemia does not develop until later in pregnancy and, therefore, does *not* play a role in this mechanism.

Later exposure to hyperinsulinemia contributes to the development of cardiac manifestations, including cardiomyopathy characterized by generalized cardiomegaly together with asymmetric septal hypertrophy, leading to functional left ventricular outflow tract obstruction. Cardiac dysfunction has a wide range of possible clinical presentations, ranging from an asymptomatic infant to a critically ill infant with either cardiac failure or severe respiratory distress that may be difficult to distinguish from respiratory distress syndrome. The cardiac hypertrophy resolves spontaneously within a few months of birth. Beta blockers are useful therapeutic agents, whereas cardiotonic agents may worsen the condition. The cardiomyopathy may be recognized in the second trimester by evidence of septal hypertrophy.

Hypocalcemia is seen in IDMs, often after 2-3 days of life, and is related to the severity of the maternal diabetes. The mechanisms are related to inadequate parathyroid hormone (PTH), excess calcitonin, and altered vitamin D metabolism. The most common physical sign is tremor, which usually resolves spontaneously, although occasional infants may require calcium supplementation.

Infants of diabetic mothers are at significantly increased risk for asphyxia for a number of reasons. Macrosomia results mainly from excess body fat in a distribution that increases the risk for shoulder dystocia, which may lead to asphyxia, brachial plexus injury, diaphragmatic paralysis, and recurrent laryngeal nerve injury.[27] In addition, in uncontrolled diabetics, increased HbA1C together with increased maternal 2,3-diphosphoglycerate (2,3-DPG) can lead to increased affinity of hemoglobin for oxygen, thereby reducing oxygen delivery to the fetal tissues.[12,21]

Although the vast majority of IDMs recover rapidly and appear to have no residual effects, type 1 diabetes is transmitted to the child in 2% of cases if the mother was insulin dependent and in 6% if the father was insulin dependent.[23] Additional long-term effects may include increased childhood and adolescent obesity, impaired glucose tolerance, and subtle neuropsychological effects.[28] Box 18.2 summarizes the major morbidity in infants of diabetic mothers.

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• BOX 18.2 Major Morbidity in Infants of Diabetic Mothers

- Macrosomia and visceromegaly
  - Birth trauma—shoulder dystocia, brachial plexus injury, diaphragmatic paralysis, recurrent laryngeal nerve injury
  - Premature birth
- Congenital malformations
  - Cardiac, central nervous system, gastrointestinal, musculoskeletal, renal
- Metabolic disturbance
  - Hypoglycemia
  - Hypocalcemia
- Hematologic
  - Polycythemia
  - Hyperbilirubinemia
- Respiratory
  - Respiratory distress syndrome
  - Transient tachypnea of the newborn
- Skeletal
  - Caudal regression syndrome

Breastfeeding in Women With Gestational Diabetes Mellitus

Breastfeeding should be strongly recommended for its multiple health benefits for the neonate and mother. It reduces the long-term risk for obesity, diabetes, hypertension, and cardiovascular disease. The inverse association between breastfeeding and obesity is dose-dependent (approximately 4% reduction in risk of being overweight per month of breastfeeding) and is seen across all age groups and ethnicities. Children who had been breastfed for at least 2 months also had lower rates of type 2 diabetes. Because of the increased risk of hypoglycemia in IDMs and the low substrate of breast milk after delivery, hypoglycemia should be aggressively monitored and treated with supplements (see Chapter 86). Among postpartum women with recent gestational diabetes mellitus, breastfeeding the infant during the 2-hour, 75-g OGTT may modestly lower plasma 2-hour glucose (5% lower on average) as well as insulin concentrations in response to ingestion of glucose.

Key Points

- Gestational diabetes (GDM) is defined as glucose intolerance beginning or first diagnosed during pregnancy.
- Pregestational diabetes refers to women with DM prior to conception.
- Women with pregestational diabetes may exhibit vascular complications, placental insufficiency, and growth restriction.
- The main perinatal risk in GDM is macrosomia, whereas pre-GDM can be associated with a variety of malformations.

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19

Obstetric Management of Prematurity

MAGED M. COSTANTINE, ANTONIO SAAD, AND GEORGE SAADE

Preterm birth is defined as a delivery that occurs at 20 weeks' gestation or later but prior to 37 weeks' gestation (from the first day of the last menstrual period). Although advancements in neonatology and obstetrical interventions have dramatically improved outcomes and reduced the burden associated with prematurity, the rate of preterm birth itself has not changed substantially over the past 40 years. From 1990-2006, the preterm birth rate *increased* to a peak of 12.6%, probably because of the increase in indicated preterm deliveries and early deliveries related to multiple gestations conceived with assisted reproductive techniques.[109] This was followed by an encouraging drop in preterm birth rate to 9.57% in 2014. However, since then there has been a reverse trend with the 2016 preliminary birth data showing a preterm birth rate of 9.85%.[109] On the other hand, the low birth weight rate declined slightly to 8.1% in 2015,[109] and the infant mortality rate remained stagnant and was reported as 5.96 infant deaths per 1000 live births in 2013, compared with 6.15 deaths in 2010.[111]

Prematurity remains a leading cause of neonatal morbidity and mortality worldwide, accounting for 60%-80% of deaths of infants without congenital anomalies. In 2013, 36.1% of all infant deaths in the United States were preterm related, second only to congenital malformations and chromosomal abnormalities among the leading causes of infant mortality.[111] Maternal race and ethnicity have a particularly strong effect on preterm-related infant mortality, with 44% of non-Hispanic black infant deaths attributed to preterm-related causes, a 3 times higher rate compared with non-Hispanic white infants.[111] However, although the preterm-related infant mortality rate was highest for non-Hispanic black women, they also experienced the largest declines since 2005, with the preterm-related infant mortality rates having declined by 22% for non-Hispanic black women, compared with a 14% decline for non-Hispanic white women.[111]

There are few obstetric interventions that successfully delay or prevent spontaneous preterm birth. Interventions to reduce the morbidity and mortality of preterm birth can be primary (directed to all women), secondary (aimed at eliminating or reducing existing risk), or tertiary (intended to improve outcomes for preterm infants). Most efforts so far have been tertiary, including regionalized care and treatment with antenatal corticosteroids, tocolytic agents, magnesium sulfate for neuroprotection, and antibiotics. These measures have reduced perinatal morbidity and mortality but essentially have no effect on the incidence of preterm birth itself. Advances in primary and secondary care, following strategies used for other complex health problems such as cervical cancer, are necessary to truly move toward eradicating prematurity-related illness in infants and children.[87]

Promising interventions such as progestin supplementation, cerclage placement, and cervical pessary insertion appear to be useful in the prevention of preterm birth in certain populations. The most pressing need is to better define the populations of pregnant women for whom these and other interventions are beneficial, and continued work to understand the complex pathophysiology of prematurity in an effort to design future interventions effective in reducing preterm birth.[125]

Prematurity

Preterm birth prior to 37 weeks' gestation may be divided into two major categories: (1) indicated preterm births and (2) spontaneous preterm births. Indicated preterm births include deliveries prompted by concerns regarding maternal or fetal well-being, processes that account for approximately 25% of all preterm births together.[56] Common reasons for these indicated early deliveries include preeclampsia/eclampsia (see Chapter 17) and nonreassuring fetal status secondary to abnormal fetal heart rate, intrauterine growth restriction (see Chapter 15), or oligohydramnios (see Chapter 24).

Spontaneous preterm births include deliveries that follow either spontaneous labor or preterm premature rupture of membranes (PPROM). Spontaneous preterm births account for approximately 70% of all preterm deliveries, with 40%-50% of these early deliveries owing to preterm labor and 25% to PPROM.[56]

The risk of neonatal mortality and morbidity is inversely related to the gestational age at the time of delivery.[6,49] A recent review of studies from the United States and other developed countries showed survival to discharge of 23%-27% for births at 23 weeks, 42%-59% for births at

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Abstract

Preterm labor and delivery remains a significant clinical problem globally, accounting for a substantial component of all neonatal morbidity and mortality. Despite important insights into the pathophysiology of preterm labor over the past several decades, effective therapeutic interventions to decrease spontaneous preterm delivery remain limited. Clearly, the development of effective screening tools to identify patients at greatest risk for spontaneous preterm delivery, primary and secondary prevention strategies, and interventions to improve neonatal outcomes are urgently needed. With the advances in neonatal care, coupled with various obstetric interventions including the use of progesterone, cervical cerclage, and pessary to prevent preterm birth in select populations, and the use of antenatal corticosteroids, magnesium sulfate, and intrapartum antibiotics all contributed to decrease in neonatal mortality and morbidities associated with preterm birth. This chapter aims to review the epidemiology and pathophysiology of preterm labor, as well as the current therapeutic strategies that may be employed in this setting.

Keywords

Preterm birth
prematurity
neonatal morbidities and mortality
pathogenesis
prevention
progesterone
cerclage
pessary

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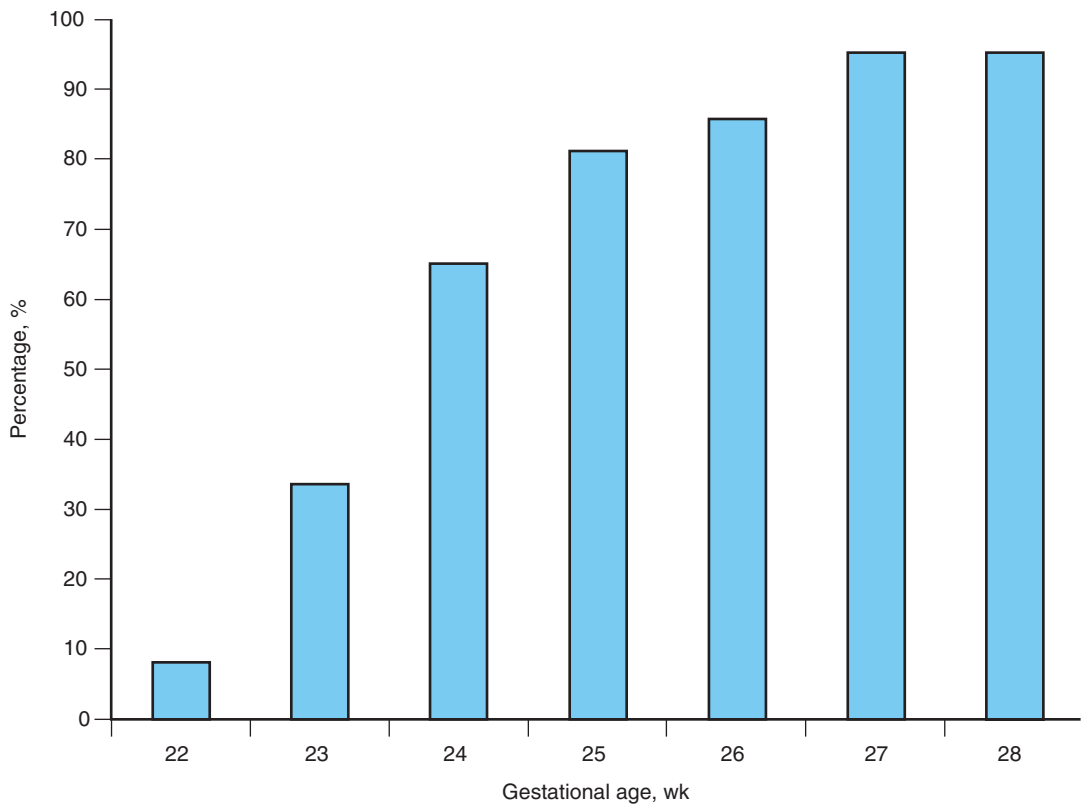
24 weeks, and 67%-76% for births at 25 weeks of gestation.[6] Gestational-age-specific neonatal mortality rates are listed in Table 19.1 (see also Fig. 19.1).[6,35,155,171,177] Survival by gender is presented in Fig. 19.2. Attention has primarily been focused on prevention of early preterm births (23-32 weeks' gestation), which represent less than 2% of all deliveries but contribute to 60% of perinatal mortality and nearly 50% of long-term neurologic morbidity. Perhaps the greatest benefit of this focus has been reaped by the extremely premature neonates. Although once considered to be nonviable, survival rates of 20%-40% have recently been noted in neonates delivered at 22-23 weeks' gestation.

Stoll et al.[172] reported that survival increased between 2009 and 2012 for infants at 23 weeks' gestation (27%-33%; adjusted RR 1.09 [95% CI, 1.05-1.14]) and 24 weeks (63%-65%; adjusted RR 1.05; 95% CI, 1.03-1.07), with smaller relative increases for infants at 25 and 27 weeks' gestation and no change for infants at 22, 26, and 28 weeks' gestation. Survival without major morbidity increased approximately 2% per year for infants at 25-28 weeks' gestation, with no change for infants at 22-24 weeks' gestation.

These babies are at risk for a wide array of complications, though, including long-term neurologic impairment.[6] Moore noted from the EPICure studies that looked at extremely preterm infants that survival of babies admitted

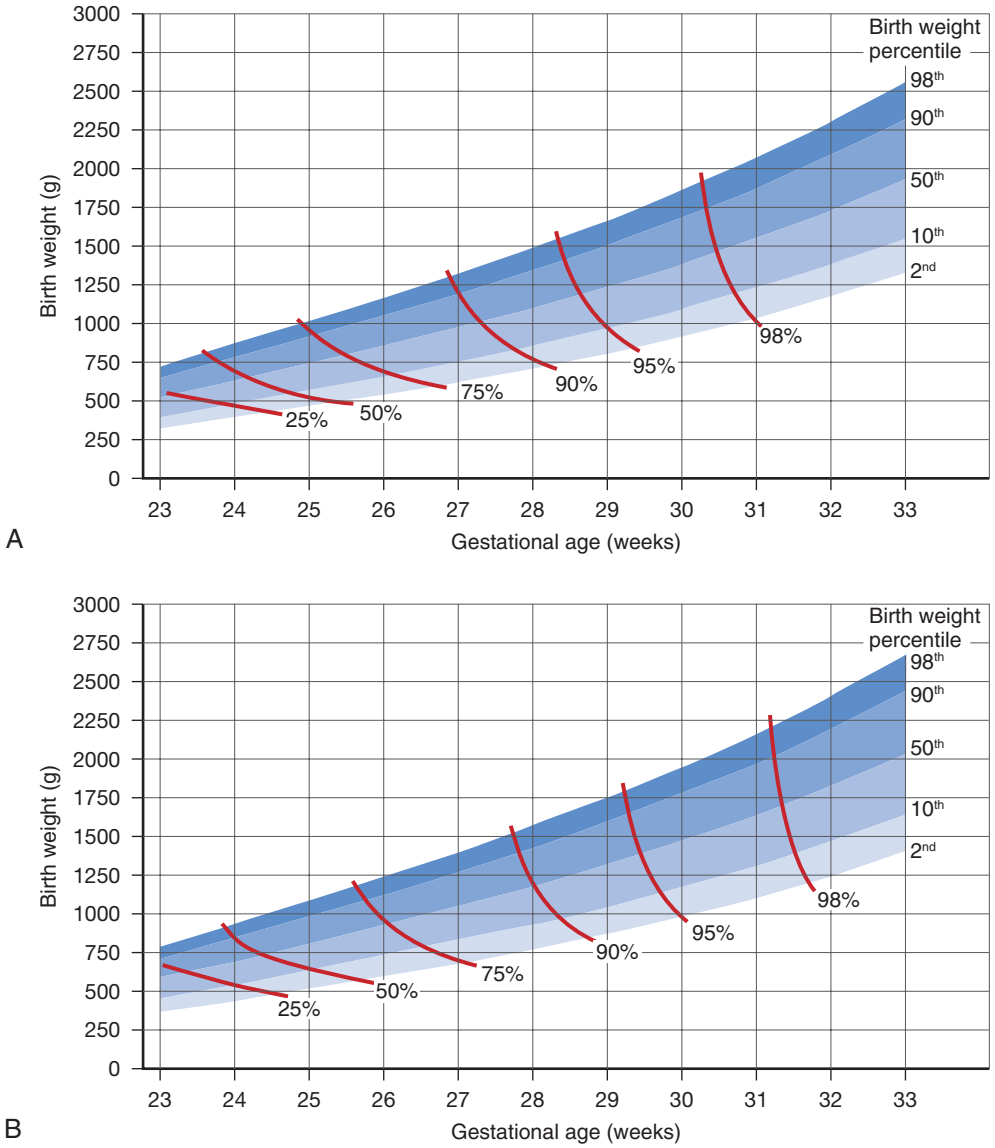
TABLE 19.1 Survival Rates by Gestational Age 2004-2007

	Survival by Gestational Age			
Gestational Age, Weeks	Japan,[89] %	Sweden,[65] % (CI)	NRN,[171] % (Range)	EPICure,[35] %
23	55	53 (44-63)	26 (2-53)	17-28
24	76	67 (59-75)	55 (20-100)	40-60
25	85	82 (76-87)	72 (56-90)	66-75
26	90	85 (81-90)	88 (60-100)	77-83
27	93	85 (81-90)	91 (75-100)	95



• **Fig. 19.1** Survival to discharge according to gestational age among very low birth weight infants born in the National Institute of Child Health and Human Development (NICHD) neonatal research network centers in 2012. (Data from Stoll BJ, Hansen NI, Bell EF, et al., for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA* 2015;314(10), 1039–1051.)

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• **Fig. 19.2** Contour plot of predicted survival according to gestational age, birth weight, and gender. The contour lines join combinations of gestational age and birth weight of equal estimated probability of survival. Birth weight percentiles are shown for information. **A,** Female. **B,** Male. (Data from Manktelow BN, Seaton SE, Field DJ, et al. Population-based estimates of in-unit survival for very preterm infants. *Pediatrics*. 2013;131[2]:e425-e432.)

for neonatal care increased from 39% (35%-43%) in 1995 to 52% (49%-55%) in 2006, an increase of 13% (8%-18%), and that survival without disability increased from 23% (20%-26%) in 1995 to 34% (31%-37%) in 2006, an increase of 11% (6%-16%).[123] A recent cohort from the Neonatal Research Network of non-anomalous infants born between 2006 and 2011 before 27 weeks showed similar patterns with overall rates of survival and intact survival (without severe impairment) of 5.1% (IQR 0-10.6) and 3.4% (IQR 0-6.9) respectively among children born at 22 weeks to 81.4% (IQR 78.2-84) and 75.6% (IQR 69.5-80) respectively among those born at 26 weeks' gestation.[155]

While extremely premature neonates contribute the bulk of perinatal mortality and morbidity, those born as late preterm (between 34 weeks 0 days and 36 weeks 6 days; 6.87% in 2015) make up the majority of preterm infants,[28] and recent evidence has emerged showing that they have increased mortality and various morbidities, including transient tachypnea of the newborn, respiratory distress syndrome (RDS), persistent pulmonary hypertension, respiratory failure, temperature instability, jaundice, hypoglycemia, feeding difficulties, and prolonged neonatal intensive care unit (NICU) stay compared with their term counterparts (Table 19.2).[28,174] These late preterm infants may also manifest long-term neurodevelopmental consequences. It is, therefore, important to remember that although morbidity is inversely related to gestational age, there is no gestational age, including term, that is wholly exempt from adverse outcomes.[157] The best outcomes remain for babies delivered at 39 weeks.

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TABLE 19.2 Neonatal Mortality and Morbidities in Infants Born Late Preterm (34-36 6/7 Weeks) Compared With Term Infants

Variable	Late Preterm Infants (%)			Full-Term Infants (%)
	34 Weeks	35 Weeks	36 Weeks	
Neonatal mortality	0.57%	0.34%	0.23%	0.06%
Mechanical ventilation or endotracheal intubation	3.6%	1.7%	0.79%	0.35%
Nasal CPAP	8.8%	5.3%	2.1%	0.26%
Use of surfactant	7.4%	4.35	2.2%	0.23%
Use of nasal oxygen	9.6%	6.5%	3.3%	0.5%
RDS	10.6%	6%	2.7%	0.36%
Sepsis work-up	31.2%	22%	14.8%	11.8%
Sepsis (culture proven)	0.64%	0.33%	0.22%	0.13%
Hypoglycemia	11.5%	5.3%	4.4%	0.26%
Feeding problems	51%	34%	22%	5.3%
Jaundice requiring phototherapy	10.3%	6%	2.4%	1.3%

CPAP, Continuous positive airway pressure; RDS, respiratory distress syndrome.
From Teune MJ, Bakhuizen S, Gyamfi Bannerman C, et al. A systematic review of severe morbidity in infants born late preterm. *Am J Obstet Gynecol.* 2011;205:374.e1-9.

While gestational age remains the major determinant of morbidity and mortality, other factors affect these rates. For example, female infants demonstrate better survival rates than male infants at any gestational age, and black neonates tend to do better than white neonates.[177] Neonatal survival rates also increase as infant birth weight increases, with 55% survival at 501-750 g, 88% at 751-1000 g, 94% at 1001-1250 g, and 96% at 1251-1500 g.[49] In addition, differences in hospital practices regarding the initiation of active treatment in infants born between 22 and 24 weeks' gestation may affect overall and intact survival among these patients.[155] The best outcomes at the limits of viability continue to be reported from Japan.

Neonatal morbidities related to prematurity also remain a significant clinical problem, including RDS, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, patent ductus arteriosus, jaundice, growth failure, cerebral palsy, disorders of cognition, and retinopathy of prematurity. The risk for these morbidities is inversely related to both gestational age at delivery and birth weight, with Table 19.3 depicting the morbidity rates according to gestational age. Use of antenatal corticosteroids (betamethasone or dexamethasone) has been shown to reduce the incidence or severity of RDS, intraventricular hemorrhage, and necrotizing enterocolitis, but rates of other adverse outcomes remain unchanged.

Cerebral palsy is an umbrella term encompassing disorders of movement and posture, attributed to non-progressive disturbances occurring in the developing fetal or infant brain. Cerebral palsy complicates approximately 2 per 1000 live births. Although the majority of cases are associated with term deliveries, the relative risk for an early preterm infant developing cerebral palsy is nearly 40 times that of a term infant. The risk of cerebral palsy is particularly high in children with extremely low birth weight (less than 1000 g), a population that also has substantially higher rates of cognitive disorders, hearing and visual disabilities, neurobehavioral dysfunction, and poor school performance (see Chapter 60).[26] The high risk of cerebral palsy in this population may be associated with the increased rate of intrauterine infection and inflammation in extreme preterm patients. Intrauterine infection and postnatal sepsis appear to play an important role in the pathophysiology of this condition. Intrauterine infection and inflammatory cytokines appear to substantially increase the risk of cell death, resulting in periventricular leukomalacia and intraventricular hemorrhage, and ultimately contributing to development of cerebral palsy.[26,186] Recently, obstetric professional societies have advocated for the use of magnesium sulfate for fetal neuroprotection. Research has shown that administration of this therapy to women at risk for imminent delivery of a fetus less than 32 weeks' gestation may reduce the risk of moderate or severe cerebral palsy by up to 45%.[7,164]

Pathogenesis

Despite exhaustive research attempts, a complete understanding of the pathogenesis of preterm labor remains elusive. It is becoming increasingly clear that the factors that lead to the development of preterm labor are distinct from those that occur with term labor and thus represent a pathologic rather than a physiologic process. To add to the complexity, preterm labor appears to involve a number of

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TABLE 19.3 Morbidity by Gestational Age for Infants Born in the NICHD Neonatal Research Network

	Gestational Age (Weeks)					
	23	24	25	26	27	28
N	496	1223	1426	1530	1811	1967
Morbidity						
Respiratory distress syndrome*	97	95	90	86	78	65
Surfactant therapy	95	90	89	84	78	67
Bronchopulmonary dysplasia						
Mild	26	26	37	35	28	16
Moderate	35	34	29	26	20	15
Severe	38	37	26	17	13	8
Patent ductus arteriosus	54	60	55	48	42	32
Grade III-IV intraventricular hemorrhage	36	26	21	14	11	7
Necrotizing enterocolitis (proven)	12	15	13	9	10	7
Late-onset septicemia	62	55	46	35	27	20

*An infant was determined to have respiratory distress syndrome if each of the following was true: required oxygen at 6 hours of life, continuing to age 24 hours; demonstrated clinical features up to age 24 hours; needed respiratory support to age 24 hours; had an abnormal chest radiograph up to age 24 hours.
Modified from data obtained between 1/1/04 and 12/31/07 from the National Institute of Child Health and Human Development (NICHD), Stoll BJ, Hansen NI, Bell EF, et al., Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126(3):443-456.

processes that all lead to the common pathway of spontaneous preterm birth.

To understand the pathophysiologic processes of preterm labor, one must be familiar with the pathway leading to normal term labor. Three main biologic events appear to be involved with the onset of spontaneous labor: cervical ripening, formation and expression of myometrial oxytocin receptors, and myometrial gap junction formation. Prostaglandins E_2 and $F_{2\alpha}$ (PGE_2 and $PGF_{2\alpha}$) are believed to be important factors involved in these events. Levels of these specific prostaglandins increase in amniotic fluid, maternal plasma, and urine during labor, wherein they have been shown to facilitate cervical ripening and to promote myometrial gap junction formation. To that end, exogenous administration of prostaglandins facilitates cervical ripening and induction of labor at any point in gestation, while administration of prostaglandin synthetase inhibitors arrests preterm labor. Although prostaglandins are clearly an important component of the parturition process, the mechanism by which this cascade of events begins is not fully understood. Several theories exist regarding the initiation of parturition, including (1) progesterone withdrawal, (2) oxytocin initiation, and (3) decidual activation.

The progesterone withdrawal theory stems primarily from studies of sheep. Endogenous progesterone is known to inhibit decidual prostaglandin formation and release. As parturition nears, the fetal adrenal axis becomes more sensitive to adrenocorticotropic hormone, which incites an increased secretion of cortisol. Fetal cortisol then stimulates trophoblast 17α-hydroxylase activity, which decreases progesterone secretion and leads to a subsequent increase in estrogen production. This reverse in the estrogen-to-progesterone ratio then results in increased prostaglandin formation, thus leading to parturition. However, although this mechanism is well established in sheep, it does not appear to be the primary initiator of parturition in humans. Despite this, it is thought that premature activation of this axis can lead to preterm birth, primarily as triggered by increased maternal physical or psychological stress or fetal uteroplacental vasculopathy (i.e., as seen with preeclampsia or intrauterine growth restriction). Supporting this theory are the increased fetal adrenal zone size and elevated corticotropic hormone levels associated with preterm delivery, particularly late preterm births.

The second parturition theory involves oxytocin, a substance known to cause uterine contractions and to promote prostaglandin release, as an initiator of labor. The number of myometrial oxytocin receptors increases substantially as women near term. Despite this, oxytocin levels themselves do not rise before labor, and the involvement of this hormone in parturition likely represents a final common pathway instead of an inciting event.

The final and most likely theory regarding preterm parturition involves premature decidual activation through processes such as inflammation and/or hemorrhage. There is a large body of evidence establishing a strong link between inflammation, such as seen in the presence of genitourinary pathogens or even with systemic infections, and spontaneous preterm delivery. Colonization or infection of the upper genital tract results in inflammation and disruption of the choriodecidual interface, initiating a cascade of events ultimately resulting in spontaneous labor. Pathogens may have

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a direct role in this process, as evidenced by the finding of bacteria (usually organisms that are hard to culture using standard techniques) within the amniotic fluid of up to two-thirds of women with preterm birth. More importantly, however, pathogens lead to inflammation that then drives the process of preterm parturition. The evidence for these events is well supported by the biochemical changes that have been observed within the amniotic fluid, trophoblast, and decidua of patients with spontaneous preterm labor. Further support for this hypothesis comes from studies of mid-trimester amniotic fluid, obtained at the time of genetic amniocentesis, which demonstrate that elevated interleukin (IL)-6 levels are often associated with subsequent spontaneous abortion, fetal death, or preterm labor. In addition, amniotic fluid levels of the proinflammatory cytokines IL-1β and tumor necrosis factor-α increase in association with preterm labor. These specific cytokines appear to enhance prostaglandin production in the amnion and decidua while also triggering expression of matrix metalloproteinases that subsequently cause the breakdown of the cervical-chorionic-decidual extracellular matrix. These processes then lead to cervical ripening, separation of the chorion from the decidua, and possible membrane rupture.

Hemorrhage, as with overt placental abruption or even more subtle bleeding, can also lead to decidual activation. Multiple studies have linked the occurrence of vaginal bleeding to an approximately fourfold increase in the risk of spontaneous preterm birth. It is likely that inflammatory and coagulation pathways converge to result in this association. Not only can inflammation or infection lead to hemorrhage secondarily, but vaginal bleeding may also be the inciting event itself, triggering thrombin production that then generates pro-inflammatory cytokines.

The strong association between inflammation and preterm birth represents a series of complex, interconnected pathways. Recognition of this association is an important advance in our understanding of the mechanisms involved in spontaneous preterm delivery and represents a potential target for therapeutic intervention.[56,87,125]

Risk Factors

The identification and management of preterm labor have been directed at defining various epidemiologic, clinical, and environmental risk factors that are related to spontaneous preterm birth. Early recognition of these risk factors (Box 19.1) may allow modification of the traditional approaches to prenatal care and ultimately may reduce the rate of preterm deliveries.

Demographics

In the United States, race is one of the most significant risk factors for preterm delivery. In 2015 birth data, black women have a prematurity rate of about 13.4%, in comparison with 8.9% for white women. The rate of preterm birth less than 32 weeks was more than double in non-Hispanic black women (3.09%) compared with non-Hispanic white women (1.27%).[109] Similarly, the rate of very low birth weight neonates (less than 1500 g), which are associated with the greatest risk of neonatal morbidity and death, is more than doubled in non-Hispanic black women (2.89%) compared with non-Hispanic whites (1.09%).[109] Other risk factors including extremes of maternal age, less education, and lower socioeconomic status, are associated with increased risk of preterm delivery.[29] However, even when these factors are controlled for, black women still have higher rates of preterm delivery.[29]

In addition to race, various behavioral factors increase the risk of preterm birth. Nutritional status, low maternal prepregnancy weight and BMI, and poor gestational weight gain are associated with increased risk. Smoking is associated with several poor pregnancy outcomes including placental abruption, intrauterine growth restriction, and preterm birth, with 10% to 20% of all preterm births attributed to maternal smoking. Substance use in pregnancy, especially cocaine, opiates, and alcohol, are other behavioral factors. Whether the pathophysiology of substance use is direct or through concurrent exposure to other lifestyle-related risks is to be determined.

Yet another behavioral factor related to preterm birth rates is the degree of physical activity and stress during

• BOX 19.1 Risk Factors Associated With Preterm Delivery

Demographic Factors

- Age
- Race
- Socioeconomic status

Behavioral Factors

- Smoking
- Substance abuse
- Poor nutrition
- Absent or inadequate prenatal care

Maternal Medical Conditions

- Poor obstetric history
- Uterine or cervical malformations (short cervix)
- Myomas
- Exposure to diethylstilbestrol
- Hypertension
- Diabetes
- Other medical conditions

Current Pregnancy Complications

- Multiple gestation
- Excess or decreased amniotic fluid
- Vaginal bleeding
- Low body mass index (<19.8 kg/m^2)
- Fetal anomalies
- Abdominal surgery
- Infection (systemic or local)

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pregnancy. Several studies have evaluated the effects of employment on preterm delivery, with disparate results ranging from an increase to an actual decrease in the risk of preterm birth in the working group. These variable results are likely related to the fact that physical activity levels probably impact the rate of preterm birth more than simple employment statistics. For example, activity in the standing position has been shown to increase uterine irritability, likely owing to uterine compression of pelvic vessels resulting in a decreased venous blood return to the heart, a phenomenon that may be temporarily relieved via contractive activity. Maternal stress also plays a role in the association between work activity and preterm birth.[33] It seems, therefore, reasonably clear that women who engage in hard, physical work for long hours under increased stress are at a greater risk of preterm birth than inactive women or those with less physically demanding jobs.

Obstetric History

A history of a prior preterm delivery is one of the most significant risk factors. The recurrence risk of preterm birth ranges from 12%-57%, depending on the number of prior preterm deliveries and the gestational age at which those deliveries occurred. For example, whereas women with one prior preterm birth have a threefold increased risk for preterm delivery in comparison with women with no such history, a six- to tenfold increased risk is seen in women with two previous preterm births.[115] Furthermore, the risk of recurrent preterm birth is increased in women with prior second-trimester losses, induced abortions, prior twin preterm birth, and prior indicated preterm birth.

Cervical and Uterine Factors

Patients with congenital Müllerian anomalies have an increased risk of preterm delivery. Approximately 3%-16% of all preterm births are associated with a uterine malformation. The incidence of preterm labor varies greatly depending on the type of uterine anomaly with unicornuate, didelphic, and bicornuate abnormalities having higher preterm labor rates (approximately 35%) compared with septate uterus (approximately 15%). In addition, these patients are at increased risk of placental abruption and PPROM.

Uterine leiomyomata have also been associated with an increased risk of preterm delivery, primarily owing to an increased incidence of antepartum bleeding and PPROM. Of the various types of myomata, submucosal and subplacental myomata appear to be most strongly associated with preterm delivery.

Cervical incompetence is another important risk factor for preterm delivery. The classic clinical description of cervical incompetence involves a history of painless cervical dilation between 12 and 20 weeks. A history of a second-trimester pregnancy loss has been the cornerstone of the diagnosis, but distinguishing between cervical incompetence and preterm labor can at times be difficult, and many times may not help in the clinical management of these patients.

Intrauterine exposure to diethylstilbestrol (DES) is a significant factor associated with congenital causes of cervical incompetence and both upper and lower genital tract structural abnormalities. An estimated 1-1.5 million women were exposed in utero to DES between the late 1940s and 1971. These women have an increased risk of preterm delivery ranging from 15% to 28%, with an increased risk of spontaneous abortion of 20%-40%. Women exposed to DES who have associated anomalies, such as T-shaped uterus, cervical incompetence, or vaginal structural anomalies, have a greater risk of preterm delivery than those who do not demonstrate these structural abnormalities. Because most women exposed to DES in utero are now older than 40, this risk factor is becoming less and less of an issue.

In addition, cervical procedures performed for the diagnosis and treatment of cervical intraepithelial neoplasia, including cold knife conization, or loop electrosurgical excision, have been associated with increased risk of preterm birth in subsequent pregnancies. A greater depth of excision was suggested to lead to greater risk of PPROM and preterm birth. However, a recent meta-analysis showed that the risk of preterm birth was only increased when these patients were compared to women without any history of cervical dysplasia and not when compared to those with history of abnormal cytology. This suggests other factors like high-risk HPV virus infection as the link toward increased preterm birth risk rather than the procedure itself.[22]

Multifetal Gestations

Multiple gestations carry a sixfold increased risk of preterm delivery compared with singleton pregnancies. In the United States, 15%-20% of all preterm births are in multifetal pregnancies (only 3% of all pregnancies). Approximately 50% of twin and nearly all of higher-multiple gestations deliver prior to 37 completed weeks, with an average length of gestation of 35.2 weeks for twins, 32.1 weeks for triplets, and 29.7 weeks for quadruplets. Owing to artificial reproductive techniques, the prevalence of multiple gestations has increased in the United States. Multiple gestations are discussed further in Chapter 21.

Bleeding

Vaginal bleeding is also associated with an elevated risk of preterm delivery. This is particularly true in the setting of placenta previa and placental abruption, but first- or second-trimester vaginal bleeding in the absence of these conditions is also associated with an increased risk of preterm delivery. The mechanism responsible for the development of preterm labor in the setting of vaginal bleeding appears to be related to thrombin deposition with subsequent production of prostaglandins and plasminogen activators that stimulate an array of degradative enzymes leading to destruction of the extracellular matrix.

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Infection

Infections of the decidua, fetal membranes, and amniotic fluid have been associated with preterm delivery (see Chapter 25).[16,23] For example, although intra-amniotic infection or chorioamnionitis complicates 1%-5% of term pregnancies, the contribution of infections to preterm birth has been estimated to be at least 25%-40% (see also Chapter 25).

There are data suggesting a link between occult upper genital tract infection and spontaneous preterm delivery even in the absence of clinical features of intra-amniotic infection. Moreover, the likelihood of a positive amniotic fluid culture or colonization of the chorioamnion in women with spontaneous preterm labor is inversely proportional to the gestational age at delivery.[16] Typical organisms associated with histologic chorioamnionitis include *Ureaplasma*, *Mycoplasma*, *Gardnerella*, *Bacteroides*, and *Mobiluncus* species.

Numerous theories exist regarding the underlying pathogenesis of intra-amniotic infection: (1) ascending infection from the vagina and cervix, (2) transplacental passage through hematogenous dissemination, (3) retrograde seeding from the peritoneal cavity through the fallopian tubes, and (4) iatrogenic means as a result of intrauterine procedures such as amniocentesis and chorionic villus sampling. There is some evidence to support each of these theories, but ascending infection is the most well-accepted theory.

The mechanism of ascending infection appears to start with excessive overgrowth of certain organisms within the vagina and cervical canal. These microorganisms then gain access to the intrauterine cavity by infecting the decidua, the chorion, the amnion, and then finally the amniotic cavity itself. In this manner, pathogens are able to cross intact membranes. The fetus then becomes infected by aspirating or swallowing infected amniotic fluid or by direct contact with the organism within the fluid, leading to localized infections such as pneumonitis, otitis, or conjunctivitis. Seeding of these areas can lead, in turn, to fetal inflammatory response syndrome and sepsis. Alternatively, sepsis may result from maternal bacteremia, leading to placental infection with subsequent spread of organisms through the umbilical cord to the fetus.

Intra-amniotic infection can also lead to preterm labor through less direct methods, namely stimulation of prostaglandin. Microorganisms, probably through the release of endotoxins (in gram-negative organisms) such as phospholipase A_2 and C or lipopolysaccharide, activate pattern-recognition receptors such as Toll-like receptors that lead to release of inflammatory cytokines such as IL-8, IL-1β, and TNF-α, which in turn stimulate the production of prostaglandins and matrix-degrading enzymes by the amnion and decidua. The amniotic fluid concentrations of prostaglandins $PGF_{2\alpha}$ and PGE_2, as well as their metabolites, are increased in patients with preterm labor, preterm premature rupture of membranes, and intra-amniotic infection.

Group B streptococcus (GBS) has been associated with an increased risk of preterm delivery, but more importantly, GBS colonization plays a major role in neonatal morbidity and death. Between 10% and 30% of pregnant women are colonized with GBS. Pregnant women colonized with GBS have higher incidence of preterm birth, PPROM, and low birth weight. Patients with urinary colonization also have positive results on cervical and vaginal cultures, possibly indicating that the presence of GBS in the urine may be a marker of more severe forms of genital tract colonization. Unfortunately, treatment of GBS genital tract colonization has never been shown to decrease the risk of preterm delivery or PPROM.[8,181]

In 2010, the Centers for Disease Control and Prevention (CDC), in conjunction with the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, revised their guidelines for the prevention of perinatal GBS disease to confirm universal screening at 35-37 weeks of gestation and intrapartum antibiotic prophylaxis for culture-positive and high-risk women. The revised guidelines also included new recommendations for laboratory methods for identification of GBS colonization during pregnancy, algorithms for screening, and intrapartum prophylaxis for women with preterm labor and premature rupture of membranes, as well as clarification of the colony count threshold required for reporting GBS detected in urine of pregnant women, updated prophylaxis recommendations for women with a penicillin allergy, and a revised algorithm for the care of newborn infants.[8,27,181]

Intrapartum GBS prophylaxis is indicated in women with: (1) prior infant with invasive GBS disease, (2) GBS bacteriuria any time during pregnancy, (3) GBS carriers through prenatal screening cultures collected at 35-37 weeks' gestation, and (4) unknown GBS culture at the onset of labor in women with any of the following: (i) preterm labor at less than 37 weeks' gestation, (ii) membranes ruptured for 18 hours or longer, (iii) intrapartum maternal fever of 38°C or higher, and (iv) intrapartum nucleic acid amplification test (NAAT) GBS positive.[8]

For women who are culture positive for GBS, intrapartum chemoprophylaxis with intravenous penicillin G (5 million units initially and then 2.5 million units every 4 hours) is recommended until delivery. Intravenous ampicillin (2 g initially, and then 1 g every 4 hours) is an acceptable alternative to penicillin G. Because of emerging resistance of GBS to macrolides, guidelines have recently been modified for women who are allergic to penicillins.[8,181] In penicillin-allergic women who are not at high risk for anaphylaxis, intravenous cefazolin (2 g initially, and then 1 g every 8 hours until delivery) is recommended. In penicillin-allergic women who are at high risk for anaphylaxis, clindamycin and erythromycin susceptibility testing of the GBS isolate is recommended. If the isolate is sensitive to both clindamycin and erythromycin, intravenous treatment with clindamycin 900 mg every 8 hours is recommended.[8] If the GBS isolate is resistant to either agent or susceptibility is unknown, treatment with intravenous vancomycin (1 g every 12 hours) is recommended. Currently, 70%-80% of cases of neonatal GBS infection in the United States occur in term

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infants; however, the case fatality rate and the burden of disease is much higher in those born preterm. In addition, half the cases are usually early in onset (within the first week of life). In addition, 10%-15% of neonatal infection cases were attributed to missed screening among mothers, and many were born to women who had tested negative for GBS before delivery. Further improvement toward eradication of GBS colonization and disease may involve universal screening in conjunction with rapid diagnostic technologies or other novel approaches, including DNA techniques for the identification of GBS. Given the complications and potential limitations associated with maternal intrapartum prophylaxis, however, vaccines are being considered to prevent neonatal GBS disease. Developing a universal vaccine has proved to be a daunting task, though, because of the variability of serotypes in diverse populations and geographic locations.

Bacterial vaginosis (BV) is yet another infection associated with an increased risk for preterm labor and delivery. It is a common lower genital tract infection found in approximately 20%-40% of African-American women and 10%-15% of white women. This condition is a clinical syndrome characterized by a decrease in the normal vaginal lactobacilli-dominant microflora and a compensatory predominance of bacteria such as *Gardnerella vaginalis*, *Prevotella*, *Bacteroides*, *Peptostreptococcus*, *Mobiluncus*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*. Characteristically, patients with symptomatic BV complain of a watery, homogeneous grayish discharge with a fishy amine odor.

As above, BV has been associated with increased risk for preterm birth, especially among African-American women in whom up to 40% of early spontaneous preterm births may be associated with BV. While some randomized clinical trials demonstrated that treating BV in high-risk patients resulted in reductions in preterm birth rates, other trials did not confirm these findings.[24,77] The majority of women with BV never manifest any signs or adverse outcomes related to the infection, and it is likely that BV is only a surrogate marker for a more important, presently unrecognized condition that may be the cause of the preterm birth.[16,23]

Many other maternal infections or colonizations have been reportedly associated with preterm birth. One of the difficult questions to address is whether these relationships are causal or associative. Gonorrhea, chlamydia, trichomonas, syphilis, and other genital pathogens are more frequently found in women who have a spontaneous preterm birth. For example, gonorrhea, chlamydia, and syphilis have all been associated with a twofold increased risk for preterm delivery, and trichomonas has been associated with a 1.3-fold increased risk. Furthermore, many other sexually transmitted infections (e.g., human immunodeficiency virus, human papilloma virus, hepatitis B, and genital herpes simplex virus) have been associated with an increased risk for spontaneous preterm birth in some, but not most, studies. Importantly, the women affected by these infections often have other risk factors for preterm birth (e.g., low socioeconomic status, malnutrition, smoking, substance abuse, bacterial vaginosis). These confounding variables make it difficult to establish causality.

Genetic Factors

Despite evidence that genetic factors contribute to the duration of gestation and the risk of preterm birth, robust associations with genetic variants have not until recently been identified. Zhange used large data sets that included the gestational duration to determine possible genetic associations.[188] They performed a genome-wide association study in a discovery set of samples obtained from 43,568 women of European ancestry using gestational duration as a continuous trait and term or preterm (<37 weeks) birth as a dichotomous outcome. In the discovery and replication data sets, four loci (EBF1, EEFSEC, AGTR2, and WNT4) were significantly associated with gestational duration. Functional analysis showed that an implicated variant in WNT4 alters the binding of the estrogen receptor. Common variants in EBF1, EEFSEC, and AGTR2 showed association with preterm birth with genome-wide significance. An analysis of mother-infant dyads suggested that these variants act at the level of the maternal genome. Previously established roles of these genes in uterine development, maternal nutrition, and vascular control support their mechanistic involvement.

Other Risk Factors

A variety of other factors have been associated with an increased risk for preterm labor (see Box 19.1), including the following:

- Extremes in the volume of amniotic fluid, including polyhydramnios or oligohydramnios
- Fetal anomalies, especially those involving multiple organ systems and central nervous system abnormalities
- Maternal abdominal surgery in the late second and third trimester
- Maternal medical conditions, such as gestational or pre-existing diabetes and hypertension (although these preterm births are often induced, not spontaneous)
- Asymptomatic bacteriuria
- Systemic infections including bacterial pneumonia, pyelonephritis, and acute appendicitis

Predicting Preterm Labor

The multifactorial nature of preterm delivery has thus far impeded efforts to decrease or even eliminate preterm birth. Indicated deliveries account for 20%-25% of all preterm births while PPROM is associated with another 25%-40% of these early deliveries. In these cases, tocolysis is usually not applicable or contraindicated. Of the remaining 40%-50% of early deliveries owing to spontaneous preterm labor, more than half occur beyond 34 weeks' gestation when the use of tocolysis is also not recommended. Consequently, only about 15%-20% of patients at risk for preterm

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birth are true candidates for treatment. A significant volume of research has focused on predicting preterm birth in this cohort of patients. Classical clinical predictors including cervical change; uterine activity; socioeconomic, demographic, and other clinical variables; and various combinations of risk scoring systems were not shown to be useful predictors of preterm birth. The use of home uterine monitoring is also not recommended. Other categories of risk factors are explored in the following paragraphs: biochemical predictors and ultrasound predictors.[29,168]

Biochemical Predictors

The biochemical processes leading to the initiation of either term or preterm labor are complicated, such that these pathways have not been fully established in humans. Despite this limitation, important insights into the pathophysiology of spontaneous preterm labor have helped to identify various biochemical markers that may predict preterm delivery.[57]

Perhaps one of the most important biochemical markers identified to date is fetal fibronectin.[145] This glycoprotein is found within the extracellular matrix that surrounds the extravillous trophoblast at the uteroplacental junction. Clinically, it serves as a prototypic example of a marker of choriodecidual disruption. Fetal fibronectin is usually absent from cervicovaginal secretions starting from the 20th week of gestation until near term. Detection of elevated cervicovaginal levels of fetal fibronectin has, therefore, been strongly associated with an increased risk for preterm delivery in high-risk patients.[59,142,168] Sensitivities in the 80%-90% range with positive predictive values of 30%-60% have been reported. For example, Goldenberg and associates demonstrated that, in asymptomatic women at 24 weeks' gestation, elevated cervicovaginal fetal fibronectin levels (greater than 50 ng/mL) were strongly associated with subsequent spontaneous preterm delivery, with ORs of 59.2 (95% CI, 35.9-97.8) for delivery before 28 weeks' gestation, 39.9 (95% CI, 25.6-62.1) for delivery less than 30 weeks' gestation, and 21.2 (95% CI, 14.3-62.1) for delivery less than 32 weeks' gestation.[59] Further supportive data comes from Tanir and associates, who prospectively confirmed the clinical value of cervicovaginal fetal fibronectin, showing that a positive fetal fibronectin test was associated with an increased likelihood of preterm delivery in women with signs and symptoms of preterm labor.[173] Quantitative fetal fibronectin testing was also evaluated in women with preterm labor symptoms, demonstrating an increasing positive predictive value for preterm birth of 19%, 32%, 61%, and 75%, with increasing fetal fibronectin thresholds of 10 ng/mL, 50 ng/mL, 200 ng/mL, and 500 ng/mL respectively.[1] While these data suggest that fetal fibronectin is a marker for spontaneous preterm delivery, trials using antibiotics in women with positive fetal fibronectin were not supportive, and no other studies showed any benefit in predicting or preventing preterm birth. While many clinicians rely on the test (usually alone or in combination with cervical length) in symptomatic women at less than 32 weeks' gestation, to justify their management in an ambulatory fashion due to the test's high negative predictive value, recent meta-analysis and review showed that testing of fetal fibronectin in singleton gestations with threatened preterm labor is not associated with prevention of preterm birth or improvement in other perinatal outcomes but is associated with other costs.[21] Therefore, screening of low-risk women with fetal fibronectin test to predict preterm birth is not recommended.[29,81,168]

Estriol is another biochemical marker that was suggested to be of use in predicting preterm delivery.[145] Estriol is a unique hormone of pregnancy that is produced almost entirely by the trophoblast using precursors derived from the fetal adrenal gland and liver. Levels of this hormone rise throughout pregnancy, with a characteristic exponential increase 2-4 weeks before the spontaneous onset of labor at term. Interestingly, patients undergoing induction of labor at term fail to demonstrate this increase in estriol, indicating that it plays a role in the onset of spontaneous labor. This finding has led to the theory that salivary estriol levels may be used to identify patients at risk for preterm delivery.[145] However, studies did not show any reduction in the preterm birth rate with the use of these assays. A variety of other serologic, salivary, cervical, and amniotic fluid markers have been evaluated as predictors for preterm delivery, including corticotropin-releasing hormone, alpha-fetoprotein, human chorionic gonadotropin, human placental lactogen, corticotropin-releasing factor, C-reactive protein, alkaline phosphatase, ferritin, placental isoferritin, progesterone, estradiol, matrix metalloproteinase, IL-6, TNFα, and granulocyte colony-stimulating factor. Each of these markers has been shown to have a modest correlation with spontaneous preterm delivery, and none is currently useful clinically.[81]

A variety of enzymes including collagenases and metalloproteinases have been studied with regard to their ability to predict preterm birth. IL-1 stimulates cervical, decidual, and other cells to produce various collagenases, which then act to break down the collagen matrix of the cervix. Serum levels of these collagenases remain relatively constant until the onset of labor, when a marked increase occurs. This increase appears to be exaggerated in women who deliver prematurely, with an up-to-eightfold greater elevation in preterm births. In addition to the collagenases, the metalloproteinases and their inhibitors have received increasing interest in regard to their role in predicting preterm birth. In particular, elevated metalloproteinase-2 (MMP-2) and MMP-8 levels have been associated with preterm labor, especially PPROM, likely owing to their role in membrane weakening through degradation of the chorioamnion basement membrane.[14,125] Granulocyte elastase is another granulocyte degradative enzyme that may play a role in parturition. Granulocytes are stimulated by IL-8 (an inflammatory marker that is elevated in amniotic fluid in labor) and then degraded by granulocyte elastase. The activity of granulocyte elastase has been shown to be increased in the cervix in both term and preterm labor, suggesting that it

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may be involved in cervical ripening and degradation of fetal membranes. Similar to the previous markers, none of these have been shown to either predict or help prevent preterm birth, therefore, they are not used clinically.[29,81,168]

Given the association of occult upper genital tract infection with early spontaneous preterm birth, a variety of serum, amniotic fluid, and cervicovaginal inflammatory markers have also been evaluated as potential markers for the prediction of spontaneous preterm delivery. Both serum and cervical IL-6 levels are significantly elevated at 24 weeks' gestation in women with subsequent spontaneous preterm birth at less than 35 weeks' gestation.[16,23] Rizzo and colleagues further characterized the inflammatory milieu of the cervix and amniotic fluid, showing that levels of several cytokines (IL-1, IL-6, TNFα) were elevated in a series of patients with preterm labor and intact membranes, a finding that was significantly associated with the presence of intra-amniotic infection.[148] In that study, cervical IL-6 was the most potent marker for infection, with an RR of 7.7 (95% CI, 3.5-17.8) in the presence of elevated levels (greater than 410 pg/mL) of this protein.[148] Serum granulocyte colony-stimulating hormone, ferritin, and lactoferrin are examples of other inflammatory markers that may be elevated in asymptomatic women who subsequently deliver prematurely. However, none of these tests is used clinically in low- or high-risk women to predict preterm birth.[16,29,81,168]

Ultrasound Predictors

Regardless of the gestational age at delivery, cervical changes occur before the onset of clinical symptoms associated with preterm labor. Detection of these changes previously involved digital examination only, a test that is problematic because of such possible factors as the introduction of infection, interobserver differences, underestimation of cervical length, and an inability to evaluate the internal cervical os when the external os is closed. In fact, detection of these changes digitally may be possible only late in the process, limiting the clinician's ability to initiate potential treatments. Ultrasonography, therefore, has several potential benefits, allowing for a more objective approach to examination of the cervix with visualization of changes earlier in the process of parturition.[137] Cervical changes visible via ultrasonography include cervical length, dilation of the internal cervical os, dynamic changes that occur in the cervix with time, the presence of intra-amniotic debris, and cervical funneling or wedging.

Transvaginal ultrasound is far superior to transabdominal ultrasound. Transabdominal ultrasound is technically more difficult because the distance between the transducer and the cervix is relatively long, particularly in obese patients. Transabdominal assessment of cervical length and internal os dilation may also be affected by bladder filling and emptying. Finally, fetal parts can cause acoustic shadowing of the cervix when looking abdominally. Transperineal ultrasonography is also effective in the assessment of cervical length, revealing findings that correlate well to those obtained via digital cervical examination and/or transvaginal imaging.[18,79,167]

In a study by Smith and colleagues, low-risk patients were observed serially via transvaginal ultrasonography, showing that the average cervical length of 37 mm remained stable between 10 and 30 weeks of gestation and then began to decrease slightly after week 32. In general, most additional studies reported lengths of more than 30 mm as normal, although this estimate depends upon the population studies and the gestational age at which the length is measured.

Iams and colleagues, in a large multicenter trial, provided the clearest insights into the relationship between cervical length and spontaneous preterm delivery.[86] In this prospective study of 2915 women with a singleton pregnancy, transvaginal sonographic determination of cervical length was obtained at 24 weeks' and again at 28 weeks' gestation. A cervical length less than the 10th percentile (26 cm) at 24 weeks was significantly associated with an increased risk for spontaneous preterm birth at less than 35 weeks' gestation (RR 6.19; 95% CI, 3.84-9.97). An inverse relationship between cervical length and the rate of preterm delivery was noted in this study. The investigators concluded that the risk of spontaneous preterm birth is increased in women who are found to have a short cervix by transvaginal ultrasonography during pregnancy.

Owen and colleagues further evaluated the use of cervical length assessment in a cohort of high-risk women screened between 16 and 18 weeks' gestation.[138] In this study, a cervical length of 25 mm or less was significantly associated with increased risk for spontaneous preterm delivery prior to 35 weeks (RR 3.4; 95% CI, 2.1-5.0). It should also be noted that, in contrast to singleton pregnancies, cervical lengths differ significantly in higher-order gestations, probably reflecting a greater risk for subsequent preterm delivery.[18,167]

Dilation of the internal cervical os and the dynamic nature of the cervix may also be assessed via transvaginal ultrasonography. While increased dilation and the presence of dynamic changes appear to correlate with an increased risk for preterm birth, studies did not show either one to improve the ability of cervical length to predict preterm birth.[29]

Ultrasound assessment of the cervix represents a relatively easy way to identify patients who may be at higher risk for spontaneous preterm delivery, but the positive predictive value of this test is relatively low, and universal screening of all pregnant women remains controversial.[29,167] Cervical length measurements have, therefore, been combined with biochemical parameters in an attempt to improve the specificity and sensitivity of these individual screening tests. However, this combined screening approach does not appear to be superior in identifying women at risk for preterm birth and guiding acute management in such situations.[130]

Prevention

Optimal management of women with a history of spontaneous preterm birth includes a thorough review of the

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patient's obstetric, medical, and social history, with particular attention paid to potentially reversible causes of preterm birth (e.g., smoking, acute infections, strenuous activities). Care for these women should also involve accurate ultrasound dating, consideration of progesterone therapy, cerclage, or pessary (depending on clinical history), and close surveillance during the pregnancy for evolving findings.

Programs attempting to decrease the rate of preterm delivery now use three main approaches: (1) education and surveillance programs, (2) cervical assessment, and (3) supplementation with progestins. Education and surveillance programs train women to recognize the symptoms of preterm labor and educate them about lifestyle changes, nutrition, and smoking cessation.

One of the largest intervention studies was conducted by Papiernik and coworkers in France from 1971-1982.[141] These investigators employed the use of a proactive educational program for the prevention of preterm delivery. The preterm birth rate in the region studied apparently fell from 5.4% to 3.7%. These findings are hard to interpret because the investigation was not a controlled trial, such that changes in antenatal care during that decade make it difficult to assume that the improvement was due solely to the educational program. In subsequent studies modeled after the Papiernik design, no statistically significant differences were identified.

Several theories may explain why these studies have failed to demonstrate significant improvements in the rates of preterm birth. First of all, the level of education and supervision may not have been adequate for the patient population under evaluation. The highest incidence of preterm delivery tends to consist of a population of lower socioeconomic status, in which education and surveillance may be more difficult to achieve. More importantly, early symptoms of premature labor are often subtle and varied, with diagnostic sensitivity less than 50%. For example, women often do not perceive contractions until labor is relatively advanced.

Home uterine activity monitoring was, therefore, proposed as a potential solution to this problem. Although some of these earlier and smaller trials of home uterine activity monitoring demonstrated a significant decrease in preterm births among enrolled subjects, trials were not convincing and were criticized due to overdiagnosis of preterm labor and the potentially biased nursing support; in addition subsequent studies have not shown a benefit. Moreover, the use of home uterine activity monitoring may be harmful in that monitoring may lead to unnecessary hospital admissions and/or intervention such as tocolysis or cerclage placement. Experts have, therefore, concluded that home uterine activity monitoring has no clinical value at this time and should not be used to manage patients outside of a randomized, controlled clinical trial.[29]

Although home uterine monitoring is no longer routinely employed, one study demonstrated more promising results in regard to the beneficial effects of preterm birth prevention clinics. Manuck and colleagues evaluated the rates of recurrent spontaneous preterm births in women assigned either to receive care in a consultative preterm birth prevention clinic (70 patients) or a routine prenatal care clinic (153 patients).[105] Women who were seen in the specialized clinic had lower rates of recurrent spontaneous preterm birth (48.6% vs. 63.4%, $p = 0.04$), delivered at a later mean gestational age (36.1 vs. 34.9 weeks, $p = 0.02$), and had lower rates of composite major neonatal morbidity (5.7% vs. 16.3%, $p = 0.03$). These findings suggest that preterm birth prevention clinics may play a role in the care of high-risk women.

Treatment

One of the primary obstacles encountered when deciding on the optimal therapeutic intervention to prevent preterm delivery is the difficulty in accurately distinguishing between preterm labor and preterm contractions. Traditionally, this distinction is made by the combination of persistent uterine contractions with change in the dilation or effacement of the cervix by digital examination. Another issue that must be addressed is how aggressively one should pursue treatment. Gestational age clearly plays an important role in this decision. Before 32 weeks' gestation, an aggressive approach seems reasonable because of the neonatal consequences of early preterm birth. However, beyond this gestational age, when neonatal morbidity and mortality rates begin to approach those of term infants, maternal treatment becomes more controversial. Many of the interventions discussed in this section have the potential for significant maternal and fetal side effects, and the risks of these adverse events must be weighed against the benefits of treatment in each individual patient.

Therapeutic interventions employed in the setting of preterm labor have the following purposes: (1) to prevent premature birth, (2) to control contractions when they do occur and delay the time from onset of contractions to the actual time of delivery, and (3) to optimize fetal status and maturation before preterm delivery. Most efforts to prevent preterm labor have not proven to be effective and, equally frustrating, most efforts at arresting preterm labor once started have also failed. Management has, therefore, focused more on preventing neonatal complications, including antenatal administration of corticosteroids for enhancement of fetal lung maturity, magnesium sulfate for fetal neuroprotection, and intrapartum antibiotics for prevention of group B streptococcal neonatal sepsis. Ensuring delivery in a medical center with an experienced resuscitation team and the availability of a high-quality newborn intensive care unit also helps to optimize neonatal outcomes.

Bed Rest

Bed rest is one of the most common interventions implemented for the prevention or treatment of threatened preterm labor, but limited data exist to demonstrate significant benefit with this recommendation. Although bed

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rest is prescribed for up to 20% of pregnancies and a wide range of conditions, there is little evidence of effectiveness. Unfortunately, no conclusive, well-performed, prospective, randomized studies exist that have independently evaluated the potential effects for the treatment or the prevention of preterm labor in singletons. Despite a lack of evidence proving that bed rest is beneficial, many obstetricians recommend bed rest for arrested preterm labor and PPROM. In Canada, although care providers have been discouraged from routinely recommending bed rest for women at risk of preterm birth because of potential adverse side effects (i.e., venous thromboembolism, muscle weakness, bone loss, and maternal depression), most providers have not incorporated these recommendations into clinical practice.[169]

McCall et al. reviewed the evidence for bed rest and concluded that "therapeutic" bed rest continues to be used widely despite evidence of no benefit and known harms. Cochrane systematic reviews do not support "therapeutic" bed rest for threatened abortion, hypertension, preeclampsia, preterm birth, multiple gestations, or impaired fetal growth. This assessment has been echoed in other comprehensive reviews. Prescribing bed rest is inconsistent with the ethical principles of autonomy, beneficence, and justice. Hence, if bed rest is used, it should be only within a formal clinical trial.[112]

Hydration or Sedation

One of the mainstays in the initial treatment of preterm labor is the use of oral or intravenous hydration. At least two theories exist in regard to the mechanism of action behind hydration as a potentially effective treatment for preterm contractions. The first theory holds that hydration inhibits the release of antidiuretic hormone through the Gauer-Henry reflex. This reflex, however, has been demonstrated only in animals. The second theory is based on the suggestion that patients with preterm labor are hypovolemic, a theory supported by the delay in delivery that may be seen when women with preterm contractions are treated with albumin in an effort to expand plasma volume. Despite these theories, few studies have prospectively evaluated the use of hydration in women with preterm contractions, and those that do exist actually suggest no benefit to this intervention. For example, in one trial, the combination of bed rest and aggressive hydration was found to be no more effective than bed rest alone in stopping contractions. When the contractions actually did stop, patients in both groups remained at equally high risk for subsequent preterm birth. Another study by Guinn and colleagues reported similar findings in a prospective, randomized trial of 179 women with preterm contractions.[67] Patients were randomized to one of three arms: observation alone, intravenous hydration, or a single dose of subcutaneous terbutaline. No significant differences were noted among the three groups in regard to the interval between intervention and delivery or the incidence of preterm birth, suggesting that intravenous hydration offers no clinical benefit.

Sedation is another strategy that has been used to differentiate between preterm contractions and true preterm labor. As with hydration, limited data document the efficacy of sedation in this clinical setting. Helfgott and associates performed a prospective comparative study of 119 women with preterm labor who were randomly assigned to treatment with hydration and sedation or to the control treatment of bed rest alone. Women in the treatment arm received a combination of 8-12 mg of intramuscular morphine sulfate and 500 mL of intravenous lactated Ringer's solution. No significant differences in contraction cessation or preterm labor rates were seen between the patients assigned to receive hydration and sedation and those assigned to bed rest alone.

Overall, current research does not support the use of hydration or sedation in the initial treatment of preterm labor. Clinically, in many cases, initial hydration with intravenous infusion of fluid occurs before initiating treatment with a tocolytic agent. In addition to being ineffective, aggressive hydration may increase the risk of fluid overload and subsequent development of pulmonary edema when used in the setting of tocolytic therapy, especially with β-sympathomimetic agents.

Progesterone

Based on the progesterone withdrawal theory of parturition initiation, use of progesterone or similar other progestins has been proposed for the prevention of preterm labor and delivery.[167]

Several randomized controlled trials have confirmed the efficacy of progesterone therapy for the prevention of preterm birth.[167] Da Fonseca and colleagues performed a double-blinded, placebo-controlled trial of 142 high-risk pregnancies in which they showed a significant reduction in preterm birth rates prior to 37 weeks' gestation in women assigned to receive weekly progesterone vaginal suppositories (13.8% compared with 28.5% in the control group, $p < 0.05$).[40] Preterm birth prior to 34 weeks was also significantly lower in the progesterone group when compared with the placebo group (2.7% vs. 18.5%, respectively, $p < 0.05$). Meis and colleagues from the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network reported similar results from a large randomized clinical trial designed to evaluate the efficacy of 17α-hydroxyprogesterone caproate for the prevention of preterm birth in high-risk women.[116] Among women receiving weekly intramuscular progesterone therapy from 16-36 weeks' gestation, the incidence of preterm birth prior to 37 weeks' gestation was 36.3%, compared with an incidence of 54.9% in the placebo group (RR 0.66; 95% CI, 0.54-0.81). The incidence of preterm birth at less than 35 weeks (RR 0.67; 95% CI, 0.48-0.93) and at less than 32 weeks (RR 0.58; 95% CI, 0.37-0.91) was also significantly decreased in women treated with progesterone when compared with placebo. Fonseca et al. screened more than 24,000 women and enrolled 1.7% of them whose

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cervical length was less than 15 mm (less than third percentile). Women randomized to 200 mg vaginal progesterone suppositories had a lower preterm birth rate (19% vs. 44%; RR 0.56; 95% CI, 0.36-0.86) compared with those randomized to placebo.[50] Hassan and colleagues screened more than 32,000 women worldwide and enrolled those with cervical length of 10-20 mm. Four hundred sixty-five women were randomized to 90 mg vaginal progesterone gel (daily until 36 weeks) and had lower rates of preterm birth before 28, 33, and 35 weeks compared with placebo. Neonatal morbidity and mortality were also lower in treated women (7.7% vs. 13.5%; RR 0.57; 95% CI, 0.33-0.99).[75]

However, as the number and size of such trials have increased, the role of progesterone in preventing prematurity has become less clear. O'Brien and colleagues conducted a randomized, double-blind, placebo-controlled, multinational trial evaluating whether prophylactic administration of vaginal progesterone would reduce the risk of preterm birth in high-risk women with a history of spontaneous preterm birth.[135] Therapy with either progesterone vaginal gel or placebo was initiated between 18 weeks and 0 days and 22 weeks and 6 days of gestation, and patients were asked to continue once-daily treatment until delivery, 37 weeks' gestation, or development of preterm rupture of the membranes. In this trial, progesterone did not decrease the frequency of preterm birth at less than or equal to 32 weeks, and there was no difference between the groups with respect to the mean gestational age at delivery, infant morbidity or mortality, or other maternal or neonatal outcome measures.[135] However, examination of a subset of this cohort in a planned secondary analysis revealed that vaginal progesterone may reduce the rate of early preterm birth and improve neonatal outcome in women with a short sonographic cervical length in addition to a history of a prior spontaneous preterm birth.[42] Moreover, the use of vaginal progesterone in high-risk women was investigated recently in the OPPTIMUM study, published in 2016. This was a large (1228 subjects), multicenter, double-masked randomized trial comparing 200 mg of vaginal progesterone per day to placebo in women at high risk for preterm birth, including those with previous spontaneous birth at less than or equal to 34 weeks' gestation, or a cervical length less than or equal to 25 mm, or those with positive fetal fibronectin test combined with other clinical risk factors for preterm birth. Progesterone supplementation did not reduce the risk of preterm birth or composite neonatal outcomes and had no long-term benefit on outcomes of children at 2 years of age. In addition, in a subgroup of women with a history of a prior spontaneous preterm birth (n = 903), there were no significant differences in the rate of preterm birth less than 34 weeks of gestation between those receiving vaginal progesterone and placebo (15.9% vs. 18.8%).[133]

Use of progesterone has also been investigated in other populations, with varying results. For example, progesterone use has been investigated in women following arrest of acute preterm labor. Rozenberg and colleagues performed an open-label, multicenter, randomized controlled trial enrolling women presenting with preterm labor symptoms and a cervical length measurement less than 25 mm.[154] After successful tocolysis, women were assigned to either receive intramuscular progesterone injections or placebo until 36 weeks' gestation, with no benefit seen in the prevention of preterm birth in the group assigned to the progesterone arm of the trial.[154]

Progesterone has also been evaluated in the setting of multiple gestations, with most studies showing no reduction in rates of preterm birth in women with twin and triplet gestations.[152,167] Progesterone use has been examined in otherwise low-risk patients with cervical shortening. In a large, multicenter, randomized controlled trial enrolling nulliparous women with cervical shortening (<30 mm), Grobman and associates within the MFMU Network showed no benefit in regard to prevention of spontaneous preterm birth in women assigned to weekly 17 α-hydroxyprogesterone caproate as compared with placebo.[62]

In addition to the controversies with the use of progesterone, these studies lead to another one regarding the use of transvaginal ultrasonography, with some experts espousing universal screening of all patients and others recommending a risk-based screening approach. Currently, the Society for Maternal Fetal Medicine and the American College of Obstetricians and Gynecologists recommend the use of intramuscular 17 hydroxyprogesterone caproate to singleton women with a history of prior spontaneous preterm birth and vaginal progesterone to women with a cervical length of 20 mm or less before 25 weeks' gestation.[29,165,167]

Cerclage

Cerclage is a procedure in which a nonresorbable suture is placed in simple purse-string fashion at the level of the internal os. It can be placed either transvaginally or transabdominally. The transvaginal approach consists mainly of two techniques: McDonald (suture placed at the cervicovaginal junction) and the Shirodkar (the suture is placed as close to the internal cervical os by dissecting the vesicocervical mucosa). The transabdominal approach is usually performed due to anatomic limitations (prior trachelectomy) or history of prior failed transvaginal approach. Indications for cervical cerclage include: history of second trimester painless cervical dilation 1 or more times that resulted in pregnancy loss in the absence of abruption or labor; second trimester findings on physical exam consistent with painless dilated cervix; history of preterm less than 34 weeks and with cervical length less than 25 mm before 24 weeks' gestation.

Cerclage is most beneficial in women with prior cervical insufficiency when placed electively before any cervical change. This case scenario leads to low rates of complication and high cerclage success rates.

The optimal time for cerclage placement is early second trimester (12-14 weeks), since miscarriage rates are more likely to occur before this interval and major anatomic anomalies (e.g., anencephaly) can be detected by this period.

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In addition, this period allows obstetricians to perform early aneuploidy testing by chorionic villus sampling. The upper limit of gestational age, by which cerclage placement is contraindicated, remains controversial. It is generally accepted that after fetal viability (23-24 weeks' gestation), complication risks outweigh the potential benefits of the intervention, and cerclage should not be attempted. Moreover, interventional trials that elucidated the efficacy of cerclage limited gestational age at 24 weeks for screening and initiation of therapies. It is not recommended to place a cerclage after 24 weeks; above this gestational age, there should be extensive counseling about benefits and risks of the procedure when the patient desires cerclage placement.

Contraindications to cerclage placement include rupture of membranes, evidence of intrauterine infection, major fetal anomalies, active vaginal bleeding of unknown cause, and active labor. Potential morbidities associated with cerclage placement include bleeding, infection, rupture of membranes, maternal soft tissue injury, spontaneous suture displacement, and the risks of anesthesia. Additional complications may be seen in association with delivery, including cervical laceration in up to 13% of cases. Rare reports of uterine rupture have also been reported in patients in whom labor occurred before suture removal. Scarring of the cervix from the procedure may also contribute to an increased incidence of cesarean delivery.

Cerclage success rates were first reported to be greater than 75%. These initial findings may have been misleading. Since pregnancy outcomes in the intervention group were compared to outcomes of prior pregnancies, the trials did not account for patients that may have a successful pregnancy even after repeated mid-trimester losses.

Several trials that followed evaluated the efficacy of cerclage in women with a history of preterm birth rather than with classical history of cervical insufficiency. The majority of these studies showed no advantage of cerclage in reducing the rates of preterm birth, PPROM, or perinatal mortality, despite being associated with higher administration rates of tocolytic agents and of hospitalization. In a large study conducted by the Royal College of Obstetricians and Gynaecologists, 1292 patients with a history of either an early delivery or a prior cervical surgery were randomly assigned to cerclage placement or expectant management.[144] Significantly fewer deliveries occurred prior to 33 weeks in the cerclage group (13% versus 17%), but a higher incidence of puerperal pyrexia was also demonstrated in this treatment group.[144] Limitations of all of these studies included the ill-defined subjective enrollment criteria and the lack of statistical power to adequately address neonatal morbidity outcomes.

As discussed, the use of transvaginal cervical sonography has greatly altered current recommendations regarding cerclage placement for singleton gestations. Cerclage placement has been shown beneficial in women with history of preterm birth and a short cervix. Several prospective studies have been conducted using cervical length shortening as a marker to determine the patient population who may best benefit from cerclage placement for the prevention of recurrent preterm birth.[4,17,19,63,176] Althuisius and colleagues reported findings from a small randomized trial comparing the efficacy of therapeutic cerclage plus bed rest with bed rest alone for the prevention of subsequent preterm birth in women with an ultrasonographically determined short cervix (less than 25 mm) before 27 weeks' gestation.[4] Use of cerclage in this study was associated with a significant reduction in the incidence of preterm birth prior to 34 weeks when compared with women treated with bed rest alone (0% vs. 44%; $p < .002$).[4] In contrast, To and colleagues, in a large multicenter randomized trial of cervical cerclage for women with an ultrasound-detected short cervix (less than 15 mm) between 22 and 24 weeks' gestation, reported that the use of prophylactic Shirodkar cerclage did not significantly reduce the incidence of preterm birth at less than 33 weeks' gestation when compared with expectant management (22% vs. 26%; $p < .44$).[176] A meta-analysis by Belej-Rak and colleagues evaluated the literature relating to the effectiveness of cervical cerclage in women with a sonographically detected shortened cervix.[17] Based on this systematic analysis of six pertinent trials, the authors reported that there was no statistically significant effect of cerclage on the rates of preterm birth (less than 37, less than 34, less than 32, and less than 28 weeks).[17] Singleton pregnancies with history of prior preterm birth have shown to have a greater than 30% risk of developing a short cervix (<25 mm) before 24 weeks.[19,136] Owen et al. randomized 302 women with a history of preterm birth and cervix length of <25 mm to either have or not have cerclage placed. In this large multicenter trial, women with cerclage had reduced perinatal death by almost 50% (8% vs. 16%), and reduced births before 24 weeks (6.1% vs. 14%) and before 37 weeks (45% vs. 60%).[136] In the same high-risk population, Berghella et al. performed a meta-analysis review that showed a 30% reduction in preterm birth rate at less than 35 weeks' gestation[20] (28% vs. 41%; RR 0.70; 95% CI, 0.55-0.89). The composite perinatal morbidity and mortality was also reduced by 36% (16 vs. 25%; RR 0.64; 95% CI, 0.45-0.95) in the cerclage group.

Cerclage placement in women with multiple gestations and short cervix (CL < 25 mm) has been associated with a twofold increase in preterm birth (RR 2.15; 95% CI, 1.15-4.01).[20] In light of these results, cerclage placement is not recommended in the setting of multiple gestation.

Removal of the cerclage is normally performed at about 36-37 weeks' gestation unless active preterm labor begins before that time. There are no prospective studies to guide management of women with cerclage in the setting of PPROM. Retrospective studies report conflicting results but have generally concluded that retaining the cerclage for 24 hours after PPROM was associated with pregnancy prolongation.[55] Due to their retrospective nature, the studies' results may have been biased due to other confounders such as preterm labor or infection. Other studies reported that cerclage retention after PPROM was associated with increased neonatal deaths due to infection, sepsis, chorioamnionitis,

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and respiratory distress syndrome.[55,101] While cerclage retention may certainly be reasonable to permit completion of a course of antenatal corticosteroids, prolonged retention should be undertaken only with extreme caution. ACOG does not recommend antibiotic prophylaxis beyond 7 days if the cerclage remains in place.

Current ACOG and SMFM guidelines recommend progesterone supplementation to all pregnant women with history of prior preterm birth.[29,167] Cerclage placement has been shown to best benefit this patient group if short cervix is noted by transvaginal ultrasound (cervical length [CL] <25 mm).[19,136] In a meta-analysis review that included 169 pregnant women with history of preterm birth and CL less than 25 mm occurring at less than 25 weeks' gestation, vaginal progesterone was shown to decrease preterm birth rates at less than 33 weeks (RR 0.54; 95% CI, 0.30-0.98).[150]

Currently, it is recommended that women with a singleton gestation and a history of prior preterm birth receive progesterone prophylaxis until term, and undergo transvaginal serial cervical surveillance early in the second trimester to determine which patients are candidates for cerclage placement.[19,85,167]

Pessaries

Use of pessaries for the prevention of preterm birth in women at risk for preterm birth has been evaluated and was first proposed in the 1950s. While several different pessary types have been used, the Arabin pessary, a flexible ringlike silicone device, has been most effective in published trials. This pessary is designed such that the smaller inner diameter should fit around the cervix snugly, thereby mechanically holding the cervix closed in an effort to prevent exposure of fetal membranes to the vaginal flora.[13] Placement of the pessary changes the inclination of the cervical canal, directing it posteriorly so that the weight of the pregnancy centers on the anterior lower segment.[13]

The PECEP trial, the largest trial to date, was a randomized controlled trial that enrolled women with cervical shortening (cervical length ≤25 mm), 192 of whom were assigned to receive an Arabin pessary with 193 assigned to expectant management.[61] Twelve women (6%) delivered before 34 weeks' gestation in the pessary arm compared with 51 women (27%) in the expectant management arm, an 82% reduction.[61] Despite these encouraging positive results, evidence from two recent RCTs did not show such benefit.[83,131] Data from two large clinical trials showed no benefit in women with asymptomatic twins with no other risk factors (not screened for short CL) that received pessaries.[103,132]

Recently, three prospective studies elaborated the role of pessaries in preventing preterm birth in women with multiple gestations and with a short cervix (CL ≤25 mm before 25 weeks' gestation).[60,103,132] The Arabin pessary was used in all the trials. Only two out of the three RCTs supported the use of pessaries in this population by significantly reducing rates of preterm birth.[60,103] A recent review pooled the above-referenced RCTs and reported no significant differences in preterm birth rates or neonatal outcomes among the group that received pessary versus no pessary group.[156]

The role of pessaries in preventing preterm birth remains unanswered. We are still awaiting several RCTs to be completed. We recommend not to use pessaries for prevention of preterm birth, and their use should be only reserved for research purposes.

Tocolytics

In the United States, up to one in eight children are born before 37 weeks.[109] Despite being poorly understood, preterm birth's impact on neonatal morbidity and mortality is detrimental, with skyrocketing health care costs,[111] emphasizing the importance in identifying an efficacious treatment for this burden. The optimal tocolytic agent remains to be determined, and RCTs evaluating their efficacy have been hindered by various obstacles. Designing clinical trials to test tocolytics is complicated in that the health of two patients must be considered. These trials also face problems related to the fact that the nature of preterm birth and its outcomes are different in the setting of early preterm labor (less than 28 weeks) as compared with late preterm labor (34-36 weeks). Maintenance tocolysis has not been shown to be effective in improving neonatal outcomes nor preventing preterm birth,[43,73] whereas short-term tocolysis has been shown to be superior to placebo.[70] Given the difficulty in predicting and preventing preterm birth, management has been focused on patients admitted for preterm labor. In the latter case, the most important intervention to date is the administration of antenatal corticosteroids.[5] Hence, the primary objective of tocolytic administration has been shifted to preserve pregnancy for at least 48 hours to allow steroid administration, magnesium for neuroprotection, or transportation to a higher level of care facility.

β-Sympathomimetic Agents

In general, β-sympathomimetic tocolytic agents are β2 selective agents. β2 receptors are located in the uterus, blood vessels, bronchioles, and liver. These agents bind to β2 receptors as agonists and activate the cyclic AMP pathway, leading to intracellular depletion of calcium. The latter decreases myometrial contractility and ultimately leads to smooth muscle relaxation. Despite being β2 selective, when administered in vivo at the dosages used pharmacologically, these agents stimulate nonselective β-receptors throughout the body, leading to many adverse effects, thus limiting their clinical use. In the United States, terbutaline is the most common β2-adrenergic agonist used in obstetrics. Ritodrine is no longer available in the US market despite being the most studied and the only FDA-approved tocolytic agent.

Ritodrine

Initial studies supported its use as an efficient tocolytic agent with minimal side effects.[119] In addition, these studies

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showed a statistically significant effect on pregnancy prolongation, with a reduction in neonatal morbidity and mortality.

Subsequent reports have not been as positive with respect to neonatal morbidity and mortality. Ritodrine treatment has still been shown to significantly delay delivery but not to significantly modify perinatal outcomes. King and associates conducted a meta-analysis involving 16 clinical trials with a total of 890 women, demonstrating that women treated with ritodrine had significantly fewer deliveries within 24 and 48 hours of the start of therapy[96]; however, no statistically significant decrease in the incidence of RDS, birth weight less than 2500 g, or perinatal death was demonstrated. Of note, these studies were completed before the use of antenatal steroid therapy had become widespread.

Ritodrine can be administered either intravenously or orally. Treatment usually begins with intravenous infusion. The patient should be closely monitored for fluid balance, cardiac status, electrolytes (including potassium and glucose), and fetal well-being. The initial infusion rate of 100 μg/min described by Barden and colleagues[15] may be too high. A study by Caritis and coworkers suggested that there is an adequate response using an initial infusion of 50 μg/min with a maximum rate of 350 μg/min.[25] With cessation of uterine activity, the rate should be reduced at hourly intervals. Due to its half-life of 1-2 hours, oral ritodrine has a rigorous dosing scheme of either 10 mg every 2 hours or 20 mg every 4 hours. Plasma levels with oral dosing are only 27% of those obtained with intravenous infusion, suggesting that a higher dose may be needed to maintain adequate plasma levels. Relative contraindications to ritodrine use include diabetes mellitus, underlying cardiac disease, use of digitalis, hyperthyroidism, severe anemia, and hypertension.

Many of the maternal side effects result from stimulation of beta receptors throughout the body. These side effects include tachycardia, hypotension, tremulousness, headache, fever, apprehension, chest tightness or pain, and shortness of breath. Serious maternal cardiopulmonary side effects reported with the use of ritodrine include pulmonary edema, myocardial ischemia, arrhythmia, and even maternal death.[15] Pulmonary edema may occur in up to 4% of patients receiving parenteral ritodrine. Predisposing factors associated with this serious complication include multiple gestations, positive fluid balance, blood transfusion, anemia, infection, polyhydramnios, and underlying cardiac disease. Pulmonary edema probably results from overhydration and activation of the renin-angiotensin system, resulting in an increase in aldosterone, and thus subsequent salt and water retention. If untreated, the pulmonary edema can progress to adult RDS. The concurrent use of corticosteroids has been associated with an increased risk for development of pulmonary edema. The two most commonly used antepartum steroids, betamethasone and dexamethasone, have minimal mineralocorticoid activity and are thus unlikely to contribute greatly to this complication. Another serious complication, peripartum heart failure, has also been reported with long-term use of β-sympathomimetics. A baseline electrocardiogram should be obtained before the start of therapy, and therapy should be discontinued when patients develop a heart rate greater than 130 beats per minute or systolic blood pressure less than 90 mm Hg.

Metabolic effects of ritodrine include hypokalemia. Hypokalemia results from increases in insulin and glucose concentrations, which drive potassium intracellularly. This imbalance is transient, resolving within 24 hours of discontinuing therapy. Total body potassium remains unchanged. Elevated serum glucose levels are the result of an increase in cyclic adenosine monophosphate, with peak levels achieved 3 hours after initiation of treatment. Serum insulin levels increase both in response to the serum glucose elevation and also because of a direct effect of β2 stimulation of the pancreas. Furthermore, β1 stimulation results in lipolysis and mobilization of free fatty acids, acetoacetate, and β-hydroxybutyrate. In patients with diabetes mellitus, diabetic ketoacidosis may occur if blood sugar concentrations are not adequately controlled.

Initial studies evaluating long-term exposure to β-sympathomimetics demonstrated no differences in Apgar scores, head circumference, or neurologic status (i.e., development of developmental delay and behavioral differences), but fetal cardiac complications have been reported. These medications readily cross the placental barrier, achieving concentrations in the fetus similar to those in maternal serum. Elevation in the baseline fetal heart rate is seen, as is a questionable increase in heart rate variability. A wide range of complications has been described, including rhythm disturbances such as supraventricular tachycardia and atrial flutter. These usually resolve within 2 weeks after cessation of therapy. Septal hypertrophy in the fetus and neonate has also been described with maternal ritodrine treatment. The degree of hypertrophy correlates with the duration of therapy, and this finding usually resolves within 3 months of age.

Other, more serious fetal complications have been described as well, including hydrops fetalis, pulmonary edema, extrauterine cardiac failure, intrauterine fetal demise, neonatal death, and myocardial ischemia. Neonatal hypoglycemia is another potential complication with β-sympathomimetics. This usually develops when delivery occurs within 2 days of treatment, and the hypoglycemia is transient, resulting from medication-induced hyperinsulinemia. Finally, neonatal periventricular-intraventricular hemorrhage may be increased with β-sympathomimetic therapy. In a retrospective study of 2827 women delivering preterm, there was a twofold increase in hemorrhage in fetuses that received beta-mimetics.[64] Ritodrine has thus fallen out of favor as a primary tocolytic agent, largely as a result of these potential complications.

Terbutaline

Terbutaline was initially studied by Ingemarsson, who randomly assigned 30 patients with preterm labor to either

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intravenous terbutaline therapy or placebo. Ingemarsson demonstrated an 80% success rate in comparison to only 20% for the placebo.[88] Unfortunately, as with other tocolytic agents, subsequent studies did not show such positive results.

Terbutaline can be administered via oral, subcutaneous, and intravenous routes. When administered intravenously, clinicians must carefully monitor the fetus, fluid balance, cardiac status, and electrolytes. The initial infusion rate is 5-10 μg/min, and the rate is gradually increased every 10-15 minutes to a maximum of 80 μg/min. Orally administered terbutaline undergoes significant first-pass metabolism in the intestinal tract, resulting in a bioavailability ranging from only 10%-15%. The mean half-life of oral terbutaline is 3.7 hours, with increased clearance noted in pregnant patients. The usual oral dosages range from 2.5-5 mg every 4-6 hours, adjusted by patient response and maternal pulse. Subcutaneous regimen is the most common route of administration, and it usually involves 250-μg doses every 20-30 minutes (four to six doses). Although subcutaneous terbutaline administration is one of the first-line tocolytic agents for preterm labor, it has no effect on actual preterm birth rates.

One possible explanation for the failure of long-term treatment with β-sympathomimetics is a phenomenon involving desensitization or downregulation of responsiveness to these agents. The use of a low-dose subcutaneous infusion pump attempts to overcome this problem. Lam and colleagues compared the use of the terbutaline pump with oral terbutaline therapy.[100] The average duration of therapy before breakthrough of preterm labor was 9 weeks with the pump and 2 weeks with oral administration of terbutaline. Total daily drug dosage was also considerably lower (3 mg versus 30 mg/day) with the pump.[100] Guinn and associates conducted a prospective, double-blind, randomized clinical trial comparing terbutaline pump maintenance therapy with placebo, demonstrating no significant differences in either the preterm delivery rate or neonatal outcomes.[68] A Cochrane review of 11 RCTs (1322 women) showed that β2 agonists were associated with decreased risk of delivery within 48 hours (RR 0.63; 95% CI, 0.53-0.75) despite having no significant effect in perinatal morbidity or mortality.[12] Another review of 95 RCTs demonstrated similar results; the probability to delay delivery within 48 hours was higher in the group of women that received β2 agonists (OR 2.41; 95% CI, 1.27-4.55). β2 agonists had higher rates of adverse effects that required physicians to opt for another alternative agent (OR 22.68; 95% CI, 7.51-73.67).[70]

Maternal side effects and complications are similar to those stated for ritodrine. Terbutaline seems to affect the maternal heart rate less than ritodrine when administered intravenously. However, both oral and intravenous forms of terbutaline are more diabetogenic than ritodrine. Interestingly, subcutaneous administration of terbutaline via pump does not appear to increase the risk of gestational diabetes but does cause elevations in blood glucose levels in patients with diabetes. Neonatal effects of maternally administered terbutaline are similar to those of ritodrine.

In 2011, a warning was released by the US Food and Drug Administration (FDA) concerning terbutaline administration to treat preterm labor secondary to serious maternal side effects.[179] Another study reported an association between antenatal exposure of the drug and offspring adverse behavioral effects.[184] Based on the above evidence, it is recommended to limit the use of terbutaline only for inpatient short-term tocolysis or for the acute management of uterine tachysystole.

Magnesium Sulfate

Magnesium sulfate has been one of the most commonly used tocolytic agents, especially since it has been shown to have fetal neuroprotective effects. Magnesium appears to have similar efficacy with fewer side effects than terbutaline.

Magnesium has tocolytic properties by acting as a calcium competitor in the sarcoplasmic reticulum, diminishing the interaction of calcium with the actin-myosin complex and interfering with myometrial repolarization.[72,98] Magnesium may also block influx of extracellular calcium and disrupt intracellular release of calcium via inositol triphosphate pathways. Ultimately, the release of acetylcholine at the neuromuscular junction is decreased, leading to decreased amplitude of motor endplate potential and leading to decreased sensitivity.

Magnesium sulfate is administered intravenously and is normally given as an initial bolus of 4-6 g over 30 minutes, followed by a maintenance infusion of 1-4 g/hr. In contrast to intravenous magnesium sulfate for tocolysis, oral magnesium therapy is not effective for the treatment of preterm labor.

Magnesium is a bivalent cation, and it is the second-most common intracellular cation.[48] Less than 1% is found extracellularly. It is most commonly found in bone (53%), followed by myocytes (27%).[185] Most extracellular magnesium is in ionized form and its serum level drops in pregnancy secondary to hemodilution of pregnancy.[99,183] It is transported across the cell membrane through a sodium-ATP-dependent transporter.

Magnesium is almost exclusively excreted by the kidneys. Approximately 75% of the infused dose of magnesium is excreted during the actual infusion, with 90% excretion by 24 hours. Magnesium is reabsorbed at the renal level by a transport-limited mechanism; therefore, the glomerular filtration rate significantly affects excretion. Serum magnesium levels of 5-8 mg/dL are considered therapeutic for inhibiting myometrial activity on the basis of in vitro studies. Once cessation of uterine activity is achieved, the patient is maintained at the lowest possible rate for 12-24 hours and then weaned off as tolerated.

Maternal side effects caused by magnesium sulfate are typically dose related. Common side effects include flushing, heat intolerance, nausea, headache, drowsiness, and blurry vision. Constant monitoring of deep tendon reflexes is mandatory to avoid toxicity. Diminished deep tendon

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reflexes occur when serum magnesium levels reach or exceed 12 mg/dL (10 mEq/L). Significant respiratory depression can occur as serum levels reach 14-18 mg/dL (12-14 mEq/L), and cardiac arrest may occur with levels greater than 18 mg/dL (15 mEq/L). In general, respiratory depression does not occur before loss of deep tendon reflexes. The toxic effects of high magnesium levels can be rapidly reversed with the infusion of 1 g of calcium gluconate.

Magnesium sulfate is absolutely contraindicated in patients with myasthenia gravis or heart block. It is relatively contraindicated in patients with underlying renal disease or a history of a recent myocardial infarction. It is also relatively contraindicated in women who are receiving calcium channel blockers.

Pulmonary edema has been reported to have an incidence of approximately 1%. The risk for pulmonary edema is increased in patients with multifetal gestations and in those receiving combined tocolytic therapy. Because of the potential risk of fluid overload and the subsequent development of pulmonary edema, periodic assessment of fluid balance is essential.

Magnesium readily crosses the placenta, achieving fetal steady-state levels within hours after the start of treatment. No significant alterations in neurologic status or Apgar scores have been reported with mean umbilical cord concentrations of 3.6 mg/dL. At a cord concentration between 4 and 11 mg/dL, though, apnea, hypotension, refractory bradycardia, respiratory depression, hypotonia, and motor depression have been reported. Long-term use of magnesium (greater than 7 days) has been shown to cause fetal bone loss in the proximal humerus, a finding of unclear significance since these cases were based on unsolicited reports to the FDA's Adverse Event Reporting System (18 cases) and epidemiologic analysis with design concerns.[80,110,114,127,161,187]

Consequently, the FDA released a warning against using magnesium sulfate for more than 5-7 days for the sole purpose of preventing or treating preterm labor. As a result, the safety drug classification for magnesium was changed from class A-D.[51] ACOG and SMFM followed with a statement advising obstetricians to continue using magnesium for the following indications[30]:

- seizure prophylaxis in preeclampsia or treatment of eclampsia,
- fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery,
- short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids in pregnant women who are at risk of preterm delivery within 7 days.

Mercer et al. reviewed the role of magnesium sulfate as a tocolytic agent.[117] Only three out of the four RCTs comparing magnesium sulfate as control or placebo evaluated its effect on delivery within 48 hours or within 7 days.[36,37,52,82] Magnesium did not affect preterm delivery within 48 hours (RR 0.75; 95% CI, 0.54-1.03). The same results were noted for delivery before 37 weeks or within 7 days. There was also no improvement in neonatal morbidities. Compared to magnesium, alternate tocolytic agents (total of 16 RCTs: beta mimetics, calcium channel blocker, and cyclooxygenase inhibitors) did not show any additional improvements in delivery at 48 hours, 7 days, preterm delivery, or low birth weight. In summary, there is no evidence supporting the use of magnesium as a tocolytic agent, even when used short term. In the meantime, no other tocolytic agent has been shown to be superior to magnesium.

Initial observational studies suggesting the beneficial role of magnesium in decreasing neonatal neurologic morbidities occurred in the early 1990s.[129,139,162] Since then, several RCTs were performed to elucidate this role.[38,107,108,120,121,153] Mittendorf et al. included women in preterm labor before 34 weeks and cervical dilation greater than 4 cm ($N = 57$) that were randomized to either magnesium or placebo.[120,121] Infant death was not increased in the neuroprotection group, but when performing a secondary analysis of magnesium sulfate versus other tocolytic agents, infant death was significantly increased in the former group. This led to early termination of the trial. This was followed by a multicenter placebo-controlled trial that included women with planned or expected delivery within 24 hours at less than 30 weeks' gestation. Infant death or cerebral palsy or both by 2 years of age was not different in the women who received magnesium.[38] Secondary analysis showed that infants exposed to magnesium had less frequent inability to walk without assistance. Another placebo-controlled trial included 564 gravid women less than 33 weeks' gestation, with planned or expected delivery within 24 hours.[108] There was no significant difference in infant death or severe white matter injury or both before discharge or in a 2-year follow-up among groups. Although there was no decrease in cerebral palsy in the long-term follow-up, the authors reported reduction in "gross motor dysfunction" or "motor" or "cognitive dysfunction" in the magnesium group. This was followed by a large multicenter trial that included 2241 gravid women at less than 32 weeks' gestation with imminent risk of delivery before 32 weeks' gestation.[153] Subjects were randomized to receive either magnesium or placebo. The magnesium treatment group had a significant reduction in moderate to severe cerebral palsy. When performing a prespecified secondary analysis, magnesium reduced cerebral palsy by greater than 30% (4.2 vs. 7.3%, $p = 0.004$). Pooling the results from the above RCTs, Doyle et al. suggested that antenatal administration of magnesium sulfate for neuroprotection decreased the incidence of cerebral palsy[44] (RR 0.71; 95% CI, 0.74-0.98). These results were confirmed in two other metanalyses.[31,34] Based on the above evidence, magnesium sulfate, when given before early preterm delivery, reduces the risk of cerebral palsy in surviving infants.

Prostaglandin Synthetase Inhibitors

Because prostaglandins appear to play a pivotal role in the pathway leading to preterm labor and delivery, attempts to interrupt this cascade of events are of utmost importance.

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Prostaglandins are 20-carbon cyclopentane carboxylic acids derived from membrane phospholipids (primarily arachidonic acid) via the enzymatic action of phospholipase A and cyclooxygenase (prostaglandin synthetase). Because a number of drugs are available that inhibit the action of prostaglandin synthetase (e.g., aspirin, ibuprofen, indomethacin, sulindac), this pathway represents a key target for pharmacologic intervention. Of these drugs, indomethacin has been the most extensively studied. It reversibly binds to cyclooxygenase.

Indomethacin

A 2005 Cochrane review that was updated in 2010 identified three trials comparing prostaglandin inhibitors to placebo in the treatment of preterm labor.[94] One RCT, despite its small sample size, showed a significantly lower rate of preterm deliveries earlier than 37 weeks' gestation (RR 0.21; 95% CI, 0.07-0.62) in women who received prostaglandin inhibitors. The authors also reported a nonsignificant trend toward lower risk of delivery before 37 weeks' within 48 hours (RR 0.20; 95% CI, 0.03-1.28) or within 7 days of receiving the tocolytic agent (RR 0.41; CI, 0.1-1.66) when receiving this class of agent. The authors concluded that these results should be taken with caution due to the small sample size involved in the review.

Another meta-analysis showed that out of 1000 gravid women receiving prostaglandin inhibitors, only 80 would deliver within 48 hours, versus 182 (for the next best treatment). The authors conclude that prostaglandin inhibitors should be considered first-line for preterm labor prior to 37 weeks' gestation.[71] In a network meta-analysis, prostaglandin inhibitors were shown to be more efficacious than placebo in delaying delivery by 48 hours (OR 5.94; 95% CI, 2.14-12.34).[70] In this analysis, the authors suggested that this class of tocolytics was more efficient than any other agent and ranked prostaglandin inhibitors in the top three most efficacious tocolytics (96% probability).

Indomethacin is usually administered orally or rectally in divided doses. A loading dose of 50 is followed by 25-50 mg orally every 6 hours for up to 48 hours. Indomethacin blood concentrations usually peak 1-2 hours after oral administration, whereas rectal administration is associated with levels that peak slightly earlier. Approximately 90% of the drug is protein bound, undergoing excretion by the kidneys unchanged. Indomethacin readily crosses the placenta, equilibrating with maternal concentrations 5 hours after administration. The half-life is approximately 15 hours in term neonates and somewhat shorter in preterm neonates.

Most studies have limited the use of indomethacin to 24-48 hours' duration because of concerns regarding the development of oligohydramnios and constriction of the ductus arteriosus. The latter of these effects may lead to fetal pulmonary hypertension and neonatal persistent pulmonary hypertension.[122] If longer therapy is required, close fetal monitoring is indicated, including weekly amniotic fluid indexes to evaluate for oligohydramnios and ductal velocity assessment to examine for ductal constriction or closure. If the amniotic fluid volume (measured as the fluid depth in the four quadrants of the uterus) falls below 5 cm or if the pulsatility index of the ductus arteriosus decreases to less than 2 cm/sec, discontinuation of therapy should be considered. Several long-term studies have evaluated the efficacy and safety of this drug.

Maternal contraindications to indomethacin use include peptic ulcer disease, allergies to indomethacin or related compounds, significant hematologic disease, hepatic or renal dysfunction, and drug-induced asthma. Major maternal side effects are minimal and infrequent. Gastrointestinal upset may occur but can be relieved by either taking the medication with meals or using an antacid.

Fetal contraindications include pre-existing oligohydramnios, gestational age greater than 32 weeks, and congenital fetal heart disease in which the fetus is dependent on the ductus arteriosus for circulation. Several fetal side effects have been reported with the use of indomethacin. It has been associated with oligohydramnios. Although indomethacin has been shown to reduce fetal urine output, these levels return to baseline within 24 hours after discontinuation. Examining the effect on renal artery blood flow, Mari and colleagues found no change in the pulsatility index in 17 fetuses during the first 24 hours of indomethacin therapy, suggesting that renal artery constriction and a decrease in renal blood flow are responsible for the reduction in urine output.[106] Regardless, oligohydramnios is usually seen with long-term therapy of more than 7 days, although this onset seems to vary from one patient to another and is somewhat unpredictable. Therefore, the amniotic fluid index should be followed while the patient is receiving therapy. Resolution of oligohydramnios usually occurs within 48 hours of discontinuation of treatment. Although persistent anuria, neonatal death, and renal microcystic lesions have been reported with prenatal indomethacin exposure, most of these infants were exposed to doses greater than 200 mg/day for up to 36 weeks of gestation with inadequate amniotic fluid volume assessment.

Another important potential complication of prenatal indomethacin exposure is the development of ductus arteriosus constriction or closure. It is theorized that ductal constriction or closure leads to the diversion of right ventricular blood flow into the pulmonary vasculature. With time, this causes pulmonary arterial hypertrophy. After birth, relative pulmonary hypertension can then cause right-to-left shunting of blood through the foramen ovale and away from the lungs, resulting in persistent pulmonary hypertension. This complication has been described with long-term indomethacin therapy but not in fetuses exposed to the drug for less than 48 hours.[54] Development of ductus arteriosus constriction can be identified by Doppler echocardiography. Moise and colleagues detected ductal constriction in 7 of 14 fetuses exposed to indomethacin in utero, with these changes seen up to 72 hours after initiation of treatment.[122] There was no correlation with maternal drug levels, and the constriction resolved within 24 hours after treatment

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was stopped. No cases of persistent pulmonary hypertension were reported in this case series. The observed effects on ductal constriction have been shown to increase with advancing gestational age, with 50% of fetuses demonstrating constriction when exposed at 32 weeks' gestation. Based on this data, indomethacin therapy should be discontinued by 32 weeks at the latest.

Yet another reported complication is an increased risk of necrotizing enterocolitis in infants exposed to indomethacin prenatally. This complication is specifically seen in neonates who are born at less than 30 weeks' gestation. Norton and coworkers performed a retrospective case-control study of 57 neonates that delivered at less than 30 weeks' gestation after recent antenatal exposure to indomethacin, comparing them to 57 matched control fetuses.[134] In this study, the incidence of necrotizing enterocolitis was 29% in the indomethacin group versus 8% in the control group. Additionally, a statistically higher incidence of grade II-IV intraventricular hemorrhage and patent ductus arteriosus was noted in the indomethacin treatment group.[134] No correlations were made in regard to duration of treatment or the time frame between exposure and delivery. Although these results are of concern, indomethacin appears to be a relatively safe and effective tocolytic agent when used with the appropriate caution (less than 48 hours duration of therapy in pregnancies only at less than 32 weeks' gestation).

Sulindac

Sulindac is another prostaglandin synthetase inhibitor that is closely related to indomethacin in structure. Although this agent has been reported to have fewer side effects than indomethacin when used for tocolysis, preliminary experiences also indicate that oral sulindac therapy may not be very useful in the prevention of preterm birth.

Kramer and colleagues conducted a randomized, double-blind study to evaluate the comparative effects of sulindac and terbutaline on fetal urine production and amniotic fluid volume.[97] Sulindac administration also resulted in a significant decrease in fetal urine flow and amniotic fluid volume. Additionally, two fetuses developed severe ductus arteriosus constriction. These data suggest that sulindac shares many of the fetal side effects associated with indomethacin.

Haas and coworkers sought to determine the optimal first-line tocolytic agent for treatment of premature labor.[71] These investigators performed a quantitative analysis that included 58 randomized controlled trials of tocolysis. They extracted data regarding delay of delivery for 48 hours and 7 days, term deliveries, adverse effects causing discontinuation of therapy, absence of RDS, and neonatal survival. A random-effects meta-analysis showed that all tocolytic agents were superior to placebo or control groups in delaying delivery both for at least 48 hours (53% for placebo compared with 75%-93% for the tocolytics) and 7 days (39% for placebo compared with 61%78% for the tocolytics). No statistically significant differences were found for the other outcomes, including the incidence of respiratory distress and rates of neonatal survival. Importantly, this decision model demonstrated that prostaglandin inhibitors provided the best combination of tolerance and delay of delivery, indicating that these agents may be considered the optimal first-line agent for tocolysis prior to 32 weeks of gestation.

Cyclooxygenase-2 Inhibitors

Both indomethacin and sulindac are nonselective cyclooxygenase (COX) inhibitors. In the setting of inflammation, cyclooxygenase-2 (COX-2) is preferentially upregulated. Given that many early cases of preterm labor and delivery are likely related to underlying occult infection or inflammation of the upper genital tract, specific targeting of COX-2 represents a logical target for tocolytic therapy. In addition, by specifically targeting COX-2, there is a theoretical potential for reduction of some of the untoward renal, gastrointestinal, and cardiac side effects that are relatively common with the nonselective COX inhibitors.

The emergence of several selective COX-2 inhibitors (e.g., celecoxib, nimesulide) led to several investigations designed to evaluate the efficacy of these agents for the treatment of preterm labor.[159,160,170] For example, Stika and colleagues reported findings from a randomized, double-blind, placebo-controlled trial of celecoxib versus indomethacin for the treatment of preterm labor.[159] In this small study of 24 women, no difference between the two agents was noted with respect to length of prolongation of pregnancy. Although a transient decrease in amniotic fluid volume was noted with both agents, mean maximal ductus arteriosus blood flow velocity, which was increased with indomethacin, was not significantly altered in women receiving celecoxib.[159] Sawdy and colleagues conducted a similar randomized double-blind, placebo-controlled study of nimesulide versus indomethacin versus sulindac for the treatment of preterm labor.[160] Similar reductions were noted among the three treatment groups with respect to amniotic fluid volume, fetal urine production, and ductus arteriosus Doppler pulsatility index over the initial 48-hour treatment period.[160] To date, no large trials have been reported that have critically evaluated the therapeutic efficacy of the COX-2 inhibitors to prevent preterm birth or reduce neonatal morbidity in women presenting with preterm labor.

Calcium Channel Blockers

Dihydropyridine calcium channel blockers (nifedipine and nicardipine) act on L-type calcium channels blocking transmembrane calcium influx into myometrial cells. Low intracellular calcium levels counteract myosin light chain kinase activation preventing myometrial contraction. The majority of clinical investigations evaluating the use of calcium channel blockers for the treatment of preterm labor have used nifedipine. Ulmsten and associates first reported the use of nifedipine as treatment of preterm labor in a study involving 10 patients, with resultant cessation of uterine activity for 3 days in all patients receiving treatment.[178] In

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a subsequent three-armed randomized control study, Read and colleagues reported that the nifedipine group had a significantly longer time interval from presentation to delivery than either ritodrine or placebo.[147] These results suggest that nifedipine is as effective as ritodrine in prolonging pregnancy, with far fewer side effects causing discontinuation of therapy.

Nifedipine can be administered orally or in a sublingual form. It is rapidly absorbed by the gastrointestinal tract with detectable blood levels attained within 5 minutes of sublingual administration. Nifedipine readily crosses the placenta, and serum concentrations of the fetus and the mother are comparable. Most studies used an initial loading dose of 10-30 mg orally, repeated every 15-20 mins for the first hour, followed by 10-20 mg every 4-8 hours.[32] Up to 30 mg can be administered per dose, but such high doses may result in more side effects. The sublingual form is usually not used for treatment of preterm labor because it acts more rapidly than the oral form, resulting in an increased risk of acute hypotension.

Contraindications to the use of nifedipine, or any of the calcium channel blockers, include hypotension, congestive heart failure, aortic stenosis, and pre-existing peripheral edema. Concurrent use of calcium channel blockers and magnesium sulfate can result in profound hypotension and hence should be avoided. Maternal side effects, including dizziness, lightheadedness, flushing, headache, and peripheral edema, result from the potent vasodilatory effects of these agents. These side effects occur in approximately 17% of patients, although they are severe enough to warrant discontinuation of therapy in only 2%-5% of women.

Studies evaluating the fetal effects of calcium channel blocker therapy have been limited to date. One obstacle that limits the performance of large trials is the potentially adverse effects that calcium channel blockers may have on uteroplacental blood flow. Although uteroplacental blood flow appears to be reduced in animal models, studies examining blood flow in humans have yet to demonstrate any significant adverse effects on fetal or uteroplacental blood flow during treatment with nifedipine. Additional studies are needed to more completely evaluate the potential fetal effects of calcium channel blocker therapy.

Several meta-analyses support the use of nifedipine as an effective acute tocolytic agent. A Cochrane review elaborating the role of calcium channel blockers in acute tocolysis included 12 RCTs ($N = 1029$ patients). The authors concluded that these agents were effective in delaying delivery for 7 days and past 34 weeks' gestation.[95] A subsequent review included 26 RCTs ($N = 2179$ patients); nifedipine was not superior to other tocolytic agents in preventing birth within 48 hours. However, when compared to β2-adrenergic agonist, it was found to delay delivery within 7 days and to prolong gestation past 37 weeks.[32] Minimal adverse effects were noted in the nifedipine group. Network meta-analysis and decision analysis suggested that nifedipine be considered as first-line tocolytic with regard to various important outcome.[70,71]

Other investigators regard nifedipine as a cost-effective option, with cost taking into account drug price together with the costs of treating adverse events.[78] Hayes and associates determined the optimal tocolytic based on a cost decision analysis.[78] A PubMed search of commonly used tocolytics was performed to determine the probability of adverse events. Cost for an agent was determined by acquisition cost together with the probability and cost of adverse events. Nineteen clinical trials yielded a cohort of 1073 patients (indomethacin 176, magnesium sulfate 451, nifedipine 176, and terbutaline 270). The probability of adverse events was 58% for terbutaline, 22% for magnesium sulfate, 27% for nifedipine, and 11% for indomethacin. Nifedipine and indomethacin were found to be the least expensive treatment options at less than $20 each, compared with $200 for magnesium sulfate and $400 for terbutaline, largely related to the cost of monitoring and treating adverse events. They concluded that if one elects to proceed with tocolysis, either nifedipine or indomethacin should be the agent of choice based on this cost decision analysis. These findings essentially agree with the recommendations by Haas and coworkers, who recommended prostaglandin inhibitors as the top three most efficacious tocolytic agents.[71]

Oxytocin Antagonists

Oxytocin antagonists have been set forth as a novel category of agents that may be useful for the treatment of preterm labor. Based on the theory that preterm labor may result from early gap junction formation coupled with a rise in oxytocin receptor concentration, oxytocin may be a pivotal hormone in the evolution of parturition. Oxytocin has been shown to be intimately involved in the physiologic pathways leading to both term and preterm labor. Whereas the role of oxytocin may represent the terminal event for a variety of pathophysiology pathways leading to preterm delivery, it represents an important central pathway that may be amenable to therapeutic intervention. Because the primary cellular targets for oxytocin are the myometrium and decidua, oxytocin antagonists have the theoretical benefit of being highly organ specific with minimal potential for adverse side effects.

Oxytocin antagonists have been shown to effectively inhibit oxytocin-induced uterine contractions in both in vitro and in vivo animal models. The initial human experience with oxytocin antagonist therapy came from several small uncontrolled studies performed in the late 1980s.[2,9] Akerlund and colleagues reported on a series of 13 patients who received a short-term infusion of an oxytocin antagonist. This therapy resulted in inhibition of premature labor in all patients, but 10 of these patients subsequently required treatment with β-agonists.[2]

Similarly, Anderson and associates reported their experience with 12 patients between 27 and 33 weeks of gestation who were treated with a competitive oxytocin receptor antagonist for 1.5-13 hours.[9] Of these 12 patients, 9 had arrest of contractions, and the remaining 3 had no change in contraction frequency.

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The most studied oxytocin antagonist is atosiban. Atosiban is a nonapeptide oxytocin analogue that competitively antagonizes the oxytocin-vasopressin receptor and is thus capable of inhibiting oxytocin-induced uterine contractions. Atosiban is typically administered intravenously. Standard dosing recommendations are for a single initial intravenous bolus of 6.75 mg of atosiban, followed by an intravenous infusion of 300 μg/min for the first 3 hours and then 100 μg/min for up to 18 hours. Maintenance therapy can be implemented at a rate of 30 μg/min via continuous infusion. It appears to have a good maternal safety profile, with rare and non-life-threatening side effects (hypersensitivity and injection site–related reactions).

Several prospective, randomized, masked clinical trials have demonstrated that atosiban is effective in diminishing uterine contractions in women with threatened preterm birth without causing significant maternal, fetal, or neonatal adverse effects.

Romero and coworkers, in a prospective, randomized, double-blind, placebo-controlled, multicenter investigation of 501 women with documented preterm labor, demonstrated that atosiban was significantly more effective than placebo in delaying delivery for 24 hours, 48 hours, and 7 days.[151] Importantly, however, the median from start of therapy to delivery or treatment failure was not significantly different between the study groups, nor were perinatal outcomes. In this trial, rates of extremely premature fetal death were higher in the atosiban group, despite not reaching statistical significance. These concerns may be explained by lack of stratification by gestation in the trial's randomization method (atosiban group had significant higher numbers of women less than 26 weeks' gestation) and the presence of other significant confounders. Moutquin and colleagues compared atosiban to ritodrine for the treatment of preterm labor.[124] In this multicenter, double-blind, randomized, controlled trial of 212 women, the investigators demonstrated that the tocolytic efficacy of atosiban was comparable to that of conventional ritodrine therapy in terms of cessation of preterm labor and neonatal outcomes, with fewer adverse side effects reported with atosiban. The potential use of atosiban for maintenance therapy in patients with arrested preterm labor has also been evaluated. Valenzuela and associates reported experience from a multicenter, double-blind, placebo-controlled trial of 513 women with arrested preterm labor.[180] Median time from start of maintenance therapy to first recurrence of labor was significantly longer for women treated with atosiban (32.6 days) than for those treated with placebo (27.6 days). Another trial by Salim and colleagues compared atosiban to nifedipine, showing that more women undergoing tocolysis with atosiban remained pregnant after 48 hours, but nifedipine had longer-lasting effects (i.e., patients more likely to remain pregnant after 7 days).[158] These data suggest that atosiban may be useful in delaying delivery 24-48 hours in the setting of preterm labor, but this delay appears to have minimal impact on neonatal outcomes.

Atosiban was not superior to β2-agonists or placebo in neonatal outcomes nor tocolytic efficacy in a Cochrane review (N = 1695 patients).[140] Lower infant birth weight and higher drug adverse effects were noted in the atosiban group (weighted mean difference, 138.31 g; 95% CI, −248.76 - −27.86; RR 4.02; 95% CI, 2.05-7.85 respectively). In the same review, compared to β2-agonists, the rates of infants born under 1500 g were higher in the oxytocin antagonist group (RR 1.96; 95% CI, 1.15-3.35). In the Haas' network meta-analysis, atosiban was superior to placebo in postponing delivery within 48 hours (OR 2.02; 95% CI, 1.1-3.8), but the same observation was noted when it was compared to other tocolytics.[70]

Further well-designed, randomized, placebo-controlled trials are needed to more clearly elucidate the role, if any, of the oxytocin antagonists in the therapeutic armamentarium for preterm labor.

Nitric Oxide Donors

Nitric oxide is a potent endogenous hormone that facilitates smooth muscle relaxation in the vasculature, gastrointestinal tract, and uterus. Interest has arisen about the potential use of nitric oxide donors (e.g., nitroglycerin and glycerol trinitrate) as tocolytic agents. Lees and colleagues compared transdermal glycerol trinitrate to ritodrine for tocolysis in a randomized investigation of 245 women with documented preterm labor between 24 and 36 weeks' gestation.[102] These investigators found no significant differences in either tocolytic effect or neonatal outcomes, but glycerol trinitrate was associated with fewer maternal side effects.

El-Sayed and colleagues evaluated 31 women with documented preterm labor before 35 weeks' gestation in a randomized comparison of intravenous nitroglycerin and magnesium sulfate.[46] Tocolytic failure (continued need for tocolysis after 12 hours of treatment) was significantly more common in patients treated with nitroglycerin than in women treated with magnesium sulfate. Importantly, 25% of the patients treated with nitroglycerin experienced significant hypotension, requiring discontinuation of treatment.

A Cochrane review in this topic included eight RCTs (N = 466 women).[45] Only one trial compared this class of drugs to placebo. Delaying delivery for 48 hours was not different among groups (RR 3.06; 95% CI, 0.74-12.63). The same observation was noted when comparison to other tocolytic agents was performed (RR 1.43; 95% CI, 0.47-4.37). Despite these results, nitrates were superior to other tocolytics in decreasing preterm delivery before 37 weeks (RR 0.69; 95% CI, 0.53-0.88) with fewer drug side effects (RR 0.47, 95% CI, 0.37-0.61).

The network meta-analysis by Haas et al. suggested that these agents will have at best 4% probability to delay delivery for 48 hours and 10% of being the best agent based on maternal side effects.[70]

Given the small number of trials available, there is insufficient data to determine whether nitric oxide donors are effective tocolytics. Therefore, clinical use of these agents for the treatment of preterm labor should only be investigational.

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Antibiotics

Before 37 weeks of gestation, PPROM complicates approximately 3% of pregnancies and accounts for one-third of all preterm births. Also, PPROM is associated with significant maternal and neonatal morbidity and mortality related to infection, umbilical cord compression, placental abruption, and preterm birth. As previously discussed, preterm labor, especially at less than 30 weeks' gestation, has been associated with occult upper genital tract infection. Many of the bacterial species involved in this occult infection are capable of inciting an inflammatory response, which ultimately may culminate in preterm labor and delivery. It is on this basis that antibiotics have been suggested as a potential therapy for the treatment or prevention of spontaneous preterm birth.

Elder and associates provided the first insights into the potential use of antibiotics to prevent preterm birth, demonstrating that treatment of asymptomatic pregnant patients with daily tetracycline therapy resulted in fewer preterm deliveries.[47] Despite these promising results, subsequent prospective trials using antibiotics in women colonized with *Chlamydia*, *Ureaplasma*, and group B streptococci have shown no significant decrease in preterm birth. The association of bacterial vaginosis with preterm birth, though, prompted renewed interest in the potential use of antibiotics to prevent preterm birth in asymptomatic women. Several prospective trials have demonstrated that antenatal treatment of bacterial vaginosis in asymptomatic women at high risk for spontaneous preterm delivery may reduce the subsequent spontaneous preterm delivery rate.[76,77] For example, Hauth and colleagues conducted a prospective, randomized, double-blind, placebo-controlled study of 624 women who were identified as being at risk for preterm delivery (e.g., history of previous preterm birth or prepregnancy weight of less than 50 kg).[76,77] These women were randomized to metronidazole (250 mg three times a day for 7 days) and erythromycin (333 mg three times a day for 14 days) therapy or to placebo. The investigators observed a significant reduction in the rate of preterm birth (49% vs. 31%) in women with bacterial vaginosis who received antibiotic treatment. In women without bacterial vaginosis, antibacterial treatment was associated with a significant *increase* in the rate of preterm birth (13.4% vs. 4.8%, $p < .02$).[76,77] Carey and coworkers further evaluated the use of metronidazole for prevention of preterm birth.[24] In a prospective, randomized, placebo-controlled study of 1704 low-risk asymptomatic women with bacterial vaginosis, treatment with metronidazole was not found to reduce the risk for preterm delivery or adverse perinatal outcomes. Based on these data, it appears that screening and treatment of bacterial vaginosis in women at high risk for preterm delivery may be an effective treatment to prevent preterm birth, but nondiscriminative screening and treatment of asymptomatic low-risk women does not appear to offer any clear benefit.

Several investigations have explored the use of targeted antibiotic therapy using fetal fibronectin as a screening tool to identify asymptomatic women at the greatest risk for early preterm birth induced by infection or inflammation.[11,58,76] Goldenberg and colleagues first explored this interesting theory.[58] In a subgroup analysis of women enrolled in a trial of antibiotic therapy for the prevention of preterm birth, 70 women with bacterial vaginosis and a positive fetal fibronectin test were randomized to receive either two courses of metronidazole treatment or placebo.[58] Patients who received metronidazole treatment had a lower incidence of preterm birth (8%) than the placebo group (16%), but this difference did not reach statistical significance ($p = .311$).[58] Despite the lack of statistical significance, this trend was compelling enough to lead to several randomized clinical trials designed to further evaluate the efficacy of antibiotic therapy in women with a positive fetal fibronectin test.[11,58,76]

In the largest of these trials, Andrews and colleagues screened 16,317 women between 21 and 25 gestational weeks with cervical or vaginal swabs for fetal fibronectin. Of the screened women, 1079 (6.6%) had a positive fetal fibronectin test (50 ng/mL or greater), 759 of whom consented to randomization to receive a 10-day course of metronidazole (250 mg orally three times per day) and erythromycin (250 mg orally four times per day) or identical placebo pills.[11] The primary outcome for this investigation was defined as spontaneous delivery prior to 37 weeks' gestation. No difference was observed in the incidence of spontaneous preterm birth prior to 37 weeks' (14.4% vs. 12.4%, $p = .43$), 35 weeks' (6.9% vs. 7.5%, $p = .76$), or 32 weeks' (4.3% vs. 2.2%, $p = .12$) gestation between the antibiotic-treated women and the placebo-treated women. Interestingly, among women with a prior spontaneous preterm delivery, the rate of recurrent spontaneous preterm birth prior to 37 weeks was significantly higher in the metronidazole plus erythromycin group than in the placebo group (46.7% vs. 23.9%, RR 1.95; 95% CI, 1.03-3.71; $p = .04$).[10]

The findings of the MFMU Network trial were consistent with those of two similar studies.[76] It is clear from these investigations that the use of antibiotic therapy in asymptomatic women with a positive cervical or vaginal fetal fibronectin test in the late mid-trimester does not decrease the incidence of spontaneous preterm delivery.

In contrast, the use of antibiotics for the treatment of acute preterm labor has had mixed results.[97,146] More than 15 investigations have been reported that evaluate the efficacy of different antibiotic regimens (i.e., ampicillin, erythromycin, clindamycin, ceftizoxime, amoxicillin-clavulanate, ampicillin plus erythromycin, ampicillin plus sulbactam, ampicillin plus metronidazole, amoxicillin-clavulanate plus erythromycin, and mezlocillin plus erythromycin) for the prevention of spontaneous preterm birth in women presenting with preterm labor and intact membranes.[97,175] These studies have yielded inconsistent results with regard to the benefits of antibiotics in prolonging pregnancy or improving short- and long-term neonatal outcomes.[97,146] The ORACLE II trial, the largest such study to date, was

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a multicenter, prospective, randomized study of antibiotics (erythromycin alone, amoxicillin-clavulanate alone, or combination of both agents) versus placebo in 6295 women with preterm labor and intact membranes.[91] This study failed to demonstrate significant prolongation of pregnancy or an improvement in a predefined composite neonatal outcome among women receiving any of the antibiotic regimens. A Cochrane review further evaluated the use of antibiotics in this population of women.[93] The reviewers concluded as follows: (1) antibiotic use is associated with a significant prolongation of pregnancy (5.4 days; 95% CI, 0.9-9.8), (2) maternal infection is decreased in women receiving antibiotic treatment (OR 0.59; 95% CI, 0.36-0.97), (3) the incidence of neonatal necrotizing enterocolitis is significantly reduced with maternal treatment using antibiotics (OR 0.33; 95% CI, 0.13-0.88), and (4) there is a trend toward a decreased risk of neonatal sepsis in the setting of maternal treatment with antibiotics (OR 0.67; 95% CI, 0.42-1.07). Surprisingly, the meta-analysis also demonstrated an increased perinatal mortality rate associated with maternal antibiotic treatment (OR 3.36; 95% CI, 1.21-9.32).[93] The authors, therefore, concluded that despite the prolongation in time to delivery, a clear overall benefit of antibiotic treatment for preterm labor has not yet been proven.[97] Antibiotics do play a clear role in prevention of neonatal sepsis caused by group B streptococci. In women perceived to be at an acute risk for preterm delivery, antibiotic therapy with appropriate agents against group B streptococci should be continued until either negative cultures are obtained or imminent delivery is no longer anticipated.

In the setting of preterm delivery caused by PPROM, antibiotic therapy remains a mainstay of treatment. Numerous investigations have shown that the use of a variety of antibiotics in this setting can result in an increased latency period from the time of membrane rupture to the time of delivery. A large, prospective, randomized clinical investigation by Mercer and coworkers conducted through the NICHD MFMU Network was designed to more clearly address the neonatal benefits of antenatal antibiotic use in women with PPROM.[118] In this trial, 614 women with PPROM were randomized to treatment with either intravenous ampicillin (2 g every 6 hours) plus erythromycin (250 mg every 6 hours) for 48 hours followed by oral amoxicillin (250 mg every 8 hours) and erythromycin base (333 mg every 8 hours) for 5 days or to a matched placebo treatment regimen. In addition to significantly increasing the latency period, the use of antibiotics in this investigation resulted in significant reductions in the incidences of RDS, necrotizing enterocolitis, and composite neonatal morbidity (defined as any of the following: fetal or infant death, respiratory distress, severe intraventricular hemorrhage, stage 2 or 3 necrotizing enterocolitis, or sepsis within 72 hours of birth).[118] In contrast, Kenyon and colleagues reported that antibiotic use in the setting of PPROM did not result in a reduction in neonatal morbidity.[90] These investigators conducted a large, multicenter, multinational investigation of 4809 women with PPROM at less than 37 weeks' gestation. Women were randomized to one of four treatment regimens for 10 days: placebo, amoxicillin-clavulanate, erythromycin, or a combination of amoxicillin-clavulanate plus erythromycin. Significant prolongation of pregnancy was noted among all antibiotic treatment groups when compared with placebo therapy. The investigators, however, noted no significant differences between the four treatment groups with regard to composite neonatal morbidity (defined as neonatal death, chronic lung disease, or major cerebral abnormality on ultrasound): placebo 15%, amoxicillin-clavulanate 14%, erythromycin 13%, and amoxicillin-clavulanate plus erythromycin 14%.[90]

Altogether, the use of antibiotics in the setting of PPROM appears to result in significant prolongation of pregnancy, with a potential reduction of neonatal short-term morbidity in certain subsets of patients (i.e., early PPROM at less than 32 weeks' gestation). On the basis of a meta-analysis, Hutzal and colleagues confirmed these conclusions, showing that antibiotics prolong pregnancy and reduce neonatal morbidity in women with PPROM at a gestation of 34 weeks or less, an effect that is not seen in women in preterm labor.[84]

Care must, therefore, be taken with the administration of antenatal and intrapartum antibiotics. Although they prolong pregnancy in the setting of PPROM, eradicate group B streptococci, and are effective in reducing the incidence of early-onset neonatal sepsis, this benefit may come at the cost of favoring the emergence of ampicillin-resistant organisms that may cause severe neonatal infections.

Corticosteroids

The use of antenatal corticosteroids for the prevention of neonatal RDS stems from original animal work performed by Liggins and Howie in the late 1960s. They initially observed that in gravid sheep given glucocorticoids to induce preterm labor, lambs demonstrated accelerated fetal lung maturity and decreased respiratory problems at birth. The investigators followed up on these interesting findings by conducting the first trial of antenatal glucocorticoid therapy in humans, showing that antenatal glucocorticoid administration (two doses of 12 mg of betamethasone given 24 hours apart) resulted in significant decreases in RDS and perinatal mortality in newborns born before 34 weeks.[104]

Since that landmark study, more than 15 additional prospective, randomized, controlled trials have confirmed this decrease in neonatal RDS related to antenatal administration of glucocorticoids (either betamethasone or dexamethasone). Roberts conducted a meta-analysis including 30 randomized controlled trials (7774 women and 8158 infants), reiterating the finding that antenatal glucocorticoid therapy significantly decreases the incidence and severity of neonatal RDS.[149] Neonatal mortality was also significantly reduced in this meta-analysis, as was the incidence of intraventricular hemorrhage and necrotizing enterocolitis. Maximal benefits were achieved when delivery

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occurred more than 24 hours but within 7 days of treatment initiation.

Despite this body of evidence, antenatal corticosteroids remained underused throughout the 1980s and early 1990s until the National Institutes of Health (NIH) convened a Consensus Development Conference on Antenatal Steroids in 1994 to review the potential risks and benefits of antenatal corticosteroid therapy. The panel concluded that sufficient data exist, demonstrating that antenatally administered corticosteroids (betamethasone or dexamethasone) significantly reduce the incidence or severity of RDS, intraventricular hemorrhage, and potentially necrotizing enterocolitis. The panel recommended that all fetuses between 24 and 34 weeks' gestation at risk for preterm delivery should be considered candidates for antenatal corticosteroid treatment. Additionally, given that treatment for less than 24 hours was also significantly associated with a decreased risk for RDS, intraventricular hemorrhage, and mortality, the panel concluded that steroids should be administered unless delivery is imminent. For patients with PPROM, treatment was recommended at less than 30-32 weeks because of the high risk of intraventricular hemorrhage.

Long-term follow-up of children at 3 and 6 years of age who were exposed in utero to antenatal corticosteroid therapy has not demonstrated any adverse effect on growth, physical development, motor or cognitive skills, or school progress. However, antenatal steroid therapy appears to be an independent risk factor for the development of asthma between 36 and 72 months of age.[143] All together, a single course of corticosteroids appears to be an efficacious and safe treatment modality to improve neonatal outcomes in patients at risk for preterm delivery.

One unresolved issue is related to the safety and efficacy of repeated steroid dosing. In animal studies, repeat courses of antenatal corticosteroids have been shown to have a deleterious effect on lung growth and organization, cerebral myelination, function of the hypothalamic-pituitary-adrenal axis, fetal growth, and retinal development. Several randomized trials have, therefore, evaluated the efficacy of repeated steroid courses in women at risk for preterm delivery.[66,182] Guinn and associates reported results from a randomized, double-blind, placebo-controlled clinical trial comparing repeated weekly betamethasone administration with a single course of betamethasone administered to pregnant women at the onset of threatened preterm delivery.[66] In this study of 502 women, no overall benefit was noted from repeated steroid courses with regard to composite neonatal morbidity (defined as any of the following: fetal or neonatal death, bronchopulmonary dysplasia, intraventricular hemorrhage, sepsis, necrotizing enterocolitis, and periventricular leukomalacia) when compared with single-course steroid administration (22.5% vs. 28.0%, respectively; $p < .16$).[66] Whereas the incidence of severe RDS was significantly lower among those infants in the repeated steroid course group (15.3%) when compared with those in the single-dose group (24.1%, $p < .01$), the incidence of severe intraventricular hemorrhage was higher in the repeated steroid course group (7.6% vs. 2.0%, $p < .06$).[66] Wapner and colleagues from the NICHD MFMU Network subsequently conducted a randomized trial of single versus weekly courses of corticosteroids for women at less than 32 weeks' gestation who were at increased risk for spontaneous preterm birth.[182] The primary study outcome was the occurrence of intrauterine fetal demise or neonatal death (scored together), severe RDS, grades III and IV intraventricular hemorrhage, periventricular leukomalacia, or chronic lung disease. No difference was noted between the study groups with respect to the primary study outcome. An important finding of this investigation, however, was a significant reduction in birth weight among infants exposed to four or more courses of steroids.[182]

Murphy and colleagues further evaluated this issue, randomly assigning 1858 women at 25-32 weeks' gestation who remained undelivered 14-21 days after an initial course of antenatal corticosteroids and continued to be at high risk of preterm birth. These patients were assigned to either receive multiple courses of antenatal corticosteroids ($n = 937$) or placebo ($n = 921$) every 14 days until week 33 or delivery, whichever came first. Multiple courses of antenatal corticosteroids did not improve mortality (around 12.5%) or neonatal morbidity, but there was a significant decrease in weight, length, and head circumference at birth in this group.[126] These results prompted the investigators to recommend against this treatment regimen.

In response to these concerns, the NIH reconvened a Consensus Development Conference in 2000 to review the available data on potential risks and benefits of courses steroid use when compared with single-dose administration.[128] It concluded that available evidence supporting the use of repeat courses of antenatal corticosteroids is limited due to study design and "methodologic inconsistencies." The panel also stated that despite possible benefit from repeated courses (especially in the reduction and severity of respiratory distress), several animal and human data suggest deleterious effects on cerebral myelination, lung growth, and function of the hypothalamic-pituitary-adrenal axis of the fetus. The panel stated that repeat courses should not be used outside of the context of a randomized trial.[128] Garite and coworkers subsequently randomized 437 patients with either singleton or twin gestations prior to 33 weeks' gestation who were judged to have a recurring threat of preterm delivery in the coming week. Women were eligible if they had completed a single course of antenatal corticosteroids prior to 30 weeks' gestation and at least 14 days before inclusion in this trial. Patients were randomized to receive either a single rescue course of betamethasone ($n = 223$) or placebo ($n = 214$).[53] Fifty-five percent of the patients in each group delivered before 34 weeks, but there was a significant reduction in the primary outcome of composite neonatal morbidity in the rescue steroid group. Neonates who received rescue-course steroids in utero also displayed significantly decreased RDS, ventilator support, and surfactant use, but perinatal mortality and other morbidities were similar in each group. These investigators concluded that

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administration of a single rescue course of antenatal corticosteroids before 33 weeks improves neonatal outcome without an associated increase in short-term risk. In 2015, Crowther performed a Cochrane meta-analysis of 10 trials (4733 women and 5700 infants).[39] The authors included trials with a repeat course of corticosteroids as early as 7 days from the initial course. The pooled results showed a significant reduction in RDS with no significant adverse outcomes. The authors noted an association with a small reduction in birth weight. We recommend that gravid women less than 34 weeks who are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was previously administered more than 14 days, should be offered a single repeat course of antenatal corticosteroids.

Recent attention has turned toward the use of antenatal corticosteroids in the late preterm period (34 0/7 weeks to 36 6/7 weeks). Recent data from the Maternal Fetal Medicine Units (MFMU) Network Antenatal Late Preterm Steroids trial supports the use of betamethasone in gravid women at high risk of late preterm birth (between 34 0/7 weeks and 36 6/7 weeks of gestation) that did not receive a prior course of antenatal corticosteroids.[69] This was a double-blind, placebo-controlled, randomized clinical trial that included women who were in preterm labor, or had preterm PROM, or had a planned delivery in the late preterm period. Administration of betamethasone led to a significant decrease in the need for respiratory support. Severe respiratory complications were significantly decreased (12.1% in the placebo group versus 8.1% in the betamethasone group; RR 0.67; 95% CI, 0.53-0.84; $P < .001$). The rates of transient tachypnea of the newborn; bronchopulmonary dysplasia; a composite of respiratory distress syndrome (RDS), transient tachypnea of the newborn and RDS; and the need for postnatal surfactant were all decreased in the intervention group. Neonatal sepsis, chorioamnionitis, or endometritis were not increased with late preterm betamethasone. Infants exposed to betamethasone had a higher rate of hypoglycemia (24.0% vs. 14.9% (RR 1.61; 95% CI, 1.38-1.88) but this did not lead to adverse events. As a result of this trial, SMFM supported the administration of a single course of betamethasone for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days and who have not received a previous course of antenatal corticosteroids.[166] When planning to administer antenatal corticosteroids in the late preterm birth period, obstetricians should be aware of the following considerations based on the methodology used in the trial. First, late preterm gravid women with clinical chorioamnionitis should not receive antenatal corticosteroids. Second, tocolysis should not be administered to delay delivery for the sole purpose of administering antenatal corticosteroids in the late preterm period. Third, no delays should occur in medically indicated late preterm delivery (e.g., preeclampsia with severe features) for the only purpose to administer antenatal corticosteroids. Since women with multiple gestations, pregestational diabetes, or who previously had received a course of corticosteroids or gave birth by cesarean at term were excluded from the trial, no recommendations can be made for this specific population group regarding benefits from late preterm antenatal corticosteroid administration.

The Global Network's Antenatal Corticosteroids Trial (ACT) was a multicountry (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia), cluster-randomized trial to improve appropriate use of antenatal corticosteroids (ACS) in low-resource settings in low-middle income countries (LMIC).[3] ACT substantially increased ACS use in the intervention clusters, but the intervention failed to show benefit in the targeted less than fifth percentile birth weight infants and was associated with increased neonatal mortality and stillbirth in the overall population. Maternal and neonatal infections were increased in the intervention clusters across all sites and increased infections are a possible partial explanation for the increase in neonatal mortality and stillbirth in the intervention clusters, especially in the African sites. The African sites appeared to have increased neonatal mortality in the intervention clusters, while the Guatemalan site had a significant reduction in neonatal mortality, perhaps related to a combination of ACS and improving obstetric care in the intervention clusters.[113] An expert group convened by WHO has concluded that there is a clear need for more efficacy trials of ACS in these settings to inform clinical practice.

The commonly used steroids for the enhancement of fetal maturation are betamethasone (two doses of 12 mg administered intramuscularly every 24 hours) and dexamethasone (four doses of 6 mg administered intravenously every 6 hours). At least one small trial suggested that betamethasone administered at 12-hour intervals is as effective as 24-hour dosing, a regimen that may be particularly useful in women who are at risk for imminent delivery.[92] Regardless of dosing, these two glucocorticoids have been identified as the most efficacious, because they readily cross the placental barrier to reach the fetal compartment. They also display the benefits of having long half-lives and limited mineralocorticoid activity.

Unresolved issues related to the use of corticosteroids include whether betamethasone is superior to dexamethasone, the efficacy and the appropriate dosing and efficacy in multifetal pregnancies. Despite these holes in knowledge, administration of antenatal corticosteroids remains one of the most important therapeutic advances and interventions in women at risk for preterm delivery.

Additional Interventions

Initial reports suggested that antenatal maternal treatment with phenobarbital or vitamin K reduced the incidence of intraventricular hemorrhage. However, these reports failed to control for the use of corticosteroids, a therapy that is known itself to significantly decrease the incidence of

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intraventricular hemorrhage. At this time, neither phenobarbital nor vitamin K appear to offer a significant advantage for the prevention of intraventricular hemorrhage beyond that observed with antenatal corticosteroids alone.[163]

Omega-3 fatty acid supplementation has also been proposed as possible intervention to prevent preterm birth. In a large, multicenter, randomized, double-masked, placebo-controlled trial, Harper and colleagues enrolled 852 women with a prior history of spontaneous preterm birth.[74] These women were assigned either to receive a daily omega-3 supplement or matching placebo, with no benefit noted in reducing preterm birth prior to 37 weeks' gestation in the treatment arm of the trial.

Summary

The epidemiology and pathophysiology of preterm labor are reviewed in this chapter, as are the current therapeutic strategies that may be employed in this setting. Despite all efforts thus far, preterm labor and delivery remains a significant clinical problem globally, accounting for a substantial component of all neonatal morbidity and mortality. Despite important insights into the pathophysiology of preterm labor over the past several decades, effective therapeutic interventions to decrease spontaneous preterm delivery remain limited. Clearly, the development of effective screening tools to identify patients at greatest risk for spontaneous preterm delivery is important to further the discovery of novel therapeutic strategies. As insights into the diverse etiologies of spontaneous preterm labor evolve, these strategies may lead to a significant reduction in the incidence of spontaneous preterm delivery, with concomitant improvement in perinatal morbidity and mortality rates. Because many of the preterm births are late preterm (≥70%), there is hope that major progress will be made in the near future.

The answer to prevention of prematurity is complex. This issue has been well summarized by Damus: "Despite the complex changing environment of perinatal care, shrinking resources and higher risk pregnancies, innovative strategies, expanded interdisciplinary partnerships, a focus on perinatal quality initiatives, more evidence-based interventions, tools to better predict preterm labor/birth, dissemination of effective community-based programs, a commitment to enhance equity, promoting preconception health, translation of research findings from the bench to bedside to curbside, effective continuing education for busy clinicians and culturally sensitive, health literacy appropriate patient education materials can collectively help to reverse the increasing rates of preterm births."[41] Measures that show demonstrable benefits in improving neonatal outcomes in preterm infants include antenatal corticosteroid therapy, administration of antibiotics to women with PPROM, and regionalization of care with a policy of prenatally transferring women to high-quality maternal-fetal units with experienced caregivers for mother and baby.

Preterm labor is a complex problem. The current treatment options are symptomatic, rather than causally directed, and the primary objective is to delay delivery long enough for a full course of antenatal corticosteroids to be administered. This has been accomplished with a variety of tocolytic drugs with different mechanisms of action (beta-mimetics, oxytocin antagonists, calcium-channel blockers). Preventive treatment with progesterone can lower the rate of preterm birth in selected high-risk groups by more than 30%. Premature rupture of the membranes is an indication for antibiotics. It has become fashionable to treat a short cervix with rest and progesterone, but the results have been inconsistent. It is time to try new approaches, and the application of the human genome is the logical step. Data are now accumulating on the important role for genetics in the timing of the onset of human labor. The use of modern genomic approaches, such as genome-wide association studies, rare variant analyses using whole-exome or genome sequencing, and family-based designs, holds enormous potential. Some progress has been made in the search for causative genes and variants associated with preterm birth, but the major genetic determinants remain to be identified. Further advances will depend on the identification of biomarkers for earlier detection of preterm labor as well as the development of effective therapeutic agents to inhibit labor when fetal compromise is not an issue.

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Key Points

- Preterm labor and delivery remains a significant problem globally, accounting for a substantial component of all neonatal morbidity and mortality.
- Effective maternal therapeutic interventions to decrease the burden of disease remain limited.
- The use of antenatal corticosteroid, magnesium sulfate therapy, and intrapartum antibiotics in women at risk of preterm delivery and administration of antibiotics to prolong latency in women with PPROM lead to improvement in neonatal outcomes in preterm infants.
- Obstetric interventions including the use of progesterone, cervical cerclage, and pessary to prevent preterm birth in select populations have contributed to a decrease in neonatal mortality and morbidities associated with preterm birth.

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20

Fetal Effects of Autoimmune Disease

ISAAC BLICKSTEIN AND CALANIT HERSHKOVICH-SHPOREN

Placental Transfer: General Remarks

The maternal-fetal interface is quite efficient in its selective exclusion of substances during the transport process from the maternal to the fetal circulation. At the same time, the placenta selectively transfers other substances, a process that is facilitated by the proximity of the respective maternal-fetal vascular systems within the placental cotyledons. Although there is no mixing of the maternal and fetal blood, the placental barrier is not impermeable, and small amounts of fetal blood, including fetal cells, gain access to the maternal circulation in most pregnancies through breaks in the fetal-maternal interface. When fetal blood cells are recognized as antigens by the maternal immunologic system, they may provoke an immune response and the production of immunoglobulins. This mechanism occurs in only a few pregnancies and is the basis of incompatibility disorders (see Chapter 23), whereby exogenous antigens such as fetal cells or incompatible blood sensitize the maternal immune system. The maternal antibodies, which are produced as a response to sensitization, cross the placenta and may destroy fetal cells. Generally, the mother is disease free, and the diagnosis is reached after the delivery of an affected infant or by screening tests.

A second type of maternal antibody that crosses the placenta and affects the fetus may arise from sensitization of the mother's immune system by her endogenous antigens, with the resultant production of autoantibodies. The mother with autoantibodies has an autoimmune disorder, and the diagnosis of the maternal disease usually precedes the diagnosis of the fetal or neonatal complication.

These generalizations describe immune processes that may affect the fetus or neonate. Although the maternal immune system may produce a wide range of immunoglobulins, only maternal antibodies of the IgG class (but not IgM or IgA) can cross the placental barrier. The common denominators of such disorders are the production of IgG in the maternal compartment, the transfer of IgG through the placenta, and the effects of these antibodies in the fetal compartment or neonate. This chapter discusses examples of such disorders.

Fetal Thrombocytopenia

Box 20.1 lists the immunologic etiologies of fetal, and consequently neonatal, thrombocytopenia. The most significant pathologies are neonatal alloimmune thrombocytopenia and immune (idiopathic) thrombocytopenic purpura (ITP). Although the two conditions have some similarities, they are distinct diseases, each with a different underlying pathogenesis (Table 20.1) (see Chapter 79).

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura in adults is often a chronic disease mediated by autoantibodies directed against cell surface components (glycoproteins) of platelets (IIb/IIIa or Ib/IX). Thrombocytopenia occurs when the platelet-antibody complexes are destroyed by the reticuloendothelial system. A low platelet count raises suspicion for ITP, but the diagnosis is reached after exclusion of other causes of thrombocytopenia by history, physical examination, blood count, peripheral blood smear, and autoimmune profile.[9] A spuriously low platelet count should be evaluated by examining a blood smear to exclude pseudothrombocytopenia caused by ethylene diaminetetra-acetic-acid–dependent platelet agglutination. The normal range of platelet counts in nonpregnant women and neonates is 150,000-400,000/μL; however, the mean counts tend to be lower during pregnancy. The prevalence of maternal ITP is one to two cases per 1000 deliveries. The potential risk of a low platelet count for the mother is bleeding; however, the risk becomes significant only when the platelet count becomes less than 20,000/μL. A maternal platelet count of greater than 50,000/μL is considered to be hemostatic during vaginal or cesarean birth.

Thrombocytopenia of the fetus or newborn is caused by active transplacental transport of the antiplatelet antibodies; however, no significant correlation has been observed between neonatal thrombocytopenia and maternal autoimmune antibodies. A low platelet count increases the risk for hemorrhage, but this seems to be more theoretical than real because intrauterine fetal hemorrhage has not

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Abstract

Two mechanisms may provoke the maternal immune system during pregnancy. First, fetal blood cells that enter the maternal circulation are recognized as antigens and may provoke an immune response and the production of immunoglobulins. Maternal antibodies cross the placenta and may destroy fetal cells. Second, autoantibodies from the mother's immune system provoked by an autoimmune disorder may cause fetal or neonatal complications. The common denominators of such disorders are the production of IgG in the maternal compartment, the transfer of IgG through the placenta, and the effects of these antibodies in the fetal compartment or neonate. This chapter discusses immune thrombocytopenic purpura (ITP), neonatal alloimmune thrombocytopenia, fetal-neonatal consequences of maternal antinuclear and antiphospholipid antibodies, myasthenia gravis, and herpes gestationis. Although the last decade has witnessed great progress in better understanding the underlying pathogenesis of most of these conditions, in many instances, however, therapy before birth and in the neonatal period remains controversial. Generally, steroids and intravenous immunoglobulins are the mainstay of these therapies. The obstetrical approach should consider the potential risk for the fetus during childbirth, and hence, tailor the best mode of delivery.

Keywords

immune thrombocytopenic purpura
neonatal alloimmune thrombocytopenia
maternal antinuclear antibodies
maternal antiphospholipid antibodies
myasthenia gravis
herpes gestationis

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TABLE 20.1 Characteristics of Neonatal Thrombocytopenia Based on Etiology

	Alloimmune Thrombocytopenia	Maternal Immune Thrombocytopenic Purpura
Cause of sensitization	Antigen on fetal platelets	Autoantibodies
Maternal platelet count	Normal	Low
Fetal platelet count	Low	Variable
Fetal risk (pregnancy)	High	Low
Fetal risk (delivery)	High	Depends on platelet count
Maternal risk	None	Depends on platelet count

• BOX 20.1 Immunologic Etiology of Fetal or Neonatal Thrombocytopenia

- Maternal production of autoantibodies
  - Immune thrombocytopenic purpura
  - Systemic lupus erythematosus
  - Drug-induced thrombocytopenia
- Neonatal alloimmune (isoimmune) thrombocytopenia
- ABO incompatibility

been reported in patients with ITP. The concern is for the potential trauma at birth and the potential risk for cerebral hemorrhage in the neonate. This serious complication is rare because the prevalence of fetal or neonatal ITP is about 10% that of maternal ITP, and less than half of these infants have platelet counts less than 20,000/μL. In the past, obstetricians performed antepartum cordocentesis (percutaneous umbilical vein blood sampling [PUBS]) or fetal scalp blood sampling to identify a fetus with a platelet count less than 50,000/μL and to deliver the fetus by the abdominal route. The current view holds that PUBS and fetal scalp sampling are unnecessary in pregnant women with known ITP even with platelet counts of 40,000/μL. Generally, when the maternal platelet count is greater than 50,000/μL, and the fetal platelet count (or the platelet count of previous offspring) is unknown, cesarean section is not indicated; a vaginal delivery is allowed, and the cesarean option is reserved for obstetric indications. If the fetal platelet count is known to be less than 20,000/μL, cesarean section is appropriate.

Treatment of ITP during pregnancy follows the guidelines published in 1996[9,20] and mainly reaffirmed later.[31] Pregnant patients with ITP and platelet counts greater than 50,000/μL throughout gestation and patients with platelet counts of 30,000-50,000/μL in the first or second trimester do not routinely require treatment.[20] Treatment in the form of glucocorticoids or intravenous immune globulin (IVIG) is indicated in patients with platelet counts less than 10,000/μL and patients with platelet counts of 10,000-30,000/μL who are in their second or third trimester or are bleeding. Intravenous immune globulin is an appropriate initial treatment for patients with platelet counts less than 10,000/μL in the third trimester and for patients with platelet counts of 10,000-30,000/μL who are bleeding. When glucocorticoid and IVIG therapy have failed, splenectomy is appropriate in the second trimester in women with platelet counts less than 10,000/μL who are bleeding. Splenectomy should not be performed in asymptomatic pregnant women with platelet counts greater than 10,000/μL.[20] Platelet transfusion is indicated for patients with counts less than 10,000/μL before a planned cesarean section and for those who are bleeding and expected to deliver vaginally. Prophylactic transfusions are unnecessary when the platelet count is greater than 30,000/μL and there is no bleeding.

Immune thrombocytopenic purpura does not preclude breastfeeding. The use of IVIG during pregnancy may improve platelet counts in the mother, but the treatment may not prevent fetal thrombocytopenia because the placental transfer of IVIG is inconsistent and mostly insufficient to reach fetal therapeutic levels.[3] A retrospective study examined the morbidity of 92 obstetric patients with ITP during 119 pregnancies over an 11-year period.[35] The authors found that most of these patients had thrombocytopenia during pregnancy. At delivery, 89% had platelet counts less than 150,000/μL. For many patients, the pregnancy was uneventful; however, 21.5% of the women had moderate to severe bleeding. In 31.1% of the pregnancies, treatment was required to increase the platelet counts. Most deliveries (82.4%) were vaginal. Platelet counts of less than 150,000/μL were found in 25.2% of the infants, including 9% with platelet counts less than 50,000/μL. Treatment for hemostatic impairment was necessary in 14.6% of the infants. During the study period, two fetal deaths occurred, including one caused by hemorrhage.[35]

After birth, the platelet count of newborns whose mothers have ITP-mediated thrombocytopenia may continue to decrease, and careful follow-up of the thrombocytopenia should be performed during the first week of life. Ultrasound imaging of the brain seems to be indicated if the count is less than 50,000/μL, even in the absence of neurologic findings. Neonates who exhibit severe thrombocytopenia (<20,000/μL) should be treated with platelet transfusion or IVIG or both. Neonates with platelet counts of 20,000-50,000/μL do not require IVIG treatment;

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however, careful platelet count monitoring is needed. Neonates with intracranial hemorrhage or any other bleeding manifestation should be treated with combined platelet transfusion and IVIG or glucocorticoid therapy, especially if the platelet count is less than 20,000/μL. Neonatal thrombocytopenia usually resolves within 4-6 weeks.

Neonatal Alloimmune Thrombocytopenia

The pathogenesis of neonatal alloimmune (also known as isoimmune) thrombocytopenia is similar to Rh disease. A mother with antigen-negative platelets is sensitized by antigen-positive fetal platelets gaining access to the maternal circulation via breaches in the placental barrier. As a result, the mother produces antiplatelet antibodies, and these IgG antibodies cross the placenta and destroy the fetal platelets. In contrast to Rh disease, 50% of neonatal alloimmune thrombocytopenia cases occur during the first pregnancy of an at-risk couple. This difference is explained by the higher immunogenicity of the platelet antigen and the smaller size of the platelets, which may facilitate their fetomaternal transfusion.

Of the several types of platelet antigens, the human platelet antigen 1a (HPA-1a) is involved in 80%-90% of neonatal alloimmune thrombocytopenia cases in whites, and HPA-5b is responsible for a further 5%-15% of the cases.[19] Among people of color (e.g., Asians), HPA-1a incompatibility is a rare cause of neonatal alloimmune thrombocytopenia, and other alloantigens (e.g., HPA-4b) are implicated.[5] The fetus acquires the antigen from the father. When the father is heterozygous, 50% of the fetuses would be affected, whereas all fetuses of a homozygous father would be HPA positive.

The prevalence of neonatal alloimmune thrombocytopenia is 0.5-2 cases per 1000 deliveries. Fetomaternal platelet incompatibility is much more frequent. The discrepancy is explained by the facilitating role of certain human leukocyte antigen (HLA) types that are associated with the development of neonatal alloimmune thrombocytopenia. HLA-DR3 is associated with a 10- to 30-fold risk for HPA-1a antibody production.

In the usual scenario, an asymptomatic woman delivers an otherwise normal infant in an otherwise uncomplicated birth. Most neonates are asymptomatic, and the thrombocytopenia is detected by a blood count performed for other perinatal causes. In some cases, neonates present with generalized petechiae, hemorrhage into abdominal viscera, excessive bleeding after venipuncture or circumcision, or, in extreme cases, abnormal neurologic manifestations secondary to intracranial hemorrhage. The platelet count commonly decreases further during the first week after birth.

The diagnosis of neonatal alloimmune thrombocytopenia involves typing platelet antigens in the newborn and in the parents to show that the mother lacks a platelet antigen that is present on the platelets of the father and the neonate. A more sophisticated test is to establish the existence of the antiplatelet antibody in the mother's serum that is directed against a platelet antigen in the father. Testing the infant is generally unnecessary if the father is available for testing.

Human platelet antigen genotyping is now available as a routine laboratory technique and can be used to identify HPA incompatibilities between mother and child. Several techniques are known, and the polymerase chain reaction with sequence-specific primers is used. New microarray technologies are expected to support routine genotyping of all known HPAs, which allows detection of incompatibilities for low-frequency antigens, increasing the sensitivity for the detection of antibodies against low-frequency antigens.

Older methods that measure the antibody associated with platelets lack adequate specificity, but newer enzyme-linked immunosorbent assays specifically detect the antiplatelet antibody. In antigen capture immunoassays, monoclonal antibodies directed against platelet antigens are used to identify various known platelet antigens individually, although these may be negative in maternal blood 2-4 weeks after delivery in 30% of the cases. Flow cytometry and polymerase chain reaction assays can also be used to identify the patient's platelet antigens. Establishing the diagnosis of neonatal alloimmune thrombocytopenia has immediate importance and implications for future pregnancies.

Management of the Neonate

In suspected cases of neonatal alloimmune thrombocytopenia, treatment should be started on the basis of the clinical diagnosis without waiting for the results of the immunologic workup. Management depends on the gestational age of the infant, the severity of the thrombocytopenia, the presence of bleeding, and the presence of additional risk factors for bleeding. Treatment is based on transfusion of random-donor, ABO-compatible and Rh-compatible, and HPA-1a-negative platelets (preferably with HPA-5b–negative platelets as well) in neonates with severe thrombocytopenia. This transfusion is compatible in approximately 90% of cases of neonatal alloimmune thrombocytopenia.[5,16,36] When random-donor platelets are unavailable, washed maternal platelets can be administered. Human platelet antigen–incompatible platelets should be used only if compatible ones are unavailable; they can be combined with IVIG treatment to achieve a transient increase in the platelet count until IVIG becomes effective.[5]

High-dose IVIG, 1 g/kg per day for 2 days or 0.5 g/kg per day for 4 days, is also effective in increasing the platelet count in most cases,[5] although the increase may be delayed for 1 or 2 days.[11] Corticosteroids were used in the past but have become less popular since the availability of IVIG. In any case, the neonatal platelet count should be closely monitored during the first days of life.

Management of a Subsequent Pregnancy

When the diagnosis of alloimmune thrombocytopenia is established, parents need to be counseled regarding risks and management of future pregnancies. The recurrence rate of neonatal alloimmune thrombocytopenia in a subsequent

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pregnancy is greater than 90%, and the risk for intracranial hemorrhage is the same or greater than in the previous pregnancy. The difference is, however, that in a subsequent pregnancy the patient and her caregivers are aware of the neonatal alloimmune thrombocytopenia affecting the first child. In the absence of screening (which has very low cost-effectiveness) for the presence of antiplatelet antibodies in maternal blood, the diagnosis is almost impossible without a history of neonatal alloimmune thrombocytopenia in a previous gestation. One exception is an incidental finding of intracranial hemorrhage during an ultrasound scan.

The risk for antenatal intracranial hemorrhage in the fetus with alloimmune thrombocytopenia is substantial enough to warrant intervention either by giving the mother weekly infusions of high-dose IVIG with or without corticosteroids (the preferred approach in North American centers) or by repeated in utero fetal platelet transfusions (the preferred approach in some European centers).[5] There is no way to predict which infant is going to have intracranial hemorrhage.[33] Antenatal therapy is aimed at increasing the number of fetal platelets regardless of the presence of a risk factor.

Although screening procedures are not indicated to detect neonatal alloimmune thrombocytopenia, a high index of suspicion is needed in certain cases (Box 20.2). Typically, a woman presents in early pregnancy with a history of delivering an infant with neonatal alloimmune thrombocytopenia or presents with some clues to the diagnosis.[27] The first step should be assessment of the father. In the heterozygous case, the status of the fetus is unknown, and direct assessment of fetal platelets is via PUBS or via genotyping cells in the amniotic fluid. The timing of the procedure and the risk involved are matters of debate. Failure to treat carries the risk for intrauterine intracranial hemorrhage, which is expected to occur in 30% of cases, with 10% of affected newborns dying and 20% experiencing neurologic sequelae secondary to intracranial hemorrhage. Percutaneous umbilical vein blood sampling has a high risk for miscarriage or fetal death. The operator must be prepared to transfuse platelets if the results show a dangerously low platelet count. If the infant is found to be HPA positive or the father is homozygous for the allele, there is a choice between serial platelet transfusions and IVIG administered to the mother.[32] Amniocentesis is performed mainly to exclude the presence of platelet antigens and thus to avoid unnecessary interventions.

• BOX 20.2 Maternal History That Merits Assessment of Alloimmune Thrombocytopenia

- Previous infant with proven alloimmune thrombocytopenia
- Fetal hydrocephalus
- Delivery of an infant with petechiae, bruising, or hemorrhage in an otherwise atraumatic delivery
- Unexplained fetal thrombocytopenia with or without anemia
- Recurrent miscarriages

Serial intrauterine platelet transfusions carry the risk of a single PUBS multiplied by the number of procedures. Because the survival of transfused thrombocytes is short, performing serial intrauterine transfusions requires repeating the procedure every week or 10 days.[32] In a study of the fetal loss rate in neonatal alloimmune thrombocytopenia managed by serial platelet transfusions, the authors found two perinatal losses in 12 pregnancies managed by a total of 84 platelet transfusions.[32] One loss was procedure related and resulted from exsanguination despite platelet transfusion. The procedure-related fetal loss rate was 1.2% per procedure but 8.3% per pregnancy. The authors calculated a cumulative risk for serial weekly transfusions of approximately 6% per pregnancy, indicating the need to develop less invasive approaches.[32]

The invasive procedure is used less often now than previously; this may be the result of favorable outcomes related to maternal treatment with high-dose IVIG (1 g/kg per week). The beneficial effect of megadose IVIG is presumably mediated by masking the antigenic effect of fetal platelets, reducing the production of antiplatelet antibodies. Intravenous immune globulin also stabilizes endothelial cells and reduces the incidence of intracranial hemorrhage even when the fetal platelet count remains low. It is debatable whether corticosteroids should be added to the IVIG management protocol.[26]

A European collaborative study of the antenatal management of neonatal alloimmune thrombocytopenia attempted to determine whether the severity of the disease in the current pregnancy could be predicted from the history of neonatal alloimmune thrombocytopenia in previous pregnancies and to assess the effects of different types of antenatal intervention.[4] The study enrolled 56 women who had had a prior infant affected by neonatal alloimmune thrombocytopenia owing to HPA-1a alloimmunization. The authors found that fetuses with a sibling history of antenatal intracranial hemorrhage or severe thrombocytopenia (a platelet count of <20,000/μL) had significantly lower pretreatment platelet counts than fetuses whose siblings had less severe thrombocytopenia or postnatal intracranial hemorrhage. Maternal therapy resulted in a platelet count exceeding 50,000/μL in 67% of cases. None of the fetuses managed by serial platelet intrauterine transfusions had intracranial hemorrhage after treatment. Several serious complications of PUBS arose, however. The results of this study suggest that the start of therapy can be stratified on the basis of the sibling history of neonatal alloimmune thrombocytopenia and support the use of maternal therapy as first-line treatment.[4]

Some patients who receive IVIG do not respond. Nonresponders cannot be recognized without PUBS, however.[10] When PUBS is planned to assess the effectiveness of therapy, the preparation for intrauterine platelet transfusion should be similar to the procedure used when PUBS is performed to diagnose neonatal alloimmune thrombocytopenia in a case with a heterozygous father (i.e., when the risk of an affected fetus is 50%). Nonresponders may be treated with either serial intrauterine platelet transfusions or steroids

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added to IVIG. It has been suggested that such assessment of treatment is unnecessary in patients who previously responded to IVIG therapy.

Alloimmune thrombocytopenia may also result from fetomaternal HLA mismatch. The meaning and treatment of this rare situation are controversial.

Fetal-Neonatal Consequences of Maternal Antinuclear Antibodies

Antinuclear antibodies (ANAs) are produced in various diseases with an immune component (Box 20.3). Antinuclear antibodies of the IgG and IgM types bind to nuclei or to nuclear components. Their presence is detected in the patient's serum, and they may be classified according to their subunits, each of which is related to the diagnosis of a disease. Anti-double-stranded DNA (anti-dsDNA) antibodies are specific for systemic lupus erythematosus. In this chapter, the maternal manifestations of these autoimmune diseases are not discussed; the focus is on neonatal lupus—a model of passively acquired autoimmunity—and the effects of the ANAs anti-Ro and anti-La.

Neonatal lupus is caused by transplacental passage of maternal autoantibodies. It is rare: Only about 1% of infants with maternal ANAs develop neonatal lupus. The infant may present with cardiac, dermatologic, hepatic, and hematologic manifestations. In children with neonatal lupus, there is commonly involvement of only one or two organ systems. The skin lesions on the face and scalp, often in a distinctive periorbital distribution, may be present at birth but usually develop within the first few weeks of life and tend to resolve in a few weeks or months without scarring.[29] Fetal heart block typically begins during the second or third trimester of pregnancy. In some instances, this begins as first- or second-degree heart block and progresses to third-degree heart block.[29] Complete heart block seems to be irreversible and may be combined with cardiomyopathy (see Chapter 77).[29] Hepatobiliary complications (10% of cases) may be manifested as liver failure occurring at birth or in utero, transient conjugated hyperbilirubinemia, or transient transaminase elevations occurring in infancy.[29] Thrombocytopenia, neutropenia, or anemia occurs in about 10% of affected infants. The noncardiac manifestations are transient and tend to resolve within months after birth. A case of neonatal lupus affecting both twins has been described.[34]

Mothers of children with neonatal lupus may have ANA-related connective tissue disease (e.g., systemic lupus erythematosus, Sjögren syndrome, undifferentiated autoimmune syndrome, or rheumatoid arthritis). The recurrence rate of neonatal lupus for a mother with anti-Ro autoantibodies, which are present in almost 95% of patients, is approximately 25%. Immunoglobulin G (IgG) autoantibodies are found alone or in combination and are directed against Ro (SSA), La (SSB), or U1-RNA (U1-RNP) antigens, and their presence increases the risk for neonatal lupus erythematosus.

Anti-Ro and anti-La autoantibodies recognize cardiac adrenoceptors and muscarinic receptors, and this recognition may explain the cardiac arrhythmia associated with these ANAs. Maternal anti-Ro and anti-La antibodies and complement components are deposited in fetal heart tissues, leading to inflammation, calcification, necrosis, and fibrosis of the conducting tissue (and, in some cases, of the surrounding myocardium).[12] The postinflammation fibrotic response to injury is quite rapid and, in most cases, irreversible. The process by which maternal anti-Ro or anti-La antibodies begin and propagate inflammation that leads to scarring of the atrioventricular node is not entirely clear. It has been proposed that the process begins with apoptosis of cardiocytes, resulting in translocation of Ro or La antigens and subsequent surface binding by maternal ANAs. This leads to a phagocytosis-mediated scarring process.[12] In addition, the anti-Ro antibodies have been shown to have arrhythmogenic activity through inhibition of calcium flux across cell membranes.[7] Animal models suggest that reactivity to the p200 region of the Ro52 protein and antibody targeting of L-type calcium channels may be associated in the developing cardiac neonatal lupus.[25] In vitro, the β-2 glycoprotein 1 seems to prevent anti-Ro binding to apoptotic cells, the urokinase-plasminogen activator/receptor system seems to activate TGF-β, and endothelin-1 secretion by macrophages seems to mediate tissue injury.[25] It also appears that fetal major histocompatibility complex is involved in the pathogenesis.[25] Interestingly, it was demonstrated that mothers of children with neonatal lupus accumulate genetic risk factors preferentially from the neonatal lupus child's grandparents.[25]

• BOX 20.3 Conditions Associated With Antinuclear Antibodies

Rheumatologic Conditions

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease
- Sjögren syndrome
- Necrotizing vasculitis

Infections

- Chronic active hepatitis
- Subacute bacterial endocarditis
- Infection with human immunodeficiency virus
- Tuberculosis

Miscellaneous Conditions

- Type I diabetes mellitus
- Multiple sclerosis
- Pulmonary fibrosis
- Silicone gel implants
- Pregnancy
- Age: older adult

Medications

- Drug-induced lupus erythematosus

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The cardiac rhythm disorders increase the risk for fetal congestive heart failure and point to the most important intervention during pregnancy, close follow-up with echocardiography and ultrasonography. Echocardiography can show the conduction defect and estimate the cardiac function.

About 10% of fetuses with congenital heart block are born with hydrops fetalis and congestive heart failure, and their prognosis is poor (see Chapter 23). Retrospective studies addressed the role of fluorinated steroids, IVIG, and hydroxychloroquine for prevention and treatment.[25] Intrauterine treatment with maternal corticosteroids may decrease the pericardial effusion or improve the symptoms of heart failure, but the heart block remains. Prophylactic treatment with IVIG awaits larger clinical trials.[13] It is possible to place an intrauterine pacemaker, but success is not ensured. Neonatal mortality rate in infants born with a congenital heart block ranges from 20%-30%; however, death may occur from late pacemaker failure later in childhood. Most neonates born with a heart block secondary to neonatal lupus require pacemaker placement in the neonatal period or later in life. Most children with neonatal lupus do not seem to develop rheumatic diseases, but follow-up has been limited to late adolescence.[13]

Fetal-Neonatal Consequences of Maternal Antiphospholipid Antibodies

Phospholipids are involved in facilitating the coagulation cascade. Antiphospholipid antibodies (APLAs) are autoantibodies against phospholipids or against plasma proteins bound to phospholipids. The most common subgroups involved in disease states are anticardiolipin antibodies, lupus anticoagulant antibodies, and anti–β_2-glycoprotein I antibodies. The hypercoagulability function of these antibodies is epitomized by the fact that they cause "bleeding in the test tube but clotting in the body," referring to their involvement in pathologic clotting. Antiphospholipid antibodies promote clotting in arteries and veins (i.e., thrombophilia) by activation of endothelial cells, via oxidant-mediated injury to endothelium, and by modulating the regulatory function of coagulation proteins.

It is common practice to use clinical and laboratory criteria for the diagnosis of APLA syndrome. According to the Sapporo criteria, patients are required to have either vascular thrombosis (venous or arterial, including neurologic disease) or fetal loss, and to show evidence of APLA either by the detection of anticardiolipin antibodies or by a positive test for lupus anticoagulant antibodies.[22] At present, one should look for the lupus anticoagulant (LAC), antiphospholipid antibody (APLA), and anti–β-2-glycoprotein I. To differentiate between persistent autoantibody response and transient responses from other causes, APLA must be detected on at least two occasions 12 weeks apart. These classification criteria are reported to have a sensitivity of greater than 75% and a specificity of nearly 100%. Patients with APLA and one major clinical criterion are considered to have APLA syndrome. Primary APLA syndrome refers to the syndrome occurring outside the setting of systemic lupus erythematosus.[30]

In women with APLA, there is a high incidence of pregnancy complications. Among women with a history of recurrent miscarriage (three or more consecutive losses of pregnancy), 15% have persistently positive test results for APLA and a rate of fetal loss of 90% when no specific treatment is given during pregnancy[22]; 25% of successful pregnancies were delivered prematurely.[22] Other potential complications of pregnancy include preeclampsia, placental insufficiency, fetal growth impairment, preterm birth, maternal thrombosis (including stroke), and complications of treatment.[8]

The pathogenesis underlying thrombosis and fetal loss in APLA syndrome remains to be established. The potential mechanisms that have been proposed include interference with the function of the coagulation cascade leading to a procoagulant state, cellular immune mechanisms, and the presence of predisposing factors. A "second hit" may be necessary for the clinical manifestation of the syndrome to occur.[22] The adverse effect of APLA syndrome on pregnancy is most likely associated with abnormal placental function.[8] Studies have shown abnormalities in the decidual spiral arteries, narrowing of the spiral arterioles, intimal thickening, acute atherosis, and fibrinoid necrosis in cases of fetal loss associated with APLA syndrome.[8] Other studies have found extensive placental necrosis, infarction, and thrombosis related to the procoagulant activity of APLAs in inducing adhesion molecules, platelet activation, and aggregation factors and the inhibition of key anticoagulant factors (see Chapter 27). The possibility of APLA-related neurologic morbidity (in the form of cerebral palsy) in the fetus or neonate is of major medicolegal importance and under investigation. At present, except from case reports, the association between fetal-neonatal thrombophilia from APLA and neurologic damage is yet to be established.

Treatment options include corticosteroids, low-dose aspirin, heparin (either fractionated or unfractionated),[6] and IVIG. These were administered either as single agents or in combination to increase the live birth rates in women with APLA syndrome. Although the available studies are flawed by small sample size, varying entry criteria and treatment protocols, and lack of standardized laboratory assays, many clinicians would treat patients with APLA syndrome with a combination of aspirin and heparin (fractionated or unfractionated).

There are few trials evaluating treatment of refractory APLA syndrome (recurrent pregnancy losses occur in 20%-30% of cases in most studies). A woman whose pregnancy fails on a prophylactic regimen should receive full anticoagulation therapy in a subsequent pregnancy.[8] If the treated pregnancy with full anticoagulation fails, some physicians advise adding glucocorticoids, IVIG, or hydroxychloroquine to the anticoagulation regimen.[8] The interested

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reader is referred to the review discussing the pathogenesis of the antiphospholipid syndrome.[21]

Myasthenia Gravis

Myasthenia gravis is an autoimmune neuromuscular disease affecting twice as many women as men, and it usually affects women in their third decade of life. The symptoms include weakness and fatigue of the skeletal muscles of the face and extremities. The diagnosis, which is beyond the scope of this chapter, involves a comprehensive neurologic workup based on clinical history and signs, improvement with anticholinesterase injection (edrophonium), determination of serum anti–acetylcholine receptor (AChR) antibody titers by radioimmunoassay, and electromyography.

In 90% of patients with myasthenia gravis, autoantibodies (usually IgG) against human AChRs are detected. The antibodies interfere with impulse conduction across neuromuscular junctions by decreasing the number of available AChRs there. Because myasthenia gravis typically affects women during reproductive years, the potential for exacerbation, respiratory failure, adverse drug response, crisis, and death during pregnancy is of great concern. Myasthenia gravis has a variable and unpredictable course during pregnancy, including exacerbation, crisis, and remission. In one study, 17% of asymptomatic patients with myasthenia gravis who were not receiving therapy before conception had a relapse; among patients receiving therapy, myasthenia gravis symptoms improved in 39%, remained unchanged in 42%, and deteriorated in 19% of the pregnancies. Myasthenia gravis symptoms worsened after delivery in 28% of the pregnancies.[1] In another study, myasthenia gravis symptoms deteriorated in 15% of the pregnancies, and a further 16% deteriorated during the puerperium.[17]

Therapy is based on anticholinesterase medications and plasmapheresis during a myasthenia gravis crisis. Other medications often have adverse effects on the disease, resulting in a long list of drugs that should be avoided in these patients. Plasmapheresis can be performed during pregnancy but may be associated with preterm birth. Of special concern are cesarean delivery and the hazards of anesthesia, which might prove very stressful for these patients. Some complications of myasthenia gravis in the form of exacerbation should be anticipated during pregnancy, including anxiety and physiologic stress of pregnancy (mainly present as hypoventilation), infection, a prolonged second stage at delivery (because the patient may become exhausted and be unable to push), and the contraindication to using magnesium sulfate in patients with preeclampsia.

Neonatal risks of myasthenia gravis include neonatal myasthenia gravis, prematurity, malformation, and death. Neonatal myasthenia gravis occurs in 10%-20% of infants born to mothers with myasthenia gravis and is caused by the transplacental transport of immunoglobulins from mother to infant. There is no correlation between myasthenia gravis severity and neonatal myasthenia gravis, and there is no correlation between maternal anti-AChR antibody titers and the occurrence of neonatal myasthenia gravis. This discrepancy is partially explained in neonatal myasthenia gravis by the protective role of α-fetoprotein, which inhibits the binding of myasthenia gravis antibody to its receptor.

The infant's symptoms are generally manifested by the third day of life in the form of respiratory distress and inadequate suck, which may gradually subside over 1-4 weeks. Rarely the disease becomes permanent when there is irreversible destruction of AChR by the maternal antibodies, or when there is production of antibodies by the infant. Analysis of data collected from the Medical Birth Registry of Norway, comparing 127 births by women with myasthenia gravis with 1.9 million births by women without myasthenia gravis, showed that women with myasthenia gravis had a higher rate of complications at delivery. In particular, the risk for preterm rupture of membranes was threefold higher in the myasthenia gravis group. Interventions during birth were also significantly increased, and the rate of cesarean section was twice that of the general population. Five children (3.9%) born to mothers with myasthenia gravis had severe anomalies, and three of them died.[23]

Herpes Gestationis

Herpes gestationis, also known as pemphigoid gestationis, is a rare autoimmune skin disease of pregnancy, occurring in less than 1 in about 50,000 pregnancies. Despite its name, herpes gestationis has no association with the herpesvirus infection. During pregnancy, IgG autoantibodies are produced against an important element in epidermal-dermal adhesion—the bullous pemphigoid antigen 2 (BPAg2, also known as BP180). It is assumed that these autoantibodies bind complement to the basement membrane of the epidermis and activate an immunodermatologic reaction that is responsible for the development of subepidermal vesiculae and bullae.[28]

Herpes gestationis is sometimes associated with other autoimmune diseases, and it seems that all these conditions have in common a relationship to HLA-B8 and HLA-DR3. Although herpes gestationis most commonly manifests during the second and third trimesters, in 25% of the cases it develops during the puerperium. There are reported cases of persistent herpes gestationis, but usually the disease spontaneously regresses after birth.[2]

Affected women usually present with inexorable pruritus associated with erythematous urticarial patches and plaques, which are typically located around the navel. The skin lesions may progress to tense vesicles and blisters, which spread peripherally. The face, palms, soles, and mucous membranes are usually unaffected. Although the symptoms usually wane toward the end of pregnancy, peripartum exacerbations do exist. Herpes gestationis may recur in subsequent pregnancies, and it may recur with menses and oral contraception.

The diagnosis is usually reached by collaboration between the attending obstetrician and an immunodermatologist.

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Treatment is directed toward alleviation of itching and suppression of blistering. Lukewarm baths or compresses may reduce the irritation, but corticosteroids (local, intralesional, or systemic) remain the primary therapeutic means. New treatment modalities including cyclosporine, IVIG, and tetracyclines postpartum have shown promising results.[28]

Herpes gestationis is associated with a greater incidence of premature birth and neonates who are small for gestational age. The infants of affected mothers may rarely have transient cutaneous manifestations, which disappear along with the clearance of maternal autoantibodies.[15,18] Blistering may increase the risk, however, for superimposed infection, thermoregulatory problems, and fluid and electrolyte imbalance. The attending neonatologist should also be aware of the medications received by the mother. The interested reader is referred to two reviews.[14,24]

Summary

This chapter discusses several examples of maternal immune-mediated conditions that may directly affect the fetus or neonate. Some of these conditions are quite rare, but some may be encountered in daily practice. From the neonatal point of view, the main mechanism of disease is transplacental transfer of antibodies from the mother to the fetus and the effect of these antibodies on fetal components. The last decade has witnessed great progress in better understanding the underlying pathogenesis of most of these conditions. In many instances, therapy remains controversial, however.

Key Points

- Maternal IgG antibodies are able to cross the placenta and affect the fetus-neonate.
- Better understanding the underlying pathogenesis of most immune conditions has not resulted in clearcut therapy before birth and in the neonatal period.

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21

Obstetric Management of Multiple Gestation and Birth

ISAAC BLICKSTEIN AND ERIC S. SHINWELL

The human female is programmed by nature to mono-ovulate, to nurture one fetus, and to take care of one neonate at a time. This natural pattern results in the relatively rare birth of twins (about 1 per 80 to 100 births) and in the extremely rare occurrence of high-order multiple gestations. The rarity of high-order multiple gestations can be appreciated by the quasi-mathematical Hellin-Zellany rule for twins, triplets, and quadruplets.[11] According to this rule, if the frequency of twins in a population is $1/N$, the frequency of triplets would be $1/N^2$, and that of quadruplets would be $1/N^3$.

The Hellin-Zellany relationship was found to be accurate as long as the population remained homogeneous and natural procreation occurred. In the middle of the twentieth century, however, it became apparent that deviations from the rule occur mainly because of racial differences in the frequency of dizygotic twinning.

This ordinary circumstance did not change until the emergence of effective treatment of infertility. Thereafter, it became clear that within an infinitely small fraction in human history, all we knew about natural multiples has been profoundly changed. Physician-made (iatrogenic) multiple gestations are now seen in most developed countries, with frequencies approaching 50% of twins and more than 75% of high-order multiple gestations. The contribution of infertility treatment can be appreciated from data of the 2015 Israel Neonatal Network. The data indicate that among infants weighing less than 1500 g, 13% of singletons were conceived by assisted reproduction compared with 51% of twins and 79% of triplets.[48] The reduced incidence of multiples among these very low birth infants is presumably a result of the new policies of embryo transfer in assisted reproduction.

Biology

Most human conceptions (>99.2%) emerge from a single zygote (i.e., monozygotic [MZ]), resulting from the fertilization of a single egg by a single spermatozoon. In the remaining cases, more than one egg is ovulated and fertilized, resulting in polyzygotic conceptions (i.e., dizygotic [DZ], trizygotic). This phenomenon occurs more often in taller, older, parous, heavier, and black women. Although direct and indirect evidence points to a genetic predisposition, the exact mechanism whereby the ovary is naturally stimulated to release more than one egg per cycle is unknown. All infertility treatments are associated, however, with ovarian stimulation and polyovulation. The contribution of infertility treatments to polyzygotic gestations has become extremely significant since the 1970s.

Most MZ conceptions result in singleton births. In a small fraction of cases (0.4% of all natural conceptions), the zygote splits to form an MZ twin gestation. The mechanism of zygotic splitting is unclear. It has been postulated (but never completely established) that all forms of assisted reproduction produce a breach in the integrity of the zona pellucida—the acellular layer of the egg—resulting in herniation of the part of the early embryo through that gap and splitting of the embryo.

The frequency of MZ splitting is also increased with all methods of assisted reproduction.[24] The true incidence of zygotic splitting after assisted reproduction is unknown. In a large study of single-embryo transfers, a sixfold increase in zygotic splitting was found. The frequency was not influenced by using fresh versus frozen-thawed embryos or by performing embryo transfers during a spontaneous versus an induced cycle.[24] A later hypothesis suggests that the potential to undergo splitting might be an inherent characteristic of the oocyte.[15]

Two points related to the issue of DZ and MZ twinning warrant further discussion. The first is the change of overall frequency of MZ conceptions. In a population comprising mainly of spontaneous gestations, the usual quoted frequency of MZ twinning is about one-third of the twin population, whereas in a population comprising a sizable proportion of iatrogenic pregnancies, one should expect one MZ pregnancy in 15-20 twin gestations.

The second point to consider is the placental arrangement (see Chapter 26). Dizygotic twins have two placentas (separate or fused), each with chorion and amnion, forming

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Abstract

The incidence of twins is continuously increasing worldwide. This is mainly a result of iatrogenic multiples following assisted reproduction. At the same time, the incidence of triplets seems to be, at present, high but steady. Since the most important disadvantage of multiples is preterm and very preterm births, the net effect is a continuing rise of prematurity. Most twins are dizygotic and, hence, have a dichorionic placenta. Less common, the very early embryo might split to create monozygotic twins. The subset of monochorionic twins is of particular interest because of the associated peculiar morbidity. It follows that chorionicity assessment by ultrasound is a critical step in the management of multiples.

Monozygotic twins have also an increased risk of malformations, some of which are among the most extraordinary anomalies (such as twin reverse arterial perfusion [TRAP] sequence and conjoined twins). It appears that all multiple pregnancies need special attention during pregnancy by experienced personnel. During pregnancy, the role of ultrasound in establishing the wellbeing of the set is indispensable. In some situations in monochorionic twins (such twin–twin transfusion syndrome, selective anomaly, selective growth restriction), intrauterine surgery may be indicated.

The risk of prematurity is plurality dependent. This has resulted in multifetal pregnancy reduction offered to expected mothers of triples and more. The risk of prematurity has direct effect on perinatal morbidity and mortality.

Most twins are born by cesarean section as are practically all higher-order multiples.

Keywords

twins
triplets
multiple pregnancy
zygosity
chorionicity

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the so-called dichorionic (DC) placenta. Placentation of the MZ twins is postulated to depend, however, on the stage of embryonic development at which the split occurs. It is believed that early splits (about one-third) result in DC placentas, whereas later splits result in monochorionic (MC) placentas. If the amnion has not yet differentiated, the MC placenta includes two amniotic sacs: the MC-diamniotic placenta (about two-thirds of the cases). If the split occurs later than 8 days after fertilization, an MC-monoamniotic placenta develops. Finally even later splits result in all varieties of conjoined twins. However, one should remember that this well-known theory has never been proved.

When describing a multiple gestation, one must differentiate between zygosity and chorionicity. Because MZ conceptions with a DC placenta cannot be differentiated clinically from same-sex DZ twins (half of DZ conceptions) who also have a DC placenta, zygosity can be determined with certainty only in the DC—unlike sex twins (all must be DZ conceptions) and in twins with an MC placenta (all must be MZ conceptions). Simple calculation reveals that we are blind to zygosity in about 45% of the cases, and zygosity determination must be performed by DNA testing. Thus nothing should be said about zygosity to parents of same-sex twins with a DC placenta.

Maternal Consequences

When discussing maternal complications during multiple gestation, two important issues should be considered. The first issue involves the significant changes in the roles of women in Western societies witnessed after World War II. The new roles in society were facilitated by effective contraception, allowing ample time to achieve education and a career. This change resulted in increased maternal age at first delivery. Because age and fecundity are inversely related, however, infertility treatment to achieve a pregnancy often becomes inevitable. Because all infertility treatments carry an increased risk of multiple gestations, the end result of these sociomedical trends is an increased age of the cohort of mothers of multiples. US data clearly show that the increase in maternal age is more striking in high-order multiple gestations than in twins and in twins than in singletons, with a net result of multiples being more often delivered to older mothers in whom chronic disease conditions have already accumulated.[6]

The second issue involves the overwhelmed maternal homeostasis. Consider the fact that the average singleton, twin, and triplet have a similar birth weight until 28 weeks (≈1000 g). By 28 weeks, the mother of twins and the mother of triplets have accumulated twice and three times the fetal mass of singletons. This excess of fetal mass must come from either existing maternal resources or from supplemental energy. During the third trimester, all maternal systems are overwhelmed, and some may be only a step away from clinical insufficiency.

Two examples vividly demonstrate the situation. The first is the increased frequency of clinically significant anemia as a result of depleted maternal iron stores or inadequate iron supplementation.[18] The incidence of anemia is significantly increased among mothers of multiples. A second example relates to the increased cardiac output. It has been estimated that in the worst-case scenario (i.e., preterm labor because of infection in a multiple gestation), the cardiac output may exceed 10 L/min (two to three times the normal value). It is understandable why cardiac function so easily turns into dysfunction when additional load—in the form of β-sympathomimetic tocolysis—is administered to a patient with multiples who experience premature contractions.[54]

Regardless of the inherent changes in maternal physiology resulting from the multiple gestation, there are some maternal disease conditions that are more frequent in these gestations. Hypertensive disorders are two to three times more frequent,[50] and their most dangerous complication—eclampsia—is six times more frequent among mothers of multiple gestations.[31] Preeclamptic toxemia occurs earlier in multiples than in singletons and often occurs in a more severe form.[17] Because triplets and other high-order multiples were rare in the past, there were scant data related to hypertensive disorders in high-order multiple gestations. With the current epidemic dimensions of multiple gestations, it has been shown that the risk of hypertensive disorders depends on plurality: The risk in triplets is higher than that in twins, and the risk in twins is higher than that in singletons.[55]

Although the data are still conflicting, the frequency of gestational diabetes also seems to be increased among mothers of multiples. Critical reading of the literature suggests that most stimulation tests to detect glucose intolerance of various degrees showed a diabetogenic effect of multiple gestations, whereas demographic analyses failed to show increased rates of gestational diabetes.[33] The latter analyses were conducted in the era before the epidemic of iatrogenic multiples, however, and before the effect of older maternal age could be documented.[33] Sivan and colleagues showed that the risk of gestational diabetes depends on plurality, as is the case for hypertensive disorders.[53] The correlation of multiple gestation with hypertensive disorders and gestational diabetes seems to point, at least in a teleologic way, to the increased placental size—hyperplacentosis—as a potential common denominator. Simões and coworkers showed that pregravid obesity appears to predispose women to gestational diabetes during twin pregnancy and that there is no advantage in terms of birth weight in twins born to diabetic mothers.[51]

All mothers of multiples are at considerably greater risk of preterm labor and delivery. Preterm contractions with or without cervical changes quite often necessitate tocolytic treatment. Many prophylactic measures, including progestogens, cervical suture (cerclage), β-sympathomimetics, bed rest, and hospitalization, were proposed to reduce preterm birth rates (see Chapter 19). All prophylactic measures failed to reduce significantly this common complication of multiple gestation. A cervical pessary has been proposed to help in cases of preterm birth in twins.[34] Expecting mothers of

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• BOX 21.1 Maternal Complications More Frequently Seen in Multiple Gestations

- Hypertensive diseases
  - Preeclamptic toxemia
  - HELLP syndrome
  - Acute fatty liver
  - Pregnancy-induced hypertension
  - Chronic hypertension
  - Eclampsia
- Anemia
- Gestational diabetes mellitus
- Premature contractions and labor
  - Complications associated with tocolysis
- Delivery-associated complications
  - Cesarean section
  - Operative delivery
  - Premature rupture of membranes
  - Postpartum endometritis
  - Placental abruption

HELLP, Hemolysis, elevated liver enzymes, low platelets.
Adapted from Blickstein I, Smith-Levitin M. Multifetal pregnancy. In: Petrikovsky BM, ed. *Fetal disorders: diagnosis and management*. New York: John Wiley & Sons; 1998:223.

TABLE 21.1 Categories of Structural Defects in Twins

Category	Defect
Malformations more common in twins than in singletons	Neural tube defects Hydrocephaly Congenital heart disease Esophageal and anorectal atresia Intersex Genitourinary tract anomalies
Malformations unique to monozygotic twins	Amniotic band syndrome TRAP sequence Conjoined twins Twin embolization syndrome
Placental malformations	Single umbilical artery Twin–twin transfusion syndrome Velamentous cord insertion
Deformations owing to intrauterine crowding	Skeletal (postural) abnormalities

TRAP, Twin reverse arterial perfusion.

multiples are frequently asked to leave work and to conduct a more sedentary lifestyle. Box 21.1 lists the most common maternal complications during multiple gestations.[13]

Fetal and Neonatal Consequences

Animal models, similar to humans, show an inverse relationship between litter size and gestational age and birth weight. In humans, the average gestational age at birth is around 40 weeks for singletons, 36 weeks for twins, 32 weeks for triplets, and 29 weeks for quadruplets. Although multiple gestations exhibit many specific complications, the consequences of prematurity are the most common.

Malformations

Most texts cite a two- to threefold increased risk of malformations among multiples. It seems that the increased risk is primarily related to MZ twinning, however, and that the malformation rate of DZ twins is similar to that of singletons.[16] The higher malformation rate among MZ twins is explained by the hypothesis of a common teratogen; that is, the one that causes the split of the zygote is also responsible for the malformation.

Malformations among multiples are grouped into four types (Table 21.1).[16] The first type includes malformations that are more frequent among multiples, notably malformations affecting the central nervous and cardiovascular systems. The second type involves malformations related to MZ twinning, such as twin reverse arterial perfusion sequence and the various forms of conjoined twins. The third type relates to consequences of placental malformations, in particular the MC placenta, resulting in the twin–twin transfusion syndrome (TTTS). Finally, the fourth type involves skeletal (postural) deformities (e.g., clubfoot, dolichocephaly, brachycephaly) that are caused by intrauterine fetal crowding.

Some malformations can have a major impact on the properly formed twin. In the twin reverse arterial perfusion sequence, the circulation of the severely anomalous acardiac-acephalic twin is entirely supported by the normal (pump) twin. Sooner or later this cardiac overload leads to cardiac insufficiency of the apparently normal twin. Another example is the case in TTTS whereby both twins might be completely normal, but the anomalous transplacental shunt of blood can cause serious morbidity in both twins. The most striking example is the case of single fetal demise in MC twins, whereby the surviving fetus might die in utero soon after the death of the first twin. Alternatively, the surviving twin can be seriously damaged (see Embryonic and Fetal Demise).

In contrast to structural malformations, chromosomal anomalies are not more frequent among multiples. Each member of the multiple gestation has the same maternal age–dependent risk for trisomy 21. By probability calculations, the risk for a mother that one of her twins will have trisomy 21 is greater, however, than that of a mother of a singleton who is at the same age. A 32-year-old mother of twins has approximately the same risk of one infant with trisomy 21 as a 35-year-old mother of a singleton.[41]

Because multiples are commonly seen in older mothers, and invasive cytogenetic procedures (amniocentesis or chorionic villus sampling) carry a much higher risk of pregnancy loss when performed in multiples, there is a genuine

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utility to maternal screening of aneuploidy to minimize the need for invasive procedures in these premium pregnancies. Screening tests such as the triple or quadruple test (second-trimester maternal serum human chorionic gonadotropin or free β-human chorionic gonadotropin, α-fetoprotein, and unconjugated estriol, with or without PAPP-A or inhibin) have a significantly lower prediction for trisomy 21 in multiples compared with singletons.[13] Thus at present, the basic screening for aneuploidy is the nuchal translucency thickness measurement.

Most structural anomalies can be detected by a comprehensive ultrasound scan. In addition, echocardiography and Doppler velocimetry can detect structural and functional cardiovascular anomalies. This ability raises the question of reduction of the anomalous twin. In multichorionic multiples, reduction is accomplished by ultrasound-guided intracardiac injection of potassium chloride. Because of the risk to the survivor in MC sets, however, highly invasive procedures are used to interrupt the umbilical circulation of the anomalous twin.

All invasive procedures (amniocentesis, chorionic villus sampling, and reduction methods) are associated with the risk of 5%-10% of membrane rupture and loss of the entire pregnancy. When an invasive procedure is considered during the second trimester, the risk of extremely preterm birth of the normal twin is apparent. This situation is exemplified in discordant lethal malformations. When one twin is anencephalic, the risk of reducing this twin should be weighed against the risk of endangering the normal fetus by preterm birth.

Embryonic and Fetal Demise

From the early days of sonography, it was clear that there are more twin gestations than twin deliveries. The early loss of one twin was eventually designated "vanishing" twin syndrome to denote the disappearance of an embryonic structure during the first trimester.[36] Many authorities consider this spontaneous reduction the natural equivalent of intentional multifetal gestation (numerical) reduction. The true frequency of vanishing twin syndrome is unknown, because many twin gestations remain unnoticed unless sonography is performed at an early stage. One estimate of frequency of vanishing twin syndrome comes from iatrogenic conceptions: Spontaneous reduction of one or more gestational sacs or embryos occurred before the 12th week of gestation in 36% of twin, 53% of triplet, and 65% of quadruplet gestations.[29] Pinborg and coworkers found that 1 in 10 singletons after IVF started as a twin pregnancy.[46] Interestingly, case-control studies on plurality-dependent spontaneous embryonic loss rates after assisted reproduction found that twin pregnancies have a two to five times lower miscarriage rate of the entire pregnancy compared with singletons.[40]

Single fetal death occurring beyond the first trimester is also more common in multiples. In DC twins, it is believed that the risk to the surviving twin is extremely low, and present only if there is an external insult such as maternal disease. Fetal death in MC twins is a totally different story.

Historically, it was believed that some ill-defined thromboplastin-like material is transfused from the dead to the live fetus—the twin embolization syndrome. The theory was that these emboli might cause fetal death or result in end-organ damage, such as brain and kidney lesions. In the early 1990s, after meticulous postmortem examinations, the embolic theory was replaced by the ischemic theory, which postulates that blood is acutely shunted from the live twin to the low-resistance circulation of the deceased fetus, causing acute hypovolemia, ischemia, and end-organ damage in the survivor. The chance of serious damage in the survivor is significant and estimated to be 20%-30%, although later estimations suggest lower figures.[45]

The diagnosis often is made some time after single fetal death, however, and the question arises whether prompt delivery is indicated to reduce the risk for the survivor. Data suggest that acute blood loss occurs just before the time of death of the surviving twin, and it is unlikely that immediate delivery of the surviving twin could decrease the associated high mortality and morbidity rates.[44] It is prudent to suggest conservative management in such cases, especially remote from term, and to use ultrasound and magnetic resonance imaging (MRI) to exclude brain lesions. MRI should be performed at 32 weeks' gestation, when white matter lesions can be better visualized.

Complications of the Monochorionic Placenta

The monochorionic (MC) placenta, by itself an anomalous structure, has three distinct pathologic structures. First, it is possible that the twins share unequal placental territories that inevitably lead to discordant growth. If the placental share of one twin is too small, selective intrauterine growth restriction (sIUGR) develops. Second, the MC placenta invariably contains interfetal anastomoses, and when there is significant unbalanced shunting, the twin–twin transfusion syndrome (TTTS) develops. Finally, most MC placentas have one umbilical cord attached to the membrane and to the side of the placenta—the so-called velamentous cord insertion. This placental anomaly is associated with growth restriction and TTTS.

TTTS is a consequence of MC twinning (see Chapter 26). TTTS is seen mainly (or only) in the diamniotic variety.[2] The extensive literature on TTTS may lead to the erroneous impression that the syndrome is frequently seen. TTTS occurs in about 10% of MC twins, and about half are of mild severity. Nonetheless, early-onset (before 20 weeks' gestation), severe TTTS, unless intensively treated, is associated with 100% mortality of both twins.

The pathology of TTTS is transplacental arteriovenous anastomoses that lead to shunting of blood from one twin (the donor) to the other (the recipient). Because all MC placentas have intertwin anastomoses, the syndrome probably occurs because of fewer compensating venovenous and arterioarterial connections. The hypovolemia of the

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donor is manifested by poor micturition (absent bladder and oligohydramnios on ultrasound scan) and signs of growth restriction. Conversely the hypervolemic recipient is surrounded by polyhydramnios and manifests signs of cardiac overload ranging from tricuspid regurgitation to cardiac insufficiency and hydrops fetalis.[58] Thus, the first stage (Quintero's) of TTTS is the twin oligohydramnios-polyhydramnios sequence (TOPS), followed by (stage II) absent urinary bladder on sonography of the donor, then pathologic Doppler values, and finally hydrops before fetal death. Intervention is at present indicated in all cases of stage II or higher. Treatment of stage I is currently controversial.

Many treatment modalities have been suggested to treat TTTS (Box 21.2).[47,58] Generally, TTTS means serious morbidity, but the specific outcome is related to the gestational age when TTTS occurred and to the severity of the syndrome. No single therapy has emerged as a treatment of choice with significantly better short-term results, which puts the clinician in a difficult position vis-à-vis the patient. Other data suggest, however, that long-term outcomes are better with laser occlusion than with amnioreduction (see Chapter 13). Nonetheless, in some instances, intervention can be used to buy time (i.e., increasing gestational age to the point of viability) rather than a true solution to the intertwin shunt. Laser treatment is technically possible from 17 weeks onward. However, most authorities maintain that laser treatment after 27-28 weeks is too risky and advocate elective preterm delivery thereafter.

Because we are unable to predict accurately which case is going to deteriorate over time, waiting may mean delivery of more mature twins who are in a worse or worsening condition. In addition, discordant fetal conditions remote from term pose difficult ethical questions: Waiting increases the risk for fetal death and long-term morbidity for the ailing twin, whereas pregnancy termination by cesarean section exposes both twins to the risk of preterm delivery.[58] Despite these difficulties, innovations in the treatment of TTTS may lead to an expected breakthrough in the future. The neonates may present with some of the problems that the twins acquired in utero, such as cardiac decompensation and renal problems. Also twins may manifest diseases that once were thought to be part of the TTTS. For example, significant differences in hemoglobin levels (at least 5 g/dL), now called twin anemia polycythemia sequence (TAPS), is found in 5% of MC twins but is more common after laser treatment (when a tiny A-V anastomosis was left behind). At present, fetal anemia is easily recognized by Doppler studies of the middle cerebral artery pick systolic velocity (MCA-PSV).[56] At birth, the donor is usually pale and anemic, whereas the recipient is polycythemic.[2] One may consider re-entry and performing laser photocoagulation of the remaining anastomosis, or at times, even blood transfusion to the anemic twin. The donor twin might be acutely distressed, with severe anemia and hypovolemic shock necessitating transfusion or exchange of blood products, or both. The recipient occasionally requires partial dilution exchange and support for cardiac failure (see Chapter 80). The long-term outcomes of TAPS are not clearly established.

• BOX 21.2 Treatment Modes of Twin-to-Twin Transfusion Syndrome

- Conservative management with careful monitoring
  - Monitoring
  - Ultrasound assessment
  - Biophysical profile
  - Doppler blood flow velocimetry
  - Fetal echocardiography
  - Cardiotocography
  - Digoxin
- Serial amnioreduction
- Septostomy
- Fetoscopic laser occlusion of placental vessels
- Selective feticide
  - Cord embolization
  - Nd:YAG laser technique
  - Fetoscopic cord ligation
  - Bipolar coagulation

Nd:YAG, Neodymium:yttrium-aluminum-garnet.

Fetal Growth

As noted earlier, multiples grow in utero to the same extent as singletons until about 28 weeks. Thereafter, during the third trimester, growth curves of multiples show a clear decelerating trend compared with the growth curve of singletons. The limited uterine capacity to nurture multiples leads to growth aberrations (see Chapter 15).[5]

The higher risk of delivering infants with low birth weight in a multiple birth is well known, as is the advantage for the multiparous patient. Analysis of population-based data related to 12,567 live-born twin pairs found that overall the risk of having at least one infant with very low birth weight (VLBW) (<1500 g) was 1:5 among nulliparous women and 1:12 among multiparous women. The risk of having both twins with VLBW among nulliparas (1:11) was double that of multiparas (1:22).[22] A similar trend and similar frequencies, but for infants with extremely low birth weight (<1000 g), were found in the analysis of triplets.[23]

The most common growth aberration in multiples is birth weight discordance.[9] Birth weight discordance occurs whenever there is difference in birth weights between the larger and the smaller infant of a multiple gestation set. When one analyzes a large series of multiples, one rarely finds that all members of the set have the same birth weight. Some variation is expected between siblings, and the magnitude of the difference—the degree of discordance—must be incorporated in the definition. The most common definition of discordance is the percent definition, whereby the birth weight disparity is calculated as a percentage of the larger infant. The definition does not refer to the actual size of the twins, however, and it can assign the same

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degree of discordance (e.g., 20%) to a twin pair weighing 1500 g and 1200 g and to a pair weighing 3000 g and 2400 g. The cumulative frequency shows that about 75% of twins exhibit less than 15% discordance, about 20% are 15%-25% discordant, and about 5% are more than 25% discordant.[9]

The definition of birth weight discordance is even more complex in triplets. Clinicians usually employ the same percent definition used for twins and calculate the difference between the largest and smallest triplet of each set, although this scheme ignores the middle-sized triplet and the true intertriplet relationship. A new description was developed in which the relative birth weight of the middle triplet was defined.[25] The middle triplet was defined as symmetric when the birth weight was within 25% of the average birth weight of the largest and smallest triplets, as low-skew when a set comprised one large and two small triplets, and as high-skew when the set comprised one small and two large triplets. The frequencies of different types of triplet discordance did not change with gestational age, suggesting three distinct types of discordant growth in triplets that are independent of gestational age (average values—symmetric 57%, high-skew 30%, low-skew 13%).[25]

An important related issue is the birth order of the smaller twin in a discordant set; it was commonly believed that the smaller twin is usually the second-born twin. It has been determined, however, that at lower levels of discordance either twin can be the smaller, but the likelihood of the second-born twin being the smaller increases with increasing discordance levels.[29] At discordance levels greater than 25%, the smaller twin was three to six times more often the second born.[20]

Data From Multiple Birth Data Sets

Population-based studies using the Israeli and the US Matched Multiple Birth Data Set have reached the following conclusions.

Levels of Discordance

Data suggest that there are three levels of discordance.[20,21] In the lowest levels (probably <25%), discordance seems to be related to the normal variation expected from the natural dissimilarities between siblings. In the highest level (probably >35%), discordance seems to be related to the exhausted uterine environment and reflects growth restriction.

The clinical approach to both levels is generally accepted: observation for the lowest degrees of discordance and intervention for the highest degrees of discordance. Between these levels are twins, constituting 10% of the entire twin population, who are of special interest, however, because of the controversies involved in their clinical management (aggressive versus conservative). The benefit of discordance would be an adaptive measure to promote maturity (i.e., delivery at a more advanced gestational age) by reducing the inevitable uterine overdistention, as has been shown in the group of twins within a total birth weight range of 3000-5000 g.[8]

Mortality

Mortality was 11 times higher among highly discordant smaller twins (>30%) compared with nondiscordant smaller twins. Risk estimates ranged from 1.1 among 15%-19% discordant twins to 2 among highly discordant twins. After accounting for the association between fetal growth and discordance, mortality risk was substantially higher among smaller and larger twins who were highly discordant (≥30%). The authors concluded that after controlling for fetal growth, smaller and larger twins affected by higher levels of birth weight discordance (>25%) remain at disproportionate risk for neonatal mortality.[26] Increasing birth weight discordance has been associated with increased risk of intrauterine death and malformation-related neonatal deaths.[28]

When it became clear that not all discordant twins have the same outcome, discordance was classified further according to the birth weight of the smaller twin. When neonatal mortality rates were compared among three groups of discordant twins (>25%), distinguished by the birth weight of the smaller twin being in the lowest 10th percentile (62.4%), in the 10th-50th percentile (32.9%), or greater than the 50th percentile (4.7%), the rate was significantly higher among pairs in which the smaller twin's birth weight was in the lowest 10th percentile (29% versus 11.1% and 11 per 1000).[14] This difference results from the higher mortality rates among the smaller, but not among the larger, twins. The authors concluded that even in severely discordant twin pairs, about 40% do not constitute a growth-restricted fetus. Identification of this group is an imperative step in the management of birth weight discordance in twin gestations and in avoiding unnecessary interventions that may lead to iatrogenic prematurity.[27,35]

An important practical issue in the assessment of growth in a multiple gestation is whether to use singleton or twin growth curves. Because so many twins and, logically, almost all infants in high-order multiple gestations weigh less than singletons of the same gestational age, it seems that multiples grow differently than singletons do and are frequently and erroneously defined as small for gestational age by singleton standards.[5] Before birth, ultrasound assessment of individual fetal growth cannot establish a pattern of growth restriction unless repeated scans are performed and deceleration or arrest of the growth pattern is established. Despite the relative accuracy achieved by ultrasound estimations of the individual fetal weight, the "plus or minus" situation that exists for each estimation can cause quite significant underestimation and overestimation of the weight difference between fetuses and lead to low positive predictive values of discordance.[19]

As is the case with singletons, growth restriction—genuine or relative—is usually managed conservatively unless signs of fetal distress are seen. Discordant growth and discordant fetal well-being sometimes go hand in hand, however. When the risk for the unaffected neonate is lower than the expected risk for the affected fetus, delivery is a clear option, as would be the case at greater than 32 weeks. Clinical dilemmas may arise, however, remote from term,

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when a decision to save the ailing fetus may endanger the healthy fetus with potential risks of extreme preterm birth.

Fetal assessment in multiples is no different from assessment in singletons, although it is more complicated. With the availability of modern equipment, fetal heart rate is currently traced for both twins at the same time. Intrapartum dual tracing is as important as during pregnancy, and when the membranes are ruptured, the presenting twin is usually traced with a scalp electrode, and the nonpresenting twin is followed with an external Doppler transducer. The fetal biophysical profile is similarly assessed individually.

Birth Weight Discordance in Monochorionic Twins

As noted previously, birth weight discordance is no longer part of the diagnostic criteria of TTTS. Twins may have a very unequal placental territory,[37] which may lead to severe discordance and growth restriction of one MC twin (selective IUGR, sIUGR). In the subset of MC twins, this may lead to death of the smaller twin with subsequent damage or death to the appropriately growing co-twin.[37,45] Selective intrauterine growth restriction in MC twins is associated with increased perinatal mortality and morbidity for both twins.[57] Selective intrauterine growth restriction is classified according to the umbilical artery diastolic flow, whereby sIUGR type I has normal diastolic flow and relatively good outcome, type II has persistent absent/reverse end-diastolic flow and is associated with a high risk of intrauterine demise of the IUGR twin and/or very preterm delivery, and type III has intermittent absent/reverse end-diastolic flow and is associated with 10%-20% risk of unexpected fetal demise of the smaller twin and 10%-20% risk of neurologic injury in the larger twin.[57] Management for types II and III is still controversial, suboptimal, and may include selective (preventive) feticide (to avoid sudden fetal death of one twin and death or damage to its co-twin).

Delivery Considerations

Almost 80%-90% of twins and practically all high-order multiple gestations initiate spontaneous labor at less than 38 weeks' gestation. Data have suggested that at least for twins, "term" by singleton standards (i.e., 40 weeks) might be inappropriate and could carry a risk similar to post-term singletons. This concept emerged from data suggesting that neonatal mortality[42] and morbidity[39] are increased after 37 completed weeks compared with singletons, and the concept that twins should be delivered by 37 or 38 weeks comes from evidence that the fetal systems of the multiple gestation are mature by this date.[1,38] This has been supported by Dodd and coworkers, who found that elective birth at 37 weeks of gestation was associated with a significant reduction in risk of serious adverse outcome for the infant in uncomplicated twin pregnancies.[30]

At present, great controversy exists regarding elective preterm (at 34-35 weeks) delivery of MC twins.[52] This initiative derived from the finding of increased prospective risk of intrauterine death in uncomplicated MC twins. The initially reported high risk was not universally confirmed,[52] however, and extensive research is currently trying to quantify this prospective risk accurately. Current Royal College of Obstetricians and Gynaecologists (RCOG) guidelines recognize this disadvantage of MC twins and recommend delivery at 36 weeks' gestation.

There are many reasons why cesarean section could be indicated in most twins and all high-order multiple gestations.[3] Because twin gestations often involve maternal and fetal complications and are often considered "premium" pregnancies, many clinicians follow the principle "no high-risk pregnancy should end with a high-risk delivery" and deliver twins by cesarean section for many subtle reasons other than clear, evidence-based indications. The decision for an abdominal birth in twins, intentionally or not, is based on qualitative variables that were not quantified by randomized trials and on quantitative variables that suggest no advantage for a cesarean delivery in most cases.[3]

Vaginal birth is permitted in twins whenever the first twin is in vertex presentation. Breech delivery of the second twin or internal podalic version of a transverse-lying second twin is still permitted.[7] Otherwise, all pairs with a nonvertex presenting twin are likely to undergo a cesarean section. Nuances on this construct consider fetal size, discordance, prior uterine surgery, and, mainly, the experience and dexterity of the obstetrician.

When a multiple birth is expected, the main neonatal problem is logistic rather than medical, because immediate neonatal treatment of an infant of a multiple gestation is not significantly different from treating a singleton except that twins come in pairs and triplets come in sets. In practical terms, this means more staff in the delivery suite, more cribs available in the nursery, and more stations ready in the neonatal intensive care unit (NICU). Delivery of several very preterm sets in a short period sometimes may occupy the entire NICU for a long period. If the availability of NICU beds lags behind the increased production of multiples, a serious public health situation may be created.

Outcome

Given the greatly increased risk of maternal and fetal complications during a multiple gestation, the overall outcome for multiples is worse compared with the outcome for singletons. The increased risk of cerebral palsy among multiples is clear: 28-45 for triplets, 7.3-12.6 for twins, and 1.6-2.3 for singletons per 1000 survivors, indicating that the greater the number of fetuses, the greater the prevalence of cerebral palsy. The increase in cerebral palsy with the number of fetuses seems to be exponential.[4]

The as-yet-unanswered question is: Are the outcomes of multiples poorer than the outcomes of singletons matched for birth weight or gestational age? Consider, for example, that the usual prophylactic dose of corticosteroids given to singletons may not be enough for twins to enhance lung maturity and reduce the risk of neonatal respiratory distress.[43]

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One way to estimate neonatal morbidity is to examine the influence of plurality on a cohort of infants with similar initial characteristics. Multivariate logistic regression analysis using all significant perinatal covariates of prospectively collected data from the Israeli national VLBW infant database ($N = 5594$: 3717 singletons, 1394 twins, and 483 triplets) has shown that respiratory distress syndrome was significantly more common in twins and triplets despite increased exposure to antenatal steroids.[48] In addition, VLBW triplets were at increased risk of death. Very low birth weight twins and triplets had no increased risk of chronic lung disease or adverse neurologic findings.[48]

Another way is to examine the influence of birth order on these variables.[49] Comparisons of outcome variables by birth order of VLBW twins, after stratification by mode of delivery and gestational age, revealed that second-born twins had increased risk of respiratory distress syndrome, chronic lung disease, and death, but not adverse neurologic findings. Mode of delivery did not significantly influence outcome.

Summary: Prevention Versus Cure

The epidemic dimensions of multiple births, and especially of high-order multiple gestations, became clear toward the end of the 1980s as an aftershock resulting from effective infertility treatment.[10] To amend this untoward consequence of infertility treatment, clinicians proposed to reduce the number of embryos during pregnancy.[32] Multifetal gestation reduction, albeit considered by many to be the ultimate paradox of medicine,[11] soon became a popular "cure" of the side effects of infertility treatment. This procedure, performed during the early second trimester via the transvaginal or transabdominal route, carries a risk of about 5% total loss and a risk for significant maternal psychological morbidity.

Multifetal gestation reduction is associated with better outcomes, however, because fewer fetuses expectedly do better than more fetuses. When clinicians refined and mastered the technique, the debate about the final number became pertinent, and the current controversy is about multifetal gestation reduction of triplets.[12]

As always in medicine, prevention is better than cure. In terms of infertility treatment, this means transferring only one embryo in in vitro fertilization programs and canceling ovulation induction cycles when more than one ripe follicle is visualized. Such preventive measures would reduce the overall success rates, although it is debatable if a multiple gestation with three or four severely premature infants constitutes success.

It is evident that multiple gestations and births are a true challenge for all medical disciplines involved in caring for the mother and fetuses and infants. At the same time, the increase in iatrogenic multiple births may have an antievolution effect with as-yet-unknown consequences.

Key Points

- Multiples are at higher risk of prematurity and fetal anomalies. Special risks are related to monochorionicity.
- All multiple pregnancies need special attention during pregnancy by experienced personnel.
- Most twins are born by cesarean section as are practically all higher-order multiples.
- The risk of prematurity has direct effect on perinatal morbidity and mortality.

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22

Post-Term Pregnancy

ISAAC BLICKSTEIN AND ORNA FLIDEL RIMON

The human gestation is said to last 266 days from fertilization or 280 days from the last menstrual period (LMP). This amounts to 40 weeks of gestation—10 lunar months, or about 9.5 calendar months. Because no one knows exactly how long any particular pregnancy should last, clinicians use statistical distributions of gestational ages to conclude that a given pregnancy should last between 37 and 42 completed weeks (called *term*). Using such a distribution, about 80% of infants are delivered at term, 10% are delivered before 37 completed weeks, and about 10% are delivered post-term (>42 completed weeks). The American College of Obstetricians and Gynecologists is strict in defining *post-term*—that is, pregnancies carried beyond what is considered to be term—as any time after 42 completed weeks from the LMP.[3]

The problem in defining the end of pregnancy is that the beginning of a pregnancy is seldom known. In contrast to conceptions that follow in vitro fertilization, in which the day of transferring the embryo is known, spontaneous pregnancy is associated with educated guessing, resulting in accuracies of about plus or minus 2-3 weeks. Ultrasound assessment, especially with earlier measurements, has increased the accuracy of pregnancy dating. Sonographic dating is now available using the crown-rump length, the biparietal diameter, and the femur length. Of these, the crown-rump length is the most accurate, because it is measured in the second half of the first trimester. The biparietal diameter is the most popular biometric value and is most accurate during the first half of the second trimester. The femur length is the most consistent marker for gestational age and is used from the beginning of the second trimester onward.

The addition of sonographic measurement has improved our educated guess of the gestational age and narrowed the margin of error to about plus or minus 1 week (especially when an early scan is performed). It is customary to use the known (but inaccurate) LMP whenever the calculations are within 1 week of the estimated age by early ultrasonography. If the first scan is done late in the second trimester, however, sonographic accuracy is much reduced. Because ultrasound assessment is not available everywhere, dating may be inferred from a series of clinical estimations (Box 22.1).

Accurate dating is important, because inaccurate dating is the most common reason for a pregnancy appearing to be post-term. Inaccurate dating may be a result of late ovulation, especially in cases of infrequent menstruation, or simply because the patient cannot accurately remember the LMP. Genuine post-term gestations may rarely be associated with anencephaly or with placental sulfatase deficiency. Both of these mechanisms point to the concept of the fetal placental clock, which involves the role of corticosteroid-releasing hormone and estriol in normal parturition and delivery.[22] Meanwhile, as prematurity rates have significantly declined in developed countries, current investigation is focused on the role of maternal-fetal adaptive immunity in triggering the onset of labor.[6]

Risks of Post-Term Pregnancy

Generally the risks of post-term pregnancy are of two types. In one type, the placenta continues to function, more or less as in the previous months, and the fetus continues to grow. This continued growth results in a large—so-called macrosomic—infant. McLean and colleagues studied 7000 infants with confirmed expected date of confinement (±7 days) and showed a gradual shift toward greater birth weight between 39 and 43 weeks' gestation.[21] These authors voiced their concern for fetal macrosomia rather than for intrauterine growth restriction (IUGR) in post-term pregnancy (see Chapter 15).

The other type, which seems to be more common, occurs when the placenta's function is reduced. When this situation is prolonged, some form of placental insufficiency results. Typically placental insufficiency is associated with a reduction in the nutrients and oxygen transferred to the fetus, leading not only to a wide range of perinatal morbidities but also to increased rates of perinatal mortality. In an attempt to quantify this rate, Divon and coworkers[12] evaluated the National Swedish Medical Birth Registry. In 181,524 singleton pregnancies with reliable dates delivered at greater than 40 weeks, the authors found a significant increase in the odds ratio for fetal death at greater than 41 weeks' gestation, but the odds ratios for neonatal mortality did not show a significant gestational age dependency. Intrauterine growth restriction was associated with significantly higher

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Abstract

Post-term refers to pregnancies carried beyond what is considered to be term—as any time after 42 completed weeks from the last menstrual period (LMP). At this point of gestation, fetal complications depend on placental function: If the placenta continues to function, fetal growth continues, and the main risk is related to macrosomia. However, in case of placental dysfunction, the risk of fetal growth restriction and hypoxygenation may increase ante- and intrapartum death. These cases are also more likely to exhibit signs of distress during labor and, hence, are associated with more instrumental and cesarean birth. Management of fetal macrosomia is complicated by inaccurate diagnosis, leading to many unnecessary cesarean deliveries to prevent one permanent brachial plexus injury in fetuses with antenatal estimated weights of 4000 and 4500 g.

Dysmaturity (postmaturity) is associated with fetal growth restriction attributable to placental insufficiency. The neonate may exhibit low weight, relative absence of subcutaneous fat, wrinkling of the skin, prominent fingernails and toenails, absence of the vernix caseosa, skin desquamation, and meconium stains. Dysmaturity is associated with increased perinatal mortality rate, antepartum and intrapartum fetal distress, increased neonatal morbidity, meconium aspiration, peripartum asphyxia, neonatal hypoglycemia, hypothermia, hyperviscosity, and polycythemia. To avoid these complications, it is customary to closely follow pregnancies after 41 weeks and to induce labor at 41-42 weeks' gestation.

Keywords

post-term
dysmaturity
macrosomia
meconium aspiration
induction of labor

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• BOX 22.1 Clinical Methods to Estimate Gestational Age

- Promote early prenatal care. The earlier the patient is seen, the more accurate is the estimation.
- Take a very careful menstrual history.
- If unknown, try to track the last menstrual period.
- Find out when the symptoms of pregnancy began.
- Perform a pelvic examination; dating by uterine size is better than nothing and often quite accurate. This is also true for dating by fundal height.
- Positive or negative pregnancy test results can help exclude unlikely dates.
- Look for heart tones with a simple Doppler. They can appear by 9-11 weeks.

odds ratios for fetal and neonatal mortality rates at every gestational age examined. This extensive study of accurately dated pregnancies documented a significant increase in fetal mortality beyond 41 weeks' gestation—an observation corroborated by many others[8]—and a significant contribution of IUGR to the perinatal mortality in these pregnancies.[12] A French review suggests that perinatal mortality increases regularly, from 0.7-5.8/1000 from 37-43 weeks' gestation.[30]

Another assessment of the Swedish population found that perinatal mortality depended on parity.[15] The stillbirth rate was highest for primiparas at 38 completed weeks (2.3%) and lowest at 40 weeks (1.2%), and then it increased to 2.36% in the post-term period, but the difference compared with multiparas was significant only from 41 weeks onward.[15] Neonatal mortality was increased at 41 completed weeks for primiparas, but for multiparas it changed significantly only after 42 completed weeks. Except for the parity effect on stillbirth, this study documented the parity-independent risk of neonatal deaths after 42 completed weeks.

The most recent Practice Bulletin of the American College of Obstetricians and Gynecologists added a relatively new definition of late term (41 0/7 to 41 6/7 weeks) and reaffirmed the definition of post-term gestations and its association to neonatal morbidity and mortality.[2]

Macrosomia

The well-known risks of macrosomic fetuses include dystocia (i.e., difficult delivery), borderline cephalopelvic disproportion necessitating instrumental or abdominal delivery, frank cephalopelvic disproportion ending in abdominal birth, traumatic delivery (shoulder dystocia) with or without birth trauma (brachial plexus injury, fracture of the clavicle), neurologic damage, and infant death. The risk of each of these complications is related to the degree of macrosomia; that is, the larger the infant, the greater the risk. It is unclear, however, what the relative contributions are of prolonged pregnancy, maternal diabetes, and obesity in producing macrosomia. In cases of gestational diabetes, it is logical to assume that if there is no placental insufficiency, the fetus would be continuously influenced by the growth-promoting effect of the maternal disease (see Chapter 18).

Management of fetal macrosomia is complicated by two factors. First, the diagnosis (clinical or sonographic) is often inaccurate; prediction and prevention of these risks are not always possible. Second, these risks are primarily, but not exclusively, associated with vaginal birth. When the diagnosis is uncertain, preventing most of the potential complications means performing many unnecessary cesarean deliveries. Rouse and colleagues[26] calculated that in nondiabetic pregnancies, 2345 and 3695 cesarean deliveries are necessary to prevent one permanent brachial plexus injury in fetuses with antenatal estimated weights of 4000 and 4500 g.

Because the medicolegal environment often fuels decision making in cases of potential macrosomia, clinicians may choose to induce labor in a diabetic patient before 40 completed weeks to avoid the development of macrosomia and its sequelae.[19] Alternatively, cesarean section is offered when the estimated fetal weight is greater than 4500 g and to diabetic mothers when the estimated fetal weight is greater than 4000-4200 g. Recently reaffirmed ACOG guidelines regarding macrosomia suggest that vaginal delivery is not contraindicated when the estimated fetal weight is less than 5000 g in the absence of maternal gestational diabetes.[4]

Dysmaturity

The dysmaturity (postmaturity) syndrome was described almost 50 years ago.[10] It affects about 20% of post-term pregnancies.[11] It is associated with arrest of fetal growth, IUGR, and is attributed to placental insufficiency. The neonate may exhibit many of the following signs: low weight; relative absence of subcutaneous fat; wrinkling of the skin; prominent fingernails and toenails (nails appear to be long, as if the infant was 8 days old); absence of the vernix caseosa; desquamation of the skin; and yellow-green discoloration of the umbilical cord, nails, and skin (Fig. 22.1). Dysmaturity was historically associated with increased perinatal mortality rate (3%-15%), antepartum and intrapartum fetal distress, increased neonatal morbidity, meconium aspiration, peripartum asphyxia, neonatal hypoglycemia, hypothermia, hyperviscosity, and polycythemia. These complications may result in developmental sequelae.

Meconium passed *in utero* may be aspirated either *in utero* or with the initial respiratory efforts of the infant, and it is uncertain which occurs in infants with meconium aspiration syndrome. The current International Consensus of the Neonatal Resuscitation Chapter Collaborators is that if the infant is not vigorous (does not have strong respiratory efforts, good muscle tone, and a heart rate >100 beats/min), the infant should first be resuscitated, and then the decision of suctioning of the mouth and nose to clear secretions is made.[25]

Obstetric management of dysmaturity and its related complications is primarily preventive. It requires close

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• **Fig. 22.1** Infant of 42 weeks' gestation. Note the prominent nails; absence of the vernix caseosa; desquamation of the skin; and discoloration of the umbilical cord, nails, and skin.

follow-up of patients approaching post-term and the consideration of avoiding a post-term situation by inducing labor during the 40th week or during late-term gestation.

During labor, oligohydramnios and meconium-stained amniotic fluid are associated with increased incidence of variable fetal heart rate decelerations. This particular type of tracing is more likely when the cord is compressed between the fetal body and the uterine wall. Some clinicians perform amnioinfusion (i.e., intra-amniotic instillation of saline) to increase the amniotic fluid volume and to dilute the meconium.

Assessment of Fetal Well-Being

All methods of assessing fetal well-being are associated with good negative predictive value and relatively poor positive predictive value; most of the tests adequately exclude signs of fetal distress. The reverse is not true because the tests are not sensitive enough to detect all truly distressed fetuses. As a result, many fetuses with suspected fetal distress are not distressed at all (see Chapter 12). Methods to assess fetal well-being include fetal heart rate monitoring without contractions (nonstress test); fetal heart rate reaction to contractions (oxytocin challenge test or contraction stress test); ultrasound assessment of fetal movements, tone, breathing movements, and amniotic fluid volume (together called the biophysical profile); and the more sophisticated Doppler velocimetry of various maternal or fetal vessels (Table 22.1).

In the past, visualization of the color of membranes via a transcervical amnioscope was used to exclude the possibility of meconium in the amniotic fluid. This procedure is no longer performed because meconium staining is no longer considered to be a reliable sign of acute fetal distress. Even the current method of assessing the nonreassuring fetal state—the amount of amniotic fluid as indicated by the amniotic fluid index (AFI)—yields equivocal results. It was found that neither the AFI nor the reduction in AFI was related to meconium staining and fetal distress.[28] In contrast, Morris and coworkers found in a large prospective study that an AFI of less than 5 cm was significantly associated with birth asphyxia, meconium aspiration, cesarean section for fetal distress in labor, cord arterial pH less than 7 at delivery, and low Apgar scores.[23] Despite the significant association with adverse outcomes, the sensitivities of AFI were only 28.6%, 12%, and 11.5% for major adverse outcome, fetal distress in labor, and admission to the neonatal unit.[23] Deciding the optimal management on the basis of fetal heart rate monitoring is also difficult because of the high frequency of nonreassuring patterns on electronic monitoring of normal pregnancies with normal fetal outcomes.[20]

All of these factors point to the need for a more holistic approach to the evaluation of the prolonged pregnancy. The first question is whether to avoid the potential complication by inducing delivery before 42 weeks. If the answer is yes, when should it be done? Finally, does such intervention reduce neonatal complications?

Should Labor Be Induced Before 42 Weeks?

The benefit of reducing potential fetal risks with induction of labor must be balanced against the morbidity associated with this procedure. Management of an otherwise uncomplicated pregnancy prolonged beyond the estimated date of confinement, when the woman presents with unfavorable cervical conditions, has been the subject of extensive research. One of the earliest studies compared two strategies for managing post-term pregnancy: immediate induction and expectant management.[24] Patients with uncomplicated pregnancies at 41 weeks' gestation were randomly assigned to either immediate induction of labor (within 24 hours of randomization) or expectant management (nonstress test and AFI assessment twice a week). Adverse perinatal outcome (neonatal seizures, intracranial hemorrhage, need for mechanical ventilation, or nerve injury) was similar in both groups (1.5% in the induction group vs. 1% in the expectant management group). There were no fetal deaths in either group, and there were no differences in mean birth weight or the frequency of macrosomia. The cesarean delivery rate was not significantly different between the groups.[24]

Systematic review with meta-analysis of 16 randomized controlled trials compared induction and expectant management for uncomplicated, singleton, live pregnancies of at least 41 weeks' gestation.[27] Patients who underwent labor induction had lower cesarean delivery rates (odds ratio 0.88; 95% confidence intervals 0.78, 0.99). No significant differences were found in perinatal mortality rates, rates of admission to neonatal intensive care units, meconium aspiration, meconium below the cords, or abnormal Apgar scores.[27] These results lead to the conclusion that labor induction at 41 weeks' gestation for otherwise uncomplicated singleton pregnancies reduces cesarean delivery rates without compromising perinatal outcomes.[26] The ACOG

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TABLE 22.1 Methods of Assessing Fetal Well-Being

Test	Method	Description	Interpretation
Nonstress test (NST)	Cardiotocography	FHR tracing in the absence of uterine contractions showing FHR accelerations (≥15 beats/min above baseline for >15 s)	Reactive (normal) NST: ≥2 FHR accelerations within 20 min, regardless of fetal movement Nonreactive NST: <2 FHR accelerations over a 40-min period
Contraction stress test (CST)	Cardiotocography	Response of FHR to uterine contractions (3 per 10 min), assuming that fetal oxygenation deteriorates transiently during contractions Contractions may be spontaneous or induced by oxytocin (OCT) or nipple stimulation	Negative (normal): no late or severe variable decelerations Positive: late decelerations after ≥50% of contractions Suspect: intermittent late decelerations or severe variable decelerations
Fetal movement	Kick counts	Perception of decreased fetal movement sometimes precedes fetal death	>5 fetal movements per 30 min is considered reassuring
Biophysical profile (BPP)	Cardiotocography and ultrasound	NST Fetal breathing movements Fetal movement Fetal tone Amniotic fluid volume	Normal: Reactive Normal: ≥1 episode of rhythmic fetal breathing of ≥30 s per 30 min ≥3 discrete body or limb movements per 30 min ≥1 episode of extension or flexion of a fetal limb per 30 min Vertical pocket of amniotic fluid >2 cm *Scoring*: 0 = abnormal, absent, or insufficient; 2 = normal *Score results*: ≥8 = normal; 6 = equivocal; ≤4 = abnormal
Umbilical artery Doppler velocimetry (systolic to end-diastolic [S/D] ratio)	Doppler ultrasound	Normally growing fetuses have low S/D ratios. In patients with intrauterine growth restriction, the ratio is high. Absent end-diastolic or reversed flow is an ominous sign	S/D ratio >4 is considered high
Amniotic fluid index (AFI)	Ultrasound	Sum of 4 vertical pockets of amniotic fluid	AFI decreases with gestational age. AFI <8 cm is considered oligohydramnios

FHR, Fetal heart rate; OCT, oxytocin challenge test.

Practice Bulletin suggests that induction of labor between 41 0/7 weeks and 42 0/7 weeks of gestation can be considered (level B conclusion) and induction of labor after 42 0/7 weeks and by 42 6/7 weeks of gestation is recommended (level A conclusion).[2] Implementation of such a policy is expected to influence neonatal morbidity. The new policy influenced the frequency of meconium aspiration syndrome, which decreased nearly fourfold from 1990 to 1992 to 1997 to 1998. The only change in neonatal characteristics was a 33% decrease in births at more than 41 weeks, with a reciprocal 33% increase in births at 38-39 weeks during 1997-1998.[31]

An equally important question is whether to induce post-term pregnancies when the woman has a favorable cervix. One study found that the cesarean section rate was not different between expectant management and immediate induction, and that 95% of the expectant group delivered within 1 week after enrollment. Maternal and fetal complications in both groups were similar, as were the mean birth weight and the frequency of macrosomia. Expectant management and immediate induction are acceptable.[9]

How Should Labor Be Induced?

When labor induction was shown to be an acceptable choice in the management of prolonged pregnancies, the question of how labor should be induced became equally pertinent. Generally, methods of labor induction include mechanical, surgical, pharmacologic, and nonpharmacologic methods (Box 22.2). All mechanical methods share a similar mode of action: local pressure, which stimulates the release of natural prostaglandins. One of the most popular

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• BOX 22.2 Methods of Labor Induction

Mechanical
- Intracervical balloon
- Stripping of the membranes

Surgical
- Artificial rupture of the membranes

Nonpharmacologic
- Nipple stimulation

Pharmacologic
- Oxytocin stimulation
- Prostaglandins (in various forms)
- Misoprostol
- Mifepristone

mechanical methods is to use a saline-filled balloon (Foley catheter or a special balloon), which exerts mechanical pressure directly on the cervix. In some designs it is possible to infuse extra-amniotic saline or prostaglandins. Ripening of the cervix after balloon insertion is not equivalent to the natural ripening, and the procedure often involves augmentation of labor with oxytocin.[18] Another popular mechanical means is stripping of the membranes. Stripping results in increased phospholipase A_2 activity and prostaglandin $F_{2\alpha}$ concentrations, and it causes mechanical dilation of the cervix, which releases prostaglandins. Nulliparas and multiparas who received weekly stripping starting at 38 weeks had significantly earlier deliveries and significantly fewer deliveries at 41 weeks or greater.[5] The combination of membrane stripping and intravaginal prostaglandin E_2 gel has been claimed to reduce post-term pregnancies and antenatal visits.[13] Recently, it was also found that antepartum membrane stripping in GBS carriers appears to be a safe obstetrical procedure that does not adversely affect maternal or neonatal outcomes.[16]

The most popular surgical method is amniotomy (artificial rupture of the membranes). It is postulated that the resultant amniorrhexis (leak of amniotic fluid) is involved in increased levels of prostaglandins. Amniotomy is more frequently successful when performed in women with a favorable cervix, however. Often oxytocin is given for augmentation of labor.

A nonpharmacologic method is nipple stimulation, which increases the level of oxytocin via the nipple–posterior pituitary neurohormonal axis. Evidence is lacking to support this method as a practical mode of labor induction. Nipple stimulation is frequently used, however, when there is a relative contraindication to oxytocin stimulation, such as cases of grand multiparity or trial of labor after a previous uterine surgery.

The simplest pharmacologic method of labor induction is oxytocin infusion. Myometrial receptors to oxytocin are scant during the first half of gestation but increase thereafter to 100-300 times the initial number. Oxytocin increases intracellular calcium levels and stimulates the contractions of myometrial smooth muscle cells. The number of receptors increases with contractions, leading to a positive feedback cycle that increases the efficiency of the uterine muscle. Two regimens of oxytocin stimulation—low dose (physiologic levels) and high dose (pharmacologic levels)—have been proposed. Both regimens are equally potent for labor induction.

Vaginal or cervical prostaglandins (prostaglandin E_2) change the composition of the extracellular cervical matrix and facilitate the process of dilation. There is, however, also some effect on the myometrium, which causes uterine stimulation as well. In a Cochrane review of 52 studies comparing prostaglandins for cervical ripening or labor induction with placebo or no treatment, it was found that vaginal prostaglandins increase the odds for a vaginal birth within 24 hours of application.[17] The oral and vaginal use of a synthetic prostaglandin E_1 analogue (misoprostol) was also reviewed.[1] The authors concluded that oral misoprostol seems to be more effective than placebo and at least as effective as vaginal dinoprostone. Safety data and appropriate dose-ranging studies are still required. It seems that in countries where misoprostol remains unlicensed for the induction of labor, many caregivers prefer the legal protection of using a licensed product. In a very recent multicenter trial, 3062 and 3044 low risk nulliparous women were assigned to either labor induction at 39 weeks or to expectant management, respectively. Adverse neonatal outcomes were similar in both groups but the frequency of abdominal births was lower in the induction group.[14a]

Post-Term Twin Pregnancies

In the usual setting, the major problem associated with twins is preterm birth (see Chapter 21). Although term is defined by the period during pregnancy after which most pregnancies end in spontaneous labor, this period is not defined for twins. Twins are delivered about 3 weeks earlier than singletons, which has raised the question of whether term occurs earlier in twins. If this is the case, many of the complications attributed to post-term singleton pregnancies are expected in twins at 38 weeks' gestation. Several arguments support this view.[7]

First, the distribution of twin births by gestational age is almost identical to that of singletons but shifted toward a lower gestational age. Second, comparison between growth patterns of twins and of singletons suggests that incremental growth reaches the near-term plateau earlier in twin pregnancies, indicating that birth weight does not significantly increase beyond 37-38 weeks' gestation. Third, morbidity increases beyond 37 weeks. The risk of cerebral palsy in singletons and twins decreases steadily until 36-37 weeks, and thereafter the risk of cerebral palsy in singletons continues to decrease, but the risk for twins increases again after 37 weeks' gestation. Fourth, perinatal death rates in twins gradually decline until 37-38 weeks' gestation and then

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increase again, in a manner similar to that observed after 40 weeks' gestation in singletons. The incidence of perinatal death seen at 38 weeks' gestation in twins was similar to that seen at 43 weeks in singletons.

These lines of circumstantial evidence seem to indicate that term occurs earlier in twins. Limiting the estimated date of delivery to 37-38 weeks may be appropriate. If 38 weeks or more for twins represents post-term, however, it does not follow that 36-37 weeks is equivalent to term in singletons. Twin deliveries around 36 weeks are still associated with increased morbidity compared with births at 38 weeks.[29] These lines of thinking were supported by Dodd and coworkers, who found that elective birth at 37 weeks of gestation was associated with a significant reduction in risk of serious adverse outcome for the infant in uncomplicated twin pregnancies.[14]

Summary

Improvement in management and outcomes of post-term pregnancies has been observed over the past two decades, which seems to be a direct result of better understanding of the associated pathology, implementation of new technologies, careful assessments of risk versus benefit of various strategies, and new methods of assessing fetal well-being and avoiding unwarranted complications.

Key Points

- Accurate dating is imperative. First-trimester ultrasound confirmation of the LMP is essential for an accurate diagnosis of post-term pregnancies.
- A plan of management is necessary for cases presenting during the 42nd week of gestation (i.e., after 41 completed weeks). This plan should be discussed with the patient and should include the pros and cons for each management option (e.g., expectant follow-up vs. labor induction).
- If a favorable cervix is found on pelvic examination during the 42nd week, induction seems to be a logical option.
- If the cervix is unfavorable, the option of labor induction should be considered. Because induction of labor may take some time, some clinicians start the induction procedure 1-2 days before 42 weeks.
- If induction is unacceptable to the patient, proactive and frequent fetal assessment should be offered. Fetal size and well-being should be carefully assessed. Nonreassuring fetal conditions must be promptly treated.
- Close intrapartum surveillance is recommended. The potential need for a neonatologist during the immediate postpartum period should be anticipated.

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23

Immune and Nonimmune Hydrops Fetalis

PAMELA M. SIMMONS AND EVERETT F. MAGANN

Hydrops fetalis (HF) is defined as the presence of excessive fetal fluid in two or more of the following spaces: abdominal ascites, pleural effusion, pericardial effusion, skin edema, polyhydramnios, or placentomegaly. The diagnosis is made by ultrasound imaging evaluating body cavities, the placenta, and the amniotic fluid volume. Classically, HF has been classified into two categories based on etiology: Immune HF accounts for an estimated 10%-24%, with nonimmune HF accounting for 76%-90% of cases and becoming increasingly the main cause of HF (Table 23.1).

Immune Hydrops Fetalis

Immune hydrops fetalis (IHF) was initially recognized as the combination of neonatal hydrops, anemia, and jaundice along with erythroblastosis and red blood cell hemolysis by Diamond and coinvestigators in 1932.[16] The pathophysiology of the IHF was explained by the work of Landsteiner and associates, who discovered the rhesus (Rh) antigen in 1940.[31] In 1941, Levine and coworkers observed that if an Rh-negative woman is exposed to red blood cells that are Rh positive, she will form antibodies that may result in transplacental passage of the antibodies to fetal red blood cells and may result in fetal hemolysis. The resultant maternal alloimmunization was initially documented by Chown and coworkers.[10]

Anti-D antibodies were proposed as a method to prevent the nonimmunized Rh-negative mother from becoming sensitized after birth. Freda and coworkers studied the efficacy of specific anti-D IgG in Rh-negative male prison volunteers who were given Rh-D-positive blood and observed that sensitization could be prevented.[21] A subsequent investigation confirmed that if prisoners were given Rh-D-positive blood and received anti-D IgG within 72 hours that alloimmunization did not occur.[20]

Genetics of the Rh System

Blood group antigens were among the first discoveries of genetic polymorphisms in human proteins.[12] Of these, the Rhesus factor (the largest of all of the blood groups) has more than 50 different described antigens, with additional discoveries likely to continue. Most of these are quantitative antigens (affecting the amounts of Rh factors expressed), although some are qualitative in nature. Not all antigens have clinical significance in pregnancy.

Three of the most concerning antigens in pregnancy, the Rh(D) and Rh(CcEe) antigens, are encoded at two human loci, found on chromosome #1 (1p36.1).[29] They can cause antibody formation in pregnancy and lead to significant hemolytic disease of the newborn (HDN) in future pregnancies. Although there are multiple nomenclature systems for maternal rhesus (DCE) status, the Fisher and Race method has clinical advantages, such as ease of use and remembrance, and was also proved genetically correct.[43] In this system, each parent contributes an allele from the Rh(D), Rh(C), and Rh(E) gene loci. In broad terms, these alleles are called D or d, C or c, and E or e. A person can be homozygous or heterozygous for each of these alleles. The genes are so closely linked on chromosome #1 that crossover between the alleles is not thought to occur.

The D antigen is a transmembrane protein with several extracellular loops located on erythrocytes and their immediate progenitors. Most alleles of the Rh(D) gene (≈170 identified) are caused by nonsense or missense mutations, although frameshift and splice-site mutations have also been reported.[57] Alleles that cause strongly reduced or complete absence of the Rh-D antigen are often called DEL or negative alleles, respectively. These include the most common European d (Rh-negative phenotype). The Rh-negative phenotype is most common in individuals of European and North American descent (15%-17%), then followed by African and Indian (3%-8%), with the rarest in Asia (0.1%-0.3%).[23,61] Thirty percent of Rh-negative Asians actually carry a DEL allele, whereas this phenotype is rare in Europeans. Other alleles may result in "partial D" antigens (qualitative). There are also alleles that produce a "weak" Rh(D) antigen. DEL, negative, partial D, and weak D alleles can be clinically significant in pregnancy and increase the risk for HDN.

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Abstract

Hydrops fetalis is the presence of excessive fetal fluid in two or more spaces. The diagnosis is made by ultrasound imaging evaluating the fetal body cavities, the placenta, and the amniotic fluid volume. Hydrops fetalis has been divided into two categories, including immune and nonimmune. Nonimmune hydrops fetalis has dominated as the main cause of hydrops fetalis since the routine implementation of anti-D immune globulin. Nonimmune hydrops fetalis has multiple etiologies, and often the diagnosis is made incidentally after a mother undergoes an ultrasound for other indications. Hydrops fetalis is the result of fetal anemia. Prediction of anemia can be assessed with ultrasound using Doppler flow studies. The objective of Doppler flow studies is to detect physiologic compensatory changes in the fetal circulation that would be associated with mild to moderate anemia. This is done by measuring the peak systolic velocity of the middle cerebral artery. Intervention with fetal blood sampling to confirm anemia and fetal blood transfusion may be done between 18-35 weeks' gestational age. This has been shown to improve overall survival and is associated with a low procedure-related fetal loss rate. Repeat ultrasound evaluation and antenatal testing is important for surveillance and timing of delivery.

Keywords

immune hydrops
nonimmune hydrops
hydrops fetalis
Rh disease
isoimmunization
fetal transfusion
PUBS
fetal anemia

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TABLE 23.1 Definition and Diagnostic Criteria for Immune and Nonimmune Hydrops Fetalis

Diagnostic Criteria	Definition
Presence or absence of red blood cell alloimmunization (immune vs. nonimmune HF)	Rh-D status Antibody screen
Plus Two or More Abnormal Fluid Collections	
Ascites	Echolucent rim encompassing entire fetal abdomen in the transverse view[4]
Pleural effusions	Unilateral or bilateral visualization of lung border[7]
Pericardial effusion	Nonphysiologic fluid ≥2 mm[17]
Skin edema	Subcutaneous edema ≥5 mm[48]
Polyhydramnios	Single deepest fluid pocket ≥8 mm AFI ≥25 cm[33]
Placentomegaly	Placenta ≥6 cm thickness[45]

AFI, Amniotic fluid index; HF, hydrops fetalis.

The D alleles are dominant over the d alleles. It is important to note that d is simply the absence of D antigen; there has been no identification of an actual d antigen. Thus, it is the presence or absence (and the extent) of the D antigen that will determine if an individual is Rh positive or Rh negative. There are significantly fewer alleles identified at the Rh(CcEe) gene. Unlike the Rh(D) alleles, the Cc and Ee alleles are codominant; both are expressed in a heterozygote state. The mutations/changes between the alleles are limited and result in amino acid changes at only five locations.[19] Partial C, c, E, and e antigens can be present, but the clinical significance of these in pregnancy is undetermined.

The Kell blood group gene, located on chromosome #7 (7q33),[29] has many polymorphisms, and its alleles encode for approximately 20-25 antigens. Behind the Rh and ABO blood group antigens, Kell antigens carry the most risk for HDN in human pregnancy. The two most common alleles are K and k. The Kell protein transverses the red blood cell (RBC) membrane only once, unlike D and CcEe. Kell antibodies work differently in the lysing of fetal RBCs than Rh and CcEe antibodies; Kell antibodies actually destroy early precursors of erythrocytes in the fetal liver and effect early proliferation of RBCs, instead of only attacking mature RBCs in fetal circulation.[13]

Because each of these antigens can lead to hemolytic disease of the newborn, knowing ethnicity may be helpful in predicting risks for fetal status in a broad sense or if the father of a fetus is unavailable. Of course, when possible, it is advisable to obtain paternal DCE antigen and/or Kell antigen genotyping in at-risk pregnancies. Certainly other antigens have been linked to HDN, but genotyping is not available for all of these blood groups. These results are of great importance in delineating the best courses of action during gestation for monitoring an at-risk fetus.

Typical methods of monitoring at-risk fetuses have included monitoring of maternal antibody titers; targeted ultrasounds to obtain serial middle cerebral artery peak systolic velocity (MCA-PSV) values and exclude the presence of hydrops, amniocentesis, or chorionic villus sampling (CVS) for fetal antigen genotyping; and/or amniocentesis to determine ΔOD450, whereas the latter is rarely used clinically anymore. Traditionally, fetal genotyping has been performed using polymerase chain reaction (PCR) on amniocytes or chorionic villi. New technology now allows for noninvasive determination of fetal Rh-D antigen status through the use of cell-free fetal DNA collection from a maternal blood sample. Although this technology is relatively new, this method of testing has proved to be very accurate (94%-97%), with high sensitivity and specificity.[5,24] Because fetal DNA is directly tested from maternal serum, it reduces the need for invasive testing, Rh-D prophylaxis, and paternal antigen genotyping in most cases.

Pathophysiology of Rh-D Isoimmunization

Alloimmunization, which was formerly known as isoimmunization, occurs when a mother develops antibodies to a paternally derived red blood cell antigen that is inherited by the fetus or from a transfusion of unmatched or mismatched blood. If this occurs, hemolytic disease of the fetus or neonate in subsequent pregnancies can occur.

In Rh alloimmunization, an Rh-D-negative mother is exposed to Rh-D-positive blood. A quantifiable amount of hemorrhage occurs between the fetus and the mother in up to 75% of all pregnancies. This may range from less than 0.1 mL of blood in 60% of pregnancies to an excess of 5 mL in less than 1% of pregnancies. In an analysis of maternal fetal hemorrhage, 0.01 mL of fetal blood was detected in the maternal circulation in 3%, 12%, and 46% in the first, second, and third trimesters of pregnancy, respectively.[6] The risk of sensitization is related to the amount of blood that passes between the fetus and mother. For 0.1 mL of blood, the risk of sensitization is 3% and for 0.4 mL, the risk rises to 22%. Rh sensitization has been reported as early as 38 days, and fetal maternal hemorrhage has been demonstrated as early as 5-6 weeks (mean maternal fetal transfusion at 8 weeks is 0.3 mL). The minimal amount of fetal blood needed to cause alloimmunization is estimated to be 0.25 mL. The greatest risk occurs at the time of delivery when that risk is approximately 17%. ABO incompatibility of the mother and fetus in pregnancy with Rh sensitization (mother O; father A, B, or AB) will reduce the sensitization risk to 2%. Additionally, 30% of Rh-negative individuals are nonresponders and will not become sensitized. Box 23.1 summarizes the numerous risk factors for maternal fetal hemorrhage during pregnancy.

Immune hydrops fetalis (IHF) is the end result of progressive red blood cell destruction, in which even with the

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recruitment of extramedullary tissue (liver and spleen), the severity of the hemolysis results in severe fetal anemia, HF, and often fetal death. Although the fetus is able to compensate for progressive anemia, one study determined that once the hemoglobin deficit has exceeded 7 g/dL, this compensatory ability of the fetus may become exhausted and IHF will ensue.[39] The concept of a fixed hemoglobin level for IHF likely needs to be adjusted for gestational age, because with advancing gestational age the mean hemoglobin value increases, going from 10.6 g/dL at 18 weeks to 13.8 g/dL at 40 weeks. It has been suggested that a hemoglobin value of less than 0.5 times the median for gestational age might be a more appropriate predictor for fetuses at significant risk for HF.

• BOX 23.1 Risk Factors for Maternal Fetal Hemorrhage During Pregnancy

- Spontaneous abortion
- Elective abortion
- Amniocentesis
- Chorionic villus sampling
- Antepartum hemorrhage
- Fetal blood sampling
- Ectopic pregnancy
- Blunt abdominal trauma
- Fetal death in utero
- Abruption
- Placenta previa with bleeding
- Cesarean delivery
- Manual removal of the placenta

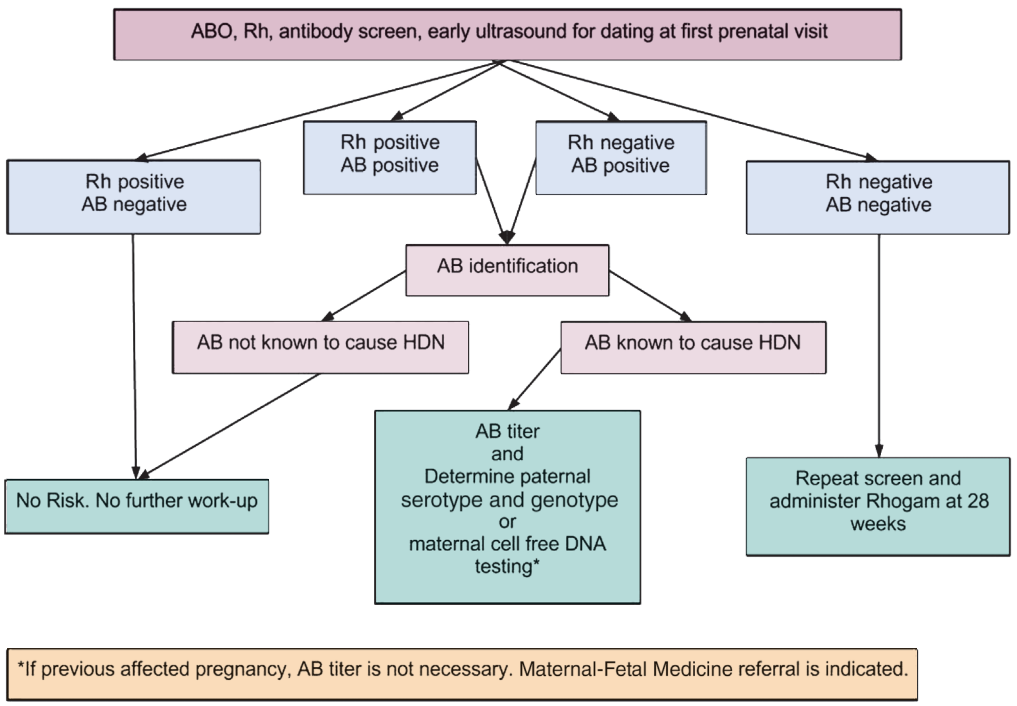
Progressive ultrasound findings of IHF include the early findings of polyhydramnios and placentomegaly, followed by hepatomegaly and pericardial effusions and late findings of ascites, scalp edema, pleural effusions, and finally, oligohydramnios.[60] Severe fetal anemia (fetal hemoglobin of ≤5 g/dL) associated with the development of HF[8] has implications on fetal survival. In a study with intravascular transfusions, the survival rate for nonhydropic fetuses was 94% compared with 74% in fetuses with hydrops.[49]

The exact mechanism that causes IHF is unknown. Proposed mechanisms include high output cardiac failure, liver dysfunction, and fetal hypoxemia from fetal anemia. It is likely that a combination of all three is responsible for fetal hydrops.

Management

Prevention

Prevention of Rh alloimmunization begins at the first prenatal visit. A careful history should be taken of any problems associated with previous pregnancies or deliveries, prior blood transfusions, or blood disorders. Initial laboratory work should include ABO typing, Rh-D status, and an antibody screen. If the mother is Rh-D negative, this should be carefully documented in the chart. If the antibody screen is positive, the antibody test and a titer of the antibody should be repeated and a determination should be made for antibodies, Rh-D, and others that are not Rh-D, to ascertain if the antibody is known to cause hemolytic disease of the newborn (Fig. 23.1). If the antibody is positive Rh-D,



• Fig. 23.1 Initial management of blood type and screen. AB, antibody; HDN, hemolytic disease of the newborn.

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then the patient should be questioned about a prior injection of anti-D immune globulin, as this could be the reason for the positive antibody titer.

Rh-Immunoglobulin Prophylaxis

Anti-D immune globulin is a passive immunoglobulin that when given to Rh-D-negative women will prevent the vast majority of cases of alloimmunization. Unfortunately, there are no other immune globulins specific for the other red blood cell antigens. After the initial screen at the first prenatal visit, a repeat Rh-D antibody screen is done at 24-28 weeks. If the antibody screen is negative, 300 μg of anti-D immune globulin is administered at that gestational age and then again within 72 hours of delivery if the neonate is Rh-D positive. Other accepted regimens are 100 μg at 28 and 34 weeks and following delivery if the neonate is Rh-D positive. Suggested doses of anti-D immune globulin for a first-trimester induced or spontaneous abortion, amniocentesis, or chorionic villus sampling, and first-trimester ectopic pregnancy, are 50–120 μg of anti-D immune globulin up to 12 weeks' gestation. After 12 weeks' gestation it is recommended to use 300 μg of anti-D immune globulin.[22,42,46] Three hundred micrograms of anti-D immune globulin will suppress the immune response of 30 mL of fetal blood or 15 mL of packed D-positive red blood cells. Women should be screened at delivery and when maternal fetal hemorrhage is suspected, to prevent an inadequate dose of anti-D immune globulin being administered and subsequent alloimmunization (Table 23.2).

Preimplantation Diagnosis

Newer techniques using molecular genetics have permitted the preimplantation diagnosis of the Rh-D status.[1] This technology has the potential to prevent Rh isoimmunization through selective transfer of Rh-D-negative embryos. In the case of severe maternal alloimmunization, the approach can prevent fetal hemolytic disease with its associated morbidity and mortality. In the first use of this technology in 2005, an unaffected Rh-negative neonate was born to an Rh-D alloimmunized mother.[50] Following intracytoplasmic sperm injection, 12 embryos were obtained, and on day 3, biopsies were performed followed by PCR. Two Rh-D-negative embryos that were subsequently transferred resulted in the delivery of a healthy Rh-D-negative infant at 39 weeks of gestation. Notwithstanding the emotional, psychological, and financial burdens of in vitro fertilization, this represents a potentially lifesaving approach for selected couples with maternal Rh alloimmunization.

Rh Alloimmunization

Detection of Rh alloimmunization begins with the initial laboratory work. Pregnant women who are Rh negative are screened for antibodies by the indirect Coombs test. This allows detection of Rh-D antibodies as well as antibodies to other atypical antigens known to cause alloimmunization. If Rh-negative women are alloimmunized to Rh-D, they need to have their anti-D titer determined, because that

TABLE 23.2 Indications for Rh Immunoglobulin Prophylaxis

Indication	Justification	Dosage (μg)	
		First Trimester	Second or Third Trimester
Spontaneous abortion/IUFD	2%-3% sensitization	50	300
Therapeutic abortion	4%-5% sensitization	50	300
Ectopic pregnancy	2%-5% sensitization	50	300
Chorionic villus sampling	50% FMH	50	300
Amniocentesis	10% FMH	300	300
Percutaneous umbilical blood sampling	40% FMH	300	300
Abruptio placenta/placenta previa	Variable	300	300
Antepartum vaginal bleeding	Variable	300	300
External cephalic version	Variable	N/A	300
Trauma	Variable	300	300
Pregnancy (28 weeks' gestation and ≤72 h postpartum)	7%-8% sensitization* 15% sensitization†	N/A	300
Delivery	50% FMH	N/A	300

FMH, Fetomaternal hemorrhage; IUFD, intrauterine fetal demise.
*First pregnancy.
†Second pregnancy.

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titer is known to roughly correlate with the severity of the disease and the need for Doppler flow studies. Although each lab sets its own standards based on experience, anti-D titers of 1:16 or greater require further assessment. If the titer is less than 1:16, the patient can be followed with monthly titers.

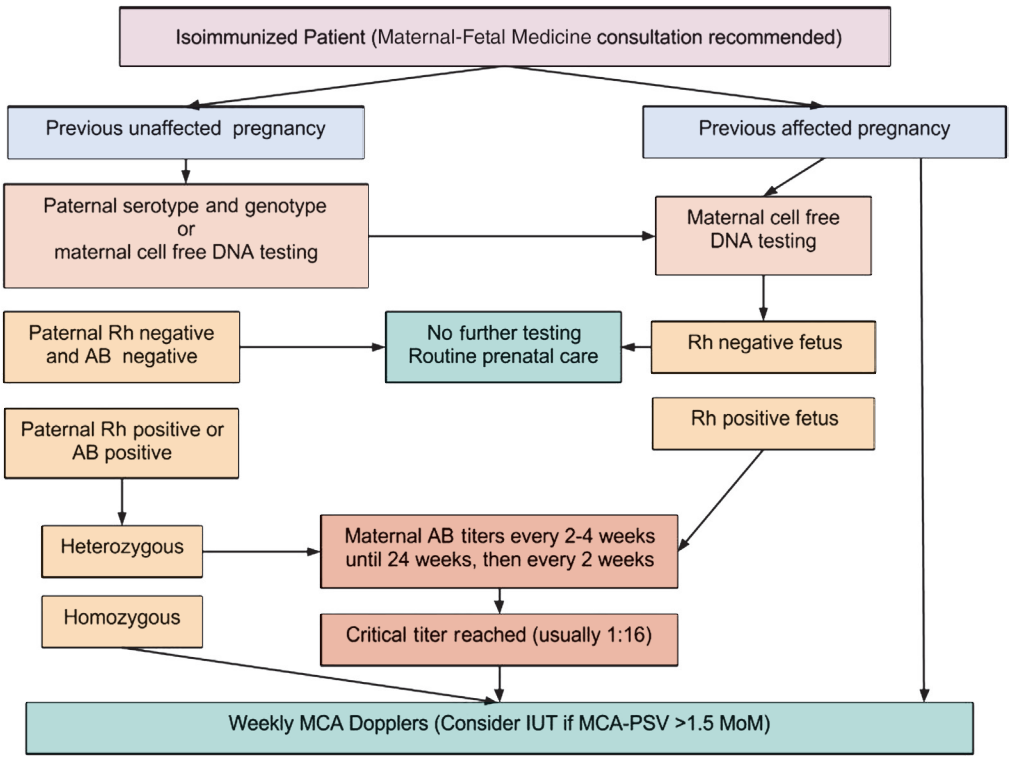
In sensitized Rh-D–negative women where the father is Rh-D positive, paternal genotyping may help clarify the fetal risk. PCR determination of paternal Rh-D status can facilitate counseling and dictate the need for intervention, because paternal heterozygosity is associated with a 50% risk of fetal Rh-D negativity, whereas homozygosity always produces an Rh-D-positive fetus, assuming correct paternity. Fetal Rh-D typing can also be done with amniocytes in the second trimester or with villi in the first trimester (Fig. 23.2). More recently, fetal Rh-D genotyping has been achieved through isolation of cell-free fetal DNA from the maternal circulation and provides a noninvasive way to directly assess fetal blood type and antibody status.

Prediction of Anemia

Cordocentesis and sampling of fetal blood is the most accurate method to determine if fetal anemia is present. However, this technique is invasive and carries a fetal loss risk of up to 3%. This has led to the use of other techniques to evaluate when the risk for fetal anemia is present so that fetal blood sampling can be undertaken. Fetal anemia had been determined previously by amniocentesis and determination of risk for fetal anemia using optical density of amniotic fluid (ΔOD450). This method used an assessment of the bilirubin content of amniotic fluid to determine the estimated level of fetal anemia. Often, a series of amniocenteses was necessary to monitor the pregnancy and determine when a more invasive cordocentesis was undertaken. With improvements in ultrasound technology, this method has been replaced by serial assessments of the peak systolic velocity (PSV) of the middle cerebral artery (MCA) in the detection of fetal anemia.[37]

The objective of Doppler flow studies is to detect physiologic compensatory changes in the fetal circulation that would be associated with mild to moderate anemia. As anemia progresses, both right and left ventricular outputs increase up to 45% with the heart rate remaining unchanged. This increases stroke volume. Progressive anemia leads to decreased blood viscosity. If the given fetal blood vessel cross-sectional area also remains unchanged, and applying Poiseuille's law (blood velocity is directly proportional to flow), increased stroke volume results in increased flow (flow being the product of velocity and the cross-sectional area).

A number of fetal vessels were evaluated by Doppler flow studies to determine which vessel would be the most predictive of fetal anemia. The MCA was selected because it is well known that the cerebral arteries respond rapidly to hypoxemia by increasing blood flow velocity to maintain cerebral perfusion. Additionally, the MCA is easy to identify with low interobserver and intraobserver variability. Mari and the Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses measured the hemoglobin concentrations in blood obtained by cordocentesis and correlated those concentrations with MCA-PSV in 111



• **Fig. 23.2** Management of the sensitized gestation. AB, Antibody; IUT, intrauterine transfusion; MCA, middle cerebral artery; PSV, peak systolic velocity.

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fetuses at risk for anemia secondary to red blood cell alloimmunization.[34] The group used a hemoglobin concentration of 5 g/dL as a threshold to calculate degrees of anemia, because fetal hydrops is rare with a hemoglobin concentration greater than 5 g/dL.[38] Strict cutoffs using receiver-operating–characteristic curves were determined to detect 100% of those fetuses with moderate to severe anemia. They found the optimal threshold was 1.29 times the median for mild anemia, 1.5 times the median for moderate anemia, and 1.55 times the median for severe anemia, with a false-positive rate of 12%. These thresholds were chosen so as to not miss any fetus with moderate or severe anemia that might result in either fetal hydrops or death (Table 23.3). Measurements of the MCA-PSV can be started as early as 16-18 weeks and should be repeated at 1- to 2-week intervals.

TABLE 23.3 Reference Values for Peak Systolic Velocity of Middle Cerebral Artery

Peak Systolic Velocity of Middle Cerebral Artery					
Gestational Age (weeks)	Multiples of the Median				
	1	1.3	1.5	1.7	2
15	20	26	30	34	40
16	21	27	32	36	42
17	22	29	33	37	44
18	23	30	35	39	46
19	24	31	36	41	48
20	25	33	38	43	50
21	26	34	39	44	52
22	28	36	42	48	56
23	29	38	44	49	58
24	30	39	45	51	60
25	32	42	48	54	64
26	33	43	50	56	66
27	35	46	53	60	70
28	37	48	56	63	74
29	38	49	57	65	76
30	40	52	60	68	80
31	42	55	63	71	84
32	44	57	66	75	88
33	46	60	69	78	92
34	48	62	72	82	96
35	50	65	75	85	100
36	53	69	80	90	106
37	55	72	83	94	110
38	58	75	87	99	116
39	61	79	92	104	122
40	63	82	95	107	126

Suppressive Therapy

Intravenous Immunoglobulin

Although most fetuses with severe Rh alloimmunization can be treated with in utero intravascular transfusions, some cannot because of gestational age (<18 weeks); they may be difficult to transfuse because of small vessels or other technical issues that may make the intravascular transfusion impractical or impossible. Maternal administration of intravenous immunoglobulin (IVIG) has been proposed as an alternative therapy until an intravascular transfusion is possible. The proposed mechanism of action is feedback inhibition of maternal antibody synthesis, blockade of reticuloendothelial Fc receptors, or blockade of placental antibody transport. There is some literature that suggests in pregnancies with severe Rh alloimmunization before 20 weeks that treatment with high-dose IVIG followed by an intrauterine transfusion after 20 weeks compared with pregnancies treated only with an intrauterine transfusion after 20 weeks had improved fetal survival.[56] In another series of four pregnancies with severe Rh alloimmunization treated with high-dose IVIG, there appeared to be no effect on the total number of transfusions or the amount of blood transfused or progression to fetal hydrops.[9] In one study of Rh-sensitized pregnancies with mild anemia treated with high-dose IVIG, benefit was observed only if treatment was started before the development of severe anemia.[25] In another, a combination of plasmapheresis and IVIG had been reported to be successful in the treatment of severe maternal red blood cell alloimmunization.[47]

Despite the high cost of treatment with IVIG, there may be a role in pregnancies less than 18-20 weeks with severe fetal anemia caused by Rh alloimmunization, either with IVIG alone or in combination with other therapies, to prolong the pregnancy so that an intrauterine transfusion can be done at a later gestational age. Unfortunately, the cost of treatment with IVIG is a limiting factor in the treatment of Rh alloimmunization.

Fetal Transfusion

Intravascular Transfusion

The first direct intravascular fetal blood transfusion for Rh alloimmunization was done by fetoscopy and described in 1984.[44] Since that time, fetoscopy is no longer used, and needle placement is by ultrasound. When screening Rh alloimmunized pregnancies, once the MCA-PSV exceeds 1.5 multiples of the median (MOM), then sampling of the fetal blood is necessary to determine if fetal anemia is present. Fetal transfusions are typically done between 18 and 35 weeks. If fetal anemia is confirmed, then an intrauterine fetal transfusion will be necessary. The blood transfused is type O, Rh(D) negative, cytomegalovirus negative, irradiated packed red blood cells, cross-matched against maternal

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blood. The usual hematocrit of the blood is around 75%, which allows for minimal blood volume to be transfused.

The procedure is done in an operating room or in close proximity to an operating room, in case there is a complication that would require an urgent delivery. For this reason, an anesthetist should see the patient before the procedure and be immediately available if there is an urgent need for an abdominal delivery. The administration of corticosteroids to accelerate fetal lung maturity should also be considered in those pregnancies starting at viability. Depending on the institution, this can be between 22 5/7 weeks and up to 34 weeks of gestation. The administration of antibiotics and/or tocolytics before the procedure is not supported by any randomized trials. The tubing and syringes used in the procedure are heparinized. The maternal abdomen is prepped, and sterile towels and sheets are used to create a sterile field. A 20- to 22-gauge echogenic tip needle is used to puncture the umbilical vein with the most desirable site being near the cord insertion site into the placenta. A free loop of cord, the intrahepatic portion of the hepatic vein, or the umbilical artery may be considered as alternatives but are less desirable sites because of fetal bradycardia and procedure-related complications that may accompany cord puncture at those sites.[44,52,55,59] Some surgeons prefer a fetal paralytic agent (vecuronium 0.1 mg/kg), which may then be injected intramuscularly or intravascularly at time of cordocentesis to prevent fetal movements. A system should be in place to report the fetal hematocrit as soon as possible. The blood sample can be confirmed using the mean corpuscular volume (MCV), which is greater than 110 μm^3 in fetal blood. The volume of blood to be transfused depends on the estimated weight of the fetus, the fetal hematocrit, and the hematocrit of the red blood cells to be transfused and the gestational age. This can be calculated using a variety of techniques, with a common calculator available online.[18] Following the blood transfusion, hematocrit assessment should be obtained. A post-transfusion hematocrit should be approximately 40% unless the gestational age is less than 24 weeks. If the gestational age is less than 24 weeks, the post-transfusion hematocrit should be 25% with repeat procedure in 48 hours.

The overall procedure-related fetal loss rate is approximately 1%, and the emergency delivery rate within 24 hours for procedure-related complications and subsequent perinatal demise is 1.8%.[30] Following the procedure, the fetus is continuously monitored for up to 4-6 hours, but that time may be extended if there are complications during the procedure or if uterine contractions develop following the procedure. Typically, the fetal hematocrit will fall approximately 1 percentage point per day, and a follow-up transfusion is likely to be necessary in approximately 2 weeks. Ultrasound evaluation of the MCA-PSV after the procedure may need to use a higher MoM cutoff of 1.69.[15]

Intraperitoneal Transfusion

Intraperitoneal transfusions are rarely performed in modern practice except when the caliber of the umbilical vessels does not permit placement of the needle for the transfusion (generally <18 weeks) or when an intravascular transfusion is technically impossible because of fetal position or the location of the umbilical cord. The infused red blood cells are absorbed into the circulation via the subdiaphragmatic lymphatic lacunae and the right lymphatic duct, making fetal respiration important for absorption to occur. Early work in sheep suggests that the time to complete absorption is about 150 hours and that the absorption rate is directly related to the transfusion volume. The higher the volume, the faster the absorption.[28] Generally, fetal intraperitoneal transfusions are less effective when fetal hydrops is present. In an assessment of intraperitoneal transfusions covering 154 fetuses treated by 270 intraperitoneal transfusions, the survival rate in the nonhydropic group increased from 35%-83% over 22 years of the study compared with the hydropic group, in whom the survival increased from 24%-42% over those same 22 years.[3]

In the literature, the size of the needle used for the transfusion has varied from a 16- to 20-gauge Tuohy needle, with the smaller needle being more commonly used when the rarely needed intraperitoneal transfusion is undertaken. The fetal abdomen is usually entered between the umbilicus and the fetal bladder to avoid the liver. The catheter tip should be free in the abdominal cavity, which can be confirmed with injected saline. Calculation of the amount of blood to transfuse is important, because if the intraperitoneal pressure exceeds the pressure of blood in the umbilical vein, there will be no blood flow and fetal demise will result.[11] This should not occur using the formula of Bowman for infused blood volume [volume = (weeks' gestation − 20) × 10 mL]. Generally, not enough blood can be given with the first transfusion, and a second transfusion may be necessary 9-10 days later. Before fetal intravascular transfusions, the transfusions were repeated every 4 weeks with delivery at 34-35 weeks. In modern practice, intraperitoneal transfusion often can be abandoned as soon as vascular access can be achieved.

Timing of Delivery

The overall timing of the delivery is somewhat controversial but is generally calculated based on severity of alloimmunization and degree of HF. If antenatal testing suggests that the fetal hemolysis is determined to be mild, then a reasonable approach would be to induce labor between 37 and 38 weeks or sooner if the fetal lung studies document lung maturity at an earlier gestational age. If the studies suggest severe alloimmunization, with fetal/neonatal survival greater than 95% in most tertiary neonatal intensive care units, the last transfusion should be given around 30-32 weeks, with delivery between 32 and 34 weeks with corticosteroids given to accelerate fetal lung maturity and to decrease the morbidity linked with preterm deliveries. Other experts have advocated that intrauterine transfusions continue up through the 35th week when there is a reasonable chance of fetal lung maturity with delivery at 37 weeks. The fetus should have continuous electronic fetal monitoring during

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labor, and a cord blood sample should be sent immediately to the laboratory following delivery for neonatal blood group, Rh typing, direct Coombs, bilirubin, hemoglobin, and hematocrit. Delivery should occur at a tertiary care facility that has adequate neonatal intensive care, blood banking, and laboratory services.

Outcome

Short Term

With improvements in ultrasound technology, improved echogenic tip needles, and level of care offered in tertiary neonatal intensive care units, perinatal survival following an intrauterine fetal transfusion has increased dramatically. These improvements are well demonstrated in two large retrospective studies from the Netherlands and Scotland.[36,54]

A retrospective review of survival in fetuses treated for anemia caused by Rh alloimmunization with intrauterine transfusions between 1988 and 1999 in the Netherlands was performed in 208 pregnant women treated with 593 blood transfusions.[54] The overall survival rate was 86%. Survival of the hydropic fetuses (78%) was significantly less than the survival of those pregnancies without hydrops (92%). Low survival rates were also observed if the first transfusion took place at less than 20 weeks and the fetus was hydropic (55%). Survival was much greater in Rh alloimmunized pregnancies (89%) compared with Kell alloimmunized pregnancies (58%). Overall fetal loss rate linked to the procedure was 4.8%.

In a retrospective review of the short-term outcomes of 116 pregnancies that underwent 457 transfusions in Scotland from 1993-2004, the rate of intrauterine death as a complication of the procedure was 2.3% for 1993-1998 and 0.8% for 1999-2004.[36] Eight infants (6.9%) were delivered by emergency cesarean as a result of a complication during the intrauterine transfusion. The survival rate of neonates from birth to discharge was 97.4%. The majority of the neonates were delivered by cesarean or vaginally at 35 weeks. Roughly 33% of neonates required some type of respiratory support following delivery. Sixteen of the neonates had an exchange transfusion following delivery, with the number of exchanges ranging from 1-4. At least one top-up transfusion was required in 54% of the neonates, with one infant requiring nine transfusions.

The short-term neonatal outcomes of intrauterine transfusion are generally very good. In the Netherlands study, pregnancies complicated by hydrops, pregnancies in which the first transfusion was undertaken at less than 20 weeks, and alloimmunization secondary to Kell had poorer outcomes. In the cohort from Scotland, there was minimal procedural loss, a low rate of emergency cesarean deliveries because of procedural complications, and no more than the expected rate of respiratory support needed secondary to gestational age of delivery at 35 weeks. All neonates were treated with phototherapy, and 16 needed exchange transfusions, primarily those who underwent an emergency delivery because of procedural problems with the intrauterine transfusions.

Long Term

More information is now becoming available on the long-term outcome of fetuses who receive intrauterine transfusions. Previously, this information had been very limited because of the small size of the studies, length of follow-up, lack of controls, and unclear criteria used to evaluate development of the child. The publication of the LOTUS study provided much-needed additional information on long-term effects of fetuses undergoing this procedure.[32]

The LOTUS study evaluated the neurodevelopment of children with hemolytic disease treated with an intrauterine transfusion. Two hundred and ninety-one children were evaluated at a median age of 8.2 years. Cerebral palsy was detected in 2.1%, severe developmental delay in 3.1%, and bilateral deafness in 1%. The overall incidence of neurodevelopmental impairment was 4.8% (14/291). The only risk factor that could be linked with neurodevelopmental delay was severe fetal HF.

The very high rate of intact survival in these at-risk pregnancies complicated by severe anemia is reassuring and confirms the relative safety of the treatment with intrauterine transfusions even in the fetus with severe hemolytic disease, including HF.

Atypical Antigens

As the incidence of Rh disease has decreased with the administration of anti-D immunoglobulin, the incidence of alloimmunization caused by other red blood cell antigens has increased. This rise is because there are no screening programs for women who are negative for these other atypical antigens that have the potential for causing hemolytic disease.

The greatest risk factor for isoimmunization of the other red blood cell antigens is a prior blood transfusion but it can also occur after a maternal fetal hemorrhage during pregnancy. Fortunately, most of the antibodies produced against these antigens are of the IgM type, do not cross the placenta, and therefore do not result in hemolytic disease of the newborn. Because of the rarity of many of these atypical antigens, there is a paucity of evidence supporting specific management algorithms. Critical titers at which time additional surveillance is undertaken are also not well established. Box 23.2 outlines a partial list of antibodies associated with HDN.

The most troublesome of the atypical antigens is the Kell antigen, which is highly immunogenic. After the reactions that occur with ABO and Rh blood groups, the Kell antigen is the most immunogenic. There are 25 Kell antigens encoded by a single gene on the 7th chromosome, with the "K" antigen being the most clinically significant. The pathophysiology of the hemolytic disease of the newborn is different from that seen with ABO and Rh sensitization.

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• BOX 23.2 Partial List of Antibodies Associated With Hemolytic Disease of the Fetus and the Newborn

Requiring Fetal Evaluation

- Rhesus: E, C, c, D (C, E, e usually associated with mild disease but may be additive to D)
- Kell: K (especially K1 and K2) can cause moderate to severe disease
- Duffy: Fy^a
- Kidd: Jk^a
- MNSs: M, S, s, U, Mi^a
- MSS: Mt^a
- Diego: Di^a, Di^b, ELO, Wr^a, Wr^b mild to severe (infrequently) disease
- P: PP_{1pk} mild to severe disease
- Public antigens: Yt^a moderate to severe
- En^a moderate
- Co^a severe
- Private antigens: Biles moderate
- Good severe
- Heibel moderate
- Radin moderate
- $Wright^a$ severe
- Zd moderate

Others (Infrequently Associated With Severe Disease)

- Coa, Co3, Ena, Far, MUT, Mur, Mv, sD, Lu^a, Lu^b, Vw, Mur, Hil, Hut, JFV, JONES, Kg, MAM, REIT, Rd, Ce, Cw, Cx, ce, Dw, Ew, Evans, G, Goa7, Hr, Hro, JAL, HOFM, LOCR, Riv, Rh29, Rh32, Rh42, Rh46, Js^a, Js^b, Kp^a, Kp^b, K11, K22, Ku, Ul^a, STEM, Tar, HJK

The Kell IgG antibodies cause destruction of erythroid precursors by macrophages in the fetal liver and can result in severe fetal anemia.[14]

Fortunately, 91% of the population is Kell negative and only 5% of the population will form Kell antibodies after a transfusion, making the disorder relatively rare. Assessment of the father's genotype, if paternity is certain, is initially undertaken because if he is Kell negative, the pregnancy is not affected and no further workup is needed. In Kell alloimmunization, early suppression of fetal RBC synthesis results in less bilirubin being released during hemolysis. Because of this, serial amniocentesis for ΔOD450 titers is not reliable or could even be misleading and should not be used. Results have suggested that MCA-PSV with a cutoff greater than 1.5 is highly predictive of severe fetal anemia as it is in the prediction of fetal anemia in Rh-D-negative mothers and should be routinely used in management.[53]

Other antibodies that have been infrequently linked with severe disease include Colton, Diego, Duffy, and MNS. Those associated with mild disease include Dombrock, Duffy, Kidd, and Gerbich. Surveillance is done with MCA-PSV using the threshold of greater than 1.5 for the diagnosis of fetal anemia.

Nonimmune Hydrops Fetalis

Although the incidence of HF has remained stable in the range of 1/1500 to 1/3800 births since the development of Rh immunoglobulin, up to 90% of cases of HF are now the result of nonimmune etiologies. Nonimmune hydrops fetalis (NIHF) defines hydrops in those fetuses whose mothers are Rh positive or that results from a nonimmune cause.[35,41,51]

Although improvements in ultrasound technology have allowed earlier diagnosis and improved understanding of underlying conditions, unfortunately the prognosis for NIHF neonates remains poor, with perinatal mortality (PNM) rates ranging from 50%-90%.[35] Maternal complications associated with NIHF include pre-eclampsia, mirror syndrome, and increased cesarean rates when NIHF is diagnosed in the antepartum period.[3,27]

Diagnosis

After ruling out fetal hydrops owing to red blood cell alloimmunization, NIHF is defined by the same ultrasonographic presence of excessive fetal fluid in two or more of the following spaces: abdominal ascites, pleural effusion, pericardial effusion, skin edema, polyhydramnios, or placentomegaly (see Table 23.1). Unlike alloimmunization, there is not a specific screening test for the multiple etiologies of NIHF, and often this diagnosis is made incidentally after a mother undergoes an ultrasound for another indication (e.g., polyhydramnios, standard fetal evaluations).

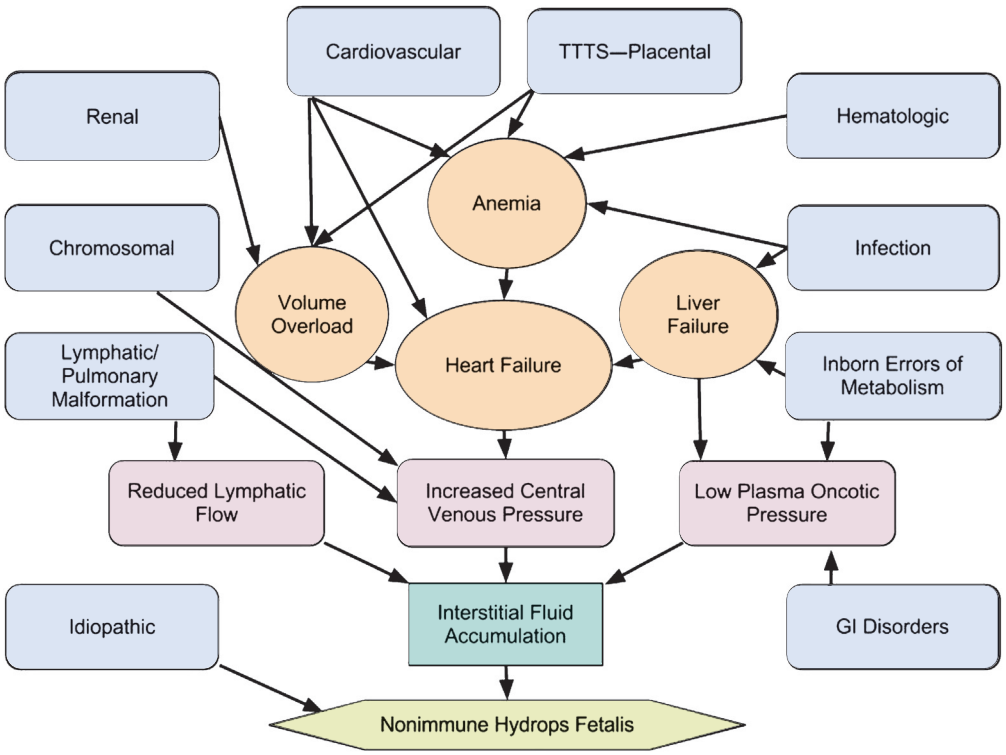
Pathophysiology

Hydrops occurs when interstitial fluid production and lymphatic return becomes imbalanced, leading to fluid accumulation in interstitial spaces within the fetus. This can result from a myriad of conditions, including those that cause reduced lymphatic flow (e.g., pulmonary masses or lymphatic malformations), lower plasma oncotic pressure (e.g., gastrointestinal anomalies, inborn errors of metabolism, liver failure), or increased central venous pressure (e.g., chromosomal abnormalities, heart failure caused by volume overload or anemia, compensatory hypoxia) (Fig. 23.3). Nonimmune hydrops fetalis rarely resolves spontaneously and, in general, carries a worse prognosis the earlier in pregnancy it is diagnosed.[2]

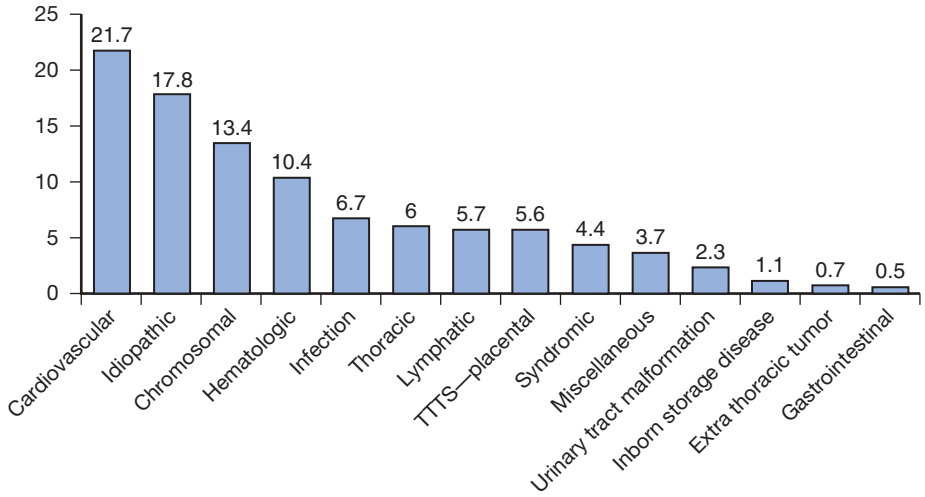
Differential Diagnosis/Etiology

Just as the pathophysiology of NIHF can result from several different pathways, the conditions or anomalies that lead to these pathophysiologic changes are vast. Fig. 23.4 summarizes 14 separate etiologies most commonly associated with NIHF and the respective percentage for which a cause is identified.[2] Within each of these categories, specific diagnoses or anomalies are further summarized in Table 23.4. In sum, greater than 100 conditions, although many are very

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• **Fig. 23.3** Pathophysiologic pathways for the development of nonimmune hydrops fetalis. TTTS, Twin–twin transfusion syndrome.



• **Fig. 23.4** Etiology of nonimmune hydrops fetalis (%). TTTS, Twin-twin transfusion syndrome.

rare, have been associated with the ultimate finding and diagnosis of NIHF.

Antepartum Evaluation

The clinical presentation of fetuses can vary depending on the underlying condition and the gestational age at which it is identified. A common finding in NIHF diagnosed before 20 weeks is a cystic hygroma, often associated with chromosomal anomalies. Common chromosomal abnormalities include Turner syndrome (45 XO) as well as trisomies 21, 18, and 13.[45] In intrathoracic masses, restrictive fetal swallowing often causes polyhydramnios, resulting in uterine size measuring larger than gestational age and prompting ultrasound evaluation.[58] Once identified, antepartum evaluation focusing on identification of the underlying cause includes a detailed history (personal and family) often with the assistance of a genetics counselor, targeted ultrasound, fetal echocardiography, middle cerebral artery Doppler peak systolic velocity (MCA-PSV) analysis, laboratory testing including evaluation of recent viral exposures, and sometimes diagnostic invasive testing. Table 23.5 summarizes the components of a full antenatal evaluation of NIHF.

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TABLE 23.4 Principal Diagnoses Associated With Nonimmune Hydrops Fetalis

Cardiovascular (21%)

Structural

- Hypoplasias (left or right heart)
- AV canal defect
- Single ventricle
- Transposition of great arteries
- Septal defects (VSD/ASD)
- Tetralogy of Fallot
- Ebstein anomaly
- Ductus arteriosus closure
- Truncus arteriosus
- Valvular (stenosis/insufficiency)

Arrythmias

- Atrial (flutter/tachyarrhythmia)
- Wolff-Parkinson-White
- Supraventricular tachycardia
- Long QT interval
- Heart block

Cardiomyopathy

- Tumors
- Neoplasias
- Myopathies
- Cardiosplenic syndromes

Infection (6.7%)

- Cytomegalovirus
- Parvovirus B19
- Syphilis
- Herpes simplex
- Rubella
- Coxsackievirus
- Leptospirosis
- Trypanosoma cruzi

Inborn Storage Disease (1.1%)

- Gaucher disease
- GM1 gangliosidosis
- Sialidosis
- Mucopolysaccharide (MPS) IVA
- Mucolipidosis type I+II
- Galactosialidosis

Idiopathic (17.8%)

Chromosomal (13.4%)

Trisomy

- 21
- 18
- 13

Monosomy

- 45, X
- 45, X (mosaic)

Duplications

- 18 q +
- 11p

Deletions

- 13 q –
- 17 q –

Triploidy

Thoracic/Extrathoracic Mass/Lymphatic (12.4%)

Mass Effect

- Diaphragmatic hernia
- Congenital pulmonary adenomatoid malformation
- Intrathoracic mass
- Pulmonary sequestration
- Chylothorax
- Airway obstruction
- Pulmonary lymphangiectasia
- Bronchogenic cyst

Skeletal Dysplasias

- Thanatophoric dysplasia
- Short rib polydactyly
- Hypophosphatasia
- Osteogenesis imperfecta
- Achondrogenesis
- Camptomelic dysplasia
- Lethal chondroplasia

TTTS-Placental (5.6%)

Twin

- TTTS
- Acardiac twin

Placental

- Umbilical vein thrombosis
- Umbilical cord angiomyxoma
- True cord knot
- Chorionic vein thrombosis
- Rare placenta disorders

Hematologic (10.4%)

- Alpha-thalassemia
- Fetomaternal hemorrhage
- Glucose-6-phosphate deficiency
- Leukemia
- Pyruvate kinase deficiency
- Red blood cell aplasias

Gastrointestinal (0.5%)

- Duodenal atresia
- Duodenal diverticulum
- Jejunoileal atresia
- Volvulus
- Imperforate anus
- Meconium peritonitis
- Intestinal malrotation
- Intestinal duplication
- Hepatic fibrosis
- Cholestasis
- Biliary atresia
- Hepatic vascular malformations
- Hepatitis
- Hepatic necrosis
- Liver tumor or cysts

Syndromic/Miscellaneous (8.1%)

- Noonan syndrome
- Arthrogryposis
- Multiple pterygium syndrome
- Neu-Laxova syndrome
- Pena-Shokeir syndrome
- Myotonic dystrophy
- Saldino-Noonan syndrome
- Francois syndrome, type III
- Familial nuchal bleb
- Elejalde syndrome
- Thoracoabdominal syndrome
- Lymphedema-distichiasis syndrome

Urinary Tract Malformation (2.3%)

- Urethral stenosis
- Urethral atresia
- Posterior urethral valve
- Finnish type nephrosis
- Edwards (prune belly) syndrome

ASD, Atrial septal defect; AV, arteriovenous; TTTS, twin–twin transfusion syndrome; VSD, ventricular septal defect.

Management

Depending on gestational age at the time of diagnosis and whether a cause for NIHF can be identified, various management options may include termination of pregnancy, invasive therapeutic intervention, or conservative management, including supportive care and monitoring of the mother and fetus. Fetal surveillance may include frequent nonstress testing or biophysical profiles on a weekly or twice-weekly basis. Because early delivery and neonatal compromise often occur, early consultation with relevant subspecialists (e.g., neonatologists, pediatric surgeons, or pediatric

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TABLE 23.5 Antenatal Evaluation of Nonimmune Hydrops Fetalis

Noninvasive Testing

Maternal History (Consider Genetics Counselor)

- Age, parity, gestational age
- Hereditary or metabolic diseases, anemia
- Recent infections or contacts
- Medication use

Maternal Laboratory Evaluation

- Complete blood cell count
- Blood type, Rh, indirect Coombs antibody screen
- Viral titers: parvovirus B19, toxoplasmosis, congenital syphilis, rubella, cytomegalovirus, herpes simplex
- Aneuploidy screening—integrated, sequential, quad, or triple screen, cell-free fetal DNA in maternal serum
- Metabolic studies, autoimmune screening, electrophoresis (if indicated)

Fetal Echocardiography

- Cardiac malformations
- Arrhythmias

Ultrasonography

- Anatomic abnormalities (cystic hygromas, thoracic masses)
- Evaluate extent of edema and/or effusions (cardiac displacement, lung hypoplasia)
- Middle cerebral artery Doppler to rule out anemia

Amniocentesis

- Karyotype
- Viral culture or PCR
- Lung maturity

Invasive Fetal Testing

Fetal Blood Sampling

- Karyotype
- Complete blood cell count, type
- Hemoglobin electrophoresis
- Viral culture or PCR
- Metabolic testing

Fetal Effusion Sampling

- Viral culture or PCR
- Protein count
- Cell count and cytology (lymphocytes)

PCR, Polymerase chain reaction.

cardiologists) is often warranted. If delivery is thought to be imminent, inpatient surveillance with the administration of antenatal corticosteroids may be indicated.

Maternal risks of conservative management include a condition known as mirror syndrome (Ballantyne syndrome).[40] If this occurs, the mother begins to demonstrate similar findings of the fetus, including generalized maternal edema, often with pulmonary involvement, thus "mirroring" the edema of the hydropic fetus and placenta. Although the pathogenesis of this condition is unknown, it is thought that the hydropic placenta causes a systemic inflammatory response as a result of increased shedding of trophoblastic debris into maternal blood.[26]

In some cases, invasive fetal therapeutic interventions may be considered. Conditions such as diaphragmatic hernia, congenital pulmonary adenomatoid malformations, or extralobar pulmonary sequestration may benefit from in utero surgery. Although paracentesis or thoracentesis may be informative for diagnostic purposes, the fluid removed from the fetal body cavity often reaccumulates in a short period of time. In these cases, shunt placement is sometimes considered, with some notable improvement in survival.

Delivery may be indicated if there is evidence of maternal mirror syndrome. Other indications for delivery include gestational age greater than 34 weeks, mature fetal lung profile, or persistent biophysical profiles of less than 6. Cesarean delivery should be reserved for routine obstetrical indications (Table 23.6). Traumatic delivery because of severe soft tissue edema often occurs; however, this risk is not negated by cesarean delivery. Given the increased frequency of nonreassuring fetal testing and labor dystocia, however, the likelihood of cesarean delivery in NIHF is increased.

TABLE 23.6 Management of Nonimmune Hydrops Fetalis

Conservative Management	Invasive Management
• Fetal surveillance—NST, BPP weekly or twice weekly • Serial growth ultrasound	• Shunt placement • Surgical repair when indicated
Hospitalize If	**Indications for Delivery**
• Fetal skin thickening • Pericardial effusion • Nonreactive NST • BPP <6 • Subjective decreased fetal movement • Anticipated imminent delivery • Administer antenatal corticosteroids	• Gestational age >34 weeks • Mature fetal lung profile • Persistent BPP <6 • Maternal compromise (mirror syndrome)

BPP, Biophysical profile; NST, nonstress test.

Prognosis

Overall survival of a fetus diagnosed with NIHF remains poor. This is largely related to the underlying etiology of

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the condition. If a structural defect is identified, or if no underlying cause is identified, the perinatal mortality rate approaches 100%. In general, PMN rates are worse when NIHF is identified early in pregnancy (<24 weeks) and, conversely, when identified, delivery and neonatal treatments may be beneficial and improve mortality. Certainly the risks associated with prematurity compound the already tenuous status of a fetus with NIHF. Given the rareness of this entity, recurrence risk is also rare, especially when the cause is something other than a hereditary factor.

Summary

Hydrops fetalis, whether from immune or nonimmune causes, represents a large spectrum of rare disorders and conditions resulting in the common pathophysiologic outcome of heart failure and interstitial fluid accumulation in the fetus. Given the seriousness of many of the underlying conditions, perinatal morbidity and mortality remain exceedingly high. Although the prognosis of IHF remains positive in those fetuses who receive intrauterine blood transfusions, treatment in NIHF is often conservative, with increased surveillance of fetal well-being but minimal improvement in short- or long-term neonatal outcomes. Invasive fetal treatment, however, is associated with improved survival in select conditions causing NIHF. All pregnancies should undergo screening for Rh alloimmunization with maternal blood typing and antibody screening. Despite improvements in technology and testing, a certain diagnosis in NIHF occurs only in approximately 67% of cases. Minimizing maternal complications such as mirror syndrome and determining the most appropriate timing for delivery remain challenging in this high-risk pregnancy population.

Key Points

- Hydrops fetalis is defined as excessive fetal fluid in two or more spaces. It can result from immune and nonimmune etiologies.
- Immune hydrops fetalis are due to blood group antigens that can form antibodies and lead to significant hemolytic disease of the newborn.
- Immune hydrops fetalis has significantly decreased after the routine implementation of Rh immunoglobulin prophylaxis with anti-D immune globulin, Rhogam.
- Fetal anemia can be predicted with Doppler flow studies by the peak systolic velocity of the middle cerebral artery and can guide the need for fetal intravascular transfusion.
- Nonimmune hydrops fetalis differential diagnosis should include chromosomal anomalies, recent viral infections, and evaluation of fetal structural anomalies with ultrasound.
- Overall prognosis is dependent on the underlying etiology. Consultation with maternal fetal medicine and neonatology with delivery in a facility capable for intervention.

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24

Amniotic Fluid Volume

PAMELA M. SIMMONS AND EVERETT F. MAGANN

Amniotic fluid surrounds the developing embryo throughout gestation, protecting the fetus and umbilical cord from trauma while allowing mobility to facilitate structural growth and development. The underlying forces that regulate amniotic fluid are exceedingly complex and dynamic, synchronizing volumes within relatively narrow ranges and providing an indirect measure of fetal well-being. Understanding the pathways of water and solute exchange provides the physiologic basis of the pathologic conditions of oligohydramnios and polyhydramnios.

Amniotic Fluid Dynamics

Several pathways for movement of amniotic fluid and solutes exist, including fetal swallowing, urination, pulmonary secretions, intramembranous movement between fetal blood and the placenta, and transmembranous movement across the amnion and chorion.[30] To understand how variations in amniotic fluid volume can affect the fetus, we must first understand fluid dynamics.

Composition

Amniotic fluid contains 98%-99% water, with its solute composition changing throughout gestation. In early pregnancy, the factors that affect amniotic fluid volume are not well known. What is known is that the osmolarity of amniotic fluid and maternal plasma are similar, suggesting that amniotic fluid is a transudate of maternal plasma originating from either placental surfaces or coming through fetal skin.[4] The fetal skin remains nonkeratinized until week 22-25, allowing it to act as a membrane through which amniotic fluid can readily pass.[63] As the fetal skin becomes keratinized and renal function matures, the hypotonic fetal urine causes the amniotic fluid osmolality to decline from 290 mOsm/kg in the first trimester to approximately 255 mOsm/kg near term.[11] Conversely, concentrations of creatinine, urea, and uric acid from the fetal urine increase progressively in the amniotic fluid. Low concentrations of proteins (principally albumin) are found in late pregnancy and provide a minor source of nutrition for the developing fetus. Near term, the amniotic fluid contains increased particulate matter from desquamated fetal skin and gastrointestinal cells, hair, vernix caseosa, stem cells, and occasionally meconium.

Production and Regulation

Surface exchange is the main component of fluid dynamics in early pregnancy before skin keratinization. Beyond 24 weeks, the surfaces in the mouth and nose can additionally act to exchange fluid, but this is not considered a major source of amniotic fluid volume regulation.[12] A fundamental source of amniotic fluid, particularly in the second half of pregnancy, is the fetal renal system. This is evidenced by the almost complete lack of amniotic fluid in fetuses with renal agenesis or bladder outlet obstructions. Secretions of the respiratory tract, fetal swallowing, and transport within and across the fetal membranes also contribute to amniotic fluid volume (Fig. 24.1).

Confirmation of a functioning renal system first starts around 8-11 weeks, when urine is initially observed in the fetal bladder. The dilute urine that is produced is thought to cause the observed drop in osmolality and sodium concentration in the amniotic fluid that persists until delivery.[4] As pregnancy advances, urinary byproducts are observed at two to three times the concentration found in fetal plasma.[32] Estimates of fetal urine output have been made by three-dimensional (3D) measurements of bladder volume at timed intervals and have been found to range from 7-70 mL/hour from 24 weeks until delivery in two separate studies.[43,80] Fetal urine production is characteristically decreased in pregnancies with abnormalities of placental function that result in intrauterine growth restriction (IUGR).[100] However, no correlation is observed between fetal weight and urine production in normal pregnancies. In normal pregnancies, low fetal urine output is not associated with lower Apgar scores, pH less than 7.25, or late decelerations in labor.[100]

Fluid is excreted from the fetal pulmonary system. Approximately 300-400 mL of fluid is secreted per day, driven by chloride ion exchange across the pulmonary epithelium.[11] It has been demonstrated in fetal sheep by Brace et al. that half of secreted lung fluid enters the amniotic fluid, and the other half is swallowed upon exiting the trachea.[10] Amniotic fluid is prevented from entering the lungs by the closed larynx, producing a new efflux of fluid

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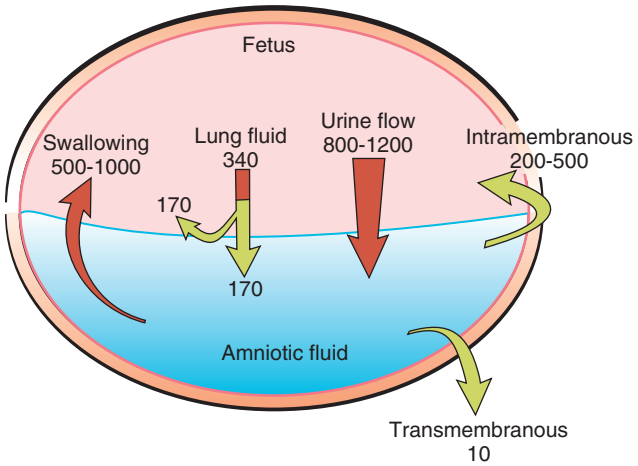
Abstract

Amniotic fluid surrounds and protects the developing fetus during pregnancy, and its volume is from surface exchange in early pregnancy and the fetal renal system in later pregnancy. The assessment of amniotic fluid volume (AFV) can be done precisely by dye-dilution techniques or measured at the time of cesarean delivery. The dye-dilution techniques require an amniocentesis, are invasive, time consuming, and require laboratory support, and the measurement at cesarean can only be done and delivery, making that technique impractical for the serial assessment of AFV. Because of these limitations AFV is estimated by ultrasound. The current techniques to estimate AFV include the subjective assessment, and the objective assessments using the amniotic fluid index (AFI) and the single deepest pocket technique (SDP). These ultrasound estimates of the AFV correlate well with normal (dye-determined or directly measured) volumes but poorly with true oligohydramnios and polyhydramnios. The use of color Doppler in estimating AFV does not help in identifying true oligohydramnios but instead labels more normal fluid volumes as oligohydramniotic. The use of the statistical method, quantile regression, is the best method to identify what is a normal AFV across gestation. In twin pregnancies, the amniotic fluid volume is best estimated using the SDP technique. The SDP technique compared to the AFI is the superior technique to use in antenatal testing to evaluate AFV in singletons. Polyhydramnios is seen with fetal anomalies, maternal diabetes, fetal macrosomia, immune and nonimmune fetal hydrops, or fetal infection, or may be idiopathic. The best ultrasound measurement to identify polyhydramnios is uncertain.

Keywords

amniotic fluid volume
amniotic fluid index
oligohydramnios
polyhydramnios
amnioreduction
single deepest pocket

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• **Fig. 24.1** Pathways for daily fluid production and removal between the fetus and amniotic fluid compartments (measured in milliliters). (From Gilbert WM, et al. Amniotic fluid dynamics. *Fetal Med Rev.* 1991;3:89. Reprinted with permission of Cambridge University Press.)

from the fetal lungs.[28] This was confirmed in an investigation by Liley et al. in which the intra-amniotic injection of contrast media resulted in, with the exception of a few cases, undetectable contrast in the fetal or neonatal lung.[2] The net amount of lung fluid entering the fetal amniotic fluid is approximately 150-200 mL per day. As further evidence of secreted lung fluid being found in amniotic fluid, the phospholipids found in amniotic fluid, which are produced by pulmonary cells, are found in the amniotic fluid. Although meconium staining is not infrequent, with rates in the literature of 7%-27% based on the population, meconium aspiration past the trachea is rare, less than 1%-5%, and is usually associated with accompanying neonatal hypoxia.[3,27] Rarely, the aspiration of amniotic fluid uncontaminated by meconium has been reported as a cause of neonatal death confirmed at autopsy.[8,37]

Analogous to renal agenesis being associated with low amniotic fluid, disruption in fetal swallowing is associated with excess amniotic fluid volume. The human fetus demonstrates swallowing around the same time that urine production begins, at 8-11 weeks,[70] and the swallowed volume increases with gestational age. The ovine model has been used historically to approximate human fetal development.[4] Studies evaluating the volume of amniotic fluid swallowed by the fetus were done primarily in sheep models and were found to range between 210 and 1085 mL/day.[83,96] Ovine studies have also shown that the amount of amniotic fluid swallowed daily in late gestation is correlated with the amniotic fluid volume, suggesting that the fetus can react and attempt to regulate its amniotic fluid surroundings. This attempted regulation is not thought to be a major controller of volume,[9] although the fetus is able to modulate its swallowing. In primate studies, esophageal ligation initially resulted in polyhydramnios, but the polyhydramnios did not persist across gestation, and at the time of delivery the amniotic fluid volume was normal.[69] Observations of swallowed amniotic fluid volume in near-term fetuses range from 210-840 mL per day (average 565 mL). This volume is equivalent to 5%-10% of the fetal body weight.[31]

Excess fluid not removed by fetal swallowing is reabsorbed via an intramembranous pathway. More specifically, this is the reabsorption of fluid and solutes from the amniotic compartment to the fetal blood via the amnion.[5] This pathway is capable of absorbing large quantities of fluid. As the fluid requirements of the fetus increase with increasing gestation, water flow from the amniotic cavity to the fetal circulation via the fetal membranes increases up to 400 mL/day.[67] This is thought to be regulated at least partially by aquaporins found in the human chorioamniotic membranes and the placenta. Aquaporins are small (26- to 34-kDa) cell membrane proteins, which regulate water flux across the cell membranes, have been found to be adaptive to abnormal amniotic fluid levels, and may represent a possible future therapeutic target for abnormal amniotic fluid volume regulation.[22,39,102] The osmotic gradient between the amniotic fluid and fetal blood also drives fluids and solutes from the amniotic fluid into the fetal blood.[32] The flow of solutes and fluid, although bidirectional, is not necessarily equal.[4,26] Vascular endothelial growth factor (VEGF) may also have an impact on intramembranous absorption of fluid.

Transmembranous movement of amniotic fluid describes the transport of water and solutes from the maternal circulation to the amniotic compartment via the placenta.[5] Overall, this has been found to be an insignificant contribution to amniotic fluid dynamics.[30]

Measurement of Amniotic Fluid Volume

The evaluation of amniotic fluid volume is important during the routine ultrasound evaluation of the fetus, because variation above or below normal is associated with increased perinatal morbidity and mortality.[18,19] Amniotic fluid volume can be measured directly at the time of cesarean delivery (with corrections made for blood contamination)[35] or by dye-dilution techniques using para-amino hippurate.[61] The direct measurement can only be done on a single occasion at the time of cesarean delivery, making it impractical for serial assessments of amniotic fluid volume, and the dye-dilution technique is invasive (requires an amniocentesis), necessitates laboratory support to calculate the amniotic fluid volume, and is also impractical for the clinical determination of amniotic fluid volume.[35] The relative accuracy of this indicator dilution technique has been validated by comparing the actual amniotic fluid volume measured at cesarean delivery with the determined by dye-dilution technique, showing only a 7% difference between the dye-determined and direct-measurement volumes (r = .99, P <.001).[57,65] Magnetic resonance imaging has also been evaluated as a means for estimating amniotic fluid volume[101]; however, this is an impractical approach to everyday screening. Although the aforementioned techniques to measure amniotic fluid volume are accurate, they

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are time consuming, cumbersome, and may require laboratory support; therefore, the volumes are usually estimated by ultrasound.

Sonographic techniques to estimate amniotic fluid volume include subjective (qualitative) estimation and semiquantitative methods: measurement of maximum vertical or single deepest pocket (SDP) and the amniotic fluid index (AFI). Advantages of sonographic estimates include that they are simple to perform; easy to teach to residents, midwives, and nurses; and are reproducible. In a study comparing all three measurements in singleton pregnancies with dye-dilution technique across different operator experiences, the accuracy of subjective and objective (sonographic) estimates was not affected by operator experience and was similarly accurate in identifying normal amniotic fluid volume. The disadvantage is that they are two-dimensional (2D) representations of a complex, 3D structure with limited significance relative to clinical outcome. Although each has been studied extensively, no technique is universally considered superior at predicting perinatal outcome. In the same study, the accuracy of estimates of all three techniques ranged from 65%-70%, and the three sonographic estimates were similar, ranging from 59%-67%. Alarmingly, none of the techniques were accurate in the identification of abnormal volumes (oligohydramnios, or low amniotic fluid, and polyhydramnios, or high amniotic fluid). The accuracy in the identification of normal volumes in twin pregnancies was dismal, ranging from 7%-29%.[54]

Subjective Estimation

Subjective estimation of amniotic fluid is based on the overall sonographic visual impression of the amniotic fluid volume by an experienced sonographer, established by visualizing echolucent pockets between the fetal parts and uterine wall without measurements. Qualitative estimation of the fluid is characterized as normal, increased, reduced, or absent.

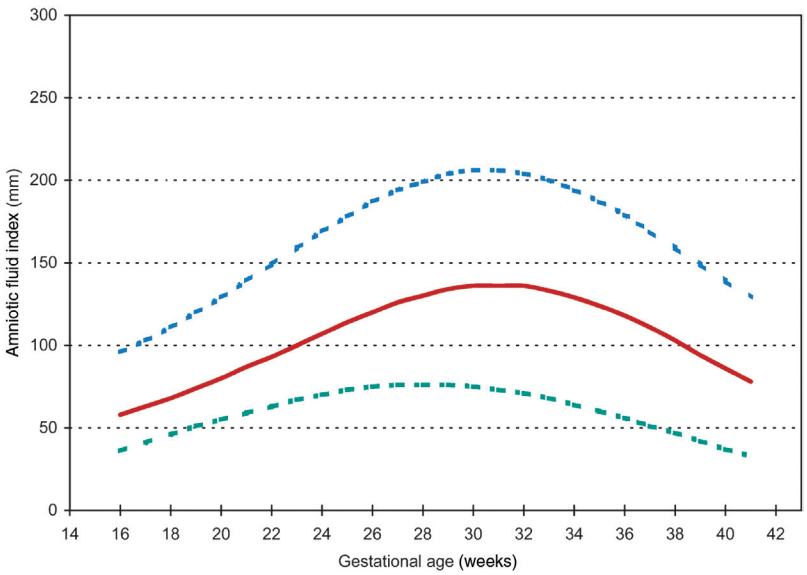
Amniotic Fluid Index Measurement

Amniotic fluid index is the summation of the vertical diameter of the largest pocket in each of the four quadrants, as proposed by Phelan and Rutherford.[82] It uses the maternal umbilicus as the central reference point and requires the transducer to be oriented in the longitudinal axis of the maternal abdomen and be kept perpendicular to the floor during scanning. The AFI correlates closely with actual amniotic fluid volume as determined by dye-dilution techniques for normal fluid volume, although it loses its predictive value at the upper and lower ends of the extreme. Moore and Cayle established the mean and outer boundaries (5th and 95th percentiles, respectively) for the AFI from 16-42 weeks' gestation in a study of 791 normal pregnancies.[71] Magann et al. also established 5th-95th percentiles, respectively, as 4.2-14.9 cm for AFI at gestational age 37-41 weeks.[48,62] Both can be seen in Fig. 24.2. The mean AFI is approximately 12-14 cm throughout most of pregnancy, declining after 33 weeks. Above the 95th percentile is approximately 20 cm and below the 5th percentile is approximately 7 cm. The absolute maximum normal AFI is less than 24 or 25 cm. Typical limits for amniotic fluid assessment by AFI are defined in Table 24.1.

TABLE 24.1 Diagnostic Categories by Measurement of the Amniotic Fluid Index

Amniotic Fluid Volume	AFI Value	Patients
Polyhydramnios	≥25 cm	2%
Normal	>8 to <25 cm	76%
Moderate oligohydramnios	≥5 to ≤8 cm	20%
Severe oligohydramnios	<5 cm	2%

AFI, Amniotic fluid index.
Data from Moore TR, Oligohydramnios. *Contemp Obstet Gynecol.* 1996;41:15.



• **Fig. 24.2** Amniotic fluid index. Four quadrant sum of deepest vertical pockets (measured in millimeters). Solid line indicates the median values, upper and lower dashed lines are the 95th and 5th percentiles, respectively. (Adapted from Moore TR, Cayle JE. The amniotic fluid index in normal human pregnancy. *Am J Obstet Gynecol.* 1990;162:1168.)

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TABLE 24.2 Diagnostic Categories by Measurement of the Single Deepest Pocket

Amniotic Fluid Volume	SDP Value	Patients
Polyhydramnios	≥8.0 cm	3%
Normal	>2 to <8 cm	94%
Moderate oligohydramnios	≥1 to ≤2 cm	2%
Severe oligohydramnios	<1 cm	1%

SDP, Single deepest pocket.
Data from Chamberlain PF, et al. Ultrasound evaluation of amniotic fluid volume: I. The relationship of marginal and decreased amniotic fluid volumes to perinatal outcomes. *Am J Obstet Gynecol.* 1984;150:245.

Single Deepest Pocket or Maximal Vertical Pocket

The single deepest vertical pocket, as originally described by Chamberlain,[40] is simply found by identifying the largest pocket of amniotic fluid after a global assessment and taking the largest vertical measurement with a horizontal measurement of 1 cm. At gestational age 37-41 weeks, the 5th-95th percentile was 2.3-6 cm for SDP according to nomograms by Magann et al.[62] Typical limits for amniotic fluid assessment by SDP are shown in Table 24.2.

Comparing Amniotic Fluid Assessment Techniques

As stated, the ideal test for sonographic assessment of amniotic fluid volume has not been firmly established. The ideal semiquantitative sonographic technique should be one that correctly identifies the patients at risk for adverse outcome. Amniotic fluid index, SDP, and a two-diameter pocket (horizontal x vertical measurements in cm^2) were compared in a study of 50 normal pregnancies between the gestational ages of 14 and 41 weeks. The prevalence of oligohydramnios as defined by AFI less than or equal to 5 cm, SDP less than 2 cm, or two-diameter pocket less than 15 cm^2 were significantly different (P <.0001) for the three techniques (8%, 1%, and 30%, respectively). The prevalence of polyhydramnios as defined by AFI greater than 24 cm, SDP greater than 8 cm, or two-diameter pocket greater than 50 cm^2 was also diagnosed with significantly different frequencies (P <.0001) (0%, 0.7%, and 3%, respectively).[62] Outcome was not assessed in this study.

Subsequently, two prospective randomized trials comparing the use of SDP versus AFI during modified biophysical profiles in complicated pregnancies were performed. Chauhan and colleagues studied 1080 women and found that AFI identified oligohydramnios in 17% of pregnancies compared with 10% identified in SDP-assessed pregnancies (P = .002).[20] However, there was no difference in delivery mode, NICU admission, umbilical artery pH, or Apgar score. Magann and colleagues had similar findings, showing oligohydramnios was identified in twice as many patients using AFI as compared with SDP in 537 pregnancies (38% vs. 17%, P <.001), resulting in a doubling of inductions of labor (30% vs. 15%, P <.001) and cesarean sections for fetal distress (13% vs. 7%, P <.05).[58] There was, however, no improvement of perinatal outcome. This was confirmed in two meta-analyses comparing the measurement of AFI to SDP.[51,74] Neither sonographic test was superior to the other. Both poorly identified abnormal volumes when compared with dye-determined or directly measured amniotic fluid volume. However, AFI overdiagnosed clinically insignificant oligohydramnios, leading to more intervention without a difference in outcome, suggesting that the single deepest pocket may be a superior sonographic assessment for antenatal testing of the at-risk pregnancy.[74]

Use of color Doppler has not been shown to aid in identification of pregnancies with adverse outcomes. Using dye-determined volume as the benchmark, Magann et al. compared grayscale ultrasonography to Doppler color ultrasonography and found that Doppler not only overdiagnosed oligohydramnios but labeled 37% of women with normal AFV as having oligohydramnios.[49]

Other Techniques

Sahin et al. attempted to apply the Cavalieri method, a mathematical approximation of volumes, to estimate amniotic fluid volume.[86] Their results correlated with concurrent AFI measurements, and although this is a promising theory, it is complicated to perform and has not been correlated with pregnancy outcome or a directly measured volume.

Three-dimensional ultrasound technology has found relevance in the evaluation of the fetus; however, it has not yet found application in the assessment of amniotic fluid. There has been only one attempt to assess third-trimester amniotic fluid volume with 3D ultrasonography. It was concluded that 3D volume datasets are reliable for determining volume; however, it was determined subjectively by the sonographer based on five volume acquisitions and compared with the value obtained during the 2D ultrasound; there was no attempt at calculating a volume based on a gold standard.[15] Interestingly, in the first trimester, growth charts have been developed for gestational sac volume and embryonic volume, the ratio of which correlates positively with gestational age.[85] Clinical applications for this data have not yet been developed, but normal versus abnormal early pregnancies are being investigated to determine if these parameters can help predict early adverse outcomes such as miscarriage.

Normal Volume and the Singleton Pregnancy

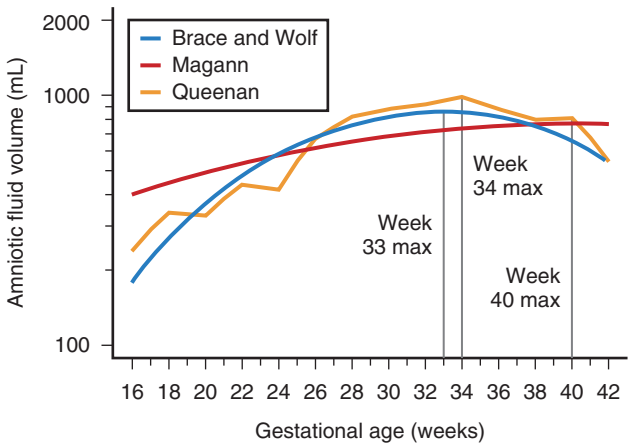
Gravid women accumulate approximately 6 L of additional fluid volume during pregnancy. Most of this fluid is associated with the conceptus: 2800 mL in the fetus, 400 mL in the placenta, and 700-800 mL of amniotic fluid.[87] The

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remainder of the fluid is associated with the maternal uterus (800 mL), breasts (500 mL), and maternal blood volume expansion (850 mL).[87] Throughout gestation, amniotic fluid volume is highly regulated, gradually increasing in the first trimester, stabilizing in the second trimester, and decreasing late in the third trimester while remaining in a relatively narrow range of volumes.

Normality can be defined in two ways. Mathematically it can represent the majority of the population as expressed by area under the curve in a Gaussian distributed population. Typically the lower and upper 5% are excluded as "abnormal." Normality can also be defined in terms of outcome. Undesired outcomes are tracked, and measurements associated with these outcomes are defined as "abnormal." This second definition is more clinically useful but much more difficult to define.

Amniotic fluid volume has been defined in both these manners. The 5th and 95th percentiles have been defined for AFI, SDP, and dye-determined techniques across gestational ages, as fluid has been found to vary significantly throughout pregnancy. Nomograms for amniotic fluid in normal pregnancies were developed by Queenan et al. in 1972 by dye-determined methods,[84] Brace and Wolfe by dye-dilution and direct measurement,[11] and Magann et al. by dye-dilution and direct measurement. (Fig. 24.3).[48,62] Two of these studies showed that amniotic fluid volume increases steadily in early gestation and remains relatively stable between 22 and 38 weeks, averaging 750-800 mL. Thereafter, amniotic fluid declines by 8% per week, with a mean volume of approximately 500 mL at 40-42 weeks. The third nomogram found that amniotic fluid volume continues to increase throughout gestation, confirming a mean volume of approximately 800 mL at term.[48] A more recent publication evaluated 1,190 normal amniotic fluid volumes (by dye-dilution and direct measurement) across gestation, comparing four statistical methods to construct gestational age-specific reference intervals for amniotic fluid. The investigators determined that quantile regression because of its flexibility and robustness, especially when data is sparse, is the preferred statistical technique to construct gestational age-specific reference for normal amniotic fluid volume (Table 24.3).[77]



• **Fig. 24.3** Comparison of normal amniotic fluid volumes (dye-determined or directly measured) across gestation. (Adapted from Magann EF, Sandlin AT, Ounpraseuth ST. Amniotic fluid and the clinical relevance of the sonographically estimated amniotic fluid volume: oligohydramnios. *J Ultrasound Med.* 2011;30:1573-1585; Brace RA, Wolf EJ. Normal amniotic fluid volume changes throughout pregnancy. *Am J Obstet Gynecol.* 1989;161:382-388; and Queenan JT, Thompson W, Whitfield CR, Shah SI. Amniotic fluid volumes in normal pregnancies. *Am J Obstet Gynecol.* 1972;114:34-38.)

A study of more than 15,000 patients done by Shanks et al. showed that AFI less than the 5th percentile versus a cutoff of 5 cm better predicts fetuses at risk for newborn intensive care (NICU) admission,[89] although this study has been criticized for its retrospective design and the variable intervals between the time the measurement was obtained and the time of delivery. Additionally, an investigation of 291 pregnancies with dye-determined volumes in which the third and fifth percentiles of the AFI were assessed to determine if either of these percentiles was superior to the fixed cutoff of less than 5 for the AFI to detect the 75 pregnancies with oligohydramnios, discovered that both the percentiles (third and fifth) and the fixed cutoff (<5) poorly identified oligohydramnios, but neither was superior to the other.[56]

Twins and Amniotic Fluid

Multifetal pregnancies are at a higher risk of perinatal morbidity and mortality than singleton pregnancies. When evaluating the health of the amniotic fluid in twin pregnancies, singleton growth curves currently provide the best predictors of adverse outcomes, and the evaluation of fluid with singleton nomograms is frequently being used. This approach appears reasonable because in the only evaluation of volume in third-trimester diamniotic twin pregnancies, the amniotic fluid volume, or each sac, was similar to that of normal singleton pregnancies.[64] Morin and Lim performed a literature review with the Diagnostic Imaging Committee of the Society of Obstetricians and Gynaecologists of Canada and suggest that the SDP should be used in each sac with standard definitions for singleton pregnancies, although they state that there is not enough evidence to suggest that one method is more predictive than the others of adverse pregnancy outcome.[72] The AFI has been used to estimate amniotic fluid volume in twins; however, when using the summated AFI (measurement of all four quadrants as is done in singletons but without taking membrane placement into consideration), the measurement poorly predicts dye-determined oligohydramnios and polyhydramnios.[1]

In a single prospective observational study of 299 diamniotic twin pregnancies, SDP was found to be constant between 17 and 37 weeks, with an increase in fetal labor intolerance and neonatal morbidity in twin pregnancies with polyhydramnios. Alternate fixed cutoffs of less than 2.2 cm for a low amniotic fluid volume and greater than 7.5 cm for a high amniotic fluid volume were suggested

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TABLE 24.3 Fitted 2.5th, 5th, 50th, 95th, and 97.5th Percentiles of Amniotic Fluid Volumes at 10-42 Weeks of Gestation Based on the Quantile Regression Method

EGA (weeks)	2.5th	5th	50th	95th	97.5th
10	10	11.67071	33	54.5	54.5
11	14.67523	17.77286	46.78348	80.00315	85.11197
12	20.88759	26.02843	64.63046	114.4997	128.7214
13	28.86455	36.72243	87.08291	159.8753	188.7096
14	38.76757	50	114.5418	217.9379	268.4339
15	50.65874	65.81518	147.2026	290.2362	370.8499
16	64.47283	83.89999	185	377.8607	498.0732
17	80	103.7623	227.5713	481.246	650.9382
18	96.88325	124.716	274.2441	600	828.619
19	114.6324	145.9388	324.053	732.7873	1028.385
20	132.6541	166.5515	375.784	877.2853	1245.544
21	150.2943	185.7025	428.0441	1030.229	1473.61
22	166.8892	202.647	479.3488	1187.546	1704.68
23	181.8158	216.8096	528.2168	1344.573	1930
24	194.5394	227.8216	573.2642	1496.338	2140.636
25	204.6493	235.533	613.2876	1637.871	2328.18
26	211.8822	240	647.3289	1764.527	2485.396
27	216.1299	241.4547	674.7173	1872.273	2606.735
28	217.433	240.2633	695.0874	1957.925	2688.672
29	215.9638	236.8802	708.3736	2019.309	2729.829
30	212	231.8045	714.7848	2055.337	2730.905
31	205.8945	225.5429	714.7645	2066	2694.441
32	198.0441	218.5812	708.9409	2052.289	2624.451
33	188.8609	211.3661	698.0733	2016.051	2526
34	178.7474	204.2954	683	1959.804	2404.752
35	168.0774	197.7177	664.5898	1886.54	2266.555
36	157.1828	191.9366	643.7017	1799.513	2117.087
37	146.3463	187.2225	621.1525	1702.055	1961.572
38	135.7982	183.8267	597.6943	1597.407	1804.597
39	125.7176	182	574	1488.587	1650
40	116.2365	182.0158	550.6572	1378.3	1500.832
41	107.4454	184.1975	528.1678	1268.871	1359.384
42	99.39999	188.9548	506.9539	1162.223	1227.244

EGA, Estimated gestational age.

Data from Ounpraseuth, ST, Magann EF, Spencer HJ, et al. Normal amniotic fluid volume across gestation: comparison of statistical approaches in 1190 normal amniotic fluid volumes. *J. Obstet. Gynaecol. Res.* 2017;43:1122-1131.

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TABLE 24.4 Estimated SDP Percentile Distributions for Each Gestational Age (299 Diamniotic Twin Pregnancies)

EGA (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th	Twin Sacs
<17	2.02	2.11	2.54	3.96	6.48	6.86	6.88	22
17-19	2.13	2.14	2.64	4.07	6.56	6.97	7.02	143
20-22	2.22	2.23	2.79	4.22	6.6	7.04	7.21	276
23-25	2.23	2.28	2.93	4.38	6.67	7.19	7.45	322
26-28	2.29	2.37	3.06	4.53	6.8	7.44	7.79	390
29-31	2.43	2.46	3.2	4.67	6.91	7.69	8.09	323
32-34	2.44	2.51	3.32	4.8	6.98	7.76	8.27	283
35-37	2.41	2.54	3.39	4.9	7.01	7.81	8.39	129

EGA, Estimated gestational age; SDP, single deepest pocket.
Data from Magann EF, Doherty DA, Ennen CS, et al. The ultrasound estimation of amniotic fluid volume in diamniotic twin pregnancies and prediction of peripartum outcomes. *Am J Obstet Gynecol.* 2007;196(6):570.

in diamniotic twin pregnancies to identify pregnancies at risk for adverse intrapartum and neonatal outcomes (Table 24.4).[57]

Hernandez et al. performed a retrospective review of 1951 twin pregnancies, both dichorionic and monochorionic, with twin–twin transfusion syndrome excluded.[33] Polyhydramnios was identified in 18% of pregnancies, defined as mild (SDP 8–9.9 cm), moderate (SDP 10–11.9 cm), and severe (SDP ≥12 cm). Pregnancy outcomes were reviewed, and polyhydramnios was not associated with preterm delivery, fetal growth restriction, NICU admission, or neonatal death in either twin. The incidence of major anomalies became more common in increasing polyhydramnios in both monochorionic and dichorionic pregnancies with a prevalence of almost 20% in severe polyhydramnios. Severe polyhydramnios was significantly associated with stillbirth in monochorionic pregnancies (27%, $P < .001$).

Assessing relative amniotic fluid volume in twin pregnancies is also important because disparity in amniotic fluid volume is a significant component of twin oligohydramnios-polyhydramnios sequence (TOPS), of which twin–twin transfusion syndrome (TTTS) is the extreme endpoint. Twin–twin transfusion syndrome carries with it a three- to fivefold increase in mortality and morbidity.[93] It is often uncovered with ultrasound evidence of discordant fetal weights and amniotic fluid in monochorionic/diamniotic twins, although it has been documented in monochorionic/monoamniotic pregnancies.[92] It may also present sonographically as a "stuck twin," with the fetus appearing to be suspended to the uterine wall with no intervening membrane visible, or there may be tightly adhered membranes that make a fetus appear wrapped in plastic wrap (Fig. 24.4). It is recommended that evaluation for twin–twin transfusion in these pregnancies should begin in the second trimester with weekly surveillance if discordant and evaluation every 2 weeks for concordant pregnancies.[17]

Abnormalities of Amniotic Fluid Volume and Their Management

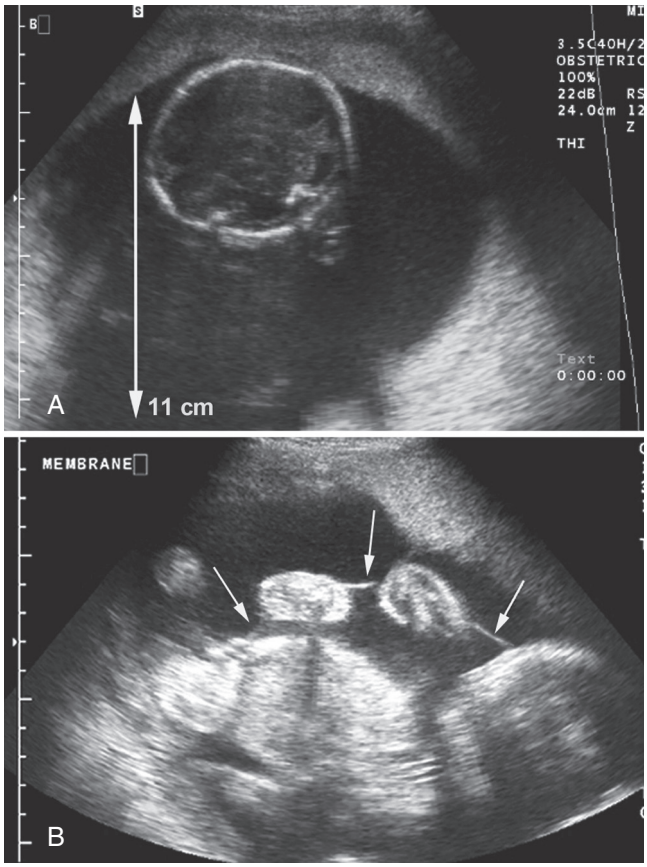
Deviation of amniotic fluid volume outside the normal range is associated with increased pregnancy loss. As early as the first trimester, low gestational sac fluid volume is predictive of increased rates of spontaneous abortion, 94% versus 8% in patients with normal sac size.[14] In the second and third trimesters, departure above or below normal volumes increases the perinatal mortality (PNM) rate (Fig. 24.5). When diagnosis was made in the third trimester, patients fared better, although there was still a 15% PNM rate.

Oligohydramnios

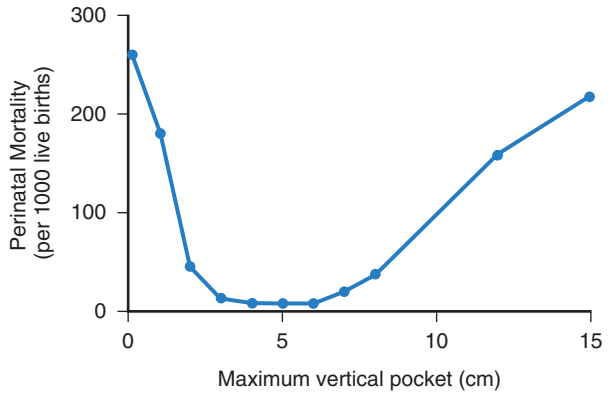
Oligohydramnios has been defined as an amniotic fluid volume that is less than 200 mL[35] or 500 mL[23] and occurs in 1%-2% of pregnancies. It is sonographically defined as an SDP less than 2 cm, AFI less than 5 cm, or a subjectively low volume. Borderline fluid has been defined as an AFI between 5 and 8 cm or 5 and 10 cm and has been associated with fetal malformations if diagnosed at age 24 and 34 weeks.[52,81]

Low amniotic fluid can be caused by underproduction or loss or can be idiopathic. Underproduction can be the result of absent or dysfunctional kidneys, urinary tract obstruction, uteroplacental insufficiency, maternal medications, or maternal dehydration. Loss is caused by rupture of membranes. Box 24.1 lists conditions associated with oligohydramnios. The clinical management of oligohydramnios should be directed toward diagnosing and alleviating remediable underlying conditions. Appropriate work-up for this abnormality is a review of the maternal history for evidence of rupture, anatomic evaluation of the renal system and bladder, and assessment of placental function and fetal growth and pulmonary status.

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• **Fig. 24.4** Appearance of "stuck twin" in twin–twin transfusion syndrome. **A,** Note fetus appears suspended to the anterior wall of uterus surrounded by large fluid collection (polyhydramnios of second twin). The membranes surrounding this twin are not visible on ultrasound examination. **B,** Note the tightly adherent membranes (*arrows*) in the donor twin sac.



• **Fig. 24.5** Perinatal mortality rate related to maximum vertical pocket (MVP) measurements in centimeters. Note the increased perinatal mortality with MVP less than 2 or greater than 8 cm. (Adapted from Harman CR. Amniotic fluid abnormalities. *Semin Perinatol.* 2008;32:288.)

Clinical Implications

Oligohydramnios increases perinatal morbidity with increased rates of IUGR (fetal weight less than the 10th percentile for gestational age, or abdominal circumference less than the 2.5th percentile), meconium-stained amniotic fluid, fetal labor intolerance, and low Apgar scores. Regardless of the etiology, fetuses in pregnancies complicated by oligohydramnios are at increased risk of adverse outcomes in the form of cord accidents, fetal lung hypoplasia, and, if in the first and second trimesters, malformations and contractures.[78] Oligohydramnios was retrospectively evaluated in 7582 fetuses in high-risk pregnancies with normal anatomy. Perinatal mortality was 11% in these pregnancies versus 0.2% in pregnancies with normal fluid based on SDP. Borderline fluid of SDP 1-2 cm was associated with an increased mortality at 3.7%.[18]

There are conflicting data that contend that the most significant risk to the normal fetus with incidental oligohydramnios is iatrogenic prematurity resulting from the subsequent rush to delivery.[68] Low amniotic fluid volume as determined by dye-dilution along with IUGR has been associated with NICU admission (OR 11.1) but no other measures of infant morbidity.[59]

Etiology

In a series by Shenker and colleagues, the most common cause of oligohydramnios was premature rupture of

• BOX 24.1 Principal Diagnoses Associated With Oligohydramnios

Fetal

- Chromosomal abnormalities
- Congenital anomalies
  - Genitourinary (renal agenesis, polycystic or multicystic dysplastic kidneys, ureteral or urethral obstruction)
- Intrauterine growth restriction
- Intrauterine fetal demise
- Postmaturity
- Premature rupture of membranes (occult or overt)
  - Preterm
  - Prolonged

Maternal

- Uteroplacental insufficiency
  - Autoimmune condition
  - Antiphospholipid antibodies, collagen vascular disease
  - Maternal hypertension
  - Nephropathy
  - Diabetic vasculopathy
  - Maternal hypovolemia
  - Preeclampsia/pregnancy-induced hypertension
- Medications
  - Prostaglandin synthetase inhibitors
  - Angiotensin-converting enzyme inhibitors

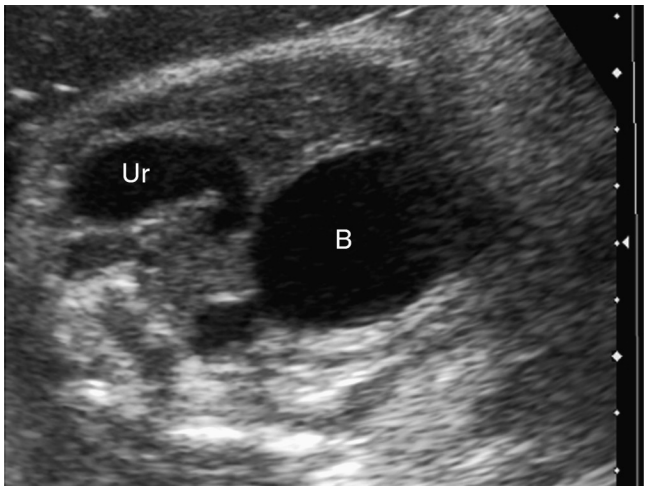
Placental

- Chronic abruption
- Placental crowding in multiple gestation
- Twin–twin transfusion
- Placental infarction

Idiopathic

Modified from Peipert JF, Donnenfeld AE. Oligohydramnios: a review. *Obstet Gynecol Surv.* 1991;46:325.

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• **Fig. 24.6** Posterior urethral valve syndrome. Male fetus with "keyhole" bladder on ultrasound. Note large bladder (*B*) and dilated ureter (*Ur*).

membranes (PROM) (50%), followed by IUGR (18%) and congenital anomalies (14%).[90] Shipp and associates noted a bimodal distribution of severe oligohydramnios, with congenital abnormalities accounting for 51% of cases occurring at 13-21 weeks' gestation, but only 22.1% at 34-42 weeks. In this series, urinary tract malformations accounted for 58.7% of all anomalies seen, with aneuploidy accounting for 4% of severe oligohydramniotic patients.[91] Genitourinary malformations associated with oligohydramnios include renal agenesis, cystic dysplasia of the kidneys, and obstructive uropathies, including posterior urethral valve syndrome. The sonographic appearance of posterior urethral valves with megacystis is shown in Fig. 24.6. Late diagnosis of oligohydramnios in pregnancies with normal anatomy has also been found to be associated with undiagnosed renal anomalies up to 9.8% of the time.[44]

Maternal use of certain medications can lead to development of oligohydramnios. Prostaglandin synthetase inhibitors (e.g., indomethacin, ibuprofen, sulindac), which are used to inhibit labor, reduce polyhydramnios, and relieve pain, also reduce the fetal glomerular filtration rate, resulting in decreased fetal urine output and oligohydramnios in up to 70% of patients. They may also decrease uteroplacental perfusion and prematurely cause closure of the ductus arteriosus. Although these effects are reversible, patients maintained on indomethacin for more than 72 hours should be evaluated with semiweekly amniotic fluid assessments and fetal echocardiography to assess the ductal flow. Angiotensin-converting enzyme (ACE) inhibitors have also been implicated as causing oligohydramnios, presumably secondary to severe fetal hypotension, reducing renal blood flow. Angiotensin-converting enzyme inhibitors are associated with producing prolonged neonatal anuria, renal anomalies, ossification defects in the fetal skull, and death; therefore, they are contraindicated in pregnancy.

Diagnostic Evaluation

Rule Out Ruptured Membranes

A sterile speculum examination should be performed on any patient suspected of having PROM. If amniotic fluid is grossly present in the posterior vagina, the diagnosis of PROM is confirmed. If only a small amount of fluid is present, it should be tested with Nitrazine paper to detect the alkaline pH of amniotic fluid. A sample should also be applied to a slide and allowed to dry. Sodium chloride in the amniotic fluid crystalizes in a "ferning" pattern, confirming the diagnosis. Cervical mucus, when applied to a slide and allowed to dry, also can create a crystalized pattern, so care should be taken to avoid collection of cervical mucus. Frequently these examinations are negative or equivocal for reasons such as chronic leakage or contaminating blood or semen, making it difficult to conclusively diagnose chronic fluid leakage. If a normal-sized fetal bladder is observed on ultrasound with concomitant severe oligohydramnios, the likelihood of PROM is high. Injection of indigo carmine diluted in sterile saline into the amniotic sac with an amniocentesis needle after placement of a tampon in the vagina can confirm the diagnosis of PROM in cases that are difficult to detect. Patients should be warned that if the fetus delivers within a few days of injection, the baby may be stained blue. Methylene blue dye has been reported to cause methemoglobinemia and hemolysis and, therefore, should not be used. Pyridium has also been reportedly used; however, the orange to red hue of the stained fluid is difficult to distinguish from bodily fluids.

Monoclonal antibodies to detect placental α-microglobulin-1 (PAMG-1) in the vagina can be used to confirm PROM. In clinical testing, the test kit AmniSure (AmniSure International LCC, Cambridge, MA) was shown to be highly sensitive (98.7%) and specific (87.5%) at detecting even minute amounts of PAMG-1 in the vagina.[42] However, false-positive results can occur if there is bleeding; false-negative results are possible if the sample is taken more than 12 hours after presumed PROM.

A group of 31 women with rupture before 24 weeks' gestation was followed for outcomes based on SDP greater than or less than 1 cm (severe oligohydramnios). The group with SDP greater than 1 cm was associated with a longer latency to a live birth in 60% of pregnancies compared to 8.3% in the group with SDP less than 1 cm. The remainder of outcomes, such as sepsis, chorioamnionitis, and abruption, was not statistically different among groups.[94] A separate study found that AFI was a poor predictor of survival in pregnancies with preterm PROM between 16 and 24 weeks.[36]

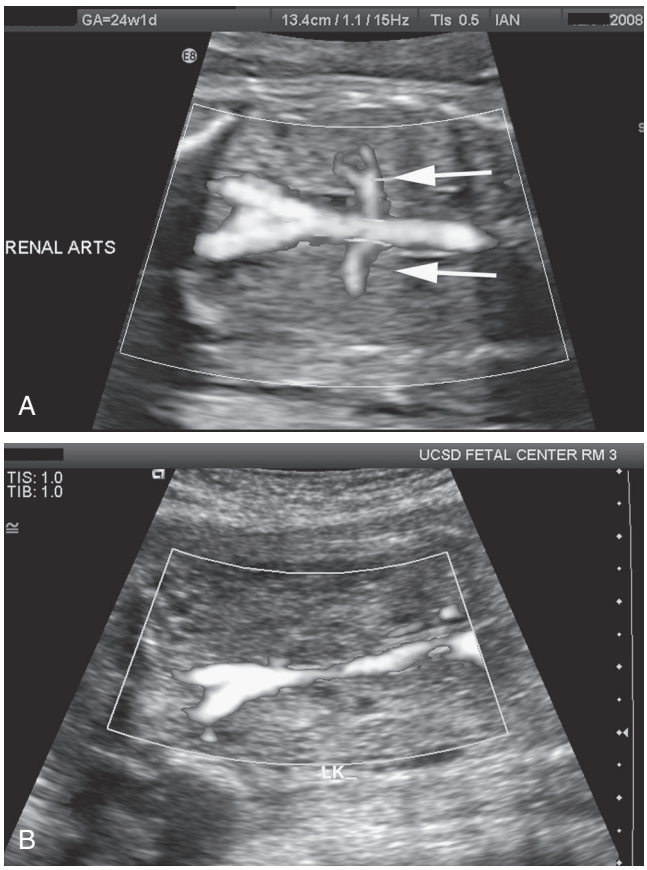
Assess Fetal Anatomy

A careful ultrasound examination with anatomic survey should be performed in cases of oligohydramnios to rule out congenital anomalies, particularly because renal and ureteral anomalies are the most common anatomic cause of severe oligohydramnios in the absence of ruptured membranes.

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The fetal urinary system should be thoroughly evaluated, paying close attention to the renal parenchyma, dimensions of the renal pelvis, and morphologic features of the fetal urinary bladder. Cardiac, skeletal, and central nervous system anomalies may coexist with primary renal anomalies and should be investigated. Chromosomal abnormalities (i.e., trisomies 18 and 21) can also present with renal anomalies, so evaluation for other signs of aneuploidy should be included and genetic amniocentesis or maternal blood for fetal cell-free DNA considered. Interestingly, isolated renal anomalies do not increase the risk of aneuploidy. With bilateral renal agenesis, virtual anhydramnios is present from 16 weeks onward. With anhydramnios, it is difficult to adequately document whether the fetal kidneys are present. In addition, the fetal adrenals can become hypertrophied and resemble renal structures. To aid in the identification of renal agenesis, Doppler imaging (Fig. 24.7) may be necessary to document the absence of renal arteries to conclusively prove renal agenesis. Transabdominal infusion of normal saline into the amniotic cavity has also been used as an adjunct in midtrimester evaluation of suspected renal agenesis. In a series by Fisk and colleagues, suspected fetal anomalies were confirmed in 90% of patients using amnioinfusion to better visualize fetal structures.[28] However, 13% of the etiologic diagnoses were changed as a result of information obtained at amnioinfusion, including the finding of kidneys in some cases of suspected renal agenesis. Aspiration of a small amount of the fluid instilled during amnioinfusion has also been used for chromosomal analysis with a 70% success rate.

Conversely, polycystic renal disease and obstructive uropathy (e.g., ureteropelvic junction obstruction) are more readily apparent but may not become evident until the late second trimester. Fortunately, unilateral renal agenesis or polycystic kidney disease rarely causes significant decreases in amniotic fluid. Magnetic resonance imaging can also be useful for assessing anatomy not well seen on ultrasound.



• **Fig. 24.7** Bilateral renal agenesis. **A**, Doppler image of normal renal arteries (*arrows*) at 24 weeks' gestation. **B**, Power Doppler image of fetal abdominal aorta and its bifurcation at 20 weeks' gestation, demonstrating bilateral absence of renal arteries. Note absence of amniotic fluid.

Assess Fetal Growth

Chronic poor placental function owing to maternal autoimmune disease, hypertension, or vasculopathy can lead to fetal growth restriction and oligohydramnios. Therefore, if PROM and congenital anomalies are excluded, IUGR resulting from uteroplacental insufficiency should be considered. In general, uteroplacental insufficiency results in asymmetric IUGR, with the fetal abdomen lagging behind the fetal head growth. However, long-standing growth restriction can produce a more symmetric picture. Early-onset symmetric IUGR is more likely to be caused by aneuploidy or congenital anomaly.

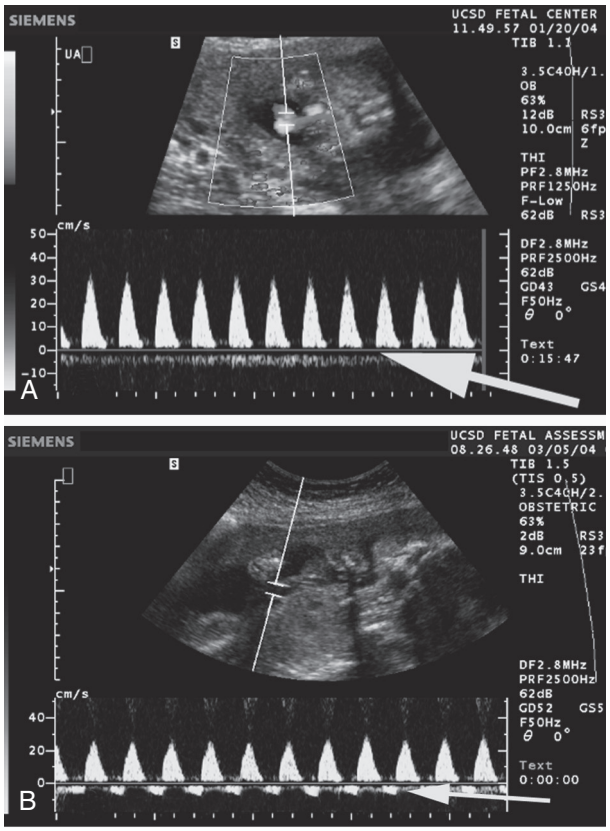
In cases of IUGR related to placental insufficiency, Doppler studies of uterine and umbilical blood flow may reveal patterns of high resistance. Absent or reverse end-diastolic flow patterns in the umbilical artery are associated with higher perinatal mortality and are demonstrated in Fig. 24.8. The fetal middle cerebral artery (MCA) can also be interrogated via Doppler and can show increased amplitude of diastolic flow as a marker of fetal hypoxia and cerebral vasodilation. Management of abnormal Doppler studies is dependent on gestational age. Pulsatility of the MCA and abnormal ductus venosus flow are late findings of fetal compromise and are indications for delivery.

In patients with IUGR with oligohydramnios, intensive fetal monitoring and hospitalization should be initiated, because the risks of fetal asphyxia and death are high. Monitoring should be continued in patients diagnosed between 26 and 32 weeks' gestation. Corticosteroids for lung maturity should be considered. Amniocentesis to assess lung maturity should be considered after 32 weeks; however, with severe oligohydramnios, this can be technically challenging. Delivery should be undertaken if the lungs are mature or if there is evidence of a deteriorating fetal status.

Assess Fetal Pulmonary Status

Prolonged oligohydramnios can result in pulmonary hypoplasia, which is associated with a high perinatal mortality. Inhibition of fetal breathing, lack of a trophic function of amniotic fluid within the airways, and simple mechanical compression of the chest are proposed as causes of pulmonary hypoplasia; however, the precise pathophysiology remains unclear.

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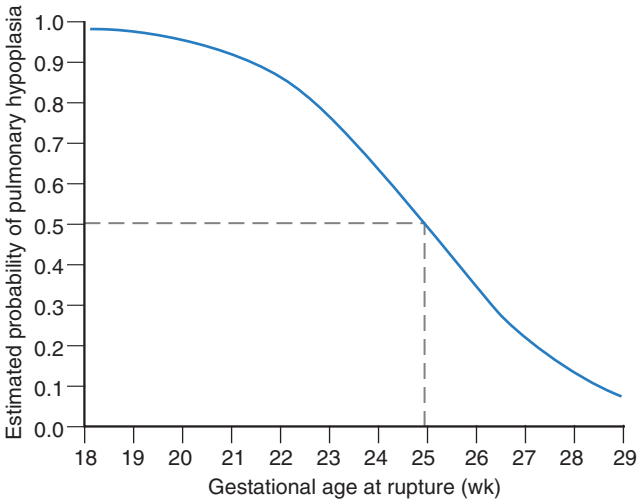


• **Fig. 24.8** Doppler umbilical artery velocimetry. **A,** Absent end-diastolic flow. Note the umbilical artery flow velocity waveform returns to zero following each fetal heart beat (*large arrow*). **B,** Reverse end-diastolic flow. Here the waveform extends below the zero line (negative flow) between the fetal heartbeats (*small arrow*).

The risk of developing pulmonary hypoplasia is greatest if oligohydramnios is prolonged and occurs during the canalicular phase of alveolar proliferation, from 16-26 weeks of gestation.[98] Improved survival is seen if there is a persistence of a fluid pocket of at least 2 cm between 20 and 25 weeks of gestation (30% survival if the pocket is <2 cm; 98% if the pocket is ≥2 cm). The estimated probability of developing pulmonary hypoplasia with severe oligohydramnios in the second trimester is illustrated in Fig. 24.9.

Several sonographic techniques have been proposed for predicting pulmonary hypoplasia, including measuring lung length and chest circumference, or evaluation of biometric ratios (e.g., thoracic-to-abdominal circumference or thoracic circumference-to-femur length). D'Alton and colleagues found a thoracic-to-abdominal circumference ratio of less than 0.08 in severe oligohydramnios virtually 100% predictive of lethal pulmonary hypoplasia.[21] Sonographically, this would have the appearance of a "bell-shaped" chest, which by itself is concerning for pulmonary hypoplasia.

Vintzileos and coworkers reviewed six current sonographic parameters for predicting pulmonary hypoplasia and found that the highest sensitivity (85%) and specificity (85%) were achieved by calculating the lung area ratio[99]:



• **Fig. 24.9** Estimated probability of development of pulmonary hypoplasia by gestational age in severe oligohydramnios (<2 cm maximum vertical pocket). *Solid line* indicates probability curve. *Dashed line* illustrates 50% probability at approximately 25 weeks' gestation. (From Vergani P, et al. Risk factors for pulmonary hypoplasia in second-trimester premature rupture of membranes. *Am J Obstet Gynecol.* 1994;170:1359.)

$$\frac{(\text{chest area} - \text{cardiac area}) \times 100}{\text{chest area}}$$

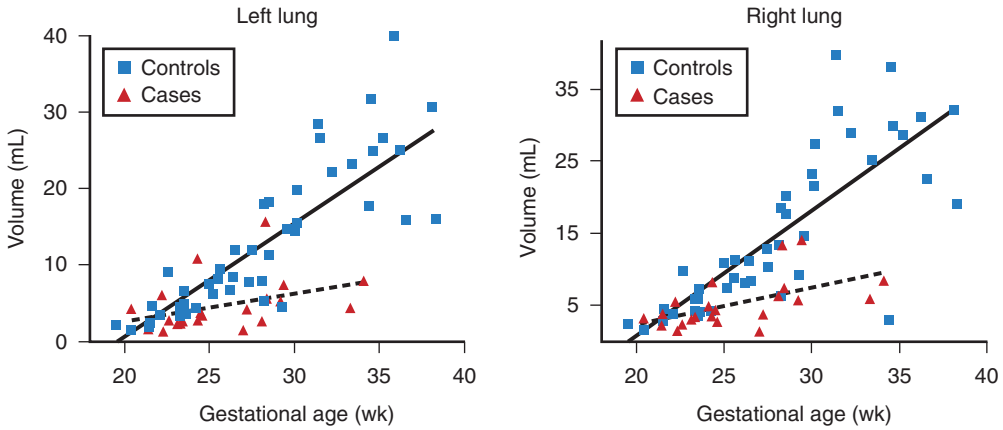
The normal lung area ratio should be greater than 66% with the heart occupying less than one-third of the fetal chest. Compared with 2D imaging techniques, 3D lung volumes have higher sensitivity (94%) but similar specificity (82%) in diagnosis of pulmonary hypoplasia. Fig. 24.10 shows total fetal lung volumes for a set of controls and cases with pulmonary hypoplasia using 3D ultrasound. Studies using magnetic resonance imaging are promising; however, nomograms for development have not been standardized.

Treatment

The management of oligohydramnios depends on the severity of the condition, the underlying cause, and the gestational age of the patient. If discovered at term, induction of labor would be a reasonable option. There is a single randomized trial evaluating induction versus expectant management in 54 patients with oligohydramnios beyond 40 weeks.[73] No difference was found in mode of delivery or neonatal Apgar score or cord blood pH.[24] However, in more than 500 maternal-fetal medicine members surveyed, 92% would recommend induction without documented lung maturity before 39 weeks, and 35% before 37 weeks, even though only one-third of respondents felt induction would decrease adverse outcomes.[88] If expectant management is chosen, there is no consensus on what fetal monitoring is best, or even if fetal monitoring is necessary; however, the use of Doppler monitoring in pregnancies thought to be at risk of placental insufficiency has shown benefit. Consistent maternal oral hydration should be encouraged.

Before term, the discovery of oligohydramnios should initiate a comprehensive sonographic evaluation if that

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• **Fig. 24.10** Scatter dot plot and regression lines of left and right lung volumes for cases with pulmonary hypoplasia (▲) and controls without pulmonary hypoplasia (■), including serial scans. (Data from Vergani P, et al. Two- or three-dimension ultrasonography: which is the best predictor of pulmonary hypoplasia? *Prenat Diagn.* 2010;30(9):834-838.)

assessment has not already been undertaken, focusing on the renal system and bladder as well as fetal growth and placental function. Chromosomal analysis can be offered to patients, and premature rupture of the membranes should be excluded. Antepartum nonstress testing or biophysical profiles along with Doppler flow studies may be useful, particularly in those pregnancies with isolated oligohydramnios and all other testing reassuring of fetal well-being in avoiding delivery of a preterm fetus or an induction in a term fetus with an unfavorable cervix.

The patient with PROM should be delivered if there is evidence of infection; otherwise, the patient can be managed expectantly with hospitalized bed rest and observation until the fetus reaches 34 weeks or has abnormal antenatal testing. Antibiotics should be administered to prolong latency and corticosteroids given to enhance lung maturity. Most deliver within a week, but those who do not can potentially remain pregnant for several weeks.

Maternal Hydration

Idiopathic oligohydramnios has been found to be responsive to maternal hydration with no difference in IV versus oral hydration acutely or long term.[55,79] The effect, however, is short-lived without continued efforts at hydration.[66] Women also placed in the left-lateral position at rest have been found to have an increase in AFI.[97] It is notable that none of the preceding studies evaluated clinically important outcomes. Maternal hydration, therefore, has a limited clinical application and may help in cases in which adequate amniotic fluid assists in outcome, such as external cephalic versions or amniocentesis.

Amnioinfusion

Prophylactic transcervical amnioinfusion has been shown to reduce the cesarean section rates when used in patients before being induced for oligohydramnios at term. Presumably this effect is achieved by reducing cord compression during labor. However, potential complications from amnioinfusion, including uterine overdistention, hypertonus, infection, and amniotic fluid embolism warrant using this modality with cautious, close monitoring. Amnioinfusion as a treatment for meconium-stained amniotic fluid is no longer recommended.

In severe second-trimester oligohydramnios, serial transabdominal amnioinfusion has been advocated as a therapeutic procedure to prevent pulmonary hypoplasia and improve outcomes. However, in Fisk and colleagues' limited series of nine patients,[28] only 33% of neonates survived. In Locatelli and associates' study of 49 women with PROM before 26 weeks, 36 underwent serial amnioinfusion.[47] They were successful in maintaining the maximum vertical pocket greater than 2 cm in 11 patients, which significantly improved perinatal outcomes: pulmonary hypoplasia was reduced from 62%-10% with no abnormal neurologic outcomes. Other small series similarly report decreased pulmonary hypoplasia, better neurologic outcomes, and overall improved survival with serial amnioinfusions.

Tissue Sealants

Application of various compounds to seal ruptured membranes has been tried since 1979. Compounds used for treating preterm PROM include platelets with thrombin or cryoprecipitate, fibrin sealants to occlude the cervical canal, gelatin plugs, synthetic hydrogels, collagen plugs, and blood patches. These treatments have been associated with poor outcomes, including fetal bradycardia and death, and remain investigational, although a few successes have been reported in repairing the amniotomy made at the time of fetal surgery. The utility in the use of tissue sealants is problematic in pregnancies complicated by preterm PROM, because the reason for the rupture is infection in a number of these pregnancies, and the use of a tissue sealant would not be appropriate in the management of these pregnancies. More study is needed before recommendations can be made for preterm PROM.

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Polyhydramnios

Polyhydramnios has been defined as an amniotic fluid volume of greater than 2000 mL[60] and occurs in 1%-3% of pregnancies. By ultrasound techniques, it has been estimated as an SDP greater than 8 cm, AFI greater than 24 or 25 cm or an amniotic fluid volume above the 95th percentile for gestational age, or a subjectively high volume of fluid. Patients with polyhydramnios may present with increased uterine fundal height, dyspnea, edema, and increased weight.

Elevated amniotic fluid can result from decreased absorption, overproduction, or be idiopathic. Decreased absorption typically results from a failure of fetal swallowing from etiologies such as tracheal atresia, tracheal or bowel obstruction, or neurologic abnormalities such as anencephaly. Chromosomal abnormalities,[13] nonimmune hydrops, and diabetes are also recognized reasons for polyhydramnios. The diagnostic workup for polyhydramnios includes an assessment for diabetes, syphilis, Rh isoimmunization, or atypical antibodies that might lead to hemolytic disease of the newborn, fetal or placental (chorioangioma) abnormalities, and work-up for infection if there has been a recent exposure or maternal history suggestive of a recent infection.

Clinical Implications

Retrospective reviews of pregnancies with polyhydramnios show an association with macrosomia, premature births, nonreactive nonstress tests, perinatal morbidity, and congenital anomalies in high-risk pregnancies with polyhydramnios.[76] One hundred eighteen pregnancies with polyhydramnios as defined by SDP greater than 8 cm with a normal fetal anatomic scan, 75-g glucose test, and TORCH serology were studied retrospectively by Abele et al.[1] Eleven of those pregnancies had postnatal abnormalities identified, with the majority being gastrointestinal atresia. In a study of 788 infants with polyhydramnios, the rate of congenital malformations was 2.3% compared with 0.13% in those with normal amniotic fluid. Those with no major congenital malformation diagnosed were at risk for the development of respiratory distress and hypoglycemia.[45]

Etiology

The prevalence of polyhydramnios is 1%-2% with 50%-60% of those pregnancies being idiopathic. Because the major pathway for removal of amniotic fluid is swallowing, it follows that congenital anomalies that interfere with swallowing or intestinal absorption (e.g., duodenal atresia) are the most common causes of polyhydramnios. The prevalence of congenital anomalies correlates with the severity of polyhydramnios, with a 2.6 times greater incidence of anomalies in severe polyhydramnios (75%) than in mild polyhydramnios (29%).[25]

Polyhydramnios has also been linked to maternal pregestational and gestational diabetes and fetal macrosomia.

• BOX 24.2 Principal Diagnoses Associated With Polyhydramnios

Fetal

- Chromosomal abnormalities
- Congenital anomalies
  - Gastrointestinal (duodenal or esophageal atresia, tracheoesophageal fistula, gastroschisis, omphalocele, diaphragmatic hernia)
  - Craniofacial (anencephaly, holoprosencephaly, hydrocephaly, micrognathia, cleft palate)
  - Pulmonary (congenital pulmonary airway malformation, chylothorax)
  - Cardiac (malformations, arrhythmias)
  - Skeletal dysplasias
- Fetal hydrops (immune or nonimmune)
- Anemia (fetomaternal hemorrhage, parvovirus infection, isoimmunization, thalassemia)
- Neuromuscular disorders (myotonic dystrophy, Pena-Shokeir)
- Neoplasias (teratomas, hemangiomas)
- Constitutional macrosomia

Maternal

- Diabetes mellitus
  - Gestational diabetes
  - Adult-onset (type 2) diabetes

Placental

- Chorioangioma
- Twin–twin transfusion

Idiopathic

Adapted from Phelan JP, Martin GI. Polyhydramnios: fetal and neonatal implications. *Clin Perinatol.* 1989;16:987; Hill LM, et al. Polyhydramnios: ultrasonically detected prevalence and neonatal outcome. *Obstet Gynecol.* 1987;69:21; Ben-Chetrit A, et al. Hydramnios in the third trimester of pregnancy: a change in the distribution of accompanying anomalies as a result of early ultrasonographic prenatal diagnosis. *Am J Obstet Gynecol.* 1990;162:1344.)

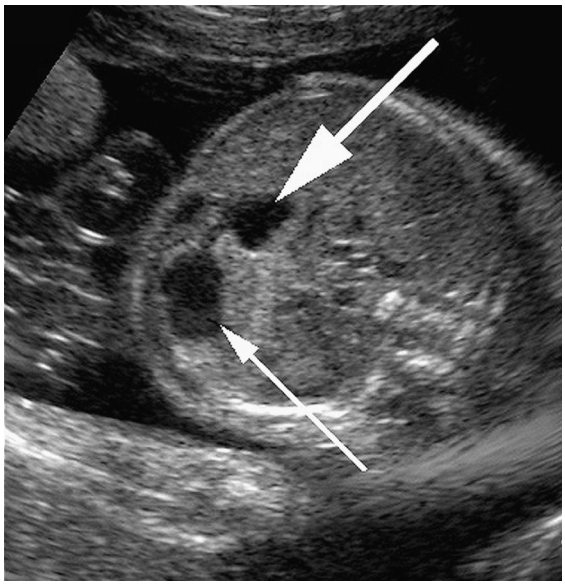
Increased fetal urination in mothers with adult-onset or gestational diabetes accounts for nearly 15% of cases of polyhydramnios.[34] Isolated polyhydramnios has not been found to be a strong independent predictor of gestational diabetes. Aneuploidy is reported in 3%-13% of pregnancies associated with polyhydramnios.[34] Development of the Rh immunoglobulin to prevent immune hydrops fetalis resulting from Rh isoimmunization (see Chapter 23) has decreased the incidence of polyhydramnios due to this condition. Box 24.2 lists conditions associated with polyhydramnios.

Diagnostic Evaluation

Assess Fetal Anatomy

A detailed sonographic evaluation should be performed to assess the fetus for possible congenital anomalies, paying particular attention to the gastrointestinal system for abnormalities that impair fetal swallowing and absorption of the fluid. With proximal obstruction (e.g., esophageal atresia,

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• **Fig. 24.11** Duodenal atresia. Note the characteristic double bubble sign within the fetal abdomen, illustrating the fluid-filled stomach (*small arrow*) and duodenum (*large arrow*) on this transverse view of the fetal abdomen.

tracheoesophageal fistula, or esophageal compression from diaphragmatic hernia or lung mass), the usual stomach "bubble" is absent. Conversely with distal obstruction, multiple cystic structures may be seen in the fetal abdomen. For example, duodenal atresia produces a characteristic "double bubble" appearance (Fig. 24.11). Decreased fetal swallowing, which may result in polyhydramnios, is associated with anencephaly, trisomy 18, trisomy 21, muscular dystrophies, fetal akinesia, and skeletal dysplasias. If polyhydramnios is present with a growth-restricted fetus, or if markers of aneuploidy are seen, evaluation for chromosomal abnormalities should be undertaken. Close surveillance is important in the pregnancy with polyhydramnios and IUGR because of the increased risk of perinatal mortality, neonatal morbidity, and neonatal mortality.[25]

Sonographic signs of fluid overload (i.e., hydrops fetalis), including ascites, pleural effusion, pericardial effusion, and skin edema, should be assessed. Polyhydramnios in hydrops fetalis may be the first presenting sign, prompting further evaluation for erythroblastosis fetalis or nonimmune hydrops.

In anatomically normal fetuses with otherwise unexplained polyhydramnios, diabetes should be suspected, particularly if there is fetal macrosomia or asymmetrically larger fetal abdominal circumference. These patients should be evaluated with a glucose tolerance test and treated accordingly. Polyhydramnios in diabetes is associated with increased perinatal morbidity and mortality beyond that of the diabetes itself.

Currently, the best technique, AFI versus SDP, to estimate polyhydramnios is uncertain. In oligohydramnios, the AFI and SDP do not label pregnancies as having oligohydramnios similarly. Magann et al. observed that in 72% of pregnancies with an AFI <5, the SDP remained normal.[53] The Cochrane review[75] concluded the SDP was superior to the AFI in antenatal testing, because the AFI increased the pregnancies diagnosed with oligohydramnios, leading to more interventions without an improvement in perinatal outcomes. With the use of the AFI and SDP in labeling pregnancies as having polyhydramnios, an overlabeling with the SDP to classify a pregnancy at having polyhydramnios has been observed. Does the use of the SDP lead to an increased number of pregnancies being labeled as having polyhydramnios without an improvement in perinatal outcomes? Future investigations are needed.

Treatment

If nonlethal congenital anomalies are uncovered, appropriate pediatric specialists should be consulted for postnatal treatment. In patients with idiopathic mild polyhydramnios (AFI of 24-40 cm), the perinatal outcome should be no different than that in patients with normal amniotic fluid volume, other than large-for-gestational-age babies (>4000 g at birth). Uterine overdistention, however, may stimulate preterm uterine contractions, and labor may ensue. These patients are at a significantly high risk for PROM and cord prolapse. They should be counseled on the signs and symptoms of preterm labor. If polyhydramnios is discovered at an early gestation, antenatal testing should be initiated at 24 weeks' gestation, although there is no consensus on what type of testing should be begun or at what interval. This can be left to the discretion of the physician. The patient should be assessed for early cervical changes if she is contracting or otherwise symptomatic. In women with severe polyhydramnios (AFI >40 cm), amnioreduction or prostaglandin inhibitors should be considered for those with significant maternal complications (difficulty breathing). There are no recommendations for induction of labor if discovered at term.

Amnioreduction

Removal of excess amniotic fluid may prolong pregnancy and reduce maternal dyspnea from the overdistended uterus in patients with severe polyhydramnios. Calderyo-Barcia and coworkers demonstrated that amnioreduction reduces the baseline tonus and contractility of the uterus by using transabdominal intrauterine pressure transducers in cases of polyhydramnios[16]; however, amniotic fluid invariably returns, making serial amnioreduction necessary. In a series by Leung and colleagues, 134 rapid amnioreduction procedures were performed on 74 patients with a maximum vertical pocket greater than 10 cm using higher flow rates (≈100 mL/min).[46] The most common reported indication for the amnioreduction was TTTS, and repeated procedures were required in 64% of cases. However, a single amnioreduction was sufficient in 70% of patients without TTTS. Complications of amnioreduction include PROM, preterm labor, abruption, fetal bradycardia, infection, and maternal hypoproteinemia.

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Prostaglandin Synthetase Inhibitors

Indomethacin reduces amniotic fluid volume by stimulating fetal vasopressin release, which has an antidiuretic effect on fetal urine production. Indomethacin is also postulated to enhance fluid reabsorption by the fetal lungs and increase transmembranous absorption of excessive amniotic fluid back to the maternal circulation. The dosing of indomethacin is generally 25 mg orally every 6 hours but can range up to 100 mg every 4-8 hours, depending on the severity of polyhydramnios and clinical response. Treatment should be discontinued once the fluid is reduced by one-third to one-half of its original volume, or when the AFI is less than 20 cm. Indomethacin is effective in reducing the amniotic fluid volume in more than 90% of cases of polyhydramnios, but complications during treatment include premature closure of the ductus arteriosus, renal complications, and necrotizing enterocolitis. Chronic ductal closure in utero can produce fetal hydrops and persistent pulmonary hypertension in the neonate. The risk of ductal constriction is 5% at 27 weeks and increases to almost 50% by 32 weeks; therefore, indomethacin treatment should be discontinued before 32 weeks to avoid iatrogenic side effects. Complications linked with indomethacin use can be minimized if the total dose of indomethacin is less than 200 mg per day and the therapy is discontinued after 48 hours of therapy.

Sulindac, a prostaglandin inhibitor sometimes used for preterm labor symptoms, has incidentally been shown to also reduce amniotic fluid volume. It has a purported advantage of less ductal closure but has not been investigated prospectively for treatment of polyhydramnios.

Close Surveillance

Idiopathic polyhydramnios, in a review of the existing literature, has been linked with a twofold to fivefold increase in the risk of perinatal mortality.[50] The ideal management of idiopathic polyhydramnios is unknown. One proposed management scheme is to do serial antenatal testing, and as long as those assessments are reassuring, then delivery probably does not need to occur before term.[95] If the idiopathic polyhydramnios resolves before term, the question of the pregnancy remaining at increased risk for perinatal mortality is also unknown.

Management of Fluid Abnormalities in Multifetal Pregnancies

Management of abnormal amniotic fluid volume in twin pregnancies does not vary much from singleton pregnancies with the single exception of twin–twin transfusion syndrome. Pregnancies with polyhydramnios-oligohydramnios sequence or those with diagnosed twin–twin transfusion syndrome should be referred to maternal-fetal medicine for evaluation and potential treatment as indicated. Laser therapy is being used with increased frequency in monochorionic diamniotic twin pregnancies complicated by twin–twin transfusion syndrome. Recommended surveillance is assessments of amniotic fluid volume every 2 weeks beginning at 16 weeks and continuing throughout the pregnancy. Surveillance recommendations for twin pregnancies are amniotic fluid assessments and growth scans every 4 weeks. The diagnosis of abnormal amniotic fluid in monoamniotic twins does not alter management of the pregnancy, as antenatal testing should begin at viability and delivery planned early.[38,95] The discovery of abnormal fluid volumes may prompt earlier evaluation of causes such as twin–twin transfusion syndrome, IUGR, and congenital anomalies. Dichorionic/diamniotic twin pregnancies should be treated as described for singleton pregnancies. In pregnancies in which polyhydramnios is found in both sacs, or in a single shared amnion, fluid reduction may be necessary for maternal comfort, and preterm labor may be encountered more frequently.[6]

The Future

Amniotic fluid also harbors fetal cells for chromosomal analysis and multiple proteins, some of which have clinical significance such as alpha-fetoprotein, phosphatidylglycerol, and interleukin-6. Amniotic fluid is now being evaluated by complex methods, such as capillary electrophoresis for early predictors of outcomes such as macrosomia and maternal gestational diabetes.[7,29] Amnion and amniotic fluid are also being used to harvest embryonic stem cells for research in all arenas of medicine, including cancer research.[41] Amniotic fluid is not only the nectar that supports a healthy pregnancy, it is a clue to maternal and fetal disease and possibly the gateway to future therapy.

Key Points

- Fetal contributions to amniotic fluid include fetal urine, lung fluid, and removal by fetal swallowing.
- Ultrasound assessments of amniotic fluid volume include amniotic fluid index and single deepest pocket.
- Both oligohydramnios and polyhydramnios may have maternal, placental, or fetal etiologies and require close monitoring for fetal well-being.

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25

Perinatal Infections and Chorioamnionitis

RICHARD POLIN AND TARA M. RANDIS

Definitions and Epidemiology

Chorioamnionitis (or intra-amniotic infection) is a major cause of fetal, neonatal, and maternal morbidity and mortality. There are strong associations between chorioamnionitis and maternal morbidity,[57] preterm birth,[46] early-onset neonatal sepsis,[67] bronchopulmonary dysplasia,[35] retinopathy of prematurity,[13,63] and diffuse white matter injury.[3] The literature supporting these associations has been inconsistent, largely because of lack of precision in the diagnosis of chorioamnionitis. Potential sites of microbial invasion include the choriodecidual space (between maternal tissues and the fetal membranes), the fetal membranes, the placenta, the amniotic fluid, the umbilical cord, and the fetus (Fig. 25.1).[28] When characteristic clinical signs are present, the condition is usually termed clinical chorioamnionitis. However, histologic chorioamnionitis (inflammation of the chorion and amnion) is three times as common as clinical chorioamnionitis confirmed by amniotic fluid culture.[17] Two main varieties of chorioamnionitis can be identified, acute chorioamnionitis and subclinical chorioamnionitis.[28] They differ in their clinical manifestations, microbiology, and risk to the fetus (Fig. 25.2). Although acute chorioamnionitis is strongly associated with early-onset sepsis, the subclinical variety may contribute to the risk of chronic lung disease and brain injury.[29,45]

Chorioamnionitis complicates 1%-4% of all pregnancies; though, the reported incidence varies widely based upon gestational age and diagnostic criteria used.[72] The prevalence of histologic chorioamnionitis ranges from 50%-70% in very low–birth weight infants to 10%-15% for infants born at term gestation. Approximately 30% of women with preterm labor and intact membranes exhibit histologic chorioamnionitis, as do 80% of women with preterm, premature rupture of membranes (PPROM). Histologic chorioamnionitis almost always represents an ascending infection of organisms colonizing the maternal birth canal. Histologic acute chorioamnionitis represents the inflammatory response of the mother and fetus to the presence of microorganisms (usually bacterial or fungal) in the amniotic cavity. Acute chorioamnionitis cannot occur before the fusion of the amnion and chorion (≈11 weeks' gestation) and is rare before 20 weeks of gestation. Before that time, a chronic choriodeciduitis can develop, which is subclinical and has been linked to an increased incidence of preterm birth, chronic lung disease, and periventricular leukomalacia. It is controversial whether the choriodeciduitis represents an infectious process or a maternal immune response to fetal antigens.[41]

As noted, histologic chorioamnionitis is three times as common as clinical chorioamnionitis, and only about two-thirds of women with suspected clinical chorioamnionitis have evidence of placental inflammation. Part of the difficulty of identifying women with chorioamnionitis is that microbial invasion of the amniotic cavity (MIAC) can be chronic and clinically silent. Furthermore, histologic chorioamnionitis can occur with negative cultures from amniotic fluid. Some of these "negative cultures" can be explained by the fastidiousness of the microorganisms found in amniotic fluid and the difficulty in recovering them using standard culture techniques. Others result from sterile inflammation, in which an immune process caused by maternal antifetal rejection leads to the infiltration of maternal lymphocytes, plasma cells, and/or macrophages.[41] Histologic chorioamnionitis has been associated with intra-amniotic infection in 72% of cases of preterm birth. However, the likelihood of neonatal sepsis in women with histologic or clinical chorioamnionitis varies dramatically with gestational age (Table 25.1).[66]

Risk Factors

Epidemiologic investigations have demonstrated several factors associated with the development of clinical chorioamnionitis, including maternal colonization with group B streptococcus (GBS), GBS bacteriuria, nulliparity, the use of internal monitoring devices, meconium-stained amniotic fluid, serial vaginal digital examinations, duration of active labor, and duration of membrane rupture.[4,58,64] Importantly, meconium-stained amniotic fluid is not only a risk factor

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Abstract

Chorioamnionitis (or intra-amniotic infection) is a major cause of fetal, neonatal, and maternal morbidity and mortality. Exposure to intrauterine inflammation increases the risk of preterm birth and the risk of long-term morbidities, including cerebral palsy, bronchopulmonary dysplasia, and retinopathy of prematurity. Administration of broad-spectrum antibiotics and prompt delivery of the fetus in the setting of acute clinical chorioamnionitis reduce both fetal and maternal morbidity. The development of more rigorous diagnostic criteria may better identify those women and fetuses most likely to benefit from antimicrobial treatment and reduce unnecessary, potentially harmful antibiotic exposure. Novel interventions to disrupt inflammatory signaling cascades in utero are greatly needed.

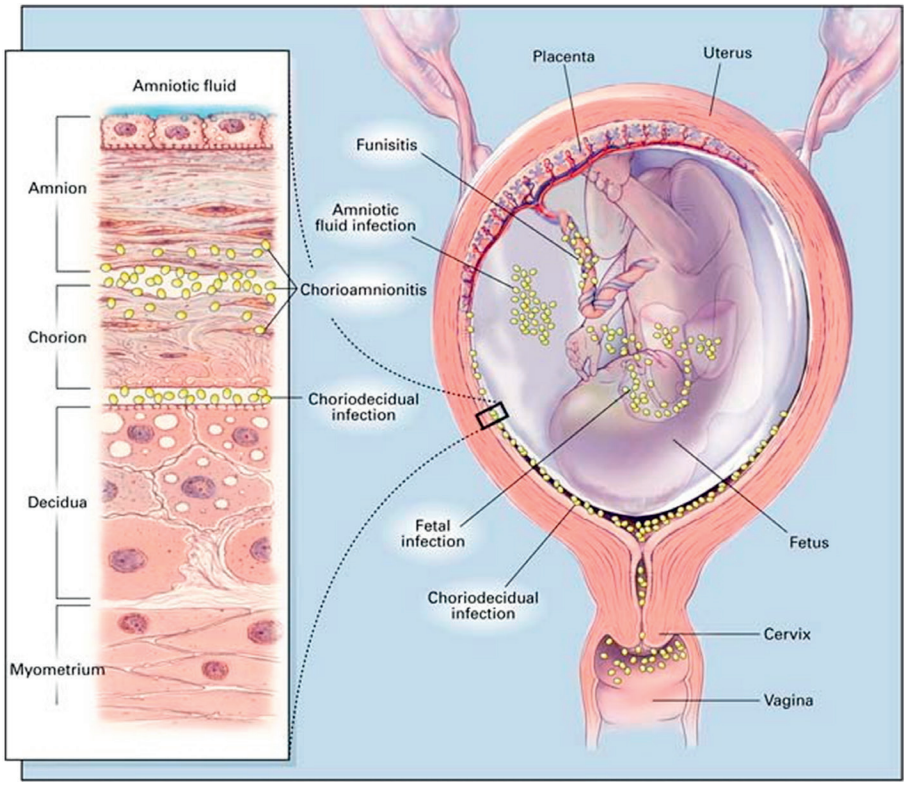
Keywords

intra-amniotic infection
fetal inflammatory response
early-onset sepsis

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TABLE 25.1 Rates of Early-Onset Sepsis According to Gestational Age and Chorioamnionitis Exposure

	22 Weeks	23 Weeks	24 Weeks	25 Weeks	26 Weeks	27 Weeks	28 Weeks
Histologic chorioamnionitis	70%	61%	59%	51%	48%	41%	34%
Clinical chorioamnionitis	28%	26%	20%	19%	19%	15%	14%
Early-onset sepsis	6%	4%	4%	2%	2%	2%	1%



• **Fig. 25.1** Potential sites of bacterial infection within the uterus. (From Goldenberg RJ, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med.* 2000;342:1500-1507. Copyright © 2000 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

Acute chorioamnionitis
Symptomatic mother

Group B *Streptococcus*
Escherichia coli
Streptococcus viridans

↓

Fulminant sepsis at birth
Respiratory distress
Cardiovascular instability

Subclinical chorioamnionitis
Preterm labor or completely asymptomatic

*Ureaplasma urealyticum**
*Mycoplasma hominis**
Gardnerella vaginalis

↓

Variable symptoms at birth
Brain injury
Chronic lung disease

*About 25% of infants <1500 g are bacteremic with one of those organisms at birth.

• **Fig. 25.2** Microbes responsible for acute and subclinical chorioamnionitis.

for chorioamnionitis but also may be a consequence of fetal stress secondary to intra-amniotic infection. There are some data to suggest that women diagnosed with chorioamnionitis during their first pregnancy are at increased risk for developing chorioamnionitis in subsequent pregnancies,[14] indicating a persistent predisposing condition or particular underlying host susceptibility. Recent gene association studies have identified single nucleotide polymorphisms in immunoregulatory genes that may influence susceptibility to chorioamnionitis.[38,52] The presence of abnormal cervicovaginal flora (e.g., bacterial vaginosis, aerobic vaginitis) during the first trimester is associated with adverse pregnancy outcomes, including early preterm birth and miscarriage and MIAC,[18,19,36] although discrete evidence linking the presence of abnormal flora of the lower genital tract with the development of acute clinical chorioamnionitis is lacking. Rather, it is hypothesized that these vaginal microbes ascend into the intrauterine cavity and induce

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a subclinical, chronic inflammatory response that in turn predisposes to preterm rupture of membranes and/or the onset of preterm labor.

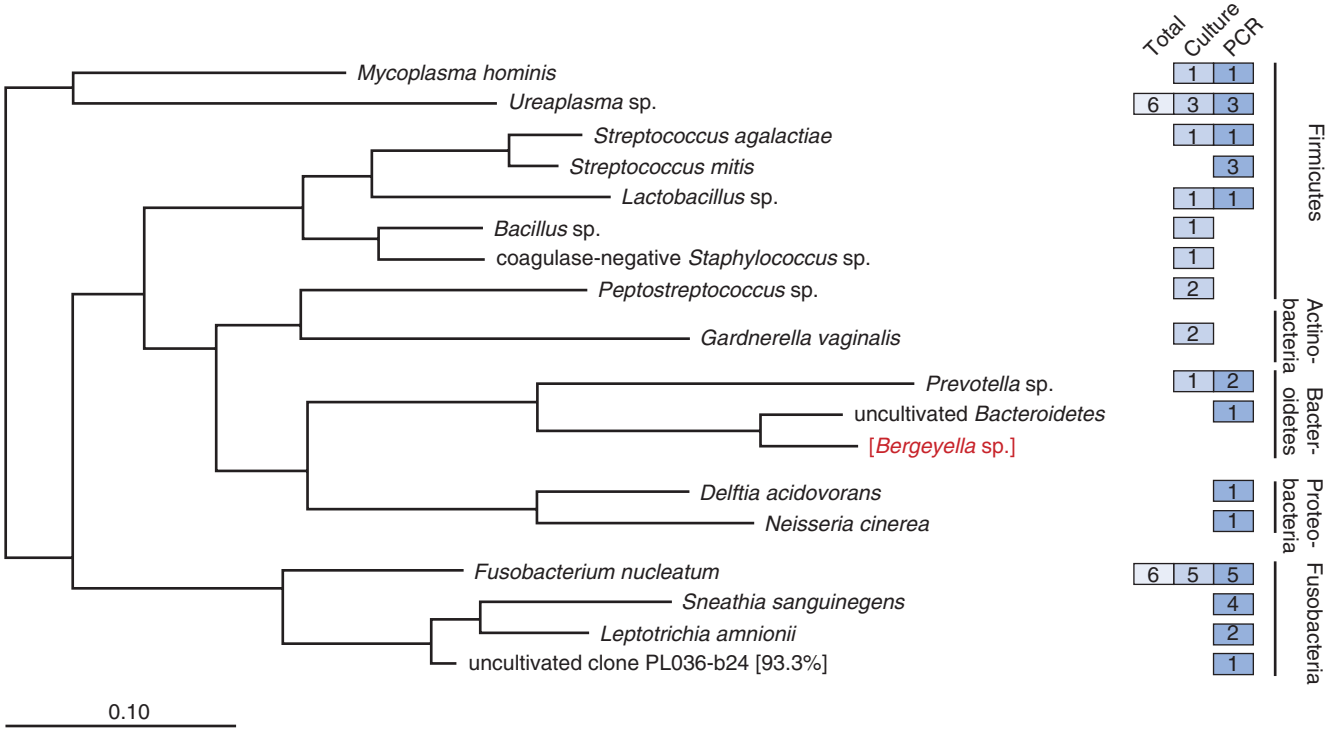
Microbiology

Chorioamnionitis is almost always polymicrobial. Using culture-based techniques, *Ureaplasma urealyticum* and *Mycoplasma hominis* are the most common organisms recovered (47% and 30%, respectively) in culture-proved chorioamnionitis.[72] Other cultivable organisms include anaerobes, such as *Gardnerella vaginalis* (25%) and *Bacteroides* (30%), and aerobes, including GBS (15%) and *Escherichia coli* (8%).[72]

Broad-range PCR has been used to identify the kinds of microorganisms found in the amniotic fluid of women with preterm labor or PPROM. Several conclusions are evident: (1) PCR-based techniques identify 30%-50% more organisms than culture-based methods; (2) five phyla are commonly represented (Fig. 25.3); and (3) the patterns of microorganisms in amniotic fluid in women with preterm labor and intact membranes are different from those found in amniotic fluid samples from women with PPROM (Figs. 25.4 and 25.5).[18] However, given the high sensitivity of PCR, the increased likelihood of detecting DNA from nonviable or environmental contaminants makes the clinical significance of this microbial diversity somewhat uncertain. Studies of the association of MIAC (using PCR-based techniques) with fetal inflammation or perinatal outcomes noted statistically significant associations with elevated concentrations of inflammatory mediators in amniotic fluid and increased rates of histologic chorioamnionitis[53] and preterm delivery.[20]

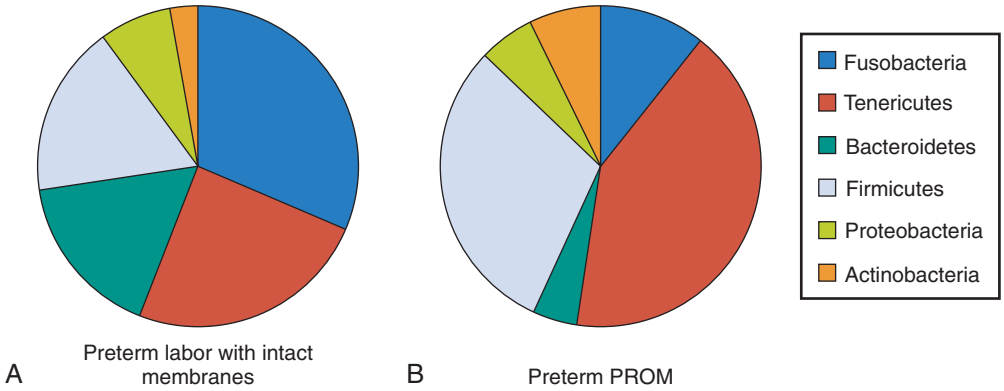
Diagnosis

Confirmation of intrauterine infection and/or inflammation requires amniotic fluid sampling and/or placental pathology. Therefore, in the vast majority of cases, the diagnosis is made using clinical criteria. The classic definition requires maternal fever (≥100.4°F or 38°C) plus two other findings, including maternal leukocytosis, maternal and fetal tachycardia, uterine tenderness, and foul-smelling or purulent amniotic fluid.[25] Individual clinical criteria have variable sensitivity and generally low specificity for

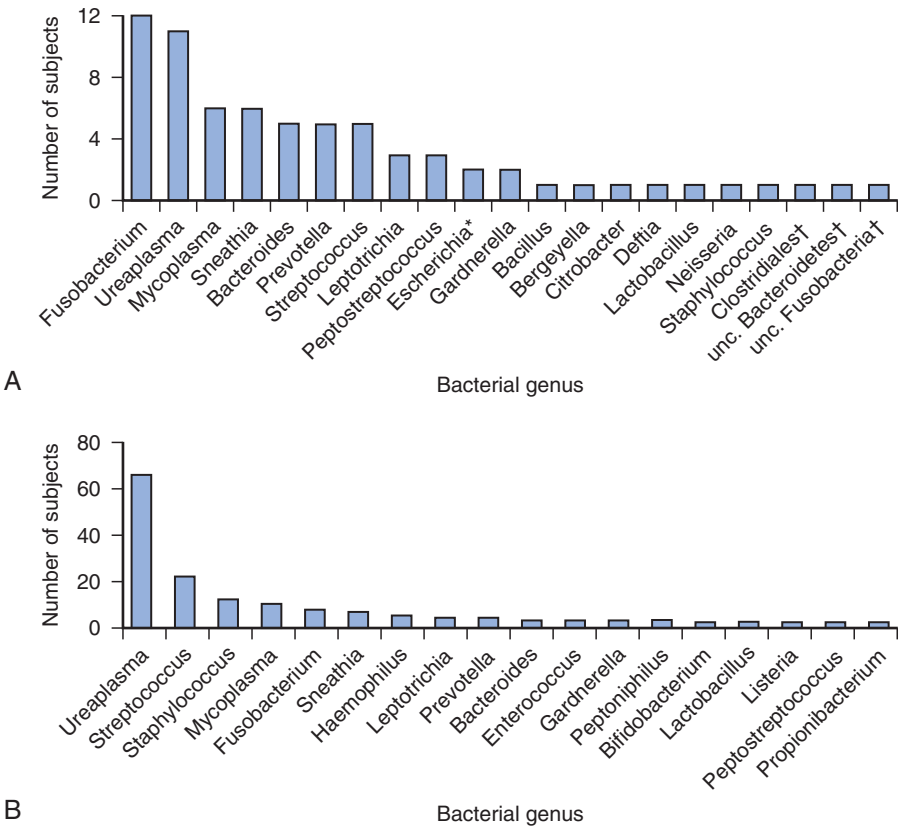


• **Fig. 25.3** Microbial diversity. Amniotic fluid specimens collected from 166 women in preterm labor with intact membranes were examined for the presence of microorganisms by both culture and polymerase chain reaction (PCR) techniques. The phylogeny of the 17 bacterial taxa identified based in a maximum likelihood algorithm is depicted. Shaded boxes indicate the number of subjects who were positive for a given taxon by culture or PCR (some samples were polymicrobial). For most individual taxa in which neither method detected all positive subjects, the total number is shown in the lightest colored box. A 99% sequence similarity cutoff threshold was used for phylotype assignment, which was based on 621 unambiguous nucleotide positions. *Bergeyella* sp. (bracketed) is included as a reference species only and was not detected in the study population. A single fungal species, *Candida albicans*, was detected by culture in *1*, subject, and by PCR in *2*, data not shown. (From DiGiulio DB, Romero R, Amogan HP, et al. Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: a molecular and culture-based investigation. *PLoS One.* 2008;3:e3056.)

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• **Fig. 25.4** Phylum-level distribution of bacterial taxa identified in amniotic fluid. Data obtained from studies using broad-range polymerase chain reaction (PCR) methods to assay amniotic fluid in the setting of either preterm labor with intact membranes, **A**, or of preterm premature rupture of the membranes (PPROM), **B**. (Data from DiGiulio DB. Diversity of microbes in amniotic fluid. *Semin Fetal Neonatal Med.* 2012;17:2-11.)



• **Fig. 25.5** Genus-level rank abundance curves of bacterial prevalence in amniotic fluid as determined by polymerase chain reaction (PCR). **A**, All 21 taxa reported in studies of women in preterm labor with intact membranes. **B**, The 18 taxa that were detected in two or more subjects in studies of women with preterm premature rupture of membranes. *Two subjects with *Escherichia* spp. were positive by both PCR and culture; in both cases *Escherichia* assignment is based on culture findings because the 16s ribosomal DNA gene is unreliable for differentiating between the genera *Escherichia* and *Shigella*. †Denotes the taxa that could not be classified to genus-level resolution because of current limitations of reference sequence databases. (Data from DiGiulio DB. Diversity of microbes in amniotic fluid. *Semin Fetal Neonatal Med.* 2012;17:2-11.)

chorioamnionitis, with little improvement in diagnostic accuracy when used in combination (Table 25.2).[54,72]

In 2016, a new descriptive term, intrauterine inflammation or infection or both (Triple I), was proposed by a panel of experts in an attempt to better define this clinical entity and to reflect the current understanding of pathophysiology, whereby inflammation does not always equal infection.[31] Suspected Triple I may be diagnosed in the presence of maternal intrapartum fever without a clear source, plus one or more of the following: maternal leukocytosis, purulent cervical drainage, or fetal tachycardia. Whether this new terminology and criteria become incorporated into routine clinical practice remains to be seen.

Maternal fever can occur as a result of intrauterine or extrauterine causes. Epidural anesthesia is associated with an increased risk of fever during labor with a relative risk of 3.34 (CI 2.63-4.23).[5,59] The general belief is that the fever associated with an epidural is noninfectious in origin; however, fever may be more likely to occur when placental inflammation is present. Fever following placement of an epidural can occur within 1 hour but almost always within 4-6 hours. It is noteworthy that fever induces an inflammatory response

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TABLE 25.2 Clinical and Amniotic Fluid Laboratory Diagnosis of Chorioamnionitis

Test	Result Suggesting Chorioamnionitis	Comments
Clinical Parameters		**Generally Nonspecific**
Fever	Temperature >100.4°F twice or >101°F once	95%-100% sensitive
Maternal tachycardia	>100/min	50%-80% sensitive
Fetal tachycardia	>160/min	40%-70% sensitive
Fundal tenderness	Tenderness on palpation	4%-25% sensitive
Vaginal discharge	Foul-smelling discharge	5%-22% sensitive
Amniotic Fluid Parameters		
Culture	Microbial growth	Diagnostic gold standard
Gram stain	Bacteria or white blood cells (>6 per high power field)	24% sensitive, 99% specific
Glucose level	<15 mg/dL	Affected by maternal hyperglycemia 57% sensitive, 74% specific
IL-6	>7.9 ng/mL	81% sensitive, 75% specific
Matrix metalloproteinase	Positive result	90% sensitive, 80% specific
White blood cell count	>30/cubic mm	57% sensitive, 78% specific
Leukocyte esterase	Positive (dipsticks)	85%-91% sensitive, 95%-100% specific

Data from Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol.* 2010;37:339-354.

in the mother, manifested by increased interleukin-6 levels. Epidural anesthesia also affects the body's thermoregulatory mechanisms by decreasing heat dissipation via sweating.

Laboratory testing may be helpful in confirming or excluding the diagnosis of chorioamnionitis, particularly when the diagnosis is uncertain. Leukocytosis has been described in 70%-90% of patients with clinical chorioamnionitis. In the absence of other signs and symptoms, isolated leukocytosis is of limited value. A number of amniotic fluid markers have been studied for the diagnosis of chorioamnionitis. These include culture, Gram stain, glucose levels, white blood cell counts, leukocyte esterase, DAMPs (damage-associated molecular patterns), soluble Toll-like receptors, matrix metalloproteinase, cytokines (e.g., TNF-α, interleukins-6 and -8, matrix metalloproteinase-8) and qualitative assessment of amniotic proteins (proteomics).[12,49] Proteomics is the characterization of the patterns of proteins and peptides in complex biologic samples (e.g., amniotic fluid). Using a newly developed technology (SELDI-TOF mass spectrometry), Buhimschi et al. demonstrated that the severity of chorioamnionitis and funisitis were significantly associated with the degree of intra-amniotic inflammation and time to delivery.[66] The development of rapid, noninvasive assays to measure biomarkers associated with MIAC in cervicovaginal fluid specimens holds promise for future diagnostics.[15]

The histopathologic findings of chorioamnionitis are well characterized and involve both maternal and fetal immune systems.[51] The initial inflammatory response occurs within 6-12 hours, is maternal in origin, and is manifested by an infiltration of neutrophils on the undersurface of the chorionic plate (acute subchorionitis). The next site of involvement occurs at the trophoblast layer of the membranous chorion (acute chorionitis). Over the next 12 to 36 hours, there is spread to the adjacent chorion and amnion (chorioamnionitis). If the infectious process is prolonged (36-48 hours) necrotizing chorioamnionitis (stage 3 acute chorioamnionitis) can result. Fetal vasculitis is an indication of a fetal inflammatory response and represents diapedesis and transmigration of fetal cells across the vessel wall in response to chemotactic agents. In preterm pregnancies, the fetal responses first appear in the chorionic plate (chorionic vasculitis), whereas in term pregnancies they are first evident in the umbilical vein (umbilical phlebitis). Stage 1 fetal inflammatory responses are characterized by neutrophils in the chorionic vessels and/or umbilical vein vasculitis; stage 2 is reached when neutrophils enter the wall of the umbilical artery (umbilical arteritis). With increasing duration of inflammation, neutrophils migrate out of the umbilical artery and vein and enter Wharton jelly to assume an arclike distribution (stage 3). Funisitis is a general term signifying inflammation of the umbilical artery and vein. It is important to distinguish umbilical arteritis from umbilical phlebitis, because the former is associated with increased concentrations of circulating fetal cytokines, whereas the latter is not. It is noteworthy that the majority of neutrophils in both the amniotic fluid and airspaces of the newborn's lungs are fetal in origin.

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Pathogenesis

Microorganisms typically invade the intrauterine space by ascending through the cervix from the lower genital tract. Retrograde migration from the abdominal cavity through the fallopian tubes, hematogenous spread through the placenta, and iatrogenic introduction via amniocentesis or chorionic villus sampling are additional mechanisms by which organisms gain access to the uterine cavity.[27]

During pregnancy, the cervical mucus plug, fetal membranes, and placenta function to protect the developing fetus from invading bacteria. The cervical mucus plug is particularly important, because it is not only an anatomic barrier but also contains numerous antibacterial peptides with bactericidal activity against potential pathogens that commonly colonize the vaginal tissues.[30] It is generally believed that once organisms gain access to the intrauterine space, they reside and replicate in the choriodecidual space before entering the amniotic fluid.[56] However, data suggest an initial intra-amniotic entry of bacteria through a restricted cervical region of membranes.[42] After replication in the amniotic cavity, microorganisms then invade the amnion and its connective tissue and progress into the chorion and decidua.

Stimulation of the innate immune response first occurs when the pathogen-associated molecular patterns of invading microorganisms are recognized by pattern recognition receptors (toll-like receptors [TLRs], NOD-like receptors (NLRs]) expressed by host epithelial cells, circulating immune cells, and perhaps most important, placental trophoblast cells.[1,32] Once stimulated, these receptors induce a cascade of proinflammatory signaling, including stimulation of Myd88 (TLRs) and inflammasome (NLRs) pathways. Subsequent production of various cytokines, chemokines, matrix-degrading enzymes, prostaglandins, and other mediators leads to inflammatory cell infiltrate, membrane rupture, cervical ripening, and in some cases the onset of labor.[2,55] Experimental evidence from animal models of intrauterine infection suggests the specific inflammatory pathway leading to the induction of preterm labor is dependent on the particular TLR activated (determined by the nature of infecting agent), as well as the route of infection (ascending versus systemic).[69] The cascade of events leading to preterm labor in the setting of intrauterine infection may be considered an adaptive host response to maintain maternal reproductive fitness.[55] This defense mechanism may also impart a survival advantage for the fetus as a means to escape a hostile intrauterine environment.

As mentioned, bacterial invasion of the amniotic cavity may be chronic, existing for several weeks without clinical symptoms. This is particularly true in infections with *Ureaplasma* spp.[55] Several investigators have documented amniotic fluid cultures positive for *Ureaplasma* in asymptomatic women undergoing genetic amniocenteses at 16-20 weeks' gestation.[68] Despite a lack of overt symptomatology, a significant portion of these women exhibited a robust inflammatory response as measured by expression of inflammatory cytokines in the amniotic fluid and subsequently went on to experience adverse pregnancy outcomes (fetal loss, preterm birth) compared with those women with sterile cultures. In fact, there is ample evidence to suggest that *Ureaplasma* spp., traditionally considered to be of relatively low virulence, may evoke a more intense host inflammatory response as compared with other pathogens associated with chorioamnionitis.[47]

Treatment

Obstetric Management

Administration of broad-spectrum antibiotics and prompt delivery of the fetus in the setting of acute clinical chorioamnionitis reduces both fetal and maternal morbidity.[26] Cesarean delivery should be performed only for standard obstetric indications, because there is no evidence it improves neonatal outcomes in the setting of chorioamnionitis and may only increase maternal complications.[22] Ampicillin and gentamicin are the most commonly prescribed antimicrobials for intra-amniotic infection, although there are no randomized trials comparing the efficacy of various antibiotic regimens. The optimal duration of therapy is unknown; however, intrapartum treatment should not be continued automatically postpartum, and the decision to extend the duration of antimicrobial therapy should be based on risk factors for postpartum endometritis.[16] It is worth noting that standard antibiotic regimens used to treat chorioamnionitis do not provide coverage against *Mycoplasma* and *Ureaplasma* spp., the most common organisms associated with intra-amniotic infection. Although there are a limited number of case reports describing reduced adverse pregnancy outcomes following treatment of documented amniotic fluid infection with genital mycoplasmas,[62] evidence for empiric therapy in the setting of acute clinical chorioamnionitis is lacking. This may reflect the differential microbial etiology of subclinical versus clinical chorioamnionitis. If cesarean delivery is performed, clindamycin (or metronidazole) is often added for anaerobic coverage.

The administration of antenatal corticosteroids to enhance fetal lung maturity in the setting of chorioamnionitis is controversial, because it is believed that the immunosuppressive effects of steroids may exacerbate maternal or neonatal infectious complications. Although randomized clinical trials addressing this issue are lacking, there are observational data to suggest that antenatal steroids may actually reduce neonatal morbidity, including severe intraventricular hemorrhage and periventricular leukomalacia in the presence of chorioamnionitis.[7]

Given that PPROM and preterm labor may be the consequence of occult intra-amniotic infection, it has been hypothesized that antimicrobial therapy may be beneficial in these circumstances despite the absence of overt signs of infection. A meta-analysis reaffirmed that administration of antibiotics and expectant management of women with PPROM is associated with a reduction in chorioamnionitis,

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prolongation of pregnancy, and decreased neonatal morbidities (early-onset sepsis, need for supplemental oxygen, abnormal cerebral ultrasound scans), but was not associated with a significant reduction in perinatal mortality.[39] Furthermore, the use of antenatal antibiotics in particular circumstances may be harmful. The administration of co-amoxiclav (ampicillin/clavulanic acid) in women with PPROM or preterm labor with intact membranes was associated with an increased risk for necrotizing enterocolitis in neonates. In addition, the use of both erythromycin and co-amoxiclav antibiotics for women with preterm labor and intact membranes was associated with an unexpected increase in the incidence of cerebral palsy at a 7-year follow-up evaluation.[40]

Management of the Exposed Infant

Most recent guidelines from the Centers for Disease Control and the American Academy of Pediatrics Committee on the Fetus and Newborn recommend that all healthy-appearing newborns born to women with a diagnosis of chorioamnionitis undergo a limited diagnostic evaluation and receive empiric antibiotic therapy until early-onset sepsis can be ruled out.[50,74]

There is growing evidence to suggest that close observation, rather than empiric antibiotic therapy, is the preferred strategy for the management of asymptomatic full-term infants exposed to chorioamnionitis.[10,34] The risk of sepsis in this population is exceedingly low given that the incidence of early-onset sepsis has declined dramatically over the last two decades (due to widespread implementation of intrapartum prophylaxis for mothers colonized with GBS and the treatment of women with chorioamnionitis with antibiotics during labor). This substantially increases the number of healthy term newborns who would need to receive antibiotics to prevent one case of sepsis.[76] Because the risk of EOS in infants born to women with chorioamnionitis is strongly dependent on gestational age, it remains prudent to empirically treat chorioamnionitis-exposed preterm infants.

Because the diagnosis of clinical chorioamnionitis is often made when fever is the only manifestation of an intrauterine infection, many infants may be unnecessarily exposed to broad-spectrum antibiotic therapy. Complicating this issue is the increased incidence of fever in women receiving epidural anesthesia.[59] Therefore, if fever is the sole manifestation of suspected chorioamnionitis, consultation with the obstetric provider is recommended to determine the level of clinical suspicion before routinely treating asymptomatic infants.

Outcomes

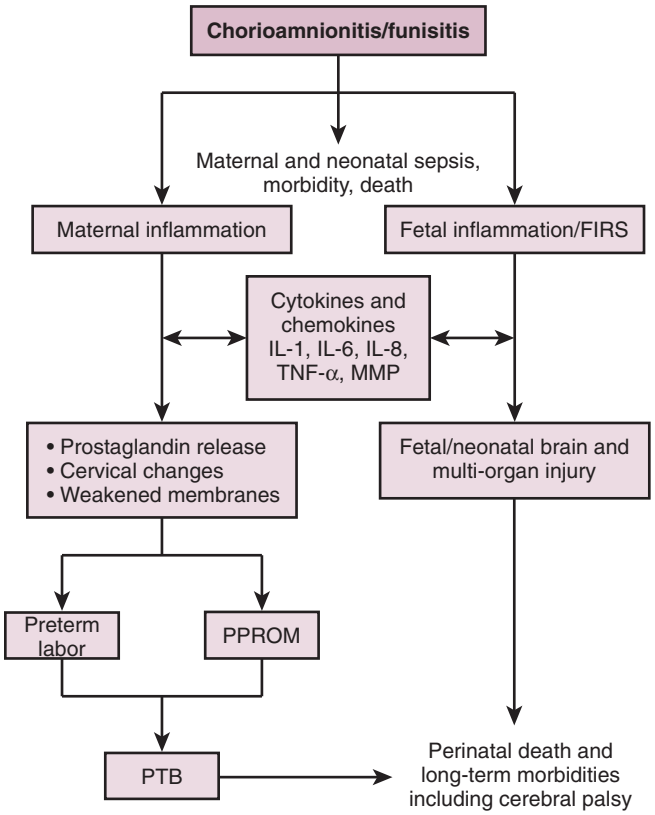
Chorioamnionitis can adversely affect the mother and her unborn infant. In pregnant women, it is associated with a twofold increase in abnormal progression of labor, an increased risk of cesarean section, postpartum hemorrhage, poor cervical dilation, and placental abruption. Surgical complications after cesarean section such as endometritis, pelvic abscess, wound infection, thromboembolism, and bacteremia are also more common in women with chorioamnionitis. The effects of intrauterine infection on the fetus depend on the duration and timing of the inflammatory process. Acute chorioamnionitis is an important risk factor for early-onset neonatal sepsis. Chronic infections, however, are often subclinical and have been associated with a wide variety of organ injury, including the brain (periventricular leukomalacia), lung (bronchopulmonary dysplasia), eye (retinopathy of prematurity), intestine (necrotizing enterocolitis), and thymus (involution and a change in cellular composition).[23] Chorioamnionitis, especially with a fetal inflammatory component, has also been associated with hemodynamic instability in the preterm newborn infant.

Chorioamnionitis is considered an important cause of preterm birth; microbiologic data suggest that up to 25% of preterm births are caused by an intrauterine infection. The evidence linking infection and preterm labor is as follows: (1) intrauterine infection (or exposure to microbial products) in experimental animals results in preterm delivery; (2) extrauterine maternal infections (e.g., pyelonephritis) are associated with preterm labor; (3) subclinical intrauterine infections are associated with preterm labor and birth; (4) patients with evidence of intrauterine inflammation (e.g., increased amniotic fluid cytokines or matrix metalloproteinases) in the midtrimester are at increased risk for preterm delivery; (5) in experimental animal models, antibiotic treatment of intrauterine infections can prevent prematurity; (6) treatment of asymptomatic bacteriuria prevents prematurity; (7) administration of antibiotics to women with preterm premature rupture of membranes prolongs gestation; (8) microorganisms can be cultured from the placenta in a high percentage of women presenting with preterm labor; and (9) polymorphonuclear infiltrations in the placenta are associated with spontaneous preterm birth. A possible mechanism for infection-associated preterm birth is shown in Fig. 25.6.[72]

Acute chorioamnionitis is a risk factor for neonatal sepsis.[76] That is not surprising given that chorioamnionitis is a key step in the pathway of most ascending infections causing early-onset sepsis. Among infants greater than or equal to 37 weeks' gestation with proven early-onset sepsis owing to *E. coli* or group B streptococcus, clinical chorioamnionitis was documented in the medical record about one-third of the time, and histologic chorioamnionitis was documented in 90%.[66] Importantly, the risk of EOS in infants born to women with chorioamnionitis is inversely correlated with gestational age. Reported rates of confirmed EOS in infants born at ≥35 weeks' gestation to mothers with clinical chorioamnionitis range from 0.47%-1.24%.[9,33,43] In contrast, rates of EOS in exposed moderate and extremely preterm infants are 5-10 times higher.[24,48,65]

Despite a large body of evidence, many studies have not shown a relationship with intrauterine infection, brain injury, and respiratory outcomes. Some of the controversy likely results from lack of precision in the definition of

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• **Fig. 25.6** Pathogenesis of chorioamnionitis: maternal and fetal response and complications. FIRS, Fetal inflammatory response syndrome; PPROM, preterm premature rupture of membranes; PTB, preterm birth. (From Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol.* 2010;37:339-354.)

chorioamnionitis and whether a fetal inflammatory response is also present. It is worth emphasizing that chorioamnionitis without evidence of fetal inflammation is unlikely to cause fetal or neonatal injury. Furthermore, the adverse effects on the newborn infant may simply be the result of preterm birth and the host of postnatal complications that affect preterm infants (e.g., respiratory distress syndrome, necrotizing enterocolitis, or intraventricular hemorrhage).

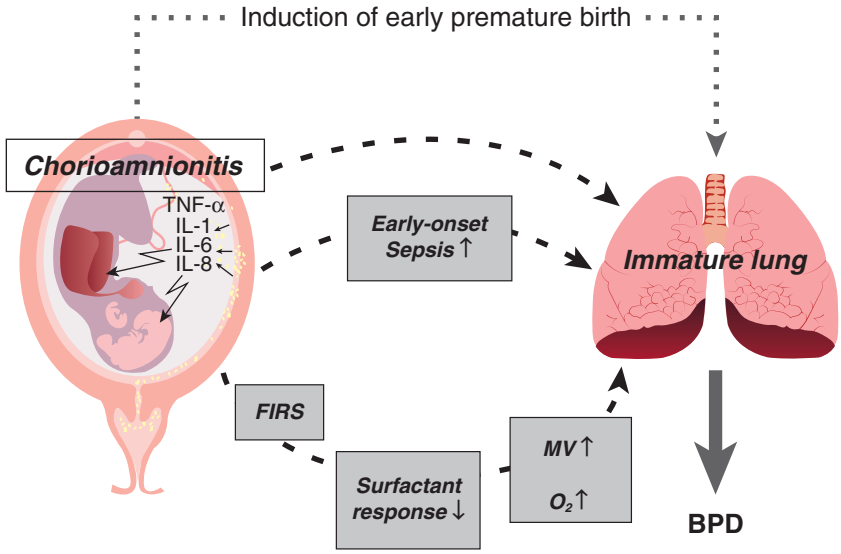
The association with antenatal inflammation and chronic lung disease is indirect and based on a number of experimental observations. In 1996, Watterberg concluded that chorioamnionitis decreased the risk of respiratory distress syndrome but increased the likelihood of bronchopulmonary dysplasia (BPD).[75] However, those data came from an era when antenatal steroids were used infrequently. In contrast, Van Marter et al. demonstrated a reduced risk of BPD in infants born to women with chorioamnionitis, but an increased risk of bronchopulmonary dysplasia in infants born from an infected intrauterine environment who were mechanically ventilated.[73] There appears to be a protective effect of antenatal inflammation on the incidence of respiratory distress syndrome, which is consistent with animal data demonstrating that both bacterial cell wall products (e.g., lipopolysaccharide) and inflammatory mediators (IL-6) accelerate surfactant production.[11,70] Been et al. demonstrated that infants born to women with histologic chorioamnionitis and a fetal vasculitis weaned from oxygen and mechanical ventilation more slowly and exhibited a decreased response to exogenous surfactant.[8] That group of infants was more likely to develop bronchopulmonary dysplasia. This study supports the importance of the additive effects of inflammation and mechanical ventilation on the risk of bronchopulmonary dysplasia. This "multiple hit model," in which both antenatal (chorioamnionitis) and postnatal factors (sepsis, surfactant production and function, mechanical ventilation) modulate the risk for bronchopulmonary dysplasia, is supported by most recent epidemiologic studies and data from experimental animal models (Fig. 25.7).[6,29,37,71]

The relationship between clinical chorioamnionitis and white matter disease is also controversial. In many studies, but not all, cytokine levels are increased in the cord blood of infants who develop periventricular leukomalacia.[78] Postmortem immunohistochemical studies on the brains of preterm infants noted an increased expression of cytokines in the periventricular region of infants with periventricular leukomalacia compared with those without evidence of brain injury.[77] More recent meta-analyses' data have noted significant associations between histologic and clinical chorioamnionitis with the risk of cerebral palsy.[60,61] However, individual studies have not been consistent in those findings. Data most supportive of that relationship have come from the ELGAN study, in which nearly 900 placentas were cultured and biopsied following the delivery of extremely low–birth weight infants.[44] Histologic chorioamnionitis was associated with ventriculomegaly and diparetic cerebral palsy. The recovery of any aerobic or anaerobic organism from the placenta significantly increased the odds ratios for both these outcomes as well as the presence of echolucent lesions on head ultrasound. Furthermore, the investigators were able to demonstrate a dose-response relationship between the number of species recovered and the risk of these morbidities.

Areas for Future Investigation

Despite improved understanding of the pathogenic mechanism by which intrauterine infection leads to adverse pregnancy outcomes, research efforts over the past few decades have yielded little in the way of effective clinical strategies for the prevention and management of intrauterine infection. The development of more rigorous diagnostic criteria may better identify those women and fetuses most likely to benefit from antimicrobial treatment and reduce unnecessary, potentially harmful antibiotic exposure. The development of sepsis calculators that combine a rigorous assessment of intrapartum risk factors together with clinical presentation, like that proposed by Puopolo and Escobar, may better identify neonates most at risk for early-onset sepsis and reduce the number of healthy infants exposed to unnecessary antimicrobial therapy.[21] Continued exploration of the protective role of a healthy vaginal

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• **Fig. 25.7** The role of chorioamnionitis in the development of bronchopulmonary dysplasia. Chorioamnionitis induces early preterm delivery of an infant with immature lungs, the major risk factor for bronchopulmonary dysplasia (BPD). Exposure to intra-amniotic inflammatory mediators renders the lung susceptible for further postnatal injuries. Chorioamnionitis with accompanying systemic fetal inflammatory response (FIRS) is known to reduce the response to exogenous surfactant administration, leading to an increased need for mechanical ventilation (MV) and supplemental oxygen (O_2). (From Thomas W, Speer CP. Chorioamnionitis is essential in the evolution of bronchopulmonary dysplasia–the case in favour. *Paediatr Respir Rev.* 2014;15(1):49-52.)

microbiome, mechanisms of abnormal colonization of the lower genital tract, and characterization of maternal/fetal immune responses to specific pathogens may help to identify those women most at risk for infectious complications of pregnancy and open the door for novel preventive strategies. Finally, exploration of potential anti-inflammatory therapies to reduce infection-related morbidities in both the mother and infant is warranted.

Key Points

- Intra-amniotic infection most frequently results from ascension of pathogens from the lower genital tract, eliciting variable inflammatory responses in both the mother and fetus.
- Exposure to intrauterine inflammation increases the risk of preterm birth and increases the risk of long-term morbidities, including cerebral palsy, bronchopulmonary dysplasia, and retinopathy of prematurity.
- Administration of intrapartum antibiotics to mothers with chorioamnionitis decreases the risk of neonatal sepsis and postpartum maternal infections. However, novel interventions to disrupt inflammatory signaling cascades *in utero* are greatly needed.

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26

Placental Pathology

RAYMOND W. REDLINE

The placenta has two opposing functions. It is the sole source of sustenance for the fetus and its sole protection against noxious external influences. It can be argued that no evaluation of a sick neonate is complete without knowing the status of the organ that has accompanied it through the preceding gestation. The specific "value added" by placental examination can be summarized under five overlapping headings:

1. Identification of immediately treatable processes: elevated risk of neonatal sepsis (histologic chorioamnionitis with fetal inflammatory response), specific infections (CMV cytomegalovirus, candida, syphilis, listeria), retained placenta, metabolic storage diseases, placental malignancies
2. Determination of the underlying cause of adverse outcomes: subclassifies preterm delivery, fetal growth restriction, and stillbirth into pathophysiologically homogenous phenotypes
3. Estimation of recurrence risk: different patterns of placental injury have distinct and widely disparate rates of recurrence varying from 0%-70%
4. Guidance for future care path(s): screening for predisposing maternal diseases, genetic testing, high-risk referral, enhanced antenatal surveillance, initiation of antenatal therapy, elective early delivery
5. Quality assurance and risk management: separating perceived from actual pathology (e.g., chorioamnionitis, abruption), uncovering subacute and chronic disorders predisposing to neonatal encephalopathy, seizures, stroke, or cerebral palsy

This chapter is not a comprehensive review of placental pathology; the reader is referred to five general references.[4,11,22,25,48] Rather, it addresses three topics: (1) the optimal use of the pathology service to obtain useful information; (2) an explanation of specific patterns of placental injury; and (3) clinicopathologic correlation (i.e., which lesions are seen in which clinical situations).

Optimal Use of Pathology Service

Because not all placentas are submitted to pathology, every obstetric service should have a specific list of situations in which a placental examination is indicated. Box 26.1 provides a list compiled by the College of American Pathologists in collaboration with a panel of neonatologists and obstetricians.[27] Because many sick neonates are transported from other hospitals, there should be a policy to ensure a timely placental examination. The best solution is to bring the placenta along with the neonate to the tertiary care center. For various reasons, the transport of the tissue specimen itself is sometimes impractical. In these cases, the slides and pathology report from the referring hospital should be requested and reviewed by the pathologist at the hospital where the neonate is to be treated. Whenever possible, placentas should be refrigerated immediately after delivery and sent without fixative to the pathology laboratory. Specimens maintained in this fashion remain useful for at least 7 days after delivery. When refrigeration within 1-2 hours of delivery is impossible, placentas should be immersed in 2-3 volumes of formalin; placentas can remain in formalin for an indefinite period before examination by the pathologist.

An informed evaluation of the placenta requires that the pathologist be aware of the clinical situation. Some mechanism, usually a form, must be established to convey this information. A proper balance should be struck between a totally open-ended form and a tedious checklist. Fig. 26.1 is an example of a form that may be useful.

Placental diagnosis requires very few special studies. Even bacterial cultures in cases of suspected chorioamnionitis rarely provide useful information beyond that which is available from placental histology and the infant's blood culture. Fungal stains of the cord and membranes may occasionally be useful for neonatal management. In certain situations, a placental karyotype may be of interest, because some data suggest that occasional cases of intrauterine fetal demise and idiopathic fetal growth restriction (FGR) may be explained on the basis of chromosomal anomalies confined to placental tissues (confined placental mosaicism).[19]

Structure, Function, and Pathologic Reaction Patterns

Overview

At the simplest level, the placenta is nothing more than fetal blood vessels and surrounding connective tissue enveloped

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Abstract

Placental pathology is an important tool for the understanding and management of disorders leading to premature delivery and birth asphyxia. Best practices include prompt submission with adequate history and timely reporting with clinical correlation. Both clinicians and pathologists need to have a thorough understanding of placental biology and the major patterns of placental injury. A successful placental pathology service will facilitate specific diagnosis, immediate management, and future genetic counseling to reduce the risk of recurrence.

Keywords

acute chorioamnionitis
maternal vascular malperfusion
fetal vascular malperfusion
maternal floor infarction
placental pathology

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Sheet filled out M.D. (printed name)_____
Gestational age (best estimate):_____
Ob index: G____ Full term____ Prem____ Ab____ Lvg____
Maternal history:
Baby (weight, Apgars, malformations, other):
Any specific questions about this placenta?

• **Fig. 26.1** Placental data sheet used to transmit clinical history to the pathologist. Each item is widely spaced on the actual full-page form to provide sufficient space for free text.

• BOX 26.1 Placental Submission Guidelines

Indications for Submission (College of American Pathologists Practice Guideline 1997): Developed by a task force of pathologists, obstetricians, and neonatologists. Indications separated into three groups as listed below.

Maternal

- Delivery at less than 37 weeks or more than 42 weeks (accepted alternative is <34 weeks)
- Systemic disorders with concern for mother or infant (hypertension, diabetes, other)
- Peripartum fever or infection
- Unexplained or excessive third-trimester bleeding
- Unexplained or recurrent pregnancy complications
- Invasive procedures with suspected placental injury
- Thick or viscid meconium
- Severe oligohydramnios/polyhydramnios

Fetal and Neonatal

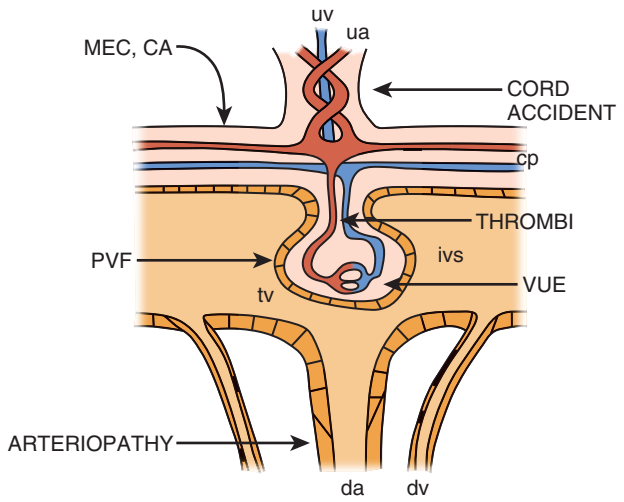
- Stillbirth or neonatal death
- NICU admission
- SGA or LGA (<10th or >90th percentile for gestational age)
- Birth depression: pH less than 7.0; Apgar score at 5 minutes less than 7; assisted ventilation greater than 10 minutes; hematocrit less than 35 mg/dL
- Neonatal seizures
- Suspected infection or sepsis
- Hydrops fetalis
- Multiple gestation (accepted alternative is all fused placentas, same-sex twins, or discordant fetal growth)

Significant Gross Placental Abnormalities

- Structural abnormalities of the placental disk or membranes
- Suspected abnormal size or weight for gestational age
- Umbilical cord abnormalities (e.g., long/short/hypercoiled/abnormal insertion/single artery)

LGA, large for gestational age; SGA, small for gestational age.

by a continuous layer of epithelium known as *trophoblast* and sitting in a pool of maternal blood called the *intervillous space*; the latter being continuously filled and drained by maternal uterine arteries and veins (Fig. 26.2). The same unit of structure is repeated in an attenuated form in the placental membranes. Early in pregnancy, the fetal vasculature and maternal intervillous space involute in that portion of the gestational sac destined to become the membranes, leaving a tough shell of fetal connective tissue and the placental trophoblast in contact with the maternal uterus. An understanding of each of these anatomic compartments and



• **Fig. 26.2** Schematic diagram of a functional unit in the placenta, with sites and patterns of injury indicated by arrows. Deoxygenated fetal blood enters the placenta via umbilical arteries (*ua*) and flows through the chorionic plate (*cp*) and stem villous arteries before entering terminal villi (*tv*). Flow into capillaries is regulated by stem villous arterioles. Postcapillary venules combine to form stem villous and chorionic plate veins, which drain into a single umbilical vein (*uv*) that carries oxygenated blood to the fetus. Maternal blood enters the intervillous space (*ivs*) via decidual arteries (*da*) lined with the trophoblast (*hatched lines*) and drains through unmodified decidual veins (*dv*). Decidual arteriopathy restricts maternal perfusion of the intervillous space. Perivillous fibrin (*PVF*) coats the villous trophoblast (*hatched lines*), preventing gas exchange. Villitis of unknown etiology (*VUE*) expands the villous stroma, increasing the diffusion distance. A cord accident compresses the umbilical vessels, causing a global decrease in fetoplacental circulation. Meconium (*MEC*) and chorioamnionitis (*CA*) may decrease villous perfusion by damaging fetal vessels in the chorionic plate. Segmental fetal vascular malperfusion (*THROMBI*) similarly decreases the distal fetal vascular bed.

their reaction patterns in abnormal pregnancies provides the basis for understanding placental pathology.

Considering the fetal circulation first, the *fetal stromal-vascular* portion of the placenta is supplied by a pair of umbilical arteries and drained by a single umbilical vein. Because there is an arterial anastomosis near the umbilical cord insertion site, the fetus is not handicapped if one of the arteries is occluded or absent (single umbilical artery). The vein is the sole supply of oxygenated placental blood for the fetus. It also has the thinnest wall and is the easiest of the three umbilical vessels to collapse. Large chorionic plate arteries and veins branching off from the umbilical vessels transmit blood through the proximal stem villi to the distal villous units, where gas exchange occurs. Decreased flow secondary to fetal malperfusion of these vessels leads to luminal occlusion (fibromuscular sclerosis) and involution of the distal vascular bed (avascular villi).[43] These changes are global in the placentas of stillborn fetuses and focal in live-born infants with occlusive placental thrombi. Each distal villous unit consists of a central mature intermediate villus and surrounding terminal villi. Mature intermediate villi contain arterioles that directly regulate flow to the distal villous capillary bed. Distal villous capillaries may occasionally rupture, leading to fetomaternal hemorrhage, but an

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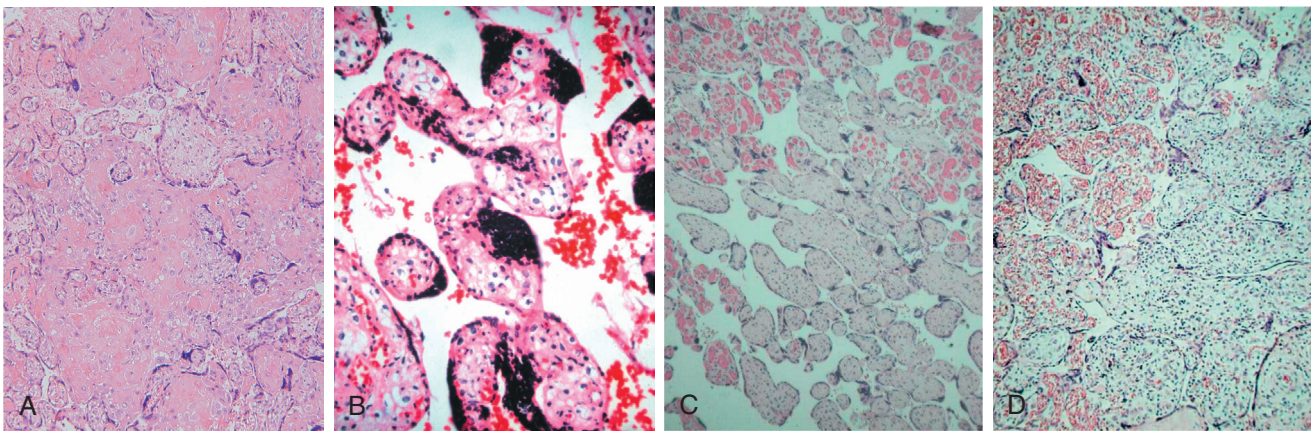
efficient mechanism for villous repair and re-epithelialization usually restricts the amount of lost fetal blood.[34]

Adequate perfusion of the *maternal uterine-trophoblastic* portion of the placenta depends on pregnancy-related increases in maternal intravascular blood volume and decreases in vascular tone. Chronic medical conditions such as renal disease, essential hypertension, and collagen vascular disease can lead to maternal malperfusion by interfering with these systemic accommodations to pregnancy.[21] To ensure adequate perfusion of the intervillous space, the human placenta has evolved a mechanism for remodeling and enlarging uteroplacental arteries.[39] The placental trophoblast grows down the lumen of these vessels, invades the vascular wall, and replaces the smooth muscle layer with a noncontractile layer of fibrinoid matrix. Failure to execute this sequence because of superficial implantation compromises perfusion, leaves the uteroplacental vessels susceptible to spasm, degeneration, and rupture, and is believed to play an important role in the pathogenesis of preeclampsia, abruptio placentae, and some cases of FGR.[6]

Intervening between the fetal and maternal circulations is the villous trophoblast. This barrier consists of a syncytial layer of terminally differentiated trophoblast specialized for gas exchange (syncytiotrophoblast) plus a few widely spaced underlying trophoblast stem cells (cytotrophoblast). In late gestation, the syncytiotrophoblast and its basement membrane fuse with the basement membrane of peripheral villous capillaries to form vasculosyncytial membranes that facilitate gas exchange. Term or near-term placentas that lack adequate vasculosyncytial membranes are at increased risk for stillbirth (sometimes called "delayed maturation").[53] Turnover of villous trophoblast is accomplished via the formation of syncytial knots, which are later released into the systemic circulation as a new trophoblast is generated. Syncytial knots form in excess of their rate of release into the intervillous circulation in placentas affected by maternal malperfusion, leading to a stereotypical histologic appearance that is easily detectable by placental examination (sometimes called "accelerated maturation").[30] It is important that maternal blood contact a nonadhesive surface to prevent activation of the coagulation system. Studies indicate that the anionic phospholipid binding protein annexin-V plays an important role in preventing the assembly of active coagulation factor complexes on the trophoblast cell membrane.[40] Antiphospholipid antibodies have been shown to displace annexin-V from the cell surface, accounting for pathology resembling preeclampsia in some affected pregnancies. Altered anticoagulant mechanisms in the intervillous space may also play a role in a poorly understood placental lesion with a very high recurrence rate known as massive perivillous fibrin deposition ("maternal floor infarction"). This lesion is characterized by an accumulation of fibrin and trophoblast-derived extracellular matrix material that surrounds terminal villi, compromising intervillous circulation and gas exchange (Fig. 26.3A).[29]

Although the two circulations are usually distinct, flow-related trauma can break down the barrier between them, leading to either fetomaternal hemorrhage or entry of maternal cells into fetal tissues. When maternal inflammatory cells cross the trophoblastic barrier, they may participate in a graft-versus-host–type response against fetal antigens in the villi. This process, known as villitis of unknown etiology (VUE), is discussed in more detail in the following.

The final placental compartment is the fluid-filled sac of membranes, which must rupture to allow vaginal delivery. Theoretically, membranes may rupture prematurely for one of two reasons: increased luminal pressure or decreased structural integrity. Increased pressure can be caused by premature contractions, cervical dilation, or polyhydramnios. Structural integrity may be compromised by trauma, inflammatory responses associated with ascending bacterial



• **Fig. 26.3** Histologic patterns of placental injury. **A,** Massive perivillous fibrin deposition. Fibrin and fibrinoid matrix encase the terminal villi. **B,** Chronic maternal vascular malperfusion (accelerated villous maturation). Numerous aggregates of syncytiotrophoblastic nuclei (syncytial knots) surround immature villi of reduced size for gestational age. **C,** Segmental fetal vascular malperfusion. Avascular villi (*lower right*) resulting from upstream vascular occlusion. **D,** Villitis of unknown etiology (*VUE*). Maternal T lymphocytes in the fetal villous stroma (*lower right*) lead to edema and fibrosis, which increase the diffusion distance between the maternal and fetal circulations.

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infection, or ischemic necrosis caused by maternal vascular compromise. The amniotic fluid contained within the sac is predominantly derived from fetal urine, and changes in fluid volume (oligohydramnios or polyhydramnios) often reflect altered fetal fluid balance. For example, maternal malperfusion can lead to fetal hypovolemia, oliguria, and subsequent oligohydramnios.[25] Significant oligohydramnios has been associated with umbilical cord compression, limb deformities, and failure of adequate lung growth.[26,28,31]

Placental membranes can also incorporate various exogenous substances suspended in the amniotic fluid, some of which, such as meconium and bacterial cell wall constituents (e.g., lipopolysaccharide), may damage the membranes and the underlying fetal vessels.[3,17] Another exogenous substance sometimes found in the membranes is hemosiderin, which can be an indicator of chronic abruption.[33]

Maternal Uterine-Trophoblastic Lesions

Muscularized maternal arteries supplying the intervillous space are susceptible to stenosis, occlusion, or rupture. Stenosis leads to chronic maternal malperfusion, which is characterized by low placental weight, increased syncytial knotting, intervillous fibrin deposition, and villous agglutination, particularly in the "watershed zones" between spiral arteries (see Fig. 26.3*B*).[21,44] Total occlusion of these arteries causes villous infarction. Although experimental studies have shown that 20%-25% of villous parenchyma can be infarcted without acute fetal compromise,[11] these studies fail to account for the impaired status of the remaining placenta in these disorders.

Rupture of the maternal arteries (abruptio placenta) may be attributed to trauma occasionally but more commonly represents ischemia-reperfusion injury with secondary rupture of the injured vascular wall. The common association of abruption with vasoactive drugs such as nicotine, and especially cocaine, is consistent with this pathogenesis.[1,32] Because muscular arteries are incompletely remodeled in preeclampsia, abruptio placenta is especially frequent in this disorder. Chronic abruption can also occur and manifests pathologically as organizing marginal blood clots, chorioamnionic hemosiderin deposition, and placental circumvallation.[33] Most evidence to date suggests that chronic abruption represents venous rather than arterial hemorrhage.

Fetal Stromal-Vascular Lesions

Fetal vessels within the umbilical cord are protected from compression by the cord matrix, a hydrated gel known as Wharton's jelly. Several processes lessen this protection: decreased hydration of the matrix secondary to maternal malperfusion; torsion of cord vessels owing to excessive coiling; and insertion of the cord vessels into the membranes, leaving them exposed to trauma.[41] The critical parameters for deciding whether a putative cord lesion is significant include thrombosis, necrosis, or hemorrhage at the proposed site of occlusion, and histologic differences in venous dilatation or cord structure proximal and distal to this site.

Large vessels in the chorionic plate and stem villi may occasionally undergo thrombotic occlusion (fetal vascular malperfusion, segmental type, see Fig. 26.3*C*).[43] Factors predisposing to thrombosis are similar to those reported in other organs, including inflammation (villitis of unknown etiology or chorioamnionitis), toxic damage (prolonged meconium exposure), stasis (chronic umbilical cord obstruction, fetal congestive heart failure), inherited predispositions to clotting (protein C and S deficiencies, maternal antiphospholipid antibodies, factor V Leiden), hyperviscosity (fetal polycythemia), and specific maternal diseases (e.g., diabetes mellitus, platelet disorders). Villi downstream from the occlusive thrombi become avascular and hyalinized. Consequences of fetal vascular malperfusion include a reduction in the size of the fetal vascular bed available for gas exchange, coexistent thromboembolic disease in the fetus, and (in rare cases) fetal consumptive coagulopathy with disseminated intravascular coagulation or thrombocytopenia.

Fetal arterioles in mature intermediate villi regulate placental resistance to fetal blood flow, the parameter evaluated in clinical pulsed-flow Doppler studies. Obliteration, stenosis, or spasm of these arterioles can have a profound impact on gas exchange.[13] These arterioles have been found to be numerically decreased in autosomal trisomies[51] and either obliterated or stenosed in patients with severe FGR.[10,13] A large proportion of placentas with these fetal arteriolar changes also show clinical and pathologic evidence of chronic maternal malperfusion.

Fetal capillaries in the terminal villi can sustain microvascular damage leading to leakage of fluid (villous edema) or blood (villous stromal hemorrhage).[13,31] Both lesions have been shown to be associated with adverse outcomes in very premature infants.[12,46] Frank rupture of these capillaries causes placental intervillous thrombi and, in some cases, hypovolemia, fetal anemia, and a compensatory increase in circulating, nucleated red blood cells (massive fetomaternal hemorrhage).[7,20] Finally, the capillary bed of distal villi can undergo adaptive angiogenesis (chorangiosis) in response to hypoxia. Chorangiosis is defined by a significant proportion of terminal villi having 10 or more capillary cross-sections, and has been associated with VUE, meconium staining, diabetes, and congenital anomalies.[2]

Inflammatory and Infectious Lesions

Acute chorioamnionitis is usually caused by cervicovaginal bacteria that either overwhelm normal cervical host defense mechanisms or gain access to the amnionic cavity after rupture of membranes.[42] The inflammatory response to bacterial infection is predominantly neutrophilic and generally involves the membranes and chorionic plate but not the chorionic villi. Acute chorioamnionitis is the most common cause of preterm labor.[15] However, few delivered infants are

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septic at birth, attesting to the effectiveness of the placenta as a protective barrier.

Histologic features can help determine the duration of infection in chorioamnionitis.[42] In the initial stages (<6 hours), maternal neutrophils enter the membranous chorion and underside of the chorionic plate (acute chorionitis). Later, maternal neutrophils infiltrate the entire chorionic plate and the full thickness of the membranes (6-24 hours). A concomitant fetal neutrophilic response, as manifested by transmigration across the fetal vessel walls, begins in the chorionic plate (fetal inflammatory response in chorionic vessels) and the umbilical vein (umbilical phlebitis) and is followed by involvement of the umbilical arteries (umbilical arteritis). Changes that occur later, such as fetal neutrophils infiltrating the umbilical cord stroma (perivasculitis) and necrosis of the amnion (necrotizing chorioamnionitis), suggest infection of greater than 24 hours duration. Finally, perivascular umbilical arcs of calcific debris, glycoprotein, and neovascularization (subnecrotizing funisitis) or a histiocytic component (subacute chorioamnionitis) suggest prolonged infection of days to weeks in duration.[35]

Infants with subnecrotizing funisitis or subacute chorioamnionitis are at increased risk for chronic lung disease. Data suggest that a severe fetal inflammatory response in chorioamnionitis may be a risk factor for severe neonatal morbidities, including bronchopulmonary dysplasia, necrotizing enterocolitis, cranial ultrasound abnormalities, and long-term neurologic impairment.[14,46,49]

The described patterns are typical for most bacteria. Unusual patterns that can suggest specific organisms are neutrophilic exudates involving the villi and intervillous space (suggestive of *Listeria monocytogenes*)[9] and microabscesses on the external surface of the umbilical cord (suggestive of *Candida albicans*).[38]

Chronic placentitis is caused by organisms that enter the villi via the maternal bloodstream. The hallmark of chronic placentitis is destructive, diffuse villitis with fibrosis and calcification.[25] Although villous inflammation is generally emphasized, these infections also involve the chorion, decidua, and other placental regions. This pattern of panplacentitis is caused by organisms of the so-called TORCH group (*Toxoplasma gondii,* rubella virus, cytomegalovirus, and herpes simplex virus), *Treponema pallidum,* other herpesviruses (Epstein-Barr virus, varicella), and a host of other parasitic and protozoan infections not commonly encountered in the United States. Distinct histopathologic features typify specific etiologic agents (e.g., increased Hofbauer cells, periarteritis, and necrotizing umbilical phlebitis in syphilis; villous plasma cells in cytomegalovirus; stromal necrosis and calcification in herpes simplex virus; and umbilical cord pseudocysts in toxoplasmosis).

Two other categories of neonatal infection that cannot be evaluated directly by placental pathology are transplacental and intrapartum infections. Transplacental infections spread to the fetus without affecting the placenta, presumably through breaks in the interhemal barrier (maternofetal transfusion). Important organisms in this category include human immunodeficiency virus (HIV), hepatitis B virus, human parvovirus B19, and enteroviruses. Intrapartum infections are acquired by the fetus during passage through a contaminated birth canal and also spare the placenta. Prominent in this category are venereal pathogens such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and human papillomavirus, and some pathogens associated with neonatal sepsis (e.g., group B streptococci and *Escherichia coli*).

Inflammatory Graft-Versus-Host–Type Lesions

Foci of idiopathic chronic villous inflammation, villitis of unknown etiology (VUE), are common in term placentas (5% of all placentas), whereas chronic infectious placentitis is rare (1-2 per 100 live births).[51] Certain features of VUE differ from infectious placentitis. Villitis of unknown etiology is confined to villi and generally involves only a fraction of the villous tree. The predominant cells in VUE are infiltrating T lymphocytes of maternal origin. Villitis of unknown etiology has a high recurrence risk and tends to occur in older women with previous pregnancies as compared with infectious placentitis, which tends to occur in younger women and rarely recurs because of acquired immunity. For these reasons many experts believe that VUE represents a graft-versus-host–type response related to the genetic differences between the mother and fetus. The chronic villous stromal inflammation associated with VUE causes placental dysfunction by increasing the diffusion distance for gas exchange (see Fig. 26.3*D*). Recent data suggest that another closely related graft-versus-host–type reaction, chronic chorioamnionitis, may play a role in some cases of idiopathic preterm labor.[24]

Developmental and Structural Lesions

A final group of lesions involves abnormalities in placental structure. As with structural abnormalities in infants, these placental lesions can represent either primary maldevelopment or secondary deformation and disruption. The uterine decidua regulates the depth of uterine implantation. Prior surgery or other uterine abnormalities can interfere with normal decidualization, leading to uncontrolled placental growth into or through the uterine wall (*placenta accreta* or *percreta*).[25] A long-held theory has been that growth abnormalities such as bilobation, accessory lobes, peripheral umbilical cord insertions, and placenta previa develop when the placenta migrates away from uterine defects toward sites with a better maternal blood supply, a process termed *trophotropism*.[4] More recent data suggest that these abnormalities may be more closely related to deficient branching of major chorionic vessels and the villous parenchyma they supply.[55]

Placental structural anomalies can also predict deformations or disruptions in the fetus. Placental amniotic bands are associated with fetal amputations.[25] Amnion nodosum, developing secondary to prolonged oligohydramnios, is

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associated with pulmonary hypoplasia.[31] Placental thrombi can be a harbinger of fetal coagulopathies such as stroke, thrombotic liver disease, renal vein thrombosis, intestinal atresia, or purpura fulminans.[25] Placental vascular anastomoses in monochorionic diamnionic twins can cause circulatory shifts leading to acute hypoxic-ischemic injury or chronic circulatory imbalance leading to twin-to-twin transfusion and discordant fetal growth.[18] Monochorionic monoamnionic twins, although rarely affected by twin-to-twin transfusion, commonly have another placental complication—entangled umbilical cords—which can lead to the death of one or both twins.

Tumors are occasionally found in the placenta. The most common placental tumor is the chorangioma, composed of proliferating fetal blood vessels. Chorangiomas can cause fetal complications by arteriovenous shunting, leading to hydrops fetalis and platelet sequestration, resulting in disseminated intravascular coagulation.[4,25] Choriocarcinomas (malignant trophoblastic tumors) can rarely arise from the villi of second- and third-trimester placentas and metastasize to the fetus.[5] The placenta can also be the site of metastasis for malignant tumors from either the mother (e.g., melanoma, adenocarcinoma) or the fetus (e.g., congenital neuroblastoma, Langerhans cell histiocytosis).

Clinical Correlation

The various anatomic, physiologic, and pathologic reaction patterns discussed above are placed in clinical context by reviewing their relative frequency in common obstetric and neonatal disease syndromes (Box 26.2).

Preterm labor and delivery are most commonly associated with pathologic evidence of acute chorioamnionitis.[15] In many cases, it can be difficult to determine whether infection develops before or after the onset of labor. Because chorioamnionitis generally triggers labor relatively rapidly, most cases that develop after prolonged membrane rupture likely represent secondary infection. Many of the remaining cases of preterm birth fall into three groups: placental abruption, chronic maternal malperfusion, and uterine structural anomalies without associated placental abnormalities (e.g., so-called cervical insufficiency).[52] As mentioned, idiopathic chronic inflammation (chronic chorioamnionitis) also may be implicated in some cases.[24]

Fetal growth restriction may either be constitutional, relating to small maternal size, malnutrition, or an anomalous fetus, or directly caused by placental disease. The most frequent placental causes of fetal growth restriction are chronic maternal vascular malperfusion and VUE.[21,45] Other, less frequent etiologies are fetal vascular malperfusion, massive perivillous fibrin deposition ("maternal floor infarction"), and confined placental chromosomal mosaicism.[19]

Intrauterine fetal demise, particularly at or near term, is often clinically unexplained. Recent studies suggest that placental examination can reveal the underlying cause or causes in up to 60%-70% of cases, much more frequently than autopsy.[23] One important group at increased risk of stillbirth are fetuses with clinical entanglements or pathologic lesions of the umbilical cord. These lesions can be diagnosed by using specific pathologic criteria.[36] Another distinct group at risk are infants whose placentas have decreased vasculosyncytial membranes (delayed villous maturation), leading to decreased placental reserve and susceptibility to transient hypoxic events.[53] The prototype for this subgroup is the infant of a diabetic mother. A less common but important cause of stillbirth is massive fetomaternal hemorrhage, which is manifested in the placenta by intervillous thrombi and increased circulating nucleated red blood cells.[7,20] Chronic fetomaternal hemorrhage and its accompanying anemia can cause congestive heart failure and hydrops fetalis. Other forms of hydrops fetalis causing stillbirth that can be identified by placental examination include infections such as human parvovirus B19, toxoplasmosis, and syphilis. Finally, a large proportion of stillbirths is associated with underlying FGR. These cases are characterized

• BOX 26.2 Clinicopathologic Correlation

Preterm Labor
- Acute chorioamnionitis (infectious)
- Abruption (acute or chronic)
- Chronic maternal vascular malperfusion ("accelerated maturation")
- Chronic chorioamnionitis (graft-versus-host type)

Fetal Growth Restriction
- Chronic maternal vascular malperfusion
- Villitis of unknown etiology
- Perivillous fibrin deposition
- Fetal vascular malperfusion
- Confined placental chromosomal mosaicism

Intrauterine Fetal Demise
- Delayed villous maturation
- Massive fetomaternal hemorrhage
- Umbilical cord accident
- Multiple or severe placental lesions

Hypoxic-Ischemic Encephalopathy
- Abruptio placentae or uterine rupture
- Umbilical cord accident
- Rupture of fetal vessels

Cerebral Palsy (Preterm)
- Severe villous edema
- Chorionic vessel thrombi
- Multiple placental lesions

Cerebral Palsy (Term)
- Segmental fetal vascular malperfusion
- VUE with stem vessel obliteration
- Severe fetal chorioamnionitis
- Meconium-associated vascular necrosis
- Multiple placental lesions

VUE, Villitis of unknown etiology.

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pathologically by severe examples of one or more than one of the processes discussed in the preceding paragraph.[8]

Central nervous system injury has been associated with several placental lesions. White matter damage, periventricular hemorrhagic infarction, and cerebral palsy in preterm infants have been linked to severe villous edema, chorionic vessel thrombi associated with histologic chorioamnionitis, and multiple placental lesions.[46] Hypoxic-ischemic encephalopathy and cerebral palsy in term infants can follow acute birth asphyxia, recurrent intermittent hypoxia, or chronic uteroplacental disease.[49] Placental findings associated with birth asphyxia include abruptio placentae, occlusive umbilical cord accidents, and rupture of fetal vessels. Recurrent intermittent hypoxia is most often related to clinical or pathologic umbilical cord problems and is commonly accompanied by an increase in circulating nucleated red blood cells in the placenta.[47] The most common chronic uteroplacental lesions associated with brain injury are those affecting large fetal vessels, including segmental fetal vascular malperfusion, villitis of unknown etiology with stem vessel obliteration, severe fetal chorioamnionitis, and meconium-associated vascular necrosis.[50] As is true for the preterm group, term infants with multiple placental lesions are also at very high risk.[49]

Umbilical Cord Coiling

Mechanisms of umbilical cord coiling include contributors from embryonic development, intrinsic properties such as growth of vessels, differential blood flow within arteries, and fetal movements.[37] Hypocoiling, defined as <1 coil/10 cm, has been associated with fetal distress, oligohydramnios, preterm delivery, intrauterine growth restriction, meconium-stained amniotic fluid, fetal heart rate (FHR) alterations, and low cord pH. Horn et al. found association of hypercoiling (>3 coils/cm) and thinning with consecutive constriction of the umbilical vessels (thin cord syndrome) and intrauterine fetal death.[16] Noncoiled umbilical cords are considered a risk factor for poor perinatal outcome and stillbirth.[54]

Summary

The placenta is the link that connects the clinical status of the neonate with underlying maternal and fetal disease processes. Careful evaluation of this organ not only provides useful diagnostic, prognostic, and therapeutic information, but also enhances overall understanding of perinatal biology. Communication among neonatologists, obstetricians, and placental pathologists brings together distinct pieces of a puzzle that none can fully solve alone. Through this process, meaningful explanations of the reasons for adverse perinatal outcomes and their chances of recurrence can be provided for concerned physicians and family members.

Key Points

- Timely examination of the placenta by someone with expertise in perinatal pathology is a critical part of neonatal care.
- Clinical context must be communicated to the pathologist for optimal interpretation.
- Placental lesions may be broadly categorized as maternal vascular, fetal vascular, inflammatory, and other.
- Individual subcategories within these broader categories have distinct significance for immediate care, explaining adverse outcomes and determining recurrence risk.
- Pathologists, neonatologists, obstetricians, and geneticists need to meet periodically to maintain quality of care.

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27

Anesthesia for Labor and Delivery

MCCALLUM R. HOYT

The goal of modern-day obstetric anesthesia practice is to provide the patient with analgesia as she requests it.[57,61] That assumes her choice is appropriate to the labor process and to the current conditions as evaluated by her obstetric provider, and has as little impact on the fetus as possible.[55] Depending on the patient's predilections, labor might be approached with prepared responses to modify pain perception, a plan to use systemic medications or nerve blocks, or some combination of these. How and whether a mother's choice has an impact on fetal well-being and neonatal outcome is the focus of this chapter, which includes a discussion of the newer anesthetic techniques. It also reviews some of the more established pain relief approaches as well as the more popular alternatives currently in vogue.

Labor Pain Characteristics and Challenges

Research has shown that the experience of pain is a complex, subjective, multidimensional response to sensory stimuli.[22] Labor pain in particular has been shown to be more intense than almost any other known pain syndrome.[45] To appreciate the complexity of providing analgesia to the laboring patient and better understand successes and expectations when doing so, a considerably abbreviated and simplistic discussion of pain is in order. A clinically useful classification of pain is to define it as being visceral or somatic. Visceral pain originates from the viscera and is often described as cramping, dull, and steady. Somatic pain is related to nonvisceral structures and is commonly described as sharp, intermittent, and well localized.[9,22] During the dilation phase, or first stage, of labor, visceral pain predominates, arising from mechanical distention of the lower uterine segment and cervical dilation. Somatic pain prevails during the descent phase, or second stage, of labor and is attributed to the distention and traction on pelvic structures surrounding the vagina as well as distention of the pelvic floor and perineum.[9,22]

The challenge when managing labor pain is to understand its very dynamic nature that may require adaptation of pain techniques to adequately manage it. Labor pain evolves rapidly over a relatively short period of time, changing not only in intensity but also from a visceral to a somatic source. To add to the challenge, not all medications are effective for all types of pain. Local anesthetics block nerve conduction and are effective where the nerves responsible for pain transmission are accessible. In labor, the nerves transmitting the pain are well described, and most of them can be reached with some form of nerve block, making this a common choice. On the other hand, opioids are very effective for visceral pain but are of little value for somatic pain.[54] Therefore, systemic opioids can aid a patient reasonably well during the first stage of labor but have little effect if used during the second stage.

Neuraxial analgesia is widely accepted as the most effective and least depressant method of providing pain relief in labor.[61] The term encompasses epidural, spinal, and combined spinal-epidural (CSE) central nervous system blocks that are only administered by those trained in anesthetic methods. With modern-day techniques, dosing can be reduced to such low levels that an analgesic state, which diminishes pain while minimizing the effect on other sensory pathways such as touch and proprioception, is possible and often the goal.[4] The lower doses result in less absorption into the maternal bloodstream, making levels barely or non-detectable. This allows the parturient to experience pain-free labor with minimal side effects to both her and the fetus while still allowing for active participation in the labor process. However, all procedures carry some risk, and as dosing methods can vary across the United States, a fetal or neonatal effect from the medications used can occur.

Despite the proven safety and efficacy of the lower-dose neuraxial techniques, not all parturients wish to use them, nor are there always practitioners available to perform these procedures. Also, not all patients are reasonable candidates for a neuraxial block for a myriad of reasons. As a result, many of the traditional, non-neuraxial approaches for labor pain management are still utilized in obstetric suites, as are some newer alternative therapies.

Techniques That Modify Pain

Although nonpharmacologic techniques do not alter the actual transmission of pain sensation, they attempt to alter the person's perception and response to it, with some measured success. Many of these approaches require preparation

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Abstract

Research has shown that the experience of pain is a complex, subjective, multidimensional response to noxious sensory stimuli. Labor pain in particular has been shown to be more intense than almost any other known pain syndrome. The American College of Obstetricians and Gynecologists in their recent "Practice Bulletin on Obstetric Anesthesia and Analgesia" state, "In the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor." The goal of modern-day obstetric anesthesia practice is to provide the patient with analgesia as she requests it. That assumes her choice is appropriate to the labor process and has as little impact on the fetus as possible. The focus of this chapter is to provide a high-level overview of obstetric anesthesia for the practicing neonatologist or pediatrician and to discuss whether a mother's choice has an impact on fetal well-being and neonatal outcome. It includes a discussion of the newer anesthetic techniques and reviews some of the more established pain relief approaches as well as the more popular alternatives currently in vogue.

Keywords

anesthesia
analgesia
neuraxial
combined spinal epidural
epidural
intrathecal spinal

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beforehand, and their effectiveness is subject to several variables. As a result, studies comparing controlled breathing techniques, hypnosis, and other nonpharmacologic methods to nerve blocks and medications are hard to evaluate.

The assumption held by proponents of alternative pain management techniques and many expectant mothers is that nonpharmacologic techniques to control pain will not have any adverse effect on the neonate and, therefore, are the safest and healthiest choices for themselves and their babies. Clinical studies have not proved this assumption to be true. Although most techniques are as benign as they appear, some can carry unintended consequences if not performed properly, making this pertinent knowledge for the well-informed neonatologist.

Nonpharmacologic Approaches

Natural Childbirth

Natural childbirth is a technique that was first defined by Ferdinand Lamaze in the 1950s and began its popular rise in the 1960s as an alternative to the heavy sedation that was often used at the time. The technique of controlled breathing and focal points to stay in a relaxed state during a contraction is based on the theory that one can modify the sensation of pain and one's response to it. Building upon the popularity of the Lamaze approach to labor pain, the Bradley technique was introduced in the 1970s as a variant and incorporated the woman's partner as her active coach. Today the term *natural childbirth* applies to any controlled breathing technique that the mother uses during labor to cope with pain and avoid pharmacologic methods.

Is natural childbirth an effective way to manage pain during labor? There is some objective evidence that Lamaze training as originally practiced is associated with β-endorphin elevations, which may help alter pain sensation.[19] What is not always appreciated is that incorrect performance can have negative consequences. If the mother deviates from the defined breathing technique and hyperventilates during her contractions, she will lower her P_{CO_2} levels. The maternal hypocapnia and resulting acute alkalosis causes the maternal oxy-hemoglobin curve to shift toward the fetal curve, thereby reducing the release of oxygen to the fetus. It also may reduce umbilical blood flow.[35] If fetal acidosis develops during the first stage of labor, it will worsen during the second stage, especially if that stage exceeds 1 hour.[63] Once hypoxia and a base deficit are present during the second stage of labor, it is difficult to reverse in utero.[63] Obviously, this series of events does not occur in every case, but the fetal tracing associated with this scenario can resemble that of cord compression. Effective analgesic techniques have been shown to improve these conditions if applied before the second stage.[51]

With the popularity of the Internet, patients today are able to find a variety of information about natural childbirth practices without any means to determine if the information presented is accurate. Several factors have come to bear upon modern-day childbirth courses that teach the Lamaze or Bradley techniques and the information that is provided. Couples are no longer willing to take the full course but try to learn the techniques in a matter of hours, if they train at all. This makes it nearly impossible to learn the pain-controlling techniques that Lamaze and Bradley described. Additionally, information provided in courses on available forms of pain relief options is variable, not only due to potential personal biases by the instructor, but also the instructor's knowledge of what is available at the local maternity units. As a result, couples may approach labor with a rigid plan that does not take into consideration informed alternatives for pain management should the fetus show signs of compromise. Unfortunately, a mother who envisions a natural childbirth for her labor often views resorting to any form of analgesia, especially an epidural, as a failure on her part. Studies show that natural childbirth preparation, including training in breathing and relaxation, did not decrease the use of epidural analgesia during labor.[5] Also, mothers who planned for an unmedicated labor but resorted to a neuraxial block frequently experienced longer labors associated with higher pain scores, which may catch them unprepared for the intensity of the process.[32]

Hypnosis

Self-hypnosis for labor and delivery, or hypnobirthing, enjoys a devoted following among those for whom the process has been successful. It requires time for training and practice and is not a choice for those with only a weekend set aside to learn it. There are two main methods of providing hypnosis in the context of pain management for childbirth: hypnotherapy delivered in person by a known practitioner, and self-hypnosis, in which the mother is trained to self-induce a state of altered consciousness. Under such a state, there is less awareness of the environment and an increased susceptibility to suggestion. These may be verbal and nonverbal communications used to achieve specific therapeutic goals.[15] In the context of childbirth, suggestions may focus on increasing feelings of safety, relaxation, and comfort, as well as potentially developing sensations of numbness.[40]

Further studies are warranted to clarify the impact of hypnosis on labor pain as current studies lack randomization, hypnotic methods are not well described, and the study populations are relatively small. A recent Cochrane database review examined 9 trials with a total of 2954. The review authors found hypnosis may reduce the overall use of analgesics but not epidural use. Also, there were no clear differences between women in the hypnosis group and those in the control group with regard to several outcomes: use of pharmacologic pain relief, spontaneous vaginal birth, and satisfaction with pain relief.[40]

Water Birth

The water birth movement holds that submersion for labor, delivery, or both, reduces the sensation of pain. It also holds that birthing from one water environment into another is less stressful for the infant. Unfortunately, there are no

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substantive studies supporting this claim. Like most alternative methods, almost everything reported in the literature is anecdotal. A Cochrane database review article indicates that immersion in water during the first stage decreases maternal requests for neuraxial analgesia and can be supported for women at low risk of complications.[12] However, immersion during the second stage of labor needs further investigation. At present, there is no clear evidence whether to support or reject a woman's decision to give birth in water.[12] Questions regarding infection and neonatal outcomes are not addressed, and large collaborative trials are needed to answer these critical issues. A 2004 review article considered three clinical concerns: water aspiration, neonatal/maternal infection, and neonatal/maternal thermoregulation in the practice of water birthing. They also looked at two practical concerns: skills and education of midwives or health professionals assisting the water birth, and emergency procedures in case of maternal collapse. They did not find sufficient evidence to caution women away from this practice.[89]

Acupuncture

This technique has most often been used to address the issue of low back pain during labor and not that of labor pain management in general. In controlled trials, acupuncture has been demonstrated to be beneficial but time consuming and without consistent results.[3] In addition, the study sizes have been small, indicating that more research is needed, although there appears to be no negative effect on the neonate.

Pharmacokinetics, Pharmacodynamics, and the Fetus

There are two classes of drugs commonly used by obstetric providers in modern practice for labor pain management that fall under the scope of this segment. They are opioids for pain relief and sedatives to relax and reduce anxiety. Under emergent surgical conditions, anesthesiologists use other classes of drugs, but these are not reviewed in any detail here. When considering the effect of any medication on the fetus, it is worth noting whether that medication has produced a cerebral effect on the mother. If so, that medication has the properties to cross the lipid blood-brain barrier and likely will cross the placental barrier to reach the fetus as the necessary transport mechanisms are the same.[90] However, the extent to which a fetus is exposed depends on many factors, such as the drug's pharmacokinetic and pharmacodynamic properties, the dose, and the mode of delivery.

Three pharmacologic characteristics are considered when weighing whether or not a medication has the properties to enter the maternal circulation from its primary site of administration and then leave that circulation to cross the placenta (see Chapter 45). These are how much of the drug is in the ionized versus the nonionized state as determined by its pH, whether it has lipophilic or hydrophilic tendencies, and whether it prefers to bind to protein.

A medication that is ionized cannot cross a membrane barrier. A drug's pKa means that 50% of the drug is ionized and 50% is nonionized. Local anesthetics as a class are weak bases (pKa = 7.6-9.1), so at physiologic pH (7.4) more of the drug is in the ionized state. The ratio by which a local anesthetic is ionized in the circulation depends on how much higher the pKa is from 7.4. For instance, a local anesthetic with a pKa of 9.1 is mostly ionized, and more will stay in the maternal circulation than a local anesthetic with a pKa of 7.6. Because only the nonionized portion of a drug will cross a membrane barrier, the amount that crosses will reproportion itself into ionized and nonionized forms once in the fetal circulation. If the fetal pH is lower than the maternal pH because of acidosis, more of the drug converts to the ionized form and cannot return to the maternal circulation. If maternal exposure to the medication persists, more of the drug passes from mother to fetus, and increasing amounts accumulate in the fetal circulation. This phenomenon is called *fetal ion trapping* and has been associated with some of the deleterious effects produced by medications in the compromised fetus.

Of the other pharmacodynamic properties mentioned, drugs that possess lipophilic properties as opposed to hydrophilic are more capable of crossing lipid-rich membranes. Most medications used in obstetrics are lipophilic but to varying degrees. For example, fentanyl and sufentanil are lipophilic opioids, but sufentanil is much more so. As a result, epidural doses of sufentanil more readily leave the epidural space to enter the maternal circulation than fentanyl.

Protein binding is the third important pharmacologic principle. A drug that binds with protein molecules remains in the maternal circulation because when bound, it becomes a bulky molecule. Only the unbound drug is free to cross a membrane and produce an effect. So excluding active transport mechanisms, it is the unbound, nonionized portion of a lipophilic medication that can cross a membrane barrier to produce an effect.

The pharmacokinetic effects of metabolism and elimination are yet another regulator of how much or even whether a drug will exert an effect on the fetal brain. Most medications undergo extensive metabolism into inactive metabolites in the maternal circulation. As a result, very little if any effect may be found. One example of a rapidly metabolized medication is succinylcholine, a depolarizing muscle relaxant. This medication is metabolized to benign metabolites by pseudocholinesterase in the maternal plasma and has a half-life of about 90 seconds. As a result, nothing reaches the fetus. However, if a drug is metabolized into an active metabolite in the maternal system and then crosses into the fetal system, that metabolite can have fetal effects. Such is the case with normeperidine, the active metabolite of meperidine.

A useful measurement that helps estimate fetal medication exposure is the ratio of the umbilical vein drug concentration to the maternal vein (UV:MV). A ratio of 1 (UV:MV = 1) means that the amounts of medication in the

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TABLE 27.1 Placental Passage of Commonly Used Anesthetic Medications

Drug	Umbilical Vein to Maternal Vein Ratio (UV:MV)
Induction Agents	
Thiopental	1.08 (range, 0.5-1.5)
Ketamine	0.54 (range, 0.4-0.7)
Propofol	0.7
Etomidate	0.5
Nondepolarizing Neuromuscular Blocking Agents	
Pancuronium	0.19
Vecuronium	0.11
Opioids	
Morphine	0.92
Meperidine	0.81 (may exceed 1.0 after 2-3 hours)
Fentanyl	0.57
Sufentanil	Levels too low to measure in humans
Butorphanol	0.84
Nalbuphine	0.97

Adapted from data from Glosten B. Anesthesia for obstetrics. In: Longnecker DE, et al., eds. *Principles and Practice of Anesthesiology*. 2nd ed. St. Louis: Mosby; 1998.

umbilical vein equal those in the maternal vein. A low ratio means that a small amount has crossed the placenta to reach the umbilical vein. For example, the nondepolarizing muscle relaxants used in general anesthesia are highly ionized, hydrophilic compounds that do not cross the membrane barrier. Their UV:MV ratios tend to be on the order of 0.1. Table 27.1 lists the UV:MV ratios of some common anesthetics.

Even if the umbilical vein levels are significant, they may not be great enough to produce any important neurobehavioral effect, because two more protective barriers exist to shield the fetal brain from medication exposure. Approximately 40%-60% of any medication entering the fetal circulation passes through the liver first and then travels through the inferior vena cava to the heart and into the circulation. The mature or nearly mature fetal liver can metabolize most drugs, and this first pass through the liver buffers the fetal brain from exposure.[26] Additionally, the unique fetal circulation dilutes most of any drug as it travels into the general circulation, and this dilutional effect can be quite protective of the fetal brain.[26]

One final clinical note for the neonatologist: Not only does the dose have an impact on how much medication enters the maternal circulation for eventual fetal distribution, but so does the mode of administration. Although it is obvious that intravenous administration achieves the highest maternal blood levels, all blocks and injections distribute some level of the drug into the maternal circulation, and they differ markedly from one another. From the greatest to the least effect on maternal blood levels, drug administration modes have the following ranking[26]:

Intravenous > Paracervical > Intramuscular > Epidural > Spinal

It should be noted that maternal local anesthetic levels after a spinal delivery are so low as to be clinically irrelevant.

Sedatives

The routine use of heavy sedatives in the active phase of labor has markedly diminished, making it unlikely that a neonatologist will be caring for a neonate with a recent exposure. In modern practice, the primary purpose of sedatives is to help the parturient rest during a prolonged latent phase of labor, but may be administered during a cesarean delivery either to an anxious patient or before the induction of a general anesthetic. Other than in the cesarean delivery scenario, enough time usually passes between administration and delivery so that any significant drug amounts clear the maternal and fetal circulations. The class of medications most often encountered today is benzodiazepines.

Benzodiazepines are most likely used in an acute situation either because of maternal self-administration or from the anesthesia provider during a cesarean section. The two most commonly encountered benzodiazepines are diazepam and midazolam. Midazolam has a low UV:MV ratio, so it does not cross to the fetus well at all, making it essentially without clinical effect when given acutely. The most common use of midazolam is during a cesarean delivery that is unplanned. Given by the anesthesia provider for its excellent anxiolytic properties, it unfortunately causes maternal amnesia that will impair the mother's recall of the delivery if administered beforehand. It is usually reserved for the highly anxious patient, and most providers attempt to delay administration until after delivery. Diazepam is another benzodiazepine that might be encountered. Unfortunately, diazepam has a high UV:MV ratio that reaches 1 within minutes and can increase to 2 within hours.[90] Metabolites are active and can remain in the system for up to 8 days. When given in the intrapartum setting for eclamptic seizures, this medication can cause hypotonia, hypothermia, and respiratory depression in the neonate.[18,44,84] Once thought to cause oral cleft malformations when used chronically during the first trimester, studies do not support this assertion.[72] Regardless, diazepam is not as commonly prescribed by the obstetric provider as it once was, and its use is usually limited to the acute management of maternal seizures. A discussion of other benzodiazepines can be found in any general pharmacologic text.

Barbiturates are used less commonly than before. Phenobarbital is rarely used but remains an option for treatment of partial or generalized tonic-clonic seizures and status epilepticus.[18] Thiopental is an anesthetic induction agent that is no longer available in the United States, making

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propofol the most frequently used. The two have similar profiles as far as neonatal effects are concerned.

Opioids

The definition of an opioid is any natural, synthetic, or semisynthetic compound that acts on the same receptors as morphine and produces similar effects. Those agents are known as pure agonists and include morphine, meperidine, and fentanyl. Those that act on only some of the receptors and may even block action on others are known as agonist-antagonists and include nalbuphine and butorphanol. Pure antagonists block action on all receptors and are not considered opioids but can reverse their actions. Naloxone defines this class.

Opioids do not block the transmission of pain but rather stimulate receptors to alter the perception of pain and one's response to that perception. For that reason, opioids are considered incomplete analgesics. There are three known opioid receptor types and a possible fourth on which these drugs act.[54,73] The μ-receptor provides the most complete analgesia but also produces most of the known side effects of opioids such as pruritus, nausea and vomiting, euphoria, dysphoria, and respiratory depression to the point of apnea. The κ-receptor mediates less intense analgesia because of what is known as a "ceiling effect." The dose-response studies performed early in the investigation of medications that stimulate this receptor determined that the curve stopped rising at a particular dose. This flattening of the dose-response curve means that more of the drug does not produce more of an expected effect. This "ceiling effect" holds not only for analgesia but also for respiratory depression. No other side effects appear to be associated with this receptor type. Both the μ- and κ-receptors have been divided into multiple subgroups. The δ-receptor mediates the effects of the endogenous endorphins, especially as they act on the spinal cord. The final receptor, called the σ-receptor, may be responsible for supraspinal effects and little is known about it to date, but research is ongoing.[68] Box 27.1 lists some of the opioids commonly used in labor and their classifications.

Opioids appear to be more effective on visceral pain than somatic pain.[54] As a result, they are more useful during the first stage of labor, which tends to be visceral in nature, than the second stage, which is more somatic.[39] Because all opioids can cross the placenta and produce an effect in the fetus, systemic opioid use has traditionally been limited to the first stage so that the opioid is metabolized from the fetus before delivery. However, not only has the selection of opioids expanded over the years, but also the thoughts on how they can be delivered. Intermittent intravenous administrations are still the mainstay on most units, but intravenous patient-controlled analgesia (IV-PCA) is offered on most obstetric units. Once thought to be taboo because of neonatal opioid-induced depression, studies show that this administration technique can be provided reasonably well.[58,76] However, because of the depressive effects, this method should be reserved for situations in which a regional technique is either not available or contraindicated.

There are several reports in the literature describing the IV-PCA technique with meperidine, fentanyl, alfentanil, and remifentanil.[56,58,76,80] Those neonates whose mothers use this technique should be watched for signs of sedation, respiratory depression, and low oxygen saturation.

• BOX 27.1 Opioids Commonly Used During Labor

Agonists

- Natural
  - Morphine
- Synthetic
  - Meperidine
  - Fentanyl
  - Sufentanil
  - Alfentanil
  - Remifentanil

Agonist-Antagonists

- Nalbuphine
- Butorphanol

Opioid Agonists

Opioid agonists that may be used on the obstetric unit are morphine, meperidine, fentanyl, sufentanil, and remifentanil.[79] Although formerly used, studies have shown that alfentanil is less effective than other opioids, such as fentanyl, for first-stage labor analgesia. In addition, when used in doses of 10 μg/kg in the mother, it can cause severe neonatal respiratory depression.[43] Morphine is the only naturally occurring agonist and, if used at all during labor, is used early. The reason is that not only is it more depressive to the neonate than any other opioid, but it may also depress uterine contractions, making it a questionable choice for labor management.[73]

Meperidine (Demerol) is a synthetic opioid with some very interesting properties. This opioid was one of the most commonly used systemically, but its use has dropped off. There is evidence that it enhances the effacement and dilation of the cervix[47] and has atropine-like properties that can produce tachycardia and myocardial depression in the mother. When injected into the epidural or spinal space, it can produce a block similar to that seen with local anesthetics, making it an option when a patient has a documented allergy to all forms of local anesthetics.[11]

When used to provide systemic analgesia, meperidine is traditionally dosed in such a way as to limit fetal exposure before delivery. The drug's duration of action is 2-4 hours, with a half-life of 3-4.5 hours. Based on that and knowing that intramuscular administration requires about 45 minutes to an hour to absorb and have an effect, meperidine is not given unless delivery is expected within the hour or beyond 3 hours. Unfortunately, estimates of delivery time are an imprecise science, and sometimes the neonate is delivered

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during peak exposure. Even so, the need for naloxone to reverse the depressive effects is uncommon under this scenario. In any case, it would probably be best to closely observe neonates exposed to this form of analgesia. Meperidine is metabolized to an active metabolite called normeperidine. The fetal liver is capable of metabolizing meperidine into its active metabolite, or it can cross the placenta and accumulate. Its half-life is 15-40 hours, so its neurologic and depressive effects can be evident for some time after delivery.

Several commonly used opioids are analogues of meperidine. They are fentanyl, sufentanil, alfentanil, and remifentanil. Although only fentanyl and sufentanil are used for anesthetic nerve blocks, fentanyl, alfentanil, and remifentanil have been used systemically in the obstetric setting. All these meperidine analogues are lipid-soluble and can cross the placenta. However, they are rapidly metabolized by the first pass through the liver to inactive metabolites, thereby making any depressive effects uncommon when these drugs are given as intermittent intravenous boluses.[62] Because of its pharmacokinetic properties, remifentanil is so short-acting that it can be used only in a continuous infusion mode. In one study, fentanyl was injected as a maternal intravenous dose of 1 μg/kg just before the start of the cesarean section, and no neonatal depressive effects were detected.[56]

Fentanyl has been used in the IV-PCA format,[48,70] as have alfentanil[48] and remifentanil,[31,56] with mild neonatal depression a common occurrence. This mode of administration is a more acceptable alternative to intermittent injections when anesthetic services are limited or neuraxial blocks are contraindicated. Generally, oxygen supplementation and observation are all that is required for the neonate after such exposure.[32,69]

One final note about the opioid agonists: All of them are associated with the suppression of fetal beat-to-beat variability, which returns to normal as the drug is eliminated, suggesting a causal effect.

Opioid Agonist-Antagonists

All medications in this category stimulate the κ-receptor and thus have a ceiling effect on respiratory depression, as previously described. However, the ceiling effect also applies to analgesic capabilities, making this class of drug limited in its effectiveness. The two most commonly used formulations on obstetric units in the United States are nalbuphine (Nubain) and butorphanol (Stadol). Both produce sedation in the mother and degrade to inactive metabolites, and although both cross the placenta, the fetal effects seem limited.[26,54] However, nalbuphine reduces fetal beat-to-beat variability and can produce a sinusoidal pattern when used.[17]

It is important to note that these two medications are markedly different in how they act on the μ-receptor. Whereas butorphanol has essentially no effect on the μ-receptor, nalbuphine actively blocks it. As a result, it can be used in small doses in lieu of naloxone to counter μ-receptor side effects such as pruritus. The danger with nalbuphine is that it can place an opioid-addicted patient into acute withdrawal at doses commonly used for labor analgesia. It can do the same to the addicted neonate.[26,54] Therefore, caution should be exercised when using this medication if there is any indication of opioid abuse in the mother or if she is in an opioid addiction maintenance program.

Because of the sedative and respiratory depressive effects of these drugs as well as the inability to produce complete analgesia, heavy intrapartum use can lead to a situation in which maternal hyperventilation during a contraction is followed by hypoventilation as the contraction recedes. This condition will produce predictable consequences for maternal oxygen and carbon dioxide levels and shifts in the oxyhemoglobin curve that can end in significant fetal acidosis that begins during the first stage and worsens during the second.[49,51,63]

Opioid Antagonists

The opioid antagonist, naloxone (Narcan), blocks the action of an opioid on all of the receptors and is commonly used to reverse adverse side effects and excessive dosing. It has a short half-life (30-45 minutes), which means that repeated boluses may be necessary at times. Naloxone is not a benign drug and has been known to cause pulmonary edema and cardiac failure in some situations, so caution should be exercised when using it.[54] It crosses the placenta, so it will reverse any opioid effect in the fetus. As with nalbuphine, it is not a medication that should be given to a mother with an opioid addiction or who is in an opioid addiction maintenance program. Not only will it produce withdrawal in the mother but in the addicted fetus as well.[49,54]

Nitrous Oxide

Despite common use in many parts of the world, few centers in the United States offered the inhalational analgesic, nitrous oxide (N_2O). But recently, U.S. institutions have considered its use, and as of 2015, 50 centers in the United States were offering it, with more considering it.[66] Nitrous oxide is a weak analgesic that, when combined with oxygen, can provide some pain relief at subanesthetic levels, making it safe to use. It is unclear exactly how N_2O provides analgesia, but what is clear is that the individual response is variable.[66] This may explain study results. A Cochrane database review examined 26 studies encompassing 2959 women.[33] Despite the studies being judged of poor quality and questionable design, those comparing N_2O against flurane derivatives, such as isoflurane and enflurane (which are not available in the United States), found the flurane derivatives provided better pain relief with fewer side effects. When N_2O was compared against placebo or no analgesia, N_2O provided better pain relief but with more side effects that included nausea, vomiting, dizziness, and drowsiness. Nitrous oxide compared against transcutaneous electrical nerve stimulation (TENS) showed no difference in effectiveness. What has not been measured to any satisfaction

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is the effect of N_2O on the mother-neonate interaction, breastfeeding, or long-term infant outcomes. Concerns over occupational exposure with N_2O use have not been validated in studies, and with newer equipment having a built-in scavenger system now available, fears are further allayed.[37,66] Nitrous oxide's utility and popularity seems to lie in that it provides a choice to mothers, which in turn may improve satisfaction scores. It is also an option when neuraxial block is contraindicated or not available and does not require anesthesia personnel to provide it.

Obstetric Nerve Blocks

Obstetric nerve blocks are invasive procedures performed by the obstetric provider to achieve analgesia in labor. Only two nerve blocks are used in obstetric practice, and these are for different goals. The paracervical block provides pain relief in the first stage of labor, whereas the pudendal block is used for analgesia during the delivery portion of the second stage.

Paracervical Blocks

The purpose of the paracervical technique is to block pain transmission via the visceral afferent fibers near the dilating cervix. This is achieved by injecting local anesthetic lateral to the cervix at the vaginal fornices. Lidocaine without epinephrine is preferred in the United States because of its relative safety.[71] In the early 1980s, US manufacturers of bupivacaine specifically contraindicated the use of the agent for paracervical blockade because of its risk for maternal cardiotoxicity.[71]

Paracervical block (PCB) was described by Europeans in the early part of the twentieth century and was first reported to be useful in providing labor analgesia in the United States in 1945. The technique became popular in the United States in the early 1960s.[71] Numerous early case series, case reports, and clinical studies demonstrated good first-stage labor anesthesia in approximately 75% of women.[71] However, careful reviews of the early reports also describe a post-blockade fetal bradycardia. Although the bradycardia has been described to be of a short duration and usually without adverse sequelae, fetal deaths have been reported.[71] Some of these deaths resulted from direct injection of local anesthetic into the fetal head, resulting in profound fetal systemic toxicity. Other theories about the etiology of the fetal bradycardia included aortocaval compression caused by maternal positioning for the block, paracervical manipulation, increased uterine activity, and local anesthetic-induced constriction of uterine blood flow in the area adjacent to the nerves blocked.[71]

Paracervical blocks are less commonly performed for labor pain in the United States today. Studies show that parturients receiving paracervical block often continue to receive subsequent analgesia and were less satisfied and less willing to have the same technique again compared against neuraxial techniques.[30] However, a PCB might be useful when neuraxial blocks are not available or contraindicated.[36] Further high-quality studies are needed to confirm the findings, assess other outcomes, and compare local anesthetic nerve blocks with various modalities for pain relief in labor.[52]

Pudendal Blocks

A pudendal block may be used for analgesia in the late stages of labor and is most typically used when an operative delivery with forceps is planned. The pudendal nerves are blocked using a transvaginal approach in which 5-10 mL of local anesthetic is injected at the site of the attachment of the sacrospinous ligament to the ischial spine. A significant potential complication of the procedure is maternal intravascular injection, so aspirations are frequently performed. Despite the avoidance of maternal injection and the typically short interval between injection and delivery, blood levels of the local anesthetic may be found in the neonate for up to 4 hours after delivery. However, studies included in a Cochrane analysis from 2012 found no significant adverse neonatal effects (based on an Apgar score of less than 7 at 5 minutes).[52]

Neuraxial Blocks

Any variety of epidural, spinal, or combination thereof falls under the general term *neuraxial block*. These nerve blocks are performed by an anesthesia provider and are the preferred techniques for cesarean deliveries, because maternal airway management is avoided, sensorium is unimpaired, and little or no medication reaches the fetus. Any manner of neuraxial block is commonly offered to parturients when labor is established. The versatility of these blocks makes them the ideal choice, as how dense the block is or how sparing is determined by which medications are used and in what manner they are dosed. In most laboring situations, only an analgesic state is desired; however, on occasion a denser block more closely resembling an anesthetic is preferred. This technical nuance defines two very different goals for the anesthesia provider. An anesthetic is that method designed to remove all sensation—pain, temperature, touch, vibratory sense, proprioception, and motor ability. The goal of an analgesic is to eliminate only the sensation of pain, leaving all other components intact. Logically, higher doses are more likely to produce the anesthetic state, whereas lower doses may produce only an analgesic state.

Techniques

How the most basic neuraxial blocks are administered has evolved over time to include several variations, of which the combined spinal-epidural and the patient-controlled epidural analgesic are just two. New on the horizon is the automated intermittent bolus approach that uses newer technology to administer boluses to the patient at preset

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intervals. It is not the purpose of this section to describe all aspects of these procedures in detail, but neonatologists should be aware of their most fundamental facts. A more in-depth description may be found in any obstetric anesthesia text.

Lumbar Epidurals

Lumbar epidural analgesia is usually initiated in either the sitting or lateral position.[67] To block the necessary nerves that transmit labor pain in the first stage (T10-L2), the back is examined for the L4-5, L3-4, or L2-3 interspaces. A placement at any of these three levels will produce the necessary nerve block. Once the epidural space is identified with the needle, a catheter is inserted through the needle and the needle is removed over the catheter. The catheter is then tested with lidocaine or bupivacaine with or without epinephrine to rule out intrathecal or intravascular catheter placement. Adequate labor analgesia is then established by bolus injection of the selected anesthetic. Analgesia is maintained with any combination of intermittent bolus injections and/or a continuous infusion. There are numerous drug combinations, concentrations, and infusion rates cited in the literature, but the prevalent trend today is to use dilute local anesthetic concentrations most often in combination with a low dose of opioid in an attempt to limit drug amounts while maintaining an analgesic state. Use of lower doses also improves the safety of the technique in that there is less of a chance of a deleterious effect on either the mother or fetus should the catheter migrate into either a vessel or the spinal space. The catheter is removed after delivery when there is no further need for analgesia or anesthesia.

Patient-Controlled Epidural Analgesia (PCEA)

First described for use in labor by Gambling et al. in 1988, PCEA allows the parturient to self-administer boluses of the epidural solution, giving her the ability to accommodate changing analgesic needs as labor progresses.[61] The anesthesia provider adjusts the program settings such as demand bolus, lockout interval, and hourly maximum rate for individual patients. Practices vary on whether a background infusion is used, but when included, will often be set at a lower rate than would be set for a conventional infusion. Patient-controlled epidural analgesia allows better dose-demand matching as labor progresses and has been shown to be associated with up to a 35% reduction in total volume of local anesthetic, especially in the first stage of labor.[61]

Intrathecal Injections (Spinals)

The word *spinal* is often replaced by the more accurate terms *intrathecal* and *subarachnoid* when anesthesia providers discuss this technique. Regardless of which term is used, intrathecal injections most often convey an image of complete paralysis and anesthesia. However, with modern dosing techniques, spinals performed for labor analgesia preserve temperature, touch, proprioception, and even mobility while providing pain relief. The procedure is the same as that described for an epidural with the exception that a smaller, styletted 25- to 27-gauge needle is used and a catheter is not left behind. The stylet is not removed until a "pop" is felt as the needle passes through the dura into the spinal space. Once the stylet is removed and the presence of cerebrospinal fluid (CSF) confirmed, the medication is injected and the needle removed.

Intrathecal injections are associated with the lowest maternal blood levels of all the analgesic methods used, resulting in clinically irrelevant fetal exposure. The most commonly used opioids for the induction of labor analgesia are highly lipophilic and travel to the μ-receptors within the central nervous system. As a result of this spread, maternal somnolence and even respiratory depression have been reported with small doses.[29] Not appropriately managing this maternal complication will have an effect on the fetus, but there is no direct effect on the fetus from the opioid as a result of the intrathecal injection. Although intrathecal opioid injections have been tried as the sole labor analgesic, they are not very effective beyond the first stage, and they may not last long enough for the labor. Additionally, should there be a need for an operative delivery or cesarean section, another anesthetic procedure would be required. To resolve this issue, spinals are now often combined with epidural catheter placements.

Combined Spinal-Epidurals (CSE)

With the CSE technique, both an epidural catheter placement and spinal injection are performed at the same interspace so that only one local skin infiltration is required. The spinal needle may go through or under the epidural needle. When the epidural tip is situated in the epidural space and before the catheter is threaded, the spinal injection is performed. After injection, the spinal needle is removed, the epidural catheter is threaded into the epidural space, and the epidural needle is removed. This procedure allows for a rapid analgesic response (the spinal), with the ability to bolus and infuse through the epidural catheter for longevity. An adaptation is to not administer a dose through the epidural catheter until the intrathecal effects begin to wear off.

Combined spinal-epidural analgesia has become increasingly popular over the past decade. Onset of analgesia is significantly faster with CSE compared with epidural analgesia by a factor of four (2-5 minutes vs. 15-20 minutes).[87] Despite studies that have addressed many of the concerns with the technique, not all anesthesia providers embrace it. However, most agree that there are some parturients for whom it is better suited, such as the rapidly progressing multiparous patient who might not be offered any analgesic otherwise. Despite studies showing that epidural catheters placed during a CSE technique are more likely to function properly,[61] a perceived detriment with the technique is that the epidural catheter is untried. Should a problem arise, anesthesia providers may forgo using the untried catheter and subject the patient to a general anesthetic. Even though the continuous infusion epidural and PCEA techniques have a slower onset of pain relief than a CSE, the epidural

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catheter is tested and functioning should there be a change in delivery plans.

Programmed Intermittent Epidural Bolusing

The development of a programmed intermittent epidural bolusing (PIEB) technique for maintenance of epidurals is based on studies suggesting that intermittent boluses, rather than continuous infusions, result in better local anesthetic spread, decrease the need for clinician-assisted epidural supplementation, and produce higher patient satisfaction.[38,88] This may be because the higher driving pressure generated by the bolus through the epidural catheter at programmed intervals results in better dispersion of medication than can be achieved with a steady, slow continuous infusion.[38] The optimal combination of bolus volume and dosing interval has yet to be determined but studies are underway.

Maternal Risks and Benefits With Neuraxial Techniques

Benefits

Every study that compares the analgesic effect achieved with a neuraxial block against any other analgesic technique, whether it is pharmacologic or nonpharmacologic, documents a superior result.[2] When done properly, these blocks allow the mother to relax and conserve her energy for the second stage of labor when she needs enough motor preservation to participate in that process. They also prevent the maternal hyperventilation often seen in response to pain and all the potential sequelae on the fetus associated with falling maternal P_{CO_2} levels.

Although the medications used with an epidural can eventually be found in the maternal circulation, measured blood levels are low. The current trend is to use very dilute local anesthetic concentrations supplemented with small opioid doses to keep maternal blood levels to a minimum. As a result, mothers typically show very little if any systemic effect from the administered medications, and such low maternal levels indicate very limited exposure to the fetus.[26]

Current studies have shown either no change or an increase in uteroplacental blood flow after epidural analgesia, provided hypotension is avoided or promptly treated.[20] Conversely, pain and the stress of labor may release excessive catecholamines into the circulation, which in turn decrease uteroplacental blood flow because of sympathetic stimulation.[42] Pain management with neuraxial analgesia decreases the level of circulating catecholamines and avoids maternal hyperventilation, which can lead to maternal hypocapnia.[2]

Maternal Side Effects

Common side effects of neuraxial analgesia are hypotension, pruritus, and some degree of motor block. Hypotension results from the sympathetic block by the local anesthetic, leading to vasodilation. It is common after any neuraxial block but frequently more severe after a spinal. It is also more common after an anesthetic dose as opposed to an analgesic one. If the hypotension is allowed to persist untreated, it would result in a decrease in uteroplacental perfusion. Thus, it would be below the standard of care not to treat hypotension when it occurs. To avoid hypotension, a fluid bolus is given before or along with the block initiation and after completion, the mother is positioned laterally or in a semi-recumbent position to prevent aortocaval compression. Decreases in blood pressure are treated with fluid boluses or intravenous vasopressors.

Pruritus is more common after spinal analgesia. The cause is unknown, but it is opioid-induced rather than histamine-related, and the incidence and severity are dose-dependent.[87] It is usually self-limited, but if severe, it can be treated with an opioid antagonist such as naloxone or the agonist-antagonist nalbuphine.

Although the goal of an analgesic dose is to avoid a motor block, some level of weakness is likely if a local anesthetic is part of the dosing mixture. As a result, the policy at many institutions is to confine the parturient to bed after the neuraxial block is placed. Although the idea of a "walking epidural" was popular some time ago, studies show that ambulation per se does not alter the labor outcome.[86] Also, most women did not care to get up once they were comfortable. As a result of this, and the fears of potential liability should a fall occur, many providers and institutions have stopped offering this option.

Other irritating side effects occur primarily because of the opioid used. Besides the pruritus, they include nausea, vomiting, sedation, and urinary retention. All are caused by stimulation of the μ-receptor (opioid) and will dissipate with time. The only hazardous opioid-induced side effect is respiratory depression, and although it is rare, health care providers should be alert for its presentation.

Maternal Risks

The anesthetic and nonanesthetic literature is full of discussions of documented as well as theoretical maternal risks resulting from neuraxial blocks. Although some are uncontested, such as epidural hematoma formation or nerve damage, others are quite fantastic, such as a reduction in the IQ of the neonate. The wide-ranging list of maternal risks includes unintentional intrathecal or intravascular injection, prolonged labor of either the first or second stage, backache, nerve damage, infection with possible abscess formation, epidural or subdural hematomas, arachnoiditis, an increased incidence of operative delivery, maternal temperature elevation, a cervical level that can affect respirations, and an impact on the cesarean section rate. Because the risks of backache, nerve damage, infection with possible abscess formation, epidural or subdural hematomas, and arachnoiditis are postdelivery problems, the reader is referred to any obstetric anesthesia text for a full discussion there. The following section considers only the maternal risks that are documented or have undergone scientific scrutiny and pose a potential problem for the fetus or neonate. Of those left, some are significant, whereas others are of questionable clinical significance. Other mentioned "risks"

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are documented to no longer be associated with neuraxial blocks but are mentioned here because the reader may not be aware of the newer literature.

Cesarean Sections

The effects of neuraxial blocks on the progress of labor, and particularly on the mode of delivery, have generated tremendous controversy. Selection bias confounded many studies, especially those that claimed epidurals increased the incidence of cesarean section. Now studies have determined that there is an association between epidurals and cesarean sections, but not causation.[75] The association occurs because in situations of a prolonged or dysfunctional labor, women are more likely to request epidural analgesia. All agree that dysfunctional labors are prolonged and very painful, and women in dysfunctional labor patterns are more likely to request some form of neuraxial block. However, dysfunctional labors are also associated with a greater cesarean delivery rate.[83] Literature has shown that neuraxial blocks are more frequently requested once a dysfunctional labor pattern is in place, and it is this labor pattern, not the neuraxial block, that places the patient at risk for cesarean delivery.[74]

Labor Prolongation

Prolongation of labor has long been blamed on neuraxial blocks. This claim is still undergoing some debate. Two meta-analyses and a Cochrane review reported no difference in the duration of the first stage of labor in women receiving epidural analgesia versus those receiving systemic opioid analgesia or no analgesia at all.[7] Conversely, a 2004 meta-analysis claimed that epidural analgesia increased the length of first stage of labor by approximately a half hour.[77] One offered explanation of this result involved the frequency of cervical examination in these studies. Full cervical dilation is considered the end point of the first stage of labor. This would only be determined by cervical examination or when the parturient complains of rectal pressure, which is likely to be later in a woman with effective neuraxial analgesia.[7] Thus, exams may be more frequently performed in the presence of an epidural to catch this end point. Clinical trials by Wong and Ohel found that the duration of the first stage of labor was significantly shorter when any form of neuraxial analgesia was administered early in labor.[7] As for the second-stage prolongation, it is generally acknowledged that there is a statistically significant average increase of about 15 minutes in the presence of an epidural.[7,74] Whether that amount of time is clinically relevant is debatable, and newer studies argue there is no prolongation at all, but the studies used for the meta-analysis are small and not of good quality.[82] Several studies suggest that a prolonged second stage of labor does not result in adverse maternal or fetal outcomes provided that the fetal status is reassuring, the mother is well hydrated and has adequate analgesia, and there is progress in descent of the fetal head.[7] Also, whether pushing is initiated immediately upon recognition of full cervical dilation or delayed until descent of the head causes an urge to push can influence the duration of time in second stage. Indeed, studies currently show that when the second stage is allowed to continue, as is more common in nulliparous patients, a vaginal delivery is more likely and the section rate is reduced by about one-half versus adhering to the usual guidelines.[24,25] The American College of Obstetricians and Gynecologists (ACOG) recommends that if an epidural is in place and there are no signs of fetal compromise, the second stage should be allowed to continue until the fetus has descended to a lower fetal station to avoid maternal exhaustion.

Operative Vaginal Deliveries

Neuraxial blocks have been associated with an increased need for operative vaginal deliveries. When studies report on the overall incidence of forceps deliveries and epidurals, there is no question that the incidence increases when an epidural is in place. However, multiple confounding factors contribute to these findings, such as high doses of local anesthetic that will relax pelvic muscles, thereby preventing proper rotation of the fetus for delivery, the method of epidural analgesia maintenance, and obstetric factors.[7] Why an obstetrician chooses a forceps delivery is not always well defined. For example, an obstetrician may request an epidural placement rather than perform a pudendal block if he or she feels that forceps are indicated for delivery. This may occur either because the obstetrician is uncomfortable performing a pudendal block or prefers the superior analgesia an epidural provides. As a result, the birth is recorded as a forceps delivery under an epidural. Impact studies have also been helpful in that they document that the introduction of a new epidural service does not increase the incidence of forceps deliveries for obstetric reasons. This strongly suggests that they have no effect.[27] However, until more well-controlled studies are performed in which the indication for the forceps delivery is documented, it will be difficult to determine precisely what the risk is or even if one actually exists.

Maternal Temperature Elevation

The gradual development of modest hyperthermia observed in laboring women with epidural analgesia is not seen in those electing other forms of analgesia or unmedicated labor.[74] Selection bias confounds the association between epidural analgesia and fever, because women at risk for fever, which may be caused by longer duration of ruptured membranes, longer labor, more frequent cervical examinations, and other interventions, are also more likely to select epidural analgesia.[74] However, even randomized trials have confirmed a higher incidence of hyperthermia in epidural-exposed women, especially nulliparous patients that suggest a causal relationship. The mechanisms of epidural-associated hyperthermia remain incompletely understood.[74] Altered thermoregulation and an antipyretic effect of opioids given to women without epidural analgesia may explain part of the phenomenon, but the most likely etiology is not an infectious one[14] but rather a noninfectious inflammation.[3,78]

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Newer studies are suggesting that a cytokine-induced inflammatory response, as is normal in labor, may be behind this phenomenon, especially interleukin 6.[10,41] The consequences of maternal hyperthermia are diverse. Obstetricians are more likely to intervene surgically in laboring women with temperature elevation, and neonatologists are more likely to evaluate neonates of febrile women for sepsis. Studies that looked at the neonatal results reported that there was no increased incidence of sepsis despite the maternal temperature elevation.[27,14] As a result, many neonatal units have adjusted their policies to require other clinical indications besides maternal temperature before a neonatal sepsis workup is initiated.

Inadvertent Injections and Excessively High Levels

Inadvertent intrathecal or intravascular injections when a neuraxial block is performed can have a serious impact on the fetus. The epidural space is a potential space that is vascular in nature. Possible catheter or needle complications include placement into a vessel or through the dura into the intrathecal space. Unrecognized misplacement with subsequent injection of a large amount of local anesthetic can cause maternal hypotension, seizures, and cardiovascular collapse from an intravascular injection, or paralysis with respiratory compromise that may lead to apnea from an intrathecal injection.[34] When an unrecognized intravascular injection occurs, the acute insult to the fetus appears to be caused by the maternal hypoxia[87] that develops during the seizure or arrest and not the high levels of anesthetic in the maternal system, although some of it is sure to cross over if uteroplacental perfusion is maintained. When a high block happens because of improper dosing or an unrecognized intrathecal injection, maternal respiratory muscles become paralyzed and inadequate respirations, including apnea, can occur. If this condition is not recognized and treated, the maternal arrest will have obvious consequences on the fetus. Fortunately, both of these complications are exceedingly rare and very preventable with attention to good technique.

Benefits and Potential Risks for the Fetus

When investigating different methods of maternal pain relief in labor, neonatal outcome has not always been at the forefront.[64] Unfortunately, many laypersons and some health care providers assume that for every negative maternal effect, there must be an associated negative fetal or neonatal effect. However, the literature does not support such a presumption. Those studies that examine the fetal and neonatal effects typically report on the presence or absence of base excess to determine the recent intrauterine environment, the intrapartum fetal heart rate (FHR), the Apgar scores, and a host of neuroadaptive examinations. These neuroadaptive examinations often require operator training and have varying abilities to determine any prolonged effect on the neonate from an intrapartum event or medication. For example, the Neurologic and Adaptive Capacity Score (NACS) has poor sensitivity to distinguish between intrauterine hypoxia and drug effects in the neonate.[6,28] The following section discusses the effects of neuraxial block on the fetus and neonate as defined by the aforementioned indicators and concludes with a brief review on breastfeeding.

Acid-Base Balance

One of the most notable benefits a fetus gains from a neuraxial block in the mother is that she no longer hyperventilates in response to painful contractions. Maternal hyperventilation in response to pain has long been known to have adverse fetal effects.[64,65] Maternal and fetal CO_2 levels are closely associated, and maternal hypocapnia as a result of hyperventilation leads to a maternal respiratory alkalosis resulting in a left shift in the oxygen dissociation curve. This leads to impaired placental transfer of oxygen to the fetus. Furthermore, a compensatory metabolic acidosis develops in the maternal side and may be conveyed to the fetus, resulting in worsening acidosis and hypoxia as labor progresses. With a functioning neuraxial block in place, these events are less likely to occur, and studies have consistently shown an improved fetal acid-base balance when an epidural is used.[64,65] Literature shows that fetal acid-base status is not only better with epidural than with systemic opioids, it is also better than with no analgesia.[65] Neonatal base excess measurement at delivery is believed to best reflect the intrauterine environment just before delivery, and studies comparing epidurals against systemic medications or alternative, nonpharmacologic labor management methods have documented that neonatal base excess levels stay within normal limits more consistently with epidural use than they do with other techniques.[63] Other findings are that amounts of meconium are less or similar upon delivery, and Apgar scores are comparable or improved when a functioning epidural is in place. These findings further support the idea of a better intrauterine environment and less stress on the fetus with an effective neuraxial block present.

Fetal Heart Rate

An alteration in fetal heart rate, most notably fetal bradycardia, can occur in approximately 10%-12% of those parturients receiving an epidural and has been a long-recognized phenomenon. It can occur within 15-45 minutes after initiation of any form of neuraxial analgesia. It has been hypothesized that as analgesia is established, there is an acute decrease in maternal plasma epinephrine levels. This acute decrease against a less rapid drop in norepinephrine levels results in a temporary imbalance of uterine tocolytic and tocodynamic forces, resulting in uterine hypertonus, decreased uterine perfusion, and ultimately, fetal bradycardia.[87] The bradycardia usually resolves with conservative therapy and is often significant enough to initiate intrauterine resuscitative measures but rarely leads to an early delivery.[8] Apgar scores are typically fine upon delivery.

The use of neuraxial opioids can also produce an effect on the fetal heart rate (FHR). Loss of beat-to-beat variability can be attributed to large doses of neuraxial opioids, but

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this side effect is also seen with systemic opioids and agonist-antagonist opioids. A comparison of analgesic techniques shows that FHR changes are more common with systemic medications.[26] More newborns of mothers receiving intravenous versus neuraxial opioids had lower 1-minute Apgar scores and needed naloxone and resuscitation.[64,65] Although studies show that the neuraxial opioid effects on FHR are temporally limited when very high doses are delivered repeatedly to the epidural space, enough can be absorbed systemically by the mother and cross the placenta. This can result in high levels in the neonate at birth and require the use of naloxone. As a result, anesthesia providers should be careful with the timing and use of neuraxial opioids during the second stage of labor.

Breastfeeding

A frequent claim made by those opposed to the use of epidurals is that this mode of pain relief will temporarily or permanently damage the neonate's ability to breastfeed.[81] Precisely how this occurs has never been elucidated, and those proposed hypotheses that seemed plausible have not withstood scientific scrutiny. Studies reporting on the effect of neuraxial medications on breastfeeding have not been randomized, and those purporting to show adverse effects of epidural analgesia received disproportionate publicity.[64,65] One of the most common theories is that medications used in the epidural space enter the maternal circulation, reaching such high levels that enough crosses to the fetus, where it remains in circulation after delivery and produces an adverse effect. The other common hypothesis is that high maternal systemic concentrations from epidural injections seep into the breast milk and affect the neonate. Reynolds reviewed 17 breastfeeding studies, from 1994-2010, looking at the effects of neuraxial blocks on breastfeeding versus other or no analgesia.[64,65] Only two studies showed a dose-related detrimental effect of epidural fentanyl, but these findings were not confirmed by other retrospective studies.[64,65] A Canadian study from 2010 showed that, with good support, a breastfeeding success rate of greater than 95% can be achieved after epidural bupivacaine plus fentanyl, with no discernible dose-related effect.[64,65] Anecdotally, some of the patients who had undergone labor without an epidural were so exhausted after delivery that they were not able to breastfeed, whereas those who had an epidural were alert.

Other studies have not measured levels but examined whether nursing policies that require a different postpartum management of patients with epidurals might have a negative influence on breastfeeding behaviors. These policies were found to minimize early postpartum maternal-infant contact. Furthermore, where early maternal-infant separation is minimized, epidural analgesia was found to have no effects on lactation success.[64,65] Although there are numerous reasons why mothers and neonates do not succeed at breastfeeding, the current peer-reviewed literature does not support the premise that neuraxial techniques have any effect on the abilities of the neonate to do so.[21]

Delivery Modes and Anesthetic Techniques

When a mother presents for labor management, and delivery is not imminent, an important role for the obstetric team is to support whatever pain-relieving choices she makes as long as there is no perceived harm to her or her fetus. However, choices are not always well-informed or circumstances dictate a change in labor management that conflicts with the mother's desires. For instance, the morbidly obese patient who has a difficult airway and a questionable fetal heart rate tracing should not pursue the water birth she planned, but be counseled on oxygen supplementation and placement of a neuraxial block in anticipation of a possible emergency cesarean section. Labor is one of the most dynamic natural events in medicine, and what may begin as a routine process can change very rapidly. As a result, analgesic techniques and management plans need to be adaptable. The following section outlines some of the anesthetic-based considerations the anesthesia provider faces when a spontaneous vaginal delivery is no longer likely.

Operative Vaginal Delivery

Over the past decade, the rate of operative vaginal delivery has significantly decreased.[13,53] There are two types: vacuum extraction and forceps delivery. The choice of instrument is often influenced by clinical circumstances, operator choice, and availability of specific instruments.[52] In the case of a vacuum extraction, it cannot be performed until the head is very low in the pelvis.[13] The extractor is generally a soft, pliable cup and the application is well tolerated by the mother so that additional analgesia is not necessary even if none was used for the labor. Some local anesthetic to the perineum in anticipation of an episiotomy may be all that is required.

Forceps application and delivery generally require some level of analgesia, and often the obstetric provider either requests a neuraxial block or performs a pudendal block. There are four levels of forceps delivery described, but the two most commonly performed are low and outlet forceps deliveries.[53,59] The placement of the forceps blades is very stimulating, and it is only in a dire emergency that an obstetric provider should perform such a delivery without some form of anesthesia in place. A pudendal block is a reasonable choice and can be performed in less time than a spinal or epidural can be administered. However, neuraxial blocks offer more complete pain relief and, in the case of an epidural or combined spinal-epidural, can be extended to a higher level should the forceps attempt fail.

Cesarean Section

Cesarean sections can be performed electively, urgently, or emergently. The form of anesthetic used is dictated by the circumstances. Most anesthesia providers prefer not to use

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a general anesthetic because of concerns with the maternal airway and potential aspiration. The incidence of failed intubation among the pregnant population is estimated to be upwards of 8-10 times that of the nonpregnant population. Studies have reported the difficult airway incidence to be between 1 in 238-750 general anesthetics, with 1:250 being the most widely quoted ratio.[60] Several factors contribute to this number. The changes of pregnancy itself as well as altered hormonal influences cause edematous airways resulting from fluid accumulation.[46] Add to this the time spent in labor, especially after many Valsalva maneuvers in the second stage, and what was once a normal airway can become swollen with obscured intubation landmarks and easily obstructed with attempts at intubation. Other changes that contribute to maternal risk during induction include those of the pulmonary system, gastrointestinal system, and body habitus over the course of the pregnancy. These changes and the often-emergent nature of an obstetric procedure may result in failed airway management, with or without aspiration. Airway fatalities have diminished secondary to the decreased use of general anesthesia for obstetric procedures and the use of rescue airway equipment such as supraglottic airway devices and video laryngoscopes.[85] Because of these airway concerns, neuraxial anesthesia is the approach of choice whenever possible for most anesthesia providers.

Neuraxial Anesthesia

In the elective or urgent situation, some form of neuraxial block is the anesthetic of choice, assuming that there are no existing contraindications (Box 27.2). If an epidural is already in place, it is an easy matter to change medications to a more concentrated, faster-onset local anesthetic. Opioids may or may not be added. Attention must still be paid to the dosing technique because moving the patient onto the operating bed may dislodge or shift the epidural catheter; therefore, test doses and aliquoted dosing amounts are still in order. If an epidural block is not in place and the need to proceed with the cesarean section is urgent or emergent, the preferred approach in most units is to perform an intrathecal injection or possibly even a combined spinal-epidural technique. These methods give a faster onset and limit the medication exposure to the fetus. All neuraxial techniques have been shown to result in better neonatal parameters than when a general anesthetic is performed.[1]

• BOX 27.2 Absolute Contraindications to Neuraxial Blocks

- Severe hypotension
  - Hypovolemia
  - Sepsis
  - Hemorrhage
- Infection at the site
- Coagulopathy or thrombocytopenia
- Maternal refusal

General Anesthesia

At what level of surgical urgency a neuraxial block should not be attempted or should be abandoned is always a topic for discussion. That decision should never be made lightly because of issues with the maternal airway, effects of anesthetics on uterine tone, and the potential impact on the fetus.[42] There are absolute contraindications to performing a neuraxial block (see Box 27.2), and when one is present, it directs the decision making. Neonatologists present at a nonelective cesarean section reasonably add the use of general anesthetics to their growing list of potential reasons for neonatal resuscitation. Fortunately, the literature supports the clinical observation that under the conditions of short incision-to-delivery times and with the current pharmacologic developments of short-acting anesthetics, the impact on the neonate is small. Those anesthetic agents that are most commonly used are further discussed.

Before the induction of a general anesthetic, the anesthesia provider usually gives the mother one or more agents to reduce the risk of aspiration, provided circumstances allow. The most commonly used agent is sodium citrate, which is an antacid taken orally just before induction. Other agents that may be given instead of or along with sodium citrate are some form of H_2-blocker, such as ranitidine, and metoclopramide. None of these medications has been shown to have an impact on the fetus.[23]

Because it is only during the induction phase and a short maintenance period to which the fetus is exposed, the anesthetics of concern are the induction agents, a rapid-onset neuromuscular blocker such as succinylcholine, a volatile agent, and perhaps nitrous oxide (N_2O) and occasionally opioids. The previous discussion on general pharmacologic properties and the UV:MV ratio should help gauge the potential impact on the fetus. Table 27.1 shows the UV:MV ratios of several of these drugs. Thiopental is no longer available in the United States, thus, propofol is now the most commonly used induction agent.[50] Ketamine and etomidate have been used as well. All cross the placenta, but there is rarely an effect seen in the neonate because of the first-pass effect through the fetal liver and the dilutional effects from the circulation. Some of propofol's benefits are its short half-life and minimal residual impact. Ketamine is generally reserved for the hemorrhaging or volume-depleted patient, because it is less cardio-depressive and produces a sympathetic response that better maintains the maternal hemodynamic state. Etomidate is generally reserved for patients with cardiac disease. All of these induction agents depress the maternal myocardium but to varying degrees. As a result, intervillous blood flow may initially decrease but will return to baseline as long as maternal blood pressures are monitored and any hypotension is treated.

To intubate and secure the airway in the most rapid manner possible, succinylcholine is the neuromuscular agent of choice, because it has the fastest onset of action. It also has the shortest duration of action as it has a half-life of 90 seconds and is metabolized in the maternal plasma by

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pseudocholinesterase to benign metabolites. As a rule, no other neuromuscular blocking agent is needed during the short time from incision to delivery, so the use of succinylcholine alone will have no effect on the fetus. However, there are times when succinylcholine is contraindicated or delivery is delayed and a nondepolarizing neuromuscular blocking agent is required. This is a different class of neuromuscular blocker from succinylcholine, but this class of medications is hydrophilic and highly ionized. As a result, little if any crosses the placenta and again, the fetus is not affected (see Table 27.1).

A volatile agent such as isoflurane or sevoflurane is administered to maintain the anesthetic state, and nitrous oxide may or may not be added. Although these agents pass to the fetus, they rarely have a direct effect unless the time from induction to delivery is prolonged. If more than 15 minutes pass since the induction, the concentrations of these agents in the fetus will equilibrate with the maternal levels, and the neonate will be depressed at delivery. Ventilatory support for a few minutes is generally all that is required as these agents are expelled through the lungs. However, it is more important for the neonatologist to note that if the uterine incision to delivery time exceeds 180 seconds, the neonate will more likely be depressed from a compromised perfusion and less so from these maintenance agents.[16]

Adjuvant Medications

Intravenous opioids or sedatives are usually not administered to the mother before delivery but on occasion it happens. Some patients demand some form of anxiolytic before the cesarean section, and in those cases a small dose of midazolam (Versed) is usual. A small dose (1-2 mg) will not have an impact on the neonate. At other times, the neuraxial block may not be adequate for the cesarean section, because either the epidural catheter is poorly positioned or insufficient time has passed for the level to rise adequately, and the anesthesia provider may administer an opioid such as fentanyl or small doses of ketamine intravenously. These medications have already been discussed, and none has a significant effect on the neonate at the dosages commonly used.

Key Points

- Neuraxial blocks are an ideal choice for labor in which the mother wants both the most effective pain relief and least effect on her baby. Maternal side effects may include hypotension and hyperthermia.
- Nonpharmacologic pain management techniques attempt to alter the patient's perception and response to noxious stimuli. Although studies evaluating the effectiveness of these techniques are small and oftentimes demonstrate inconsistent results, they do not appear to negatively impact the fetus.
- The pain management technique most often employed by the obstetrician outside the blockage of nerve transmission is intravenous injection of medication such as sedatives and opioids, which will cross the placenta and enter the fetal circulation. Impact on the fetus depends on the pharmacokinetic and pharmacodynamic properties of the drug, how much is given, and the timing of administration with delivery.
- Should a general anesthetic be necessary for a delivery, the technique employed assumes a short induction to delivery time, thereby minimizing fetal exposure and use of short-acting medications with minimal to no ability to cross the placenta.

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28

Physical Examination of the Newborn

TOM LISSAUER AND ANNE HANSEN

Immediately after a baby is born, all parents want to know, "Is my baby all right?" A quick initial physical examination of all newborns should be performed in the delivery room to ensure that there are no major anomalies or birth injuries, that the newborn's lips and body appear pink, and that breathing is normal. This primary survey must include a brief look at the entire body. This usually allows the clinician to reassure the parents that their infant looks well and appears normal.

Many serious congenital anomalies will have been identified prenatally, their presence anticipated, and a management plan made before delivery. If the newborn is sufficiently preterm or small for gestational age, has a significant problem diagnosed prenatally or at birth, or is unwell (e.g., respiratory distress), the newborn must be admitted to an intermediate or intensive care nursery.

If not already informed prenatally, the parents will be eager to hear if they have a boy or girl. Rarely, there may be uncertainty about the infant's gender, in which case it is important not to guess but to inform the parents that further evaluation is required before the gender can be determined.

During the first few hours after birth, healthy newborns are usually alert and reactive and will suck at the breast. This behavior provides an initial opportunity for the mother to form a close attachment with her infant and to establish breastfeeding. Medical interference during this time should be kept to a minimum.

Routine Examination

Every infant should undergo a "routine examination of the newborn," a detailed physical examination performed by a trained health care provider, within 24 hours of birth.[2] The objectives of the examination are listed in Box 28.1. The prevalence of the most common significant congenital abnormalities is shown in Table 28.1. Some are detected prenatally, but many are first noted in the delivery room or during the routine examination of the newborn. They are described briefly in this chapter; detailed descriptions are found elsewhere in the book. In some countries, for example, the United Kingdom, health professionals are trained according to a standardized National Neonatal and Infant Physical Examination Screening Programme and results recorded on a standardized checklist in the medical records and Parent Child Health Record.[37]

Preparation

Before approaching the mother and infant, the mother's and infant's medical and nursing records should be reviewed. Relevant items are listed in Box 28.2.

Introduction to the Parents

The health care provider should introduce himself or herself to the mother or, preferably, to both parents and explain the purpose of the examination. It is usually best to start by asking if there are any problems with feeding or any other worries about the infant. Before starting the examination the health care professional must conduct hand hygiene and ensure that the newborn can be examined in a warm, private area with good lighting.

Order of the Examination

The exact sequence in which the newborn is examined is flexible so long as the entire body is examined at some stage. If the newborn is quiet, take the opportunity to listen to the heart and examine the eyes. It is often convenient to start by making general observations of the newborn's appearance, posture, and movements while undressing him; then to conduct the examination from head to foot; then to remove the diaper to examine the genital region, femoral pulses, and hips; and finally to pick him up and turn him over to examine the back and spine and assess tone in the prone position (Fig. 28.1).

Measurements

The infant's growth parameters and gestational age should be noted. The birth weight percentile should be ascertained from the gestation-specific growth chart, using growth charts from the World Health Organization (WHO) or Centers for Disease Control and Prevention (CDC) (www.CDC.gov/growthcharts). The 10th-90th percentile for weight at 40

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Abstract

This chapter describes the components of the routine physical exam of the newborn. It covers both normal and abnormal findings and refers the reader to relevant chapters for more in depth coverage where appropriate. After reviewing basic measurements and components of the general appearance of the newborn, it covers the exam from head to toe, ending with the neurologic assessment, behavioral evaluation, assessment of gestational age, limitations of the exam, and the role of the exam in health promotion and discharge planning.

Keywords

newborn infant
routine physical exam
neurologic assessment
gestational age assessment
limitations of physical exam
health promotion
discharge planning

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• BOX 28.1 Objectives of Routine Examination of the Newborn

- Detect congenital abnormalities.
- Determine whether any of the wide range of nonacute neonatal problems is present, and initiate their management or reassure the parents.
- Check for potential problems arising from maternal disease, familial disorders, or problems during pregnancy.
- Provide an opportunity for the parents to discuss any questions about their infant.
- Initiate health promotion for the newborn (e.g., breastfeeding, prevention of sudden unexplained infant death syndrome safe transport in cars).
- Ensure an appropriate plan is in place for outpatient monitoring of hyperbilirubinemia.
- Ensure that a follow-up plan is in place for parents with child protection issues, mental health problems, substance abuse, severe learning difficulties, or other social concerns.

TABLE 28.1 Prevalence of Significant Congenital Anomalies

Anomaly	Prevalence Per 1000 Live Births
Congenital heart disease	6-8 (0.8 identified in the first day of life)
Hypospadias	4
Down syndrome	1.3
Talipes equinovarus	1.1
Development of dysplasia of the hip	0.7-1.1 (about 7/1000 have abnormal initial examination)
Cleft lip and palate	0.8
Spina bifida/ anencephaly	0.5

weeks' gestation for a female is 2.7-3.85 kg (mean, 3.2 kg) and male is 2.8-4.0 kg (mean, 3.3 kg). If the infant's gestational age is uncertain, it can be determined (±2 weeks' gestational age) using a standardized scoring scheme. Infants often lose weight over the first few days of life, but a loss of >10% of birth weight is a cause for concern.

The head circumference should be measured with a disposable tape measurer at its maximal occipital frontal circumference and plotted on a gestation-specific growth chart to identify microcephaly or macrocephaly and to serve as a reference for future measurements. However, the measurement can change markedly in the first few days because of molding of the head during delivery. The 10th-90th percentile is 32-35 cm for females and 33-36 cm for males at 40 weeks.

The infant's length may also be recorded, but because the hips and lower legs need to be held extended, unless a length board is used, the length is rarely measured accurately enough to identify short stature or serve as a reliable

• BOX 28.2 Mother's and Infant's Records

Items of Particular Relevance in the Mother's and Infant's Medical and Nursing Records are:

- Maternal age
- Details of previous pregnancies, complications, and any medical problems experienced by those children
- History of maternal disease and medication taken during pregnancy
- Maternal occupation and social background
- History of maternal drug or alcohol abuse, socially high-risk circumstances (e.g., severe learning difficulties, maternal mental health problems, domestic violence, child protection issues, unsatisfactory home conditions)
- Family history of medical problems
- Results of pregnancy screening tests (e.g., blood tests including maternal syphilis and hepatitis B surface antigen, prenatal ultrasound scans)
- Results of special diagnostic procedures (e.g., noninvasive prenatal testing, amniocentesis, chorionic villus sampling)
- Problems during labor and delivery (e.g., prolonged rupture of membranes, maternal fever)
- Infant's condition at birth and if resuscitation was required
- Infant's birth weight
- Infant's gender
- Gestational age and if there is any uncertainty about it
- Any concerns about the infant from nursing staff or parents (e.g., feeding concerns)

reference value when measured routinely. The length of the arms and legs relative to that of the trunk is observed, although short limbs from skeletal dysplasias can be difficult to appreciate in the immediate newborn period.

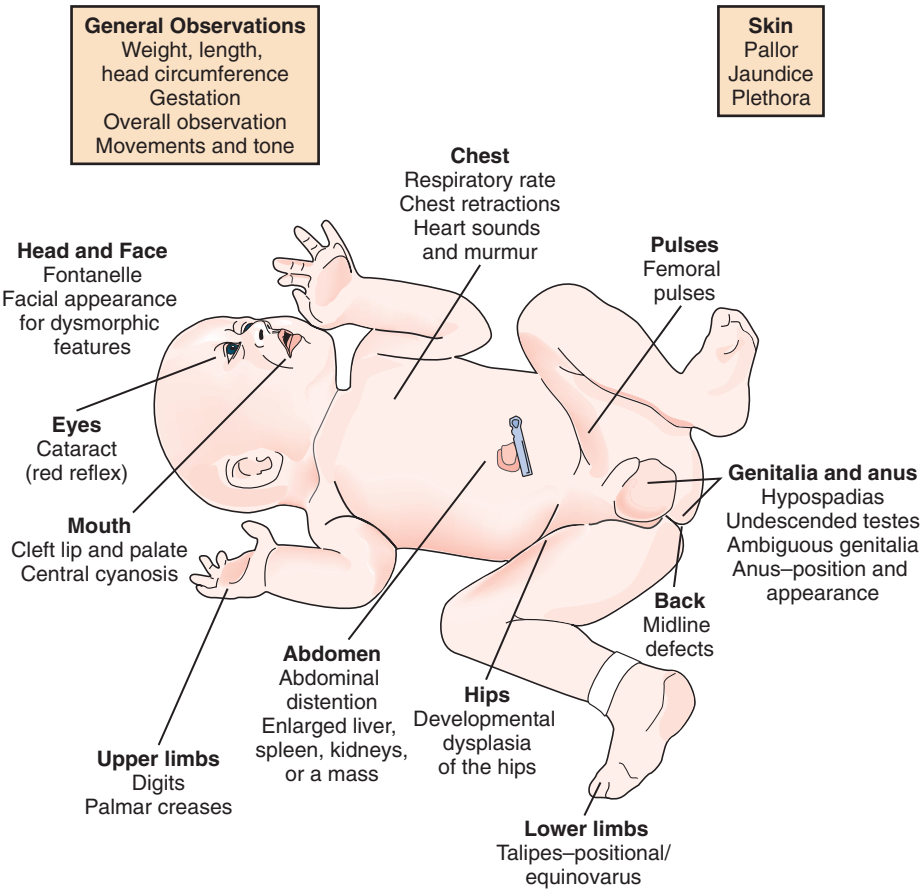
General Observation of Appearance, Posture, and Movements

Much valuable information can be gleaned by simply observing the newborn. Central cyanosis is best observed on the tongue. If present, it requires urgent investigation. If there is any doubt, the newborn's oxygen saturation should be checked with a pulse oximeter. Polycythemic infants (central hematocrit >65%) sometimes appear cyanotic because of the high concentration of reduced hemoglobin in their blood, even though they are adequately oxygenated. Acrocyanosis, peripheral cyanosis confined to the hands and feet, is common during the first day of life and is of no clinical significance. A blue discoloration of the skin, often with petechiae, can affect the presenting part in a face or breech presentation or the head and neck if the umbilical cord was wrapped around the infant's neck. This can be distinguished from central cyanosis because the tongue remains pink.

Syndromes

The facial appearance is observed. If the face is abnormal, does the newborn have a syndrome? Down syndrome is by far the most common syndrome. The characteristic facies are often difficult to recognize in the immediate neonatal

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• **Fig. 28.1** Main features of routine examination of the newborn.

period, especially in preterm infants, but other abnormalities, such as hypotonia, flat occiput, bilateral single palmar creases, and a pronounced sandal gap (an abnormal spacing between the first two toes), can be appreciated at birth. In some cases, the parents will need to be informed of the concern before the results of the chromosome analysis are available.

Many hundreds of syndromes have been described. When the diagnosis is uncertain, a book or computer database should be consulted and advice sought from a clinical geneticist (see Chapter 30).

Assess the face for asymmetry, particularly when crying, to identify facial palsy and asymmetric crying facies. In peripheral facial palsy, babies are unable to wrinkle their forehead or close their eye completely. Most are traumatic and resolve within a few weeks. Asymmetric crying facies is usually due to congenital absence of the depressor anguli oris muscle on one side of the mouth. These infants can wrinkle their foreheads and close their eyes; there is an association with congenital heart disease.

Skin

Inspect the skin for color, texture, rashes, and birthmarks. Cracked, peeling skin is common, especially in post-term infants. The infant may be plethoric from polycythemia or unduly pale from anemia or shock. If there is a concern for polycythemia or anemia, the hemoglobin concentration or hematocrit should be measured. Jaundice within the first 24 hours of birth, unless mild, is most likely to be hemolytic and requires urgent investigation and treatment. It may also be a feature of congenital infection. Manage according to guidelines.

The following newborn skin conditions are benign, self-limited, and do not need any treatment: Neonatal urticaria (erythema toxicum) is a common rash that usually starts on the second or third day of life. It consists of white pinpoint papules at the center of an erythematous base. Eosinophils are present on microscopy. The lesions migrate to different sites, and the rash resolves around the fifth day. Neonatal pustular melanosis is present from birth, contains neutrophils, and is more common in black infants. The top of the pustule is readily removed by wiping, revealing denuded skin, and may easily be mistaken for staphylococcal infection. The denuded skin becomes hyperpigmented and takes several months to fade.

Milia are benign white cysts that may be present on the nose and cheeks from retention of keratin and sebaceous material in the pilaceous follicles. Small white pearls may be visible along the midline of the palate (Epstein pearls). Cysts of the gums (epulis) and on the floor of the mouth (ranula) are mucus-retention cysts.

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In harlequin color change, there is longitudinal reddening down one half of the body and a sharply demarcated blanching down the other side. This lasts for a few minutes. It is thought to be due to vasomotor instability.

Mongolian blue spots are blue-black macular discolorations at the base of the spine or on the buttocks. They occasionally also occur on the legs and other parts of the body. They are most common in black or Asian infants and fade slowly over the first few years of life. They are of no clinical significance but are occasionally misdiagnosed as bruises; their presence and distribution at birth should therefore be recorded.

Café au lait spots are common, but more than three may indicate an underlying disorder such as neurofibromatosis type 1 or McCune-Albright syndrome.

Several vascular anomalies can be present at birth, some of which may be of long-term significance. The classification system has changed recently to more accurately reflect two distinct pathologic groups; malformations (errors in vasculogenesis), which may be associated with other anomalies, for example, Sturge-Weber and Klippel-Trénaunay syndromes, and tumors (proliferating endothelium).[35]

Vascular malformations are present at birth. The macular stain of infancy or nevus simplex, previously called "capillary hemangiomas" or "stork bites," are pink macules caused by distention of dermal capillaries and seen on the upper eyelids, the mid forehead, or the nape of the neck. They occur in 40%-60% of infants and gradually fade during the first year, although those on the neck may persist but become covered with hair.

Port-wine stains or "nevus flammeus" are caused by a vascular malformation of capillaries in the dermis. They may be anywhere on the body, are usually unilateral or segmental, and do not cross the midline. The face is a common site, along the distribution of the branches of the trigeminal nerve. They do not fade but grow with the child and become darker. When these lesions are disfiguring, their appearance can be improved using laser therapy.

Vascular malformations may be associated with other anomalies. If the port-wine stain affects the ophthalmic distribution of the trigeminal nerve, it is associated with intracranial vascular anomalies (Sturge-Weber syndrome) in about 10% of cases and, therefore, the infant should be evaluated for glaucoma and brain lesions.

Klippel-Trénaunay syndrome is an uncommon vascular malformation associated with a vascular anomaly typically causing overgrowth of the lower extremities. Larger and more complex lesions can involve the capillaries, veins, arteries, or lymphatics and may require referral to an interdisciplinary vascular anomalies center.[31]

The most common benign tumors of infancy are infantile hemangiomas (strawberry nevus). They are not usually visible at birth but become visible from proliferation of blood vessels in the first few weeks after birth, gradually increase in size until 3-15 months of age, and then slowly regress as they involute. If necessary, *topical* propranolol may be given to hasten their regression. If they cause airway compromise or gastrointestinal bleeding, they may require treatment with *oral* propranolol, sometimes combined with laser therapy. Diffuse liver hemangiomas can cause profound hypothyroidism and, therefore, thyroid function should be followed. Hemangiomas in the distribution of a beard can be associated with airway lesions.

Head

The shape of the head should be noted. It may be asymmetric from the infant's intrauterine position or molded from squeezing through the birth canal. Newborns who have been in the breech position in utero often have a prominent occipital shelf. After cesarean birth without labor the infant's head shape is round and symmetric. The fontanelle and sutures are palpated. The size of the anterior fontanelle is variable. If the fontanelle is tense when the newborn is not crying, this may be from elevated intracranial pressure, and cranial ultrasonography should be performed. A tense fontanelle can also be a sign of meningitis; therefore, a lumbar puncture should also be considered if concerns are raised by the history or physical exam. After delivery, the sagittal suture is often separated and the coronal sutures are overriding. The posterior fontanelle is often open but small. Bruising and abrasions after vacuum or forceps deliveries, from scalp electrodes, or from fetal blood sampling are relatively common (see Chapter 29). A caput succedaneum is bruising and edema of the presenting part of the head. It may extend beyond the margins of the skull bones. A cephalohematoma is caused by bleeding between the periosteum and the skull bone. It is confined within the margins of the skull sutures, usually overlying the parietal bone, and does not cross the midline. These conditions may take several weeks to resolve.

In subgaleal hemorrhage, there is bleeding between the galea aponeurosis and periosteum. Vacuum extraction and coagulopathy are risk factors. The head may have a boggy appearance with anterior displacement of the ears and a "wave sign" if fluid is pushed from one side of the head over to the other. Early recognition and treatment is paramount because of the potential for a large volume of blood loss causing hypovolemic shock.

Craniosynostosis is premature fusion of one or more of the cranial sutures, usually resulting in a markedly asymmetric skull with a palpable ridge along the suture line. It may be isolated, but if more than one suture is involved, it is often part of a syndrome (e.g., Crouzon or Apert syndrome). Because it can restrict brain growth, surgery may be required nonurgently to avoid neurologic impairment and to improve cosmetic outcome.

Eyes

The eyes should be checked both externally and with an ophthalmoscope. The size, slant, and position of the eyes should be noted. A coloboma is a defect in the normal tissue in or around the eye that can involve the lid, cornea,

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iris, retina, or optic disc. Defects internal to the pupil can only be diagnosed by ophthalmologic examination. It may be an isolated abnormality or part of the CHARGE syndrome (*c*oloboma, *h*eart disease, *a*tresia choanae, *r*estriction of growth or development, *g*enitourinary tract abnormality, *e*ar anomalies). The red reflex should be elicited using an ophthalmoscope held about 8 inches from the infant's eyes and focused on the pupil. During this part of the examination the room may need to be darkened. The eyes will usually open if the infant is awake, if the infant's head is supported in the examiner's hand and raised to about 45 degrees, or if the infant is held over the parent's shoulder. If the infant is asleep, the eyelids can be gently opened, although this is often made more difficult by the application of ophthalmic antibiotic ointment and/or swelling of the eyelids, which is common in newborns and resolves during the first few days of life. The red retinal reflex can be seen if the lens is clear but not if it is opaque from a congenital cataract or enlarged and hazy from congenital glaucoma. In dark-skinned infants, the reflex is often more yellow than red. A white pupillary reflex (leukocoria) is an important presentation of retinoblastoma. If the red reflex is abnormal, an ophthalmologist should be consulted directly. Congenital cataract is the most common form of preventable childhood blindness. The American Academy of Pediatrics (AAP) recommends referral to an ophthalmologist for all infants with a family history of significant eye disease regardless of examination findings.

Subconjunctival hemorrhages are common. They occur during delivery and resolve in 1 to 2 weeks. There may also be a mucoid discharge from the eyes in the first few days of life, which resolves spontaneously. If more prolonged, it is often from a blocked or incompletely canalized nasolacrimal duct. The eyelids can be cleansed with clean water. This condition must be contrasted with the erythematous, swollen eyelids with purulent eye discharge seen in conjunctivitis. On the first day of life, gonococcal infection is the most likely etiology of conjunctivitis but is rare in high-income countries. In the United States and many other countries, all infants are given eye prophylaxis against gonococcal conjunctivitis. Conjunctivitis may also be caused by *Chlamydia trachomatis*, but this is rare on the first day, usually presenting on days 5-14 of life.

Ears

The shape, size, and position of the ears are checked. Normally placed ears are positioned so that the top third of the ear is level with a line drawn from the inner to the outer canthus of the eye. Low-set or abnormal ears are characteristic of a number of syndromes. Malformations of the ear may be associated with hearing loss. Skin tags anterior to the ear (preauricular tags) and accessory auricles should be removed by a plastic surgeon. Preauricular tags are usually isolated and benign, but they warrant arranging for a hearing screen[21] if practicing in a setting where universal newborn hearing screens are not performed. Preauricular tags are sometimes associated with other dysmorphic features, renal anomalies, a family history of deafness, or a maternal history of gestational diabetes. When a preauricular tag is associated with other abnormalities or risk factors, a renal ultrasound is recommended.[29] A renal ultrasound examination for an isolated preauricular tag or other minor ear anomaly is no longer recommended.[18]

Congenital ear deformities, in which there is normal development of the ear cartilage but abnormal architecture, may resolve spontaneously, but splinting of the ears in the early neonatal period has been recommended to avoid the need for surgery and improve cosmetic appearance.[27] In some of these patients, surgery is eventually performed.

Mouth and Palate

The mouth is observed for size, position, and symmetry. The palate must be inspected, including posteriorly, to exclude a cleft palate. The whole of the palate needs to be visualized, which may require a flashlight and depression of the tongue. If cleft lip and palate are recognized prenatally, the parents will be forewarned and counseled about the likely appearance and management. When diagnosed at birth, the parents will need to be reassured about the good cosmetic results after surgical repair. Before-and-after photographs of other children are often helpful. Assistance in establishing feeding may be required. The infant will need to be referred to a multidisciplinary craniofacial service.

Micrognathia describes a small mandible and may be associated with glossoptosis and a U-shaped, posterior cleft palate (Robin sequence), which may cause upper airway obstruction and feeding difficulties. It can be syndromic or nonsyndromic.

Neck

Redundant skin over the posterior neck together with a flat occiput is a feature of Down syndrome. A webbed neck is a feature of Turner syndrome, which may also be associated with lymphedema of the feet. A short, webbed neck may indicate abnormalities of the cervical spine (Klippel-Feil syndrome). Cystic hygromas are soft, fluctuant swellings usually in the posterior triangle that transilluminate.

Breathing and Chest

Breathing and chest wall movement are observed. Breathing should be normal, with no signs of respiratory distress (i.e., respiratory rate greater than 60 breaths per minute, retractions of accessory respiratory musculature, flaring of the alae nasi, or grunting). If the breathing is normal, it is rare for significant abnormalities to be detected on auscultation. If the infant has respiratory distress, further evaluation is required immediately. Normal term infants may have periodic breathing with pauses of up to 10 seconds between periods of regular breathing.

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Breast enlargement can occur in newborns of either sex. A small amount of milk ("witch's milk") may be discharged.

Heart

The normal heart rate is 120-160 beats per minute in term infants but can drop to as low as 85 beats per minute during sleep. The heart sounds should be loudest on the left side of the chest. Heart murmurs can be heard in about 2% of newborns at the routine examination.[1] Most are innocent and originate from a patent ductus arteriosus or tricuspid regurgitation[4] or turbulence generated by the acute angle at the pulmonary artery bifurcation. It can be challenging to differentiate innocent murmurs from those caused by significant heart lesions. Features of innocent and significant murmurs are listed in Box 28.3.

The usefulness of electrocardiograms and chest radiographs in helping to distinguish innocent from significant murmurs is limited. The neonatal electrocardiogram and chest radiograph are difficult to interpret, and these tests have rarely been found to change decisions based on the clinical examination.[24]

If a heart murmur is thought to be significant or cannot confidently be diagnosed as innocent, the infant should be referred directly for echocardiography. The management of infants with an innocent murmur depends on the availability of echocardiography. If echocardiography is readily available, it provides parents with a definitive diagnosis without delay. If echocardiography is not readily available, a follow-up medical examination should be arranged soon after discharge and the parents warned to seek medical assistance if their infant becomes symptomatic with poor feeding, labored breathing, cyanosis, or lethargy. The United States and some other countries have instituted universal oxygen saturation–based screening for critical congenital heart disease.[32]

Femoral pulses are best palpated when the infant is quiet. Pulses feel diminished if there is coarctation of the aorta. Of note, if the ductus arteriosus is still patent, femoral pulses may feel normal even in the setting of a coarctation. If coarctation is suggested clinically, further evidence may be obtained by comparing the systolic blood pressure in the upper and lower extremities. A decrease of more than 20 mm Hg in the legs is significant. Postductal oxygen saturation may be low. If a duct-dependent cardiac lesion is suspected, urgent cardiac consultation is indicated.

Most innocent murmurs disappear in the first year of life, usually in the first 3 months. However, any mention of a heart murmur can create considerable parental anxiety, which sometimes continues for years. This can be minimized by the manner in which the murmur is described to parents.

• BOX 28.3 Features of Neonatal Heart Murmur

Features of an Innocent Murmur

- Soft (grade 1/6 or 2/6) murmur at left sternal edge
- No audible clicks
- Normal pulses
- Otherwise normal vital signs and clinical examination

Features Suggesting a Murmur Is Hemodynamically Significant

- Pansystolic
- Loud (≥ grade 3/6)
- Harsh quality
- Best heard in the upper left sternal edge
- Abnormal second heart sound
- Femoral pulses difficult to feel
- Other abnormality of vital signs or clinical examination

(For recordings of innocent and significant murmurs, see Reference 38.)

Abdomen

Observe for abdominal distention, asymmetry, and signs of umbilical inflammation. For abdominal palpation, the infant must be relaxed. The abdomen is palpated to identify any masses. The liver is normally palpable 1-2 cm below the right costal margin. The spleen tip and kidneys are sometimes palpable; assess for enlargement. If palpation of the abdomen reveals abnormally large renal masses or an enlarged bladder in a male infant, ultrasonography is required urgently to identify urinary outflow obstruction. Most cases of urinary outflow obstruction are now detected on prenatal ultrasound screening, as are other major abnormalities of the kidneys and urinary tract. Although controversial, siblings of children with vesicoureteric reflux have been recommended to be screened for this condition because approximately 27% are also affected.[33]

Umbilical hernias are common, especially in black infants. No treatment is indicated, because they usually resolve within the first few years of life. Observe for a hernia in the inguinal canal. The incidence of inguinal hernias is approximately 4% in term infants and occurs in about 13% of infants born at less than 33 weeks' gestational age. Optimal timing for repair of inguinal hernias in infants remains controversial, as definitive data is lacking. They are commonly repaired prior to discharge home to avoid incarceration of the hernia, but early repair in preterm infants must be balanced against the risk of postoperative apnea and other complications after general anesthesia.[28]

Single umbilical artery occurs in about 0.3% of newborns.[17] It may be identified on prenatal ultrasound scanning. It is associated with an increased risk of adverse perinatal morbidity[34] and mortality,[13] chromosomal abnormalities,[34] and congenital malformations, particularly of the genitourinary and cardiovascular system. A single umbilical artery has been associated with asymptomatic renal anomalies in 2%-10%, but the yield is low from ultrasound screening of the kidneys and urinary tract when this is an isolated finding,[7,11,17,26] and most renal abnormalities identified are transient or mild. The yield is further reduced by routine prenatal ultrasound screening for congenital anomalies of the kidneys and urinary tract. It is probably

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best reserved for those who also have other anomalies on physical examination.

Genitalia

In boys, the penis is checked for length and the position of the urethral orifice. The penis may appear to be short if buried in suprapubic fat. If less than 2 cm long it meets diagnostic criteria for a micropenis, suggesting congenital hypopituitarism. In hypospadias, the urethral meatus is in an abnormal position, usually on or adjacent to the glans penis, but may be on the penile shaft or perineum. The foreskin is hooded because of ventral foreskin deficiency. Ventral curvature of the shaft of the penis (chordee) may be present. Glandular hypospadias without ventral curvature may not require treatment, but more severe forms require corrective surgery. A specialist opinion should be sought before circumcision, because the foreskin may be required for corrective surgery.

The testis may feel enlarged on palpation; this is usually from a hydrocele, which can be confirmed on transillumination with a bright light. Hydroceles are relatively common in boys and usually resolve spontaneously. Bilateral testes should be palpated and that they have fully descended into the scrotum determined. A testicle is described as undescended if the testis has failed to descend from its embryologic position from the urogenital ridge on the posterior abdominal wall through the inguinal canal to the scrotum. Undescended testes may lie along the normal line of descent but have not reached the scrotum, or they may be ectopic, having deviated from the line of descent. Undescended testes are expected in preterm infants. About 4% of full-term male infants have an undescended testis at birth; by 3 months, about 1% are still undescended, with little reduction thereafter. An undescended testis should be assessed at about 6 weeks of age. If still undescended, referral to a pediatric surgeon or urologist is indicated. If both testes are undescended, the infant should be assessed regarding the possibility that the infant is a virilized female with congenital adrenal hyperplasia or other disorders of sex development.

Neonatal testicular torsion is usually due to prenatal torsion and occurred sometime before delivery. In that situation, the testis is hard, black, and nontender, and is not salvageable because it has already undergone infarction. A pediatric surgeon should be consulted urgently to decide if the torsion occurred recently enough that the testis may be salvaged. Many pediatric urologists will perform surgical fixation of the contralateral testis.

In girls, the clitoris and labia minora are prominent if the infant is preterm but are covered by the labia majora at full term. There may be a white vaginal discharge or small amount of bleeding from maternal hormone withdrawal. There may also be prolapse of a ring of vaginal mucosa. These resolve spontaneously.

The anus is also inspected to check that its position, appearance, and tone are normal and that it is patent.

Passage of urine and meconium should be monitored and recorded; both occur within 24 hours of birth in most term newborns.

Limbs and Hands and Feet

The limbs, hands, and feet are examined for general appearance, symmetry, and posture. Observe for spontaneous movement of all four limbs. Observe for limb reduction defects.

Examination of the hands and feet will identify extra digits (polydactyly), fused digits (syndactyly), or bent digits (clinodactyly). Extra digits are usually connected by a thin skin tag but can be completely attached and contain bone. Extra digits should be removed by a plastic surgeon; many pediatricians tie off thin skin tags with a silk thread, but this may leave a stump of skin. Polydactyly may be familial, but it can also be part of a syndrome.

About 45% of infants with trisomy 21 have single palmar transverse creases. Unilateral single palmar transverse creases are also observed in about 4% of normal infants, but bilateral single palmar creases occur in less than 1% of chromosomally normal infants.

Brachial plexus lesions cause lack of active movement of the affected limb; passive movement is not painful or restricted. The most common is Erb palsy from an upper root palsy (C5, C6, and sometimes C7). The arm is held adducted and internally rotated and pronated with flexion of the wrist, in the "waiter's tip" position. Injury to the lower brachial plexus roots (C8 and T1) results in weakness of the hand flexors of the wrist and fingers, described as a "claw hand," but is rare.

Although most brachial plexus injuries resolve, a significant proportion do not fully recover by 6 months of age. Those that do not recover steadily during the first 2 months of life or are severe should be seen by a specialist, because surgical repair may be indicated. Accompanying respiratory symptoms may be secondary to damage to phrenic nerve roots.

Clavicle fractures most often occur during difficult delivery of the shoulders. In the newborn period it is typically identified because the infant appears to be uncomfortable with decreased movement of the arm on the affected side. After several weeks, it may be diagnosed when a lump is seen or palpated on the clavicle, resulting from callus around the fracture. Clavicular fractures require only supportive care such as mild pain control and pinning the sleeve of the newborn outfit to the contralateral shoulder to provide relative immobilization for comfort. The fracture heals without treatment.

In positional talipes equinovarus, the feet are turned inward from intrauterine compression, commonly associated with oligohydramnios. The foot is of normal size and can be fully abducted and dorsiflexed to the neutral position, and the dorsal surface of the foot can be brought into contact with the anterior lower leg by passive manipulation. If this maneuver can be performed, the parents can be

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shown passive exercises and no further treatment is required. Feet in the calcaneus valgus position are usually due to positional deformation in utero. It should be possible to dorsiflex the foot to bring its dorsal surface into contact with the anterior lower leg and to achieve normal plantar flexion. If this can be achieved, spontaneous resolution can be expected. With talipes equinovarus, the affected foot may be shorter than normal. The entire foot is inverted and supinated, and the forefoot is adducted. The heel is rotated inward and in plantar flexion. The position of the foot is fixed and cannot be corrected completely. It may be secondary to oligohydramnios, a feature of a malformation syndrome, or of a neuromuscular disorder such as spina bifida. The infant must be referred to a pediatric orthopedic surgeon; early treatment with plaster casting and bracing usually avoids the need for surgery.

Hips

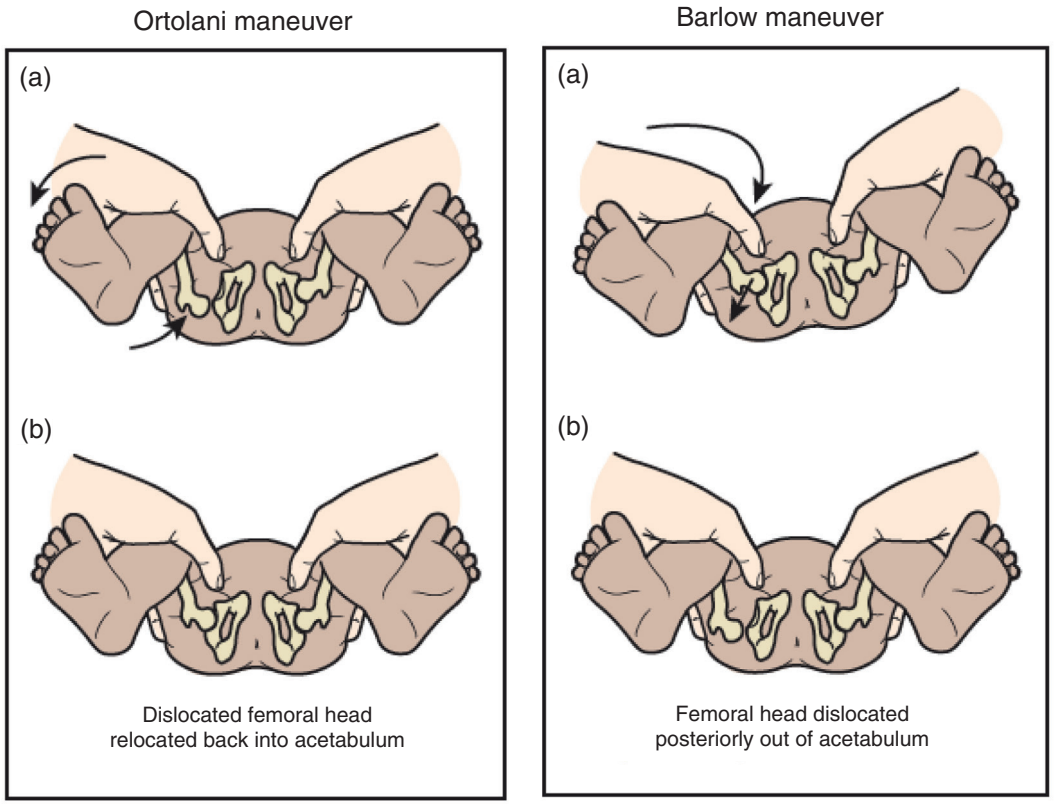
The hips are checked for developmental dysplasia of the hip (DDH). In this condition, on clinical examination in the neonatal period, the hip may be:

- dislocated (subluxated) but reducible, when the posteriorly dislocated femoral head can be returned to the acetabulum, as identified in the Ortolani maneuver.
- dislocatable, when the femoral head is in the acetabulum at rest but is dislocatable posteriorly out of the acetabulum, as identified in the Barlow maneuver.

Other signs of DDH, namely asymmetric thigh or buttock (gluteal) creases, limb length discrepancy, and limited hip abduction are usually only evident beyond the neonatal period; the Ortolani and Barlow tests are usually negative after 3 months of age.

Checking for DDH is best left toward the end of the examination because the procedure is uncomfortable. To successfully perform this examination, the infant must lie supine on a flat, firm surface and be relaxed, because crying or kicking results in tightening of the muscles around the hip.

First, the Ortolani maneuver is performed (Fig. 28.2). The hips and knees are flexed to 90 degrees, and the pelvis is stabilized with one hand. With the other hand, the examiner's index and middle fingers are placed over the greater trochanter and the thumb placed along the middle thigh. The hip is abducted whilst applying gentle upward leverage by lifting the trochanter anteriorly. A dislocated hip will return with a clunk into the acetabulum. This is best felt but can sometimes also be observed. Then the Barlow maneuver is performed (Fig. 28.2). Using the same hand position, the hip is gently adducted while pressure is gently



• **Fig. 28.2** Checking for DDH. In the Ortolani maneuver, on abduction of the hip, the dislocated femoral head is relocated into the acetabulum. In the Barlow maneuver, on adduction of the hip, the femoral head is gently dislocated posteriorly out of the acetabulum.

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applied posteriorly. If the hip is dislocatable, the femoral head will be palpated to slide out of the acetabulum.

Little force is required for these procedures; excessive force can damage the hip. During the test, clicks might be elicited but are not of long-term consequence. Any newborn with DDH should be checked for a neuromuscular disorder, and the spine should be examined to exclude spina bifida.

The hips of most infants with an abnormal neonatal hip examination at birth or 2 weeks of age resolve without intervention by 4 weeks of age. The risk for DDH is increased in female infants, in those with a positive family history, and in those with a breech presentation in the third trimester. The risk is also increased in infants with a neuromuscular disorder. The absolute risk for a positive result on routine examination of the newborn is shown in Table 28.2.[22,23]

Back and Spine

The entire back and spine are inspected and palpated for midline and other defects and for curvature of the spine. Spina bifida is often diagnosed prenatally. Affected infants must be referred to a neurosurgical service. A nevus, swelling, or tuft of hair along the spine or middle of the skull requires further evaluation, because it might indicate an underlying abnormality of the vertebrae, spinal cord, or brain. Ultrasound or magnetic resonance imaging delineates the anatomy. Small, blind ending sacrococcygeal dimples are common and harmless. Unusually large dimples, those without a visible base or positioned above the clefts of the buttocks, should be investigated because they might extend into the intraspinal space and place the infant at increased risk for meningitis.[14]

TABLE 28.2 Absolute Risk of Developmental Hip Dysplasia Based on Abnormal Physical Exam of the Newborn

Newborn Characteristics	Risk Per 1000 Newborns
Overall	
All newborns	11.5
Boys	4.1
Girls	19
Positive Family History	
Boys	6.4
Girls	32
Breech Presentation	
Boys	29
Girls	133

Data from American Academy of Pediatrics. Clinical practice guideline: early detection of developmental dysplasia of the hip. *Pediatrics.* 2000;105:89.

Posture and Muscle Tone

Observe the newborn's posture and tone. Is the infant moving all four limbs fully, and are they held in a normal, flexed position? Do the limbs feel normal on passive movements? Infants who were in an extended breech position in utero sometimes maintain this posture for some days after birth. The newborn is picked up under the arms while supporting the head. A hypotonic newborn will feel as if slipping through one's hands. Most newborns support some of their weight with their feet. When an infant is turned prone, the infant can lift the head to the horizontal position and straighten the back. Hypotonic newborns flop down like a rag doll.

A detailed neurologic examination is required only if an abnormality has been detected. Some pediatricians routinely elicit a Moro reflex, during which sudden head extension causes symmetric extension followed by flexion of all limbs. However, if normal movement of all four limbs has been observed, no further information will be gained from this procedure. Because infants appear to find it unpleasant and parents are often alarmed and upset by it, many pediatricians omit the Moro reflex test from the routine examination.

Concluding the Exam

Most newborns are found to be normal on routine examination. The parents should be reassured that the examination was normal, and any concerns they have about their newborn should be addressed fully. Parents should be informed of any abnormalities detected on examination. This may be upsetting and should be handled with sensitivity by giving a full explanation and allowing time for discussion.

Detailed Neurologic Assessment

If a neurologic concern is raised based on the history, prenatal imaging, physical exam, or postnatal course, a more detailed neurologic assessment should be performed, directed toward the area of concern. The infant's neurologic evaluation combines elements of the standard neurologic examination and a developmental assessment of gestational age[12] (Box 28.4). It also highlights the marked effect of

• BOX 28.4 Neurologic Evaluation

- General appearance
- Level of consciousness
- Head, spine, extremities
- Cranial nerves
- Motor: strength, tone, movements
- Deep tendon reflexes
- Primitive reflexes: Moro, grasp, suck, root
- Autonomic: heart rate pattern, respiratory pattern, bladder function, bowel function

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gestational age on neurologic development. With experience, the examiner can accomplish a standard neurologic evaluation with minimal or no discomfort to the infant—an important skill, especially in fragile premature infants.

Level of Alertness

Healthy term newborns cycle between states of alertness. In the preterm, there are cycles of activity and sleep, of regular and irregular respiration, and of the absence or presence of eye movements, but they tend to occur independently rather than in distinct states of alertness. For optimal neurologic examination, a term infant should be alert and not crying. Abnormal levels of consciousness, lethargy, stupor or coma, and hyperalert states can be associated with hypoxic-ischemic encephalopathy and many other congenital or acquired disorders affecting the brain. Hyperalert state can also be due to drug withdrawal. The cry may be abnormal (e.g., high-pitched from cerebral irritation, excessive from drug withdrawal).

Inspection

The physical component of the neurologic examination includes visual inspection and palpation of the head, spine, and extremities. The head is palpated to ascertain the presence of deformities, the position of the skull sutures, and the size and shape of the fontanelles.

The size and shape of the head provide important information regarding the occurrence of an insult to the fetal brain. When fetal brain growth has been compromised, head size is decreased relative to body weight and length. A large head at birth could be due to a wide range of etiologies. If the sutures are widely spaced it could be from raised intracranial pressure, for example, from obstructive hydrocephalus. Postnatally, a rapidly expanding head with widely separated sutures indicates raised intracranial pressure from cerebral edema; epidural or subdural hemorrhage; or acquired, progressive hydrocephalus, which may follow intraventricular hemorrhage in a premature infant.

Cranial Nerves

Despite the inability of the examiner to communicate verbally with the infant, the functions of most of the 12 cranial nerves can be determined in the newborn infant (Table 28.3). Indeed, cranial nerve evaluations can be conducted even in extremely premature infants.

Cranial nerve I (olfactory) is typically not examined given its rare involvement in a disease process and the infant's inability to provide an appropriate response.

Vision (cranial nerve II [optic]) is assessed both subjectively and objectively. Healthy full-term and older premature infants fixate on and track the examiner's face, a red ball, a card with concentric black and white circles presented about 25 cm from the infant's face, or other optokinetic stimuli. Horizontal eye movements are more easily elicited than are vertical eye movements.

The pupillary light reflex also assesses optic nerve integrity. It is a subcortical function and requires an intact efferent limb, specifically the autonomic component of cranial nerve III (oculomotor). Those nerves that subserve extraocular movements include cranial nerves III, IV, and VI (oculomotor, trochlear, and abducens, respectively).

Eye movements in all directions of gaze occur spontaneously or can be induced with oculocephalic maneuvers (doll's eye reflex). The doll's eye reflex is typically elicited with the infant in the supine position by simply turning the

TABLE 28.3 Cranial Nerve Examination

Nerve	Name	Function	Evaluation Method
I	Olfactory (and tract)	Smell	Not tested
II	Optic (and retina)	Visual acuity and fields	Face or red woolen ball or black and white concentric circles
III	Oculomotor response, lid elevation	Extraocular movements; pupillary reflex	Observation of tracking; doll's eye reflex
IV	Trochlear	Extraocular movements	Observation of tracking; doll's eye reflex
V	Trigeminal	Mastication; facial sensation	Corneal and suck reflexes; nasal stimulation
VI	Abducens	Extraocular movements	Observation of tracking; doll's eye reflex
VII	Facial	Facial expression; taste	Nasal stimulation; corneal and sucking reflexes
VIII	Auditory	Hearing; spatial orientation	Sounds and behavioral response
IX	Glossopharyngeal	Swallowing; vocalization	Sucking and swallowing reflex; gag reflex; quality of cry
X	Vagus	Swallowing; vocalization	Sucking and swallowing reflex; gag reflex; quality of cry
XI	Spinal accessory	Head and shoulder movement	Observation
XII	Hypoglossal	Tongue movement	Observation; atrophy; fasciculations

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head from one side to the other, whereupon the eyes will deviate in the opposite direction. Vertical eye movements can be ascertained by flexing or extending the head. Alternatively, the infant can be held vertically and rotated clockwise or counterclockwise. The eyes will deviate in the direction opposite the spin. Rotation in the axial plane induces vertical eye movements.

The eyes are observed for the presence or absence of ptosis. Unilateral or bilateral ptosis occurs as a consequence of dysfunction either of cranial nerve III, which innervates the palpebral muscle (upper eyelid only), or of ascending sympathetic nerves, which course through the neck to innervate the tarsal plates (both eyelids). Oculomotor nerve dysfunction producing ptosis is often associated with ipsilateral pupil dilation, whereas sympathetic nerve dysfunction producing ptosis is associated with ipsilateral pupil constriction (Horner syndrome).

Cranial nerve V (trigeminal) has both sensory and motor functions. Corneal and facial sensations can be tested if indicated with a wisp of cotton applied to each cornea to elicit a rapid blink or to the nares to elicit a facial grimace. The motor component of cranial nerve V subserves jaw (mandibular) opening and closure, which are best tested by observing the infant's sucking ability.

Cranial nerve VII (facial) controls all superficial facial movements, including eyelid closure, and taste, which is rarely tested. Facial movements occur spontaneously and are a component of the sucking and rooting reflexes. Tickling the nares with a wisp of cotton should induce facial grimacing, whereupon either unilateral or bilateral facial paresis will become apparent.

Cranial nerve VIII subserves both hearing (auditory) and vestibular functions (see Chapter 59). Hearing is tested either subjectively or objectively, the latter by the evoked otoacoustic emissions or automated auditory brainstem response as used in newborn hearing screening. Subjective testing at crib side can be accomplished with the use of voice, ideally the mother's, or a bell or rattle, observing for a change in heart rate or respirations, and possibly an orienting response. Initially, the sound should be of low intensity, increasing in loudness until a response is obtained. The vestibular component of cranial nerve VIII is not specifically tested other than through its interaction with brainstem pathways that subserve reflex eye movements.

The functions of cranial nerves IX and X (glossopharyngeal and vagus, respectively) are combined to control swallowing function and vocalization. Voluntary motor functions are tested by observing the infant's sucking and swallowing abilities. In addition, the position and movement of the soft palate are observed with a flashlight. Decreased movement of the soft palate or absent gag reflex suggests dysfunction of cranial nerves IX or X. During the oral evaluation, cranial nerve XII (hypoglossal) function is tested by examining the tongue and noting its position, movement, and bulk. Atrophy of the tongue is observed as scalloping of its margins. The presence of tongue fasciculations may be noted, consisting of random, wormlike movements best appreciated along the lateral tongue margins and which may be observed in spinal muscular atrophy. Tongue fasciculations must be distinguished from tremors, the latter consisting of normal rhythmic movements of the structure accentuated by its protrusion during crying.

Cranial nerve XI (spinal accessory) is a pure motor nerve. It innervates the sternocleidomastoid muscle of the neck to produce either lateral or anterior flexion of the head, depending on contraction of one or both muscles. The nerve also innervates the trapezius muscle of the shoulder to produce shoulder elevation. These functions typically are tested by simple observation of head and shoulder movements.

Motor Function

The motor system examination includes tests of skeletal muscle posture, tone, and movement. During the initial period of general observation, the position of the extremities is noted for flexion, extension, or neutral postures. Healthy, full-term infants typically exhibit flexion of the arms at the elbows and of the legs at the knees. Fisting of the hands, including adduction and infolding of the thumbs, is usual. However, there is varied movement of the fingers, including moving the thumb away from the palm. This contrasts with the persistently adducted thumb (cortical thumb) in a tightly fisted hand, with few finger movements seen in infants with cerebral injury genetic disorders or some severe malformations.

Limb position and posturing are relatively symmetric, although the infant manifests spontaneous movements that are often asymmetric and jerky. Limb posture (flexion or extension) is also influenced by the position of the head. If the head is turned to one side, there is often extension of the ipsilateral arm and leg and flexion of the contralateral extremities (asymmetric tonic neck reflex). While prone, the full-term infant maintains a flexed posture of the arms and legs, with resultant elevation of the pelvis as well as hip and knee flexion.

Tone is characteristic of skeletal muscle because of an intrinsic resistance to stretch that can be either active or passive. Muscle at rest resides in a state of partial relaxation, and energy is required for its full contraction. Elongation requires further muscle relaxation and concurrent contraction of the opposing or antagonistic muscle. Thus, normal muscle tone depends on a sophisticated interaction between agonistic and antagonistic muscles, which are influenced by innervating peripheral nerves (sensory and motor) as well as by the central nervous system. Given the strategic role played by skeletal muscle in neurologic function, it is not surprising that alterations in muscle tone represent the clinical hallmark of a variety of neurologic disease processes.

The assessment of muscle tone includes observation of the infant's posture and movement as well as the production of an active or passive range of motion. If feasible, the infant should be suspended in the horizontal plane and the attitude and posture of the head, trunk, and extremities

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observed. Thereafter, the infant is held in the vertical plane to ascertain the extent and symmetry of flexor tone of the extremities. While the infant lies supine, the upper and lower extremities are extended and flexed to ascertain the presence and extent of resistance. Head control can be determined by lifting the supine infant from the surface by the shoulders.

Increased resistance to passive movement indicates hypertonicity (rigidity, spasticity), whereas reduced resistance and unrestricted movement indicate hypotonicity. In this regard, the neurologic component of the Dubowitz and Ballard scoring systems for determining gestational age largely reflects the maturation of muscle tone in premature infants, from the weak, low tone, and extended posture of very premature infants to the active, flexor tone, and posture of the term infant. Infants who are hypertonic often exhibit an opisthotonic posture related to obligate extension of the back and neck when suspended in either the vertical or horizontal plane because of high tone in axial extensors compared with flexors. Scissoring of the legs might be evident from hypertonia in the hip adductors. In contrast, the hypotonic infant, when held in the vertical plane, tends to slide through the examiner's hands. In the horizontal plane, the infant drapes down from the examiner's hand.

Hypotonia should not be equated with weakness, which is a reduction in muscle strength or power, whether it is partial (paresis) or complete (paraplegia) paralysis. Muscle weakness is ascertained through observation of spontaneous or sensation-induced movements of the extremities. Although muscle hypotonia and weakness often occur together, hypotonia can be seen in the absence of weakness (e.g., cerebellar dysfunction), and weakness can occur when muscle tone is normal or even increased (e.g., spastic paralysis).

Deep Tendon Reflexes

Deep tendon reflexes are elicited as they are for older children and adults. The limb should be positioned in partial flexion and the appropriate tendon tapped with an infant reflex hammer. The head should be maintained in the neutral position to prevent inducing an asymmetric tonic neck response, which produces asymmetric reflex activity. Typically, upper extremity deep tendon reflexes are more difficult to elicit than lower extremity reflexes. In newborn infants, the Achilles tendon is not tapped directly; the reflex is elicited by tapping a thumb positioned on the plantar surface of the partially dorsiflexed foot.

Interpretation of the results of testing deep tendon reflexes is more problematic in neonates than older children but may help to confirm an asymmetric lesion. A few beats of ankle clonus are common and usually normal in the neonatal period if not sustained. Eliciting plantar responses is not worthwhile, because their interpretation is problematic, owing in part to multiple competing reflexes in the foot (plantar grasp, stepping, placing).[16] At this age, the plantar response is usually said to be extensor, but it mainly depends on the location and strength of the stimulus applied; a gentle stimulus will often induce a flexor response.

Developmental Reflexes

The most frequently elicited primitive or developmental reflexes include the rooting, sucking, palmar grasp, and Moro responses. These reflexes are fully developed and strong in the healthy, full-term newborn and typically disappear in the months to follow. Their persistence beyond the anticipated age of disappearance is an indicator of underlying central nervous system dysfunction. Other primitive reflexes include the crossed extension (where a limb withdraws by contracting of the flexor muscles and relaxation of the extensors and the opposite occurs in the other limb), the placing reflex (when there is flexion followed by extension when the infant is held upright and the dorsum of a foot is moved along the under edge of a table), and stepping reactions (when the soles of the feet of an infant held upright touch a flat surface she will take steps by placing one foot in front of the other), all of which make their appearance by 36-38 weeks' postmenstrual age.

Behavioral Evaluation

Behavioral assessment tools, such as the Neonatal Behavioral Assessment Scale (NBAS), the Assessment of Preterm Infants' Behavior (APIB), and the NICU Network Neurobehavioral Scale (NNNS), are formalized screening measures designed to determine neurobehavioral disturbances, identify individual behavioral differentiation and regulation patterns in newborns, or differences among groups of newborns. They are also used to guide referrals for further specialty assessment, care, and interventions, and to support families and caregivers in their understanding of their newborn's individuality. Performing any of the currently utilized assessments requires some degree of training, and in several cases, formal certification. Assessments commonly evaluate movement and postural patterns; muscle tone and strength; activity levels; simple and complex reflex behaviors; sensory functions; social attention and interaction; attention to objects; thresholds to behavioral disorganization; irritability; consolability; state range; and stability including sleep, quality of cry, and habituation or response decrement to repeated stimuli. As an example, for the assessment of consolability, the upset infant's response to different modalities of calming is assessed. It takes longer to console an infant with brain injury than it might a healthy infant. Visual and auditory response decrements are elicited with different stimuli, such as a bright light, and a rattle or bell, respectively. Response decrement is an indicator of cortical inhibitory function. It demonstrates the brain's ability to learn to diminish behavioral responses to repetitive stimuli. Failure to respond initially to the sensory stimulation or a lack of habituation may suggest cortical and/or sensory dysfunction or sedation. A highly reactive, dysregulated neurobehavioral profile may be an indicator of increased risk for

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neurologic and/or physiologic issues. A milder form of dysregulation may indicate temperament differences. Newborn group studies have also identified ethnocultural background differences in regulation. The timing of assessments depends on infants' medical complexity; ill or infants born preterm require serial assessments to track progress and recovery. The examinations should be performed in the presence of the parents and key caregivers to maximize appreciation of the infant's current strengths and vulnerabilities. In the hands of well-trained specialists, these assessments can be used to guide clinical care decisions and advocate for appropriate outpatient developmental services, as well as to optimize parent understanding of their infant.[8,36]

Assessment of Gestational Age

Formal assessment of gestational age is unnecessary for the routine newborn examination. The best guide to an infant's gestational age is an early antenatal ultrasound evaluation combined with information about the mother's last menstrual period. An evaluation of the clinical methods of assessing gestational age showed that clinical methods had 95% confidence intervals of 17 days, whereas the antenatal ultrasound had 95% confidence intervals of less than 7 days.[30] Clinical assessment is most important for infants whose gestational age is unknown or discrepant with their growth.

Gestational age can be assessed using physical and neurologic criteria, because they progress in an orderly fashion with increasing gestation. Although physical criteria allow distinction of infants with gestational ages older than 34 weeks, neurologic assessments are required to differentiate infants at earlier gestations. A combined scoring system for assessing gestational age was developed by Dubowitz and Dubowitz.[12] Its disadvantage is that it involves assessing 11 physical criteria and 10 neurologic findings. Ballard and colleagues abbreviated it to include 6 neurologic and 6 physical criteria to shorten the time taken. The revised Ballard examination (Fig. 28.3) includes assessment for extremely premature infants and is the most widely used.[5] Regardless of the method used, the assessment of gestational age using physical and neurologic criteria is accurate only to ±2 weeks, with a tendency toward overestimation in extremely premature infants.

The Premature Infant

The neurologic signs in premature infants differ markedly with postmenstrual age. In normal premature newborn infants, pupil responses to light are present, although sluggish, between 28 and 32 weeks' gestation and seldom present before 28 weeks (Table 28.4). Oculocephalic (doll's eye) reflexes are complete and even exaggerated in infants as immature as 24-25 weeks. Corneal and gag reflexes are present in premature infants as is facial grimacing to nasal stimulation.

The newborn's responsiveness to the environment depends not only on the state of health but also on the postmenstrual age. Infants of 25-30 weeks' gestation typically show intermittent arousal with external stimulation, and their waking periods are relatively short when compared with full-term infants. By 31-32 weeks' gestation the premature infant exhibits reasonable alertness during wakeful stages. By term, the infant remains alert for prolonged periods during wakefulness and readily responds to visual, auditory, and tactile stimulation.

A notable difference in the neurologic status of the premature and full-term neonate is that of muscle tone. As indicated by the Dubowitz and Ballard scoring systems for gestational age, the more premature the infant at birth, the greater the muscle hypotonicity (see Fig. 28.3). The hypotonicity is especially apparent when measuring the popliteal and heel-to-ear angles and when executing the scarf sign.

At and before 28 weeks' postmenstrual age, a premature newborn is extremely hypotonic. When held in vertical suspension, the infant does not extend the head, trunk, or

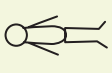
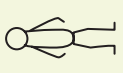
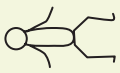
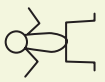
TABLE 28.4 Neurologic Maturation of the Fetus and Newborn

Function	26 Weeks	30 Weeks	34 Weeks	38 Weeks
Resting posture	Flexion of arms Flexion or extension of legs	Flexion of arms Flexion or extension of legs	Flexion of all limbs	Flexion of all limbs
Arousal	Unable to maintain	Remain briefly	Remain awake	Maintain awake
Rooting	Absent	Long latency	Present	Present
Sucking	Absent	Long latency	Weak	Vigorous
Pupillary reflex	Absent	Variable	Present	Present
Traction	No response	No response	Head lag	Mild head lag
Moro	No response	Flexion or extension of legs	Flexion or extension of legs	Complete
Withdrawal	Absent	Withdrawal only	Crossed extension	Crossed extension

From Fenichel GM. *Neonatal neurology*. 4th ed. New York: Churchill Livingstone; 2007.

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NEUROMUSCULAR MATURITY

	−1	0	1	2	3	4	5
Posture							
Square window (wrist)	 >90°	 90°	 60°	 45°	 30°	0°	
Arm recoil		 180°	 140°–180°	 110°–140°	 90°–110°	 <90°	
Popliteal angle	 180°	 160°	 140°	 120°	 100°	 90°	 <90°
Scarf sign							
Heel to ear							

PHYSICAL MATURITY

Skin	Sticky, friable, transparent	Gelatinous red, translucent	Smooth pink, visible veins	Superficial peeling and/or rash, few veins	Cracking pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel–toe 40–50 mm: −1 <40 mm: −2	>50 mm no crease	Faint red marks	Anterior transverse crease only	Creases ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola 1–2 mm bud	Raised areola 3–4 mm bud	Full areola 5–10 mm bud	
Eye/ear	Lids fused loosely: −1 tightly: −2	Lids open; pinna flat, stays folded	Sl. curved pinna; soft; slow recoil	Well-curved pinna; soft but ready recoil	Formed and firm instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty; faint rugae	Testes in upper canal; rare rugae	Testes descending; few rugae	Testes down; good rugae	Testes pendulous; deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
−10	20
−5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

• **Fig. 28.3** Assessment of gestational age using the revised Ballard method. (From Ballard JL, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr.* 1991;119:417.)

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extremities. The maturational change from hypotonia of the small premature infant to the predominantly flexion posture of the full-term infant is manifest first in the legs and later in the arms and head. By 34 gestational weeks, the infant lies in a froglike position while supine; the legs are flexed at the hips and knees, but the arms remain extended and relatively hypotonic. The maturational changes in muscle tone must be taken into account when evaluating newborns of varying gestational ages.

Developmental reflexes appear at specific ages of gestation to become fully developed and strong in the healthy full-term infant (see Table 28.4). The sucking and rooting reflexes do not develop until 33-36 weeks' gestational age. The palmar and plantar grasp responses become apparent at about 28 weeks and are strong by 36 weeks. The Moro reflex appears at 24-26 weeks and evolves through 38 weeks, at which age the entire abduction-adduction response is present.

Interpretation of the Neurologic Examination

Interpreting the findings from a neurologic examination of a newborn infant is difficult, because the interpretation is markedly affected by the infant's postmenstrual and chronologic age as well as the infant's level of alertness. The neurologic examination has been widely studied as a predictor of subsequent neurodevelopmental problems, but it is limited because many abnormal neurologic signs may be transient and significant neurologic abnormalities may take weeks or months to become manifest. Serial examinations are more informative than a single examination.

However, in spite of its limitations in specificity and in predicting prognosis, the neurologic examination is useful when considered in conjunction with a history, with or without neuroimaging, suggestive of a neurologic problem. Neurologic abnormalities that are persistent, severe, or asymmetric place the infant at increased risk of neurodevelopmental problems. The neurologic examination may be helpful in delineating the extent of neurologic deficits (e.g., after hypoxic-ischemic encephalopathy), which also informs management planning. Multiple neurologic abnormalities are more likely to be more significant than isolated abnormalities. Preterm infants who have significant abnormalities on neurologic examination at term are at higher risk of neurodevelopmental problems than those with a normal examination.

Limitations of the Routine Examination

Examination of a newborn in the delivery room and at a routine examination will identify a number of problems, many of which are transient, although some are permanent and significant. However, some significant abnormalities will not be identified. Sometimes this is because of inexperience of the examiner, or the examiner has not managed to overcome the difficulty of performing a satisfactory examination in an unsettled baby (e.g., getting a good view of the eyes and red reflex, hearing a heart murmur, or testing for DDH). However, some significant abnormalities will not be identified, because they will not be evident during the routine physical examination.

Parents might become upset or angry when it becomes evident at a later stage that their child has a significant problem. They need to be made aware that not all abnormalities can be detected at the initial examination. This situation also stresses the importance of clear documentation of the routine examination for future reference. Some of the major limitations of the clinical examination are considered below.

Jaundice

Jaundice usually develops after 24 hours of age, unless caused by hemolysis or congenital infection. Significant jaundice can develop at several days of age even though the infant was not clinically jaundiced only 1 or 2 days earlier (see Chapter 91).

Eye Abnormalities

The outcome for vision following surgery for congenital cataracts is improved if surgery is performed before 8 weeks of age.[9] However, only approximately 35% of congenital cataracts are identified on the routine examination.[20] This demonstrates the difficulty in early recognition of eye abnormalities during the routine examination of the newborn, compounded by the rarity of serious eye conditions, occurring in only 4 per 10,000 live births.[6]

Congenital Heart Disease

About 6-8 infants per 1000 live births have congenital heart disease. There are multiple limitations of the routine examination in identifying significant structural heart disease.

The first is that the newborn examination may be normal when the infant has a significant or even lethal structural heart lesion. At the time of the newborn examination, the pressure in the right side of the heart is still relatively high, and the ductus arteriosus may still be patent. Infants with a ventricular septal defect (the most common congenital heart lesion) or other heart lesions might not have a heart murmur at the routine examination, because the pressure difference between the left and right sides of the heart is insufficient to generate turbulent flow at this stage.

A second reason is that infants with duct-dependent lesions will not present clinically with heart failure, shock, cyanosis, or death until the ductus arteriosus closes days to weeks after birth. Femoral pulses may be palpable at the initial examination because of blood flow through the ductus arteriosus.

An additional limitation is that a heart murmur may be heard, but because most are innocent, it is not always

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appreciated that the murmur is from a significant heart lesion. Prenatal diagnosis of some severe heart lesions and the increasing availability of echocardiography should reduce, but will not eliminate, failure to identify structural heart lesions before discharge from the hospital.

Pulse oximetry screening assists the detection of ductal-dependent lesions.[15,19,25] The AAP recommends universal screening and recommends further assessment if any of the following criteria are met:[32]

- Any oxygen saturation (SpO_2) is less than 90%.
- Oxygen saturation is less than 95% in both extremities on three measures, each separated by 1 hour.
- There is a greater than 3% absolute difference in oxygen saturation between the right hand and either foot on 3 measures, each separated by 1 hour.

Developmental Dysplasia of the Hip

As a screening test, clinical examination for DDH is problematic. Ideally, all affected infants should be identified in the neonatal period, because early treatment prevents or reduces the need for surgery. However, about 1%-2% of term infants have an abnormal hip examination, but the incidence of DDH is only approximately 1 in 1000 live births; most infants identified clinically have mild instability, which resolves. An additional problem is that a significant proportion of infants who subsequently require surgery are not identified in the neonatal period.

An examiner might fail to identify DDH at the initial examination, because the examination is suboptimal as the infant is not relaxed. However, in some infants with a flat acetabular shelf, the clinical examination may be normal in the neonatal period, but the dysplasia progresses with age.

Two strategies can improve the detection rate of DDH in newborn infants. The hip examination can be performed by pediatric orthopedists, or imaging of the hips can be performed. Ultrasound will identify DDH, including a shallow acetabular shelf. However, ultrasound has a high false-positive rate and is only helpful in the first 5 months of life before femoral head ossification occurs. Alternatively, a hip radiograph will identify DDH but only after 4-6 months of age when the femoral head secondary center of ossification forms.

The evaluation and referral for DDH remains controversial. The American Academy of Orthopedic Surgeons published a guideline in 2014 with a goal of initiating prevention and/or detection of dislocated hips by 6–12 months of age[22]:

- Infants with normal hips should have serial hip exams up to 6 months of age, and those with risk factors (breech presentation, family history, or clinical instability) should have imaging studies before 6 months of age.
- Infants with a positive instability exam should have hip ultrasound imaging before 6 weeks of age to guide the decision to initiate brace treatment.
- Infants over 4 months of age who need hip imaging should have an AP pelvis radiograph instead of ultrasound. The AAP updated the 2000 Clinical Practice Guideline with an AAP Clinical Report in 2016.[23]

Health Promotion

The routine examination is an opportunity to promote preventive health care.

Prevention of Sudden Unexpected Infant Death Syndrome

All parents should be advised that infants should sleep on their backs and that overheating and parental smoking are risk factors. Also, bed sharing and cosleeping should be avoided. Attention to preventive measures has markedly reduced the incidence of sudden unexpected infant deaths in many countries.

Promotion of Breastfeeding

Mothers should be encouraged in, and assisted with, breastfeeding. Lactation consultants are helpful in promoting breastfeeding, especially for mothers of infants who are preterm, ill, or have difficulties with breastfeeding for any other reason.

Hearing, Vision, and Other Screening

Universal hearing screening should be performed per hospital protocol. Children with increased risk for deafness (e.g., family history, malformations of the ear including skin tags and pits) must receive early hearing testing. Infants at increased risk for issues related to vision should be referred to an ophthalmologist. Parents should be given advice about early detection of hearing and vision loss. Other screening tests, including biochemical tests, should be performed according to local guidelines.

Discharge

The discharge physical examination is an opportunity not only to recheck that the infant is well and that any previously identified or ongoing medical issues have been resolved but to also ensure that the mother and infant are ready for discharge. The American Academy of Pediatrics has published details of the criteria that should be met before discharge.[10] These include checking that the infant's vital signs are normal and have been stable for at least 12 hours; that the infant has urinated and passed a stool, completed at least two successful feeds, and has been screened and monitored for sepsis based on maternal risk factors; and that maternal blood test results (hepatitis B surface antigen, HIV, syphilis) have been checked. If the infant is jaundiced, the bilirubin should be measured and a management and follow-up plan should be in place. The importance of immunizations can be emphasized, specifically the hepatitis B vaccine, which is generally given prior to discharge home (see Appendix C).

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Hearing, blood spot screening, and pulse oximetry screening for critical congenital heart disease should have been performed or arrangements should be in place. A suitable car seat should be available. The AAP recommends that preterm infants be tested for desaturation/respiratory obstruction in a car seat prior to discharge. However, it should be explained that an infant can pass a car seat challenge and still have desaturations in the car seat at another time. Therefore, neonates should be observed while in the car seat and only remain in it for the duration of the trip. It should be explained that a car seat is not designed to be a safe position for infants to sleep once out of the vehicle. The clinician must also ensure that the parents are able to care adequately for their infant and that the infant is going to a suitable environment. Relevant follow-up care for the infant should also be in place. If a term baby is discharged early (<48 hours), a follow-up visit with a health care professional within 48 hours should be in place.

Key Points

A routine physical exam:

- should be performed on every newborn by a trained health care provider within 24 hours of birth,
- should include examination of all parts of the body and measurement of growth parameters,
- should allow minor and major abnormalities to be identified and addressed whether pre- or postnatally diagnosed,
- will not identify all abnormalities, but identification is maximized by specific training of health providers,
- is a time for thoughtful discussion with parents about their concerns, as the birth of a baby is an emotionally charged and vulnerable time for many parents,
- is an opportunity for health promotion and to check that appropriate discharge planning is in place.

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29

Birth Injuries

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Birth injuries are those sustained during the birth process, which includes labor and delivery. They may be avoidable, or they may be unavoidable and occur despite skilled and competent obstetric care, as in an especially hard or prolonged labor or with an abnormal presentation. Fetal injuries related to amniocentesis and intrauterine transfusions and neonatal injuries after resuscitation procedures are not considered birth injuries. However, injuries related to the use of intrapartum monitoring of the fetal heart rate and collection of fetal scalp blood for acid-base assessment are included. Factors predisposing the infant to birth injury include macrosomia, prematurity, cephalopelvic disproportion, dystocia, prolonged labor, abnormal presentation, and certain operative deliveries, particularly vacuum extraction. The fetus may also sustain injury, including death, if the mother is involved in a motor vehicle collision.[10] Fetal deaths may occur from maternal cardiovascular instability, uterine rupture, placental abruption, hemorrhage, and direct injury to the fetus. Although usually protected by maternal soft tissues, the uterus, and amniotic fluid, the fetus may be subjected to the same acceleration-deceleration forces as the mother. This may result in full-thickness bowel injury and fulminant disseminated intravascular coagulation. Thus, a thorough physical examination of the infant is critical after a maternal motor vehicle collision to identify any internal injury that may have occurred.

The significance of birth injuries may be assessed by review of mortality data. In 1981, birth injuries ranked sixth among major causes of neonatal death, resulting in 23.8 deaths per 100,000 live births. During the ensuing decade, because of refinements in obstetric techniques and the increased use of cesarean deliveries over difficult vaginal deliveries, a dramatic decline occurred in birth injuries as a cause of neonatal death. Statistics for 1993 revealed a reduction to 3.7 deaths per 100,000 live births; because of the emergence of other conditions, birth injuries ranked 11th among major causes of neonatal death. The most recent figures available (for 2013-2014) identify only 10 leading causes of neonatal and postneonatal death, with no mention of birth injuries.[54]

Despite a reduction in related mortality rates, birth injuries still represent an important source of neonatal morbidity and neonatal intensive care unit admissions. Of particular concern are severe intracranial injuries after operative vaginal delivery (vacuum-assisted and forceps delivery) and failed attempts at operative vaginal delivery.

The clinician should consider the broad spectrum of birth injuries in the differential diagnosis of neonatal clinical disorders. Although many injuries are mild and self-limited, others are serious and potentially lethal. This chapter describes conditions that can be managed by observation only, as well as those that require more aggressive intervention. In addition to assuring timely institution of therapy when indicated, recognition and documentation before discharge from the hospital will help avoid inappropriate suspicion of inflicted injury (child abuse) at a later date.

Injuries to Soft Tissues

Erythema and Abrasions

Erythema and abrasions frequently occur when dystocia has occurred during labor as a result of cephalopelvic disproportion or when forceps have been used during delivery. Injuries caused by dystocia occur over the presenting part; forceps injury occurs at the site of application of the instrument. Forceps injury frequently has a linear configuration across both sides of the face, outlining the position of the forceps. The affected areas should be kept clean to minimize the risk for secondary infection. These lesions usually resolve spontaneously within several days with no specific therapy.

Petechiae

Occasionally petechiae are present on the head, neck, upper portion of the chest, and lower portion of the back at birth after a difficult delivery; they are observed more frequently after breech and precipitous deliveries and tight nuchal cord.

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Abstract

Over the last few decades, the number of birth injuries as a cause of neonatal death has dramatically declined as a direct result of improvements in prenatal care and obstetric techniques. However, despite a reduction in related mortality rates, birth injuries still represent a major cause of neonatal morbidity and neonatal intensive care unit admissions. Birth injuries may be avoidable or unavoidable, and they can occur even with skilled and competent obstetric care. Factors that predispose an infant to birth injury include macrosomia, prematurity, cephalopelvic disproportion, dystocia, prolonged labor, abnormal presentation, and certain operative deliveries, particularly vacuum and forceps extraction. The fetus may also sustain injury, including death, secondary to maternal trauma. After a difficult birth, a thorough physical examination of the infant is critical to identify any injury that may have occurred. The clinician should consider the broad spectrum of birth injuries within the differential diagnosis of neonatal clinical disorders. Although many injuries are mild and self-limited, others are serious and potentially lethal. In addition to assuring timely institution of treatment when indicated, recognition and documentation before discharge from the hospital will help avoid inappropriate suspicion of inflicted injury (child abuse) at a later date.

Keywords

birth injury
newborn
delivery
birth trauma
fracture

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Etiology

Petechiae are probably caused by a sudden increase in intrathoracic and venous pressures during passage of the chest through the birth canal. An infant born with the cord tightly wound around the neck may have petechiae only above the neck.

Differential Diagnosis

Petechiae may be a manifestation of an underlying hemorrhagic disorder. The birth history, early appearance of the petechiae, and absence of bleeding from other sites help to differentiate petechiae caused by increased tissue pressure or trauma from petechiae caused by hemorrhagic disorders (see Chapter 79). The localized distribution of the petechiae, absence of subsequent crops of new lesions, and a normal platelet count exclude neonatal thrombocytopenia. The platelet count also may be low because of infection or disseminated intravascular coagulation. Infections may be clinically distinguished from traumatic petechiae by the presence of other signs and symptoms. Disseminated intravascular coagulation usually is associated with excessive and persistent bleeding from a variety of sites. Petechiae usually are distributed over the entire body when associated with systemic disease.

Treatment

If the petechiae are caused by trauma, neither corticosteroids nor heparin should be used. No specific treatment is necessary.

Prognosis

Traumatic petechiae usually fade within 2 or 3 days.

Ecchymoses

Ecchymoses may occur after traumatic or breech deliveries. The incidence is increased in premature infants, especially after a rapid labor and poorly controlled delivery. When extensive, ecchymoses may reflect blood loss severe enough to cause anemia and, rarely, shock. The reabsorption of blood from an ecchymotic area may result in significant hyperbilirubinemia (Fig. 29.1).

Treatment

No local or systemic therapy is necessary. The rise in serum bilirubin that follows severe bruising may be decreased by the use of phototherapy (see Chapter 91). Ecchymoses rarely result in significant anemia.

Prognosis

The ecchymoses usually resolve spontaneously within 1 week.

Subcutaneous Fat Necrosis

Subcutaneous fat necrosis is a rare form of panniculitis seen mostly in term or post-term infants characterized by well-circumscribed, indurated lesions of the skin and underlying tissue (see Chapter 87).



• **Fig. 29.1** Marked bruising of entire face of a 1490-g female infant born vaginally after face presentation. Less severe ecchymoses were present on extremities. Despite use of phototherapy from the first day, icterus was noted on the third day, and exchange transfusions were required on the fifth and sixth days.

Etiology

Although subcutaneous fat necrosis can occur without any obvious cause, it is most commonly seen in association with perinatal asphyxia. Other etiologic factors that have been implicated include cold exposure, localized skin trauma, obstetric trauma, preeclampsia, gestational diabetes, maternal or fetal risk of thrombosis, maternal cocaine use, hypothermia, prostaglandin E administration, brown fat deficiency, meconium aspiration, sepsis, and intrapartum calcium channel blocker administration. It can also occur as a complication of therapeutic hypothermia for perinatal asphyxia or in newborns undergoing surgical procedures.[34,69] Many affected infants are large and have been delivered by forceps or after a prolonged, difficult labor involving vigorous fetal manipulation. The distribution of the lesions usually is related to the site of trauma, which explains the frequent involvement of shoulders and buttocks. One suggested mechanism of pathogenesis proposes that diminished in utero circulation and mechanical pressure during labor and delivery result in vascular compromise to specific areas, which eventually causes localized fat necrosis. In maternal cocaine use during pregnancy, it has been postulated that cocaine may decrease placental perfusion with subsequent hypoxemia and alteration of the maternal and fetal pituitary-adrenal axes.[12]

Pathology

Histopathologic studies reveal initial endothelial swelling and perivascular inflammation in the subcutaneous tissues. This is followed by necrosis of fat and a dense granulomatous inflammatory infiltrate containing foreign body–type giant cells with needle-shaped crystals resembling cholesterol.

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Clinical Manifestations

Necrotic areas usually appear between 6 and 10 days of age but may be noted as early as the second day or as late as the sixth week. They occur on the cheeks, neck, back, shoulders, arms, buttocks, thighs, and feet, with relative sparing of the chest and abdomen. The lesions vary in size from 1-10 cm; rarely, they may be more extensive. They are irregularly shaped, hard, plaquelike, and nonpitting (Fig. 29.2). The overlying skin may be colorless, red, or purple with no local tenderness. The affected areas may be slightly elevated above the adjacent skin; small lesions may be easily movable in all directions. Fever may be seen in a small subset of infants with subcutaneous fat necrosis.

This condition may be associated with hypoglycemia, hypertriglyceridemia, hypercalcemia, nephrocalcinosis, anemia, and thrombocytopenia. Marked symptomatic hypercalcemia may develop in infants with subcutaneous fat necrosis at 3-4 weeks of age; this has been characterized by vomiting, weight loss, anorexia, fever, somnolence, and irritability, with serum calcium levels as high as 17.3 mg/dL. The treatment includes intravenous hydration, calcium-wasting diuretics such as furosemide, potassium citrate to inhibit renal stone formation, and corticosteroids. Successful short-term treatment with bisphosphonates (e.g., pamidronate or etidronate) has been reported to control hypercalcemia.[45] Investigators have suggested extra renal production of 1,25-dihydroxyvitamin D by the granulomatous cells of fat necrosis as a possible mechanism for the hypercalcemia.



• **Fig. 29.2** Subcutaneous fat necrosis in a 2900-g term infant delivered vaginally; pregnancy, labor, and delivery were completely uncomplicated. Note nodular lesion located on right buttock and surrounded by erythema (*darkened area*). (Courtesy of Dr. Rajam Ramamurthy, Cook County Hospital, Chicago.)

Differential Diagnosis

The differential diagnosis includes lipogranulomatosis and sclerema neonatorum, which carry a potentially grave prognosis, and nodular nonsuppurative panniculitis, which is usually associated with fever, hepatosplenomegaly, and tender skin nodules.

Treatment

Most of these lesions require only observation. Surgical management is not indicated, with the exception of extensive ulcerated lesions.

Prognosis

The lesions slowly soften after 6-8 weeks and completely regress within several months. Occasionally minimal residual atrophy, with or without small calcified areas, is observed. Affected infants should be followed closely during the first 6 weeks for potential development of hypercalcemia. It is important to treat this complication without delay to prevent central nervous system (CNS) and renal sequelae.

Lacerations

Accidental lacerations may be inflicted with a scalpel during cesarean section. They usually occur on the scalp, buttocks, and thighs, but they may occur on any part of the body. If the wound is superficial, the edges may be held in apposition with butterfly adhesive strips. Deeper, more freely bleeding wounds should be sutured with the finest material available. Rarely, the amount of blood loss and depth of wound require suturing in the delivery room. After repair, the wound should be left uncovered unless it is in an area of potential soiling, such as the perineal area. Healing is usually rapid, and complications are rarely seen.

Injuries to the Head

Skull

Caput Succedaneum

Caput succedaneum, a frequently observed lesion, is characterized by a vaguely demarcated area of edema over that portion of the scalp that was the presenting part during a vertex delivery.

Etiology

Serum or blood or both accumulate above the periosteum in the presenting part during labor. This extravasation results from the higher pressure of the uterus or vaginal wall on those areas of the fetal head that border the caput. Thus, in a left occiput transverse presentation, the caput succedaneum occurs over the upper and posterior aspect of the right parietal bone; in a right-sided presentation, it occurs over the corresponding area of the left parietal bone.

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Clinical Manifestations

The soft swelling is usually a few millimeters thick and may be associated with overlying petechiae, purpura, or ecchymoses. Because of the location external to the periosteum, a caput succedaneum may extend across the midline of the skull and across suture lines. After an especially difficult labor, an extensive caput may obscure various sutures and fontanelles.

Differential Diagnosis

Occasionally, a caput succedaneum may be difficult to distinguish from a cephalhematoma, particularly when the latter occurs bilaterally. Careful palpation usually indicates whether the bleeding is external to the periosteum (caput) or beneath the periosteum (cephalhematoma). Iatrogenic encephalocele is an infrequent complication of vacuum extraction delivery and may present like a caput succedaneum initially. Imaging should be considered in every child with a large caput succedaneum that does not diminish in 48-72 hours or with enlargement of the swelling more than 24 hours after delivery, especially when there are neurologic deficits and hemodynamic instability.[38]

Treatment

Usually no specific treatment is indicated. Rarely, a hemorrhagic caput may result in shock and require blood transfusion.

Prognosis

A caput succedaneum usually resolves within several days.

Cephalhematoma

Cephalhematoma is an infrequently seen subperiosteal collection of blood overlying a cranial bone. The incidence is 0.4%-2.5% of live births, with a higher frequency in infants born to primiparous mothers.

Etiology

A cephalhematoma is caused during labor or delivery by a rupture of diploic blood vessels that traverse from skull to periosteum. Repeated buffeting of the fetal skull against the maternal pelvis during a prolonged or difficult labor and mechanical trauma caused by use of forceps and vacuum suction devices in delivery have been implicated. Petrikovsky and associates described seven infants in whom cephalhematoma or caput succedaneum was identified prenatally before onset of labor.[56] Occurrence of premature rupture of membranes in five of the pregnancies suggests an etiology of fetal head compression by the uterine wall, resulting from oligohydramnios subsequent to the ruptured membranes.

Clinical Manifestations

The bleeding is sharply limited by periosteal attachments to the surface of one cranial bone; there is no extension across suture lines. The bleeding usually occurs over one or both parietal bones. Less often, it involves the occipital bones and, very rarely, the frontal bones. The overlying scalp is not discolored. Because subperiosteal bleeding is slow, the swelling may not be apparent for several hours or days after birth. The swelling is often larger on the second or third day, when sharply demarcated boundaries are palpable. The cephalhematoma may feel fluctuant and often is bordered by a slightly elevated ridge of organizing tissue that gives the false sensation of a central bony depression. It may be associated with an underlying linear, nondepressed skull fracture in a small percentage of infants.

Radiographic Manifestations

Radiographic manifestations vary with the age of the cephalhematoma. During the first 2 weeks, bloody fluid results in a shadow of water density. At the end of the second week, bone begins to form under the elevated pericranium at the margins of the hematoma; the entire lesion is progressively overlaid with a complete shell of bone.

Differential Diagnosis

Cephalhematoma must be distinguished from other birth complications such as subgaleal hematoma, caput succedaneum, vacuum caput, leptomeningeal cyst, or congenital anomalies such as meningoceles. It may be differentiated from caput succedaneum by (1) its sharp periosteal limitations to one bone, (2) the absence of overlying discoloration, (3) the later initial appearance of the swelling, and (4) the longer time before resolution. Cranial meningocele is differentiated from cephalhematoma by pulsations, an increase in pressure during crying, and the demonstration of a bony defect on a radiograph. An occipital cephalhematoma may be confused initially with an occipital meningocele and with cranium bifidum because all occupy the midline position.

Treatment

No therapy is indicated for the uncomplicated cephalhematoma, as more than 80% resolve by gradual hemolysis and resorption in 3-4 weeks. When the hematoma does not resolve spontaneously, it may get organized, and calcification may be seen. It may still get absorbed slowly and often disappears over 3-6 months. Persistent calcification that is not resolved by time may be an indication for surgical excision.[28] Rarely, a massive cephalhematoma may result in blood loss severe enough to require transfusion. Significant hyperkalemia[41] and hyperbilirubinemia may result from resolving hematoma, necessitating appropriate treatment. The most common associated complications are skull fracture and intracranial hemorrhage. Linear fractures do not require specific therapy, but radiographs should be taken at 4-6 weeks to ensure closure and exclude formation of leptomeningeal cysts; depressed fractures require immediate neurosurgical consultation. Routine incision or aspiration of a cephalhematoma is contraindicated because of the risk for introducing infection. Rarely, bacterial infections of cephalhematomas occur, usually in association with septicemia and meningitis. Focal infection should be suspected when a sudden enlargement of a static cephalhematoma

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• **Fig. 29.3** Massive, persistently enlarging cephalhematoma in a 13-day-old female infant delivered by midforceps after occiput-posterior presentation. Surgical drainage revealed 300 mL of yellowish material that cultured as *Escherichia coli*.

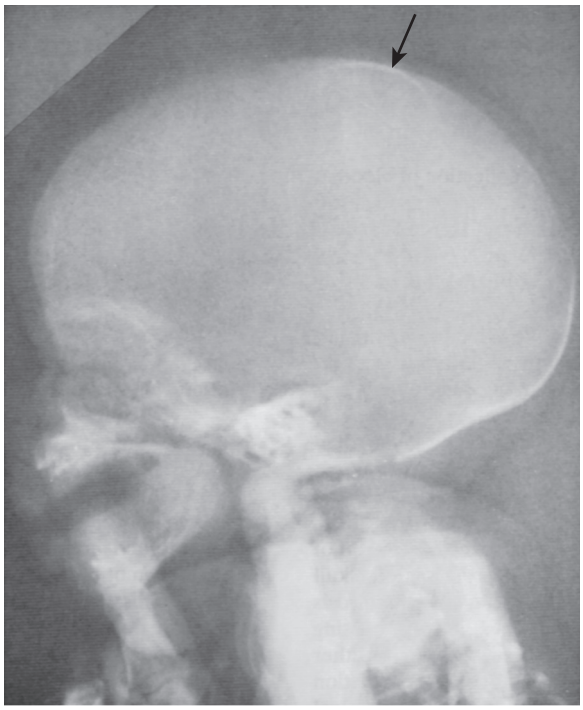
occurs during the course of a systemic infection, with a relapse of meningitis or sepsis after treatment with antibiotics, or with the development of local signs of infection over the cephalhematoma (Fig. 29.3). Diagnostic aspiration may be indicated. If a local infection is present, surgical drainage and specific antibiotic therapy should be instituted. Osteomyelitis of the underlying skull may be a rare concurrent problem.[50] The diagnosis may be suggested by periosteal elevation and overlying soft tissue swelling on skull radiographs. Additional rare complications that may accompany an infected cephalhematoma and osteomyelitis include venous sinus thrombosis and cerebellar hemorrhage.[13] Magnetic resonance imaging (MRI) may be used to detect these two intracranial complications, whereas computed tomography (CT) is the best imaging modality to identify the permeative bone erosion and destruction of osteomyelitis.[13]

Prognosis

Most cephalhematomas are resorbed within 2 weeks to 3 months, depending on their size. In a few patients, calcium is deposited (Fig. 29.4), causing a bony swelling that may persist for several months and, rarely, up to several years. Radiographic findings persist after the disappearance of clinical signs. The outer table remains thickened as a flat, irregular hyperostosis for several months. Widening of the space between the new shell of bone and the inner table may persist for years; the space originally occupied by the hematoma usually develops into normal diploic bone, but cystlike defects may persist at the sites of the hematoma for months or years. Rarely, a neonatal cephalhematoma may persist into adult life as a symptomless mass, the cephalhematoma deformans of Schüller.

Subgaleal Hemorrhage

Subgaleal hemorrhage is a collection of blood in the soft tissue space between the galea aponeurotica and the



• **Fig. 29.4** Calcified cephalhematoma (*arrow*) in left parietal region of 5-week-old girl. Infant weighed 1410 g at birth and was delivered rapidly because of prolapsed cord. Hard left parietal swelling was detected at 5 weeks by nurses during feeding.

periosteum of the skull (Fig. 29.5). The incidence is about 4 per 10,000 noninstrumented deliveries, with higher incidence after instrumental deliveries. Ng and colleagues have reported an incidence of 64 per 10,000 deliveries when vacuum extraction is performed.[55]

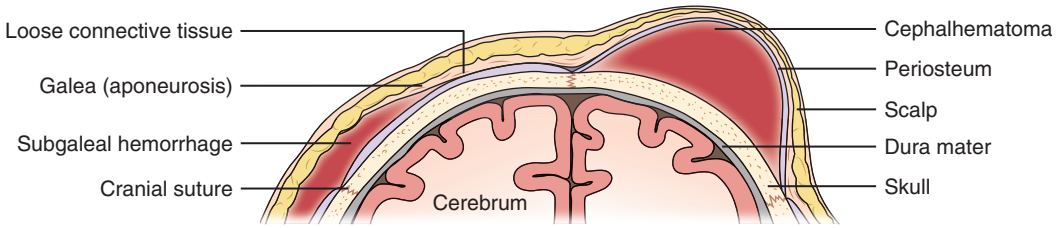
Etiology

The most common predisposing factor is difficult operative vaginal delivery, particularly midforceps delivery and vacuum extraction.[72] The risk for subgaleal hemorrhage may be reduced by use of softer silicone vacuum cups instead of the original rigid metallic ones. The major risk factors include coagulopathies, prematurity, macrosomia, fetal dystocia, precipitous labor, intrapartum hypoxia, male sex, cephalopelvic disproportion, prolonged labor, and nulliparity.

Mechanism of Injury

When vacuum is used, the mechanism of injury is thought to be the vacuum traction pulling the scalp away from stationary bony calvarium, thus avulsing open the subgaleal space and causing the bridging vessels to tear and bleed into the subgaleal space. The loose connective tissue of the subgaleal space is extremely expansive and extends over the entire area of the scalp. The space can accommodate the entire neonatal blood volume (250 mL or more in a term baby), leading to hypovolemic shock, disseminated intravascular coagulation, and multiorgan failure, resulting in death in 25% of the cases.[73]

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• **Fig. 29.5** Subgaleal hemorrhage and cephalhematoma.



• **Fig. 29.6** Clinical manifestations of subgaleal hemorrhage. Note anteriorly displaced ear.

Clinical Manifestations

Early manifestations may be limited to pallor, hypotonia, and diffuse swelling of the scalp. The development of a fluctuating mass straddling cranial sutures, fontanelles, or both is highly suggestive of the diagnosis. Because blood accumulates beneath the aponeurotic layer, ecchymotic discoloration of the scalp is a later finding.[27] This is often associated with pitting edema and progressive posterior spread toward the neck and lateral spread around the ears, frequently displacing the ears anteriorly (Fig. 29.6). Periorbital swelling and ecchymosis also are commonly observed. Eventually, hypovolemic shock, multiorgan failure, and signs of cerebral irritation develop. Massive lesions can cause extracranial cerebral compression, which may lead to rapid neurologic decompensation.[5] The clinician should be aware of occasional "silent presentation," in which a fluctuant mass is not apparent initially despite serial clinical examinations.[55] Subgaleal hemorrhage should be considered in infants who show signs of hypoperfusion and falling hematocrit after attempted or successful vacuum delivery even in the absence of a detectable fluctuant mass. Close monitoring is particularly important in those infants who are considered stable enough to allow admission to the normal newborn nursery.

Radiographic Manifestations

Standard radiographs of the skull may identify possible associated fractures. Computed tomography scanning may demonstrate abundant epicranial blood, parieto-occipital bone dehiscence, bone fragmentation, and posterior cerebral interhemispheric densities compatible with subarachnoid hemorrhage.[27]

Differential Diagnosis

In contrast with cephalhematoma, subgaleal hemorrhage is characterized by its more diffuse distribution, more rapid course, significant anemia, signs of central nervous system (CNS) trauma (e.g., hypotonia, lethargy, seizures), and frequent lethal outcome.

Treatment

Prompt restoration of blood volume with fresh frozen plasma or blood is essential. In the presence of continued deterioration, neurosurgery may be considered as a last resort. A bicoronal incision allows for exposure of the subgaleal space. Bipolar cauterization of any bleeding points can then be accomplished, and a drain can be left in the subgaleal space.

Prognosis

Although nearly 25% of infants with subgaleal hemorrhage die, long-term prognosis for survivors is generally good. More experience with aggressive and timely neurosurgical intervention may help to improve outcomes.

Skull Fractures

Fracture of the neonatal skull is uncommon, because the bones of the skull are less mineralized at birth and thus more compressible. In addition, the separation of the bones by membranous sutures usually permits enough alteration in the contour of the head to allow its passage through the birth canal without injury.

Etiology

Skull fractures usually follow a forceps delivery or a prolonged, difficult labor with repeated forceful contact of the fetal skull against the maternal symphysis pubis, sacral promontory, fifth lumbar vertebrae, or ischial spine. They have also been described after vacuum-assisted vaginal delivery.[33] Most of the fractures are linear. Depressed fractures are associated with forceps application. However, they may occur spontaneously after cesarean section or vaginal delivery without forceps. Factors that also have been implicated include pressure on the fetal skull by a maternal bony prominence (e.g., sacral promontory) or uterine fibroid, a fetal hand or foot, or the body part of a twin. Occipital bone fractures usually occur in breech deliveries as a consequence

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• **Fig. 29.7** Depressed skull fracture in term male infant delivered after rapid (1-hour) labor. Infant was delivered by occiput-anterior presentation after rotation from occiput-posterior position.

of traction on the hyperextended spine of the infant when the head is fixed in the maternal pelvis.

Clinical Manifestations

Linear fractures over the convexity of the skull frequently are accompanied by soft tissue changes and cephalhematoma. Usually, the infant's behavior is normal unless there is an associated concussion or hemorrhage into the subdural or subarachnoid space. Fractures at the base of the skull with separation of the basal and squamous portions of the occipital bone almost always result in severe hemorrhage caused by disruption of the underlying venous sinuses. The infant may then exhibit shock, neurologic abnormalities, and drainage of bloody cerebrospinal fluid from the ears or nose.

Depressed fractures are visible, palpable indentations in the smooth contour of the skull, similar to dents in a ping-pong ball (Fig. 29.7). The infant may be entirely free of symptoms unless there is an associated intracranial injury.

Radiographic Manifestations

The diagnosis of a simple linear or fissure fracture is seldom made without radiographs in which fractures appear as lines and strips of decreased density. Depressed fractures appear as lines of increased density. On some views, they are manifested by an inward buckling of bone with or without an actual break in continuity. Either type of fracture may be seen on only one view. CT imaging is the optimal diagnostic modality if a skull fracture and possible underlying injury are suspected.

Differential Diagnosis

Occasionally, the fragments of a linear fracture may be widely separated and may simulate an open suture. Conversely, parietal foramina, the interparietal fontanelle, mendosal sutures, and innominate synchondroses may be mistaken for fractures. In addition, normal vascular grooves, "ripple lines" that represent soft tissue folds of the scalp, and lacunar skull may be mistaken for fractures.

Treatment

Uncomplicated linear fractures over the convexity of the skull usually do not require treatment. Fractures at the base of the skull often necessitate blood replacement for severe hemorrhage and shock in addition to other supportive measures. If cerebrospinal fluid rhinorrhea or otorrhea is present, antimicrobial coverage is indicated to prevent secondary infection of the meninges.

Small (<2 cm) "ping-pong" fractures may be observed without surgical treatment. Loeser and associates reported three infants with depressed skull fractures in whom spontaneous elevation of the fractures occurred within 1 day to 3½ months of age.[44] Follow-up at 1-2½ years revealed normal neurologic development in all three.

Several nonsurgical methods have been described for elevation of depressed skull fractures in certain infants:

1. A thumb is placed on opposite margins of the depression, and gentle, firm pressure is exerted toward the middle. After several minutes of continuous pressure, the area of depression gradually disappears.[61]
2. A hand breast pump is applied to the depressed area. Petroleum jelly placed on the pump edges ensures a tighter seal, and gentle suction for several minutes results in elevation of the depressed bone.[64]
3. A vacuum extractor is placed over the depression and a negative pressure of 0.2-0.5 kg/cm^2 is maintained for about 4 minutes.[63]

Because these methods are technically easier and less traumatic, they may be preferable to surgical intervention in a symptom-free infant with an isolated lesion.

Comminuted or large fractures associated with neurologic signs or symptoms should be treated by immediate surgical elevation of the indented segment to prevent underlying cortical injury from pressure. Other indications for surgical elevation include manifestations of cerebrospinal fluid beneath the galea and failure to elevate the fracture by nonsurgical manipulation.

Prognosis

Simple linear fractures usually heal within several months without sequelae.

Basal fractures carry a poor prognosis. When separation of the basal and squamous portions of the occipital bone occurs, the outcome is almost always fatal; surviving infants have an extremely high incidence of neurologic sequelae.

The prognosis for a depressed fracture is usually good when treatment is early and adequate. When therapy is delayed, especially with a large depression, death may occur from pressure on vital areas of the brain. Because the natural history of depressed skull fractures in neonates has not been clearly elucidated, the outcome is uncertain for infants with smaller lesions managed either by simple observation or by surgery after significant delays.

Intracranial Hemorrhage

See Chapter 53.

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Face

Facial Nerve Palsy

Facial nerve palsy in the neonate may follow birth injury or rarely may result from agenesis of the facial nerve nucleus. The latter condition occasionally is hereditary but usually is sporadic.

Etiology

Traumatic facial nerve palsy most often follows compression of the peripheral portion of the nerve, either near the stylomastoid foramen through which it emerges or where the nerve traverses the ramus of the mandible. The neonate is vulnerable to these injuries because of the superficial course of the extracranial facial nerves. The nerve may be compressed by forceps, especially when the fetal head has been grasped obliquely. The condition also occurs after spontaneous deliveries in which prolonged pressure was applied by the maternal sacral promontory. Less frequently injury is sustained in utero, often in association with a mandibular deformity, by the persistent position of the fetal foot against the superior ramus of the mandible. An extremely rare cause is the pressure of a uterine tumor on the nerve.

This condition may occur rarely with simultaneous ipsilateral brachial plexus palsy, most likely secondary to compressive forces during delivery.[17] Contributing factors include prolonged second stage of labor and midforceps delivery.

Traumatic facial nerve palsy may follow a contralateral injury to the CNS such as a temporal bone fracture or hemorrhage, tissue destruction, or both to structures within the posterior fossa. This CNS injury is less frequent than peripheral nerve injury.

Clinical Manifestations

Paralysis is usually apparent on the first or second day but may be present at birth. It usually does not increase in severity unless considerable edema occurs over the area of nerve trauma. The type and distribution of paralysis are different in central facial paralysis compared with peripheral paralysis.

Central paralysis is a spastic paralysis limited to the lower half or two-thirds of the contralateral side of the face. The paralyzed side is smooth and full and often appears swollen. The nasolabial fold is obliterated, and the corner of the mouth droops. When the infant cries, the mouth is drawn to the normal side, the wrinkles are deeper on the normal side, and movement of the forehead and eyelid is unaffected. Usually other manifestations of intracranial injury appear, most often a sixth cranial nerve palsy.

Peripheral paralysis is flaccid and, when complete, involves the entire side of the face. When the infant is at rest, the only sign may be a persistently open eyelid on the affected side, caused by paralysis of the orbicular muscle of the eye. With crying, the findings are the same as in a central facial nerve injury, with the addition of a smooth forehead on the involved side. Because the tongue is not involved, feeding is not affected.

A small branch of the nerve may be injured, with involvement of only one group of facial muscles. Paralysis is then limited to the forehead, eyelid, or mouth. Peripheral paralysis caused by nerve injury distal to the geniculate ganglion may be accompanied by a hematotympanum on the same side.

Differential Diagnosis

Central and peripheral facial nerve palsies must be distinguished from nuclear agenesis (Möbius syndrome). The latter frequently results in bilateral facial nerve palsy; the face is expressionless and immobile, suggesting muscle fibrosis. Other cranial nerve palsies and deformities of the ear, palate, tongue, mandible, and other bones may be associated with Möbius syndrome. Congenital absence or hypoplasia of the depressor muscle of the angle of the mouth also may simulate congenital facial palsy and has been associated with an increased incidence of other congenital anomalies.

Treatment

No specific therapy is indicated for most facial palsies. If the paralysis is peripheral and complete, initial treatment should be directed at protecting the cornea with an eye pad and instilling artificial tears every 4 hours. The functional state of the nerve should be followed closely. Falco and colleagues proposed the following comprehensive approach[20]:

1. Distinguish developmental from acquired lesions on the basis of the birth history and a detailed physical examination. Patients thought to have developmental palsy should be examined with radiologic and electrodiagnostic studies and brainstem-evoked response as appropriate.
2. Because of the expected 90% likelihood of complete spontaneous recovery, patients should be observed for 1 year before surgical intervention is considered. If recovery is suggested by physical examination or serial electromyography, observation without surgery may be delayed until the second birthday. Infants who require surgery are best treated with decompression or neuroplasty or both.

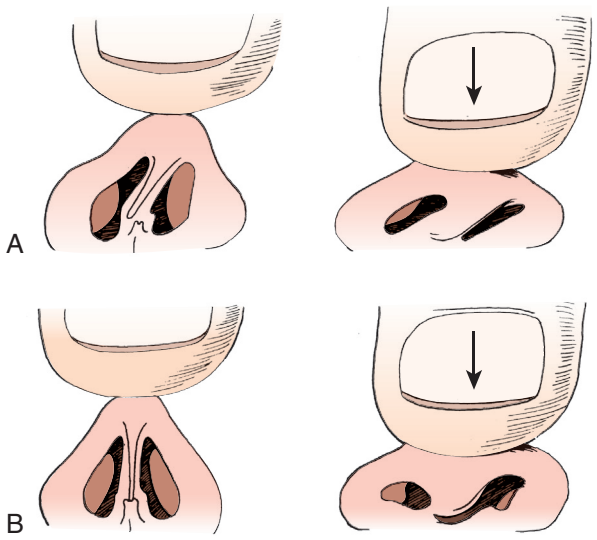
Prognosis

Most facial palsies resolve spontaneously within several days; total recovery may require several weeks or months. Electrodiagnostic testing is beneficial in predicting recovery; repeatedly normal nerve excitability indicates a good prognosis, but decreased or absent excitability early in the course suggests a poor outlook. The subsequent appearance of muscle fibrillation potentials indicates nerve degeneration. The prognosis in surgically treated infants worsens with increasing age at treatment.

Fractures and Dislocations of Facial Bones

Facial bone fractures may occur during passage through the birth canal, during forceps application and delivery, and during obstetric manipulation (most often the Mauriceau

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• **Fig. 29.8** Result of finger compression, **A**, when nasal septum is dislocated. Normal septal relationship, **B**, results in no nasal deviation with pressure. (Modified from Daily W, et al. Nasal septal dislocation in the newborn. *Mo Med.* 1977;74:381.)

maneuver for delivery of the fetal head in a breech presentation). Manipulation may result in mandibular fractures and mandibular joint damage but is rarely severe enough to cause separation of the symphysis of the mandible. Fracture of the nose may result in early respiratory distress and feeding difficulties. The most frequent nasal injury is dislocation of the cartilaginous part of the septum from the vomerine groove and columella. This may result from intrauterine factors such as a uterine tumor or persistent pressure on the nose by fetal small parts or during delivery from pressure on the nose by the symphysis pubis, sacral promontory, or perineum. The presence of nasal septal dislocation may be differentiated from the more common normal variant of a misshapen nose by a simple compression test in which the tip of the nose is compressed (Fig. 29.8).[15] In the presence of septal dislocation, the nostrils collapse and the deviated septum becomes more apparent; in the normal nose, no nasal deviation occurs with compression.

Infants who sustain nasal trauma during the birth process may demonstrate stridor and cyanosis, even in the absence of septal dislocation. Miller and coworkers noted high nasal resistance in three such infants, only one of whom was found to have septal dislocation.[51] The authors postulated the presence of edema and narrowed nasal passages from compression forces on the midface during delivery. The problem may be exaggerated by repeated nasal suctioning or transnasal bronchoscopy. These procedures and oral feeding should be avoided until the infant re-establishes normal nasal ventilation. Pulse oximetry measurements are useful in monitoring these infants.

Treatment

Fractures of the maxilla, lacrimal bones, and nose warrant immediate attention, because they unite quickly, with fixation in 7-10 days. Nasal trauma may require surgery. While waiting, the pediatrician should provide an oral airway to relieve respiratory distress. Fractures of the septal cartilage also may be reduced by simple manual remolding, but most are associated with hematomas that should be promptly incised and drained. The surgeon can visualize the deformity with an infant nasal speculum, place a septal elevator in the nose, and guide the septal cartilage into the vomerine groove; an audible and palpable click indicates return of the septum into position. For simple nasal positional deformity with no evidence of respiratory distress, steri-strip method (tapes are applied from the septal pyramid/vomer junction anchored to the cheek to straighten the columella and widen the nasal aperture) may be attempted for a few days unless septal dislocation is identified soon after birth.[74]

Early reduction and immobilization are advised for a displaced fracture of the mandible because rapid, firm union may occur as early as 10-14 days. Usually, adequate alignment can be achieved with an acrylic mandibular splint and circum-mandibular wires, which are maintained in place for 3 weeks. In more severe cases with canting of the mandibular alveolar ridge, perialveolar wires below the infraorbital rims have been used with excellent results. This procedure can prevent canted occlusion and possible facial asymmetry as the child grows, thus avoiding later extensive and costly reconstructive surgery.[60]

Prognosis

If the fracture is reduced and fixated within a few days, rapid healing without complication is the usual course. If treatment is inadequate, missed, or delayed, subsequent developmental deformities are common. Ankylosis of the mandible in the second year of life is thought to result from birth trauma to the temporomandibular joint. A young child has been described with unilateral mandibular hypoplasia, which was thought to have resulted from fibrous ankylosis caused by perinatal trauma to the condylar cartilage of the ipsilateral temporomandibular joint.[8] Other deformities may not become apparent until adolescence or young adulthood.

Eyes

See Chapter 95. Mechanical trauma to various regions of the neonatal eye usually occurs during abnormal presentation in dystocia from cephalopelvic disproportion or as a result of inappropriate forceps placement in normal deliveries. Most of the injuries are self-limited and mild and require no specific treatment.

Eyelids

Edema, suffusion, and ecchymoses of the eyelids are common, especially after face and brow presentations or forceps deliveries. Severely swollen lids should be forced open by an ophthalmologist for examination of the eyeball;

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retractors may be necessary. These findings usually resolve within a week without treatment.

A less common injury is laceration, including disruption of the lacrimal canaliculus. This has been associated with multiple upper-eyelid lacerations, including a full-thickness vertical wound lateral to the punctum and a full-thickness laceration through the lower eyelid with transection of the canaliculus after a low forceps delivery. Microsurgical repair of the lacrimal system and eyelids, including lacrimal intubation with a silicone stent, has been successful. Follow-up at 14 months revealed normal tear drainage with no amblyopia or residual deformity.[32]

An infant has been reported with superficial eyelid lacerations caused by an internal fetal monitoring spiral electrode.[42] At delivery, the electrode was attached to the eyelid. Marked facial edema related to brow presentation apparently obscured the lacerations until 14 hours of age, when much of the edema had resolved. Periorbital edema was believed to have protected the infant from more serious injury to the eyelid and globe.

Lagophthalmos, the inability to close an eyelid, is an occasional finding thought to result from facial nerve injury by forceps pressure. It is usually unilateral. The exposed cornea should be protected by an eye pad and frequent use of methylcellulose drops. The condition usually resolves within a week.

Orbit

Orbital hemorrhage and fracture may follow direct pressure by the apex of one forceps blade, most often in high forceps extractions. In most instances, death occurs immediately. Surviving infants demonstrate traumatic eyelid changes, disturbances of extraocular muscle movements, and exophthalmos. The presence of the latter two findings warrants immediate ophthalmologic consultation. Subsequent management also may require neurosurgical and plastic surgery consultations.

Sympathetic Nervous System

Horner syndrome, resulting from cervical sympathetic nerve trauma, frequently accompanies lower brachial plexus injury. The syndrome consists of miosis, partial ptosis, slight enophthalmos, and anhidrosis of the ipsilateral side of the face. Although small, the pupil reacts to light. The presence of neurologic signs indicating brachial plexus injury helps distinguish this syndrome from intracranial hemorrhage as a cause of anisocoria. Pigmentation of the ipsilateral iris is frequently delayed to several months of age; occasionally, pigmentation never occurs. Resolution of other signs of the syndrome depends on whether the injury to the nerve is transient or permanent.

Subconjunctival Hemorrhage

Subconjunctival hemorrhage, characterized by bright red patches on the bulbar conjunctiva, is a relatively common finding in the neonate. It may be found after a difficult delivery but often is noted after easy, completely uncomplicated deliveries. This finding is considered to result from increased venous pressure in the infant's head and neck, produced by obstruction to venous return consequent to compression of the fetal thorax or abdomen by uterine contractions during labor. If the infant is otherwise well, management consists of reassuring the parents. The blood is usually absorbed within 1-2 weeks. As the blood pigments break down and are absorbed, the color changes from bright red to orange and yellow.

External Ocular Muscles

Injury involving the external ocular muscles may result from direct trauma to the cranial nerve (in the form of compression or surrounding hemorrhages) or from hemorrhage into the muscle sheath, with subsequent fibrosis. The sixth cranial nerve (abducens) is the most frequently injured cranial nerve because of its long intracranial course; the result is paralysis of the lateral rectus muscle. This injury may follow a tentorial laceration with extravasation of a small amount of blood around the intracranial portion of the nerve. The involvement may be mild and transient; internal strabismus noted at birth may resolve gradually within 1-2 months. The seventh cranial nerve may be injured simultaneously with the sixth nerve by compression with forceps. Improvement in lateral gaze of the affected eye may appear within 1-2 months. Alternate patching of either eye in the severely affected infant maintains visual acuity until, with time, maximal improvement has occurred. At 6 months, the degree of nerve regeneration may be evaluated. Some infants subsequently require surgical repair of the strabismus.

Fourth cranial nerve (trochlear) palsy occurs infrequently. It may follow small brainstem hemorrhages with nuclear damage. The affected muscle is the superior oblique, which mainly turns the eye inferiorly and medially. This condition is difficult to identify in the newborn infant. Surgical correction may be necessary later.

Third cranial nerve (oculomotor) palsy, when complete, causes paralysis of the inferior oblique and medial, superior, and inferior rectus muscles. This results in ptosis, a dilated fixed pupil, and outward and downward deviation of the eye, with inability to adduct or elevate up and in, or up and out, or to depress down and out. This palsy also may occur in partial form, with or without pupillary involvement. Partial palsies may recover function spontaneously within several months, whereas complete palsies usually require surgical intervention.

Optic Nerve

The optic nerve may be injured directly by a fracture in the region of the optic canal or from a shearing force on the nerve, with resultant hemorrhage into the nerve sheath. The latter injury seldom is recognized because of the more apparent and severe changes in the sensorium. Occasionally, a fracture through the optic foramen results in formation of callus, which slowly compresses the nerve. A difficult forceps delivery is a frequent preceding event.

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Cornea

A diffuse or streaky haziness of the cornea is relatively common. This is usually caused by edema related to the birth process but also may follow use of a silver nitrate solution more concentrated than 1%. The haziness usually disappears in 7-10 days. When it persists, a rupture of the Descemet membrane has probably occurred, usually because of malpositioning of forceps at delivery. The consequence of a ruptured Descemet membrane is a leukoma or diffuse white opacity of the cornea. This results from interstitial damage of the substantia propria by fluids entering through the tear in the membrane. These leukomas are often permanent and, despite patching of the contralateral eye and use of glasses, are accompanied by a high incidence of amblyopia and strabismus.

A ruptured Descemet membrane has been reported after a prolonged delivery in which low forceps were used after unsuccessful attempts at vacuum extraction.[6] Because of significant corneal astigmatism at 2 months of age, a gas-permeable hard contact lens was applied.[68] Patching of the contralateral eye was continued. Assessment of visual acuity at 13 months, with the use of spatial frequency sweep visual-evoked potentials, demonstrated an excellent visual result.

Intraocular Hemorrhage

Trauma at birth may result in retinal hemorrhage, hyphema, or vitreous hemorrhage, with retinal hemorrhage the most common. The cause is most likely compression of the fetal head, resulting in venous congestion. The fetal head is compressed two to four times more forcefully than other fetal parts during the second stage of labor. Retinal hemorrhage is more common in primiparous deliveries and after forceps or vacuum extraction; it is rare after cesarean section. It may occur in normal deliveries. The most common lesion is the flame-shaped or streak hemorrhage found mainly near the disk and sparing the macula and extreme periphery. A majority of cases resolve within 2 weeks with no residual effects. Rarely, hemorrhages may take up to 6 weeks to resolve. It is critical to identify birth-related retinal hemorrhages and document their presence on the infant's chart to avoid subsequent suspicion of child abuse. Retinal hemorrhages may reduce the resolving power of the macula, either bilaterally to produce nystagmus or unilaterally to produce amblyopia, which may not always respond to prolonged covering of the fixing eye with improvement of the amblyopic eye.

Hyphemas and vitreous hemorrhages usually result from misplacement of forceps and often are associated with ruptures of the Descemet membrane. One infant has been described in whom a hyphema developed in one eye after spontaneous delivery.[58] The hyphema usually is clear of gross blood within 5 days; during this time the infant should be handled gently and fed frequently to minimize crying and agitation. If blood persists or secondary hemorrhage occurs, systemic administration of acetazolamide (diamox) and surgical removal of blood may be necessary.

Vitreous hemorrhage is manifested by large vitreous floaters, blood pigment seen with the slit lamp, and an absent red reflex. The prognosis is guarded; if resolution does not occur in 6-12 months, surgical correction should be considered.

Ears

The proximity of ears to the site of application of forceps makes them susceptible to injury at birth. Most of the injuries are mild and self-limited, but serious injuries may occur because of slipping or misplacement of forceps (Fig. 29.9).

Abrasions and Ecchymoses

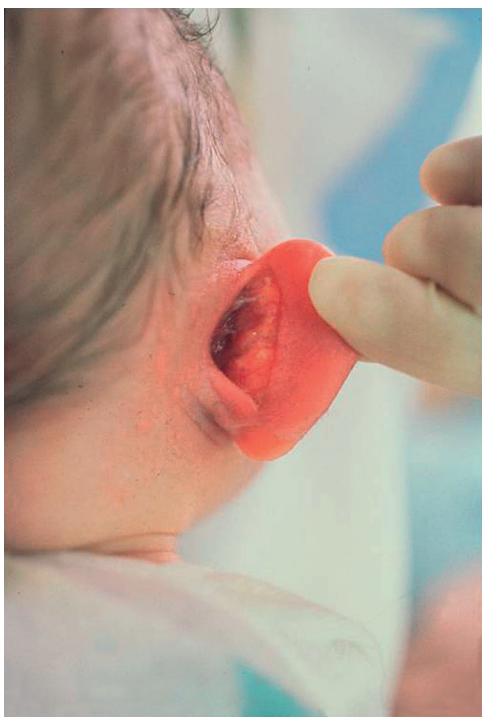
Abrasions must be cleansed gently to minimize the risk for secondary infection. Ecchymoses, if extensive and involving other areas of the body, may result in hyperbilirubinemia.

Hematomas

Hematomas of the external ear, if not treated promptly, liquefy slowly and are followed by early organization and development of cauliflower ear. Wide incision and evacuation of the hematoma may be indicated.

Lacerations

Lacerations of the auricle may be repaired by the pediatrician if they are superficial and involve only skin. After



• **Fig. 29.9** Extensive avulsion and laceration of auricle in term infant, resulting from forceful traction of misplaced forceps.

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thorough cleansing and draping, the wound edges are sutured with interrupted 6-0 or 7-0 nylon sutures, with exact edge-to-edge approximation. If the laceration involves cartilage, surgical consultation should be obtained because of the tendency toward postoperative perichondritis, which is refractory to treatment and leads to subsequent deformities. A sterile field and more meticulous presurgical preparation are essential. A contour pressure dressing is applied postoperatively.

Vocal Cord Paralysis

Unilateral or bilateral paralysis of the vocal cords related to birth injury is uncommon in the neonate.

Etiology

Unilateral paralysis may be a consequence of excessive traction on the head during a breech delivery or lateral traction with forceps in a cephalic presentation. The recurrent laryngeal branch of the vagus nerve in the neck is injured. The left side is involved more often because of this nerve's lower origin and longer course in the neck. Bilateral paralysis may be caused by peripheral trauma involving both recurrent laryngeal nerves, but more frequently it is caused by a CNS insult such as hypoxia or hemorrhage involving the brainstem. Infants with vocal cord paralysis following instrumental delivery may have associated injuries such as subdural hemorrhage.[22]

Clinical Manifestations

An infant with a unilateral paralysis may be completely free of symptoms when resting quietly, but crying is usually accompanied by hoarseness and mild inspiratory stridor. When associated with difficulty in feeding and clearing secretions, concurrent involvement of the 12th (hypoglossal) cranial nerve should be suspected, particularly if the tongue on the ipsilateral side does not protrude and demonstrates fasciculations. Hypoglossal paralysis also has been described in association with ipsilateral upper brachial plexus injury.[30] Affected infants demonstrate difficulty in sucking, with swelling and immobility of the affected side of the tongue. Bilateral paralysis results in more severe respiratory symptoms. At birth, the infant may have difficulty in establishing and maintaining spontaneous respiration; later, dyspnea, retractions, stridor, cyanosis, or aphonia may develop.

Differential Diagnosis

Unilateral paralysis of the vocal cords must be distinguished from congenital laryngeal malformations that produce neonatal stridor. A history of difficult delivery, especially involving excessive traction on the fetus, may suggest laryngeal paralysis; previously, the diagnosis was confirmed only by direct laryngoscopic examination. The availability of the flexible fiberoptic laryngoscope at the bedside has facilitated earlier diagnosis without disrupting the infant's environment. Serial examinations to monitor progress also can be conducted with ease, because the infant need not be transported to the operating room.

Bilateral paralysis also must be distinguished from a number of causes of respiratory distress in the neonate (see Chapter 66); stridor should suggest the larynx as the site of disturbance. Direct or flexible fiberoptic laryngoscopy is necessary to establish the diagnosis.

Treatment

Infants with unilateral paralysis should be observed closely until there is evidence of improvement. Gentle handling and frequent small feedings aid in keeping the infant quiet and minimizing the risk for aspiration. Bilateral paralysis necessitates immediate tracheal intubation to establish an airway. Tracheostomy is required subsequently in most patients. Laryngoscopic examinations then should be performed at intervals to look for evidence of return of vocal cord function; early extubation may be attempted if complete return occurs within a short time.

Prognosis

Unilateral paralysis usually resolves rapidly without treatment, and complete resolution occurs within 4-6 weeks. Glossolaryngeal paralysis or paresis resulting from birth injury should resolve spontaneously by 6 months of age. Recognition of this subtle condition is important for two reasons. First, its self-limited course is encouraging, thus avoiding needless alarm in the parents with concern about more ominous conditions such as Werdnig-Hoffmann disease. Second, unnecessary invasive and aggressive procedures can be avoided.

The prognosis for bilateral paralysis is more variable. If untreated, a funnel deformity may develop in the lower sternal area; this may appear as early as the 15th day of life. After tracheostomy, a decrease in the severity of the deformity may occur within several weeks. Some affected infants subsequently regain normally shaped chests; others may have residual fixed depressions occasionally severe enough to require surgical correction. The recovery of vocal cord function varies in time and degree. Some infants may show partial recovery within a few months, with several years elapsing before complete movement of the cords is restored. Other infants who have been followed for years show no improvement. Bilateral paralysis of central origin may improve completely if it is caused by cerebral edema or hemorrhage that rapidly resolves.

Injuries to the Neck, Shoulder Girdle, and Chest

Fracture of the Clavicle

See Chapter 97. The clavicle is the most frequently fractured bone during labor and delivery. Most clavicular fractures are of the greenstick type, but occasionally the fracture is complete.

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Etiology

The major causes of clavicular fractures are difficult delivery of the shoulders in vertex presentations and extended arms in breech deliveries. Vigorous, forceful manipulation of the arm and shoulder usually has occurred. However, fracture of the clavicle may also occur in infants after apparently normal labor and delivery.[39] It has been suggested that some fetuses may be more vulnerable to spontaneous birth trauma secondary to forces of labor, maternal pelvic anatomy, and in utero fetal position.

Clinical Manifestations

Most often a greenstick fracture is not associated with any signs or symptoms but is first detected after the appearance of an obvious callus at 7-10 days of life. Thus, most neonatal clavicular fractures are diagnosed at discharge or at the first follow-up visit. Complete fractures and some greenstick fractures may be apparent shortly after birth; movement of the arm on the affected side is decreased or absent. Deformity and, occasionally, discoloration may be visible over the fracture site with obliteration of the adjacent supraclavicular depression as a result of sternocleidomastoid muscle spasm. Passive movement of the arm elicits cries of pain from the infant. Palpation reveals tenderness, crepitus, and irregularity along the clavicle. Moro reflex on the involved side is characteristically absent. Radiographs confirm the diagnosis of fracture.

Differential Diagnosis

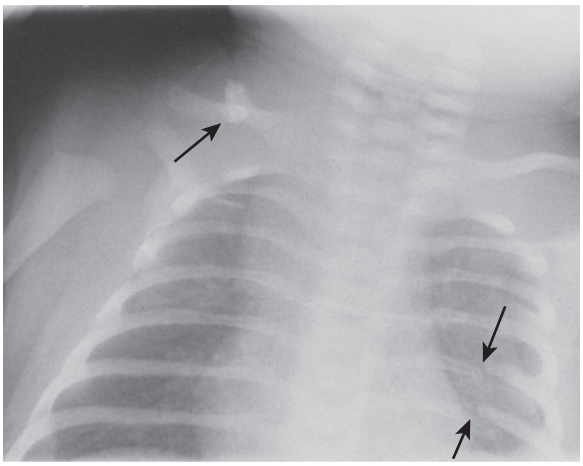
A similar clinical picture of impaired movement of an arm with an absent Moro reflex may follow fracture of the humerus or brachial palsy. The fracture is confirmed by radiographs; palsy is accompanied by additional clinical findings. Rarely, an infant may present with a congenital pseudoarthrosis of the clavicle, which may be difficult to distinguish from a fracture. Pseudoarthrosis classically appears as a painless lump on the clavicle, with no associated tenderness or limitation of mobility of the shoulder and arm. Radiography reveals disruption of the affected clavicle, with enlargement of the end of the bone. The etiology is uncertain. Recommended treatment options include observation only or surgical excision of the cartilaginous cap at about 4 or 5 years of age, followed by alignment of bone fragments and, if necessary, bone grafting or internal fixation.

Treatment

Therapy is directed toward minimizing the infant's pain. The affected arm and shoulder should be immobilized with the arm abducted more than 60 degrees and the elbow flexed more than 90 degrees. A callus forms, and pain usually subsides by 7-10 days, when immobilization may be discontinued.

Prognosis

The prognosis is excellent, with growth resulting in restoration of normal bone contour after several months.



• **Fig. 29.10** Chest radiograph of a 4905-g girl delivered by midforceps after right shoulder dystocia. On the 11th day, a prominent mass was noted in the right midclavicular region. Radiograph reveals a right midclavicular fracture (*top left arrow*) with slight superior angulation and incidental fractures of left fifth and sixth ribs (*bottom right arrows*). (From Mangurten HH, et al. Incidental rib fractures in a neonate. *Neonat Intensive Care.* 1999;12:15.)

Fracture of Ribs

Rib fractures related to labor and delivery are exceedingly rare.

Etiology

Risk factors are similar to those related to fracture of the clavicle, including macrosomia, a primigravida mother, shoulder dystocia, and delivery by midforceps or vacuum extraction.

Clinical Manifestations

Specific clinical manifestations are often absent, making diagnosis difficult, unless a chest radiograph is obtained for other reasons, including suspected clavicular fracture (Fig. 29.10),[48] respiratory distress, or cyanosis.

Mechanism of Injury

This injury is initiated when the anterior shoulder is impacted behind the symphysis pubis, with the other shoulder attempting to descend into the posterior compartment of the pelvis (Fig. 29.11).[48] This results in compression forces on the fetal arms and thorax, leading to spontaneous rib fractures on the same side as the posterior shoulder (Fig. 29.12).

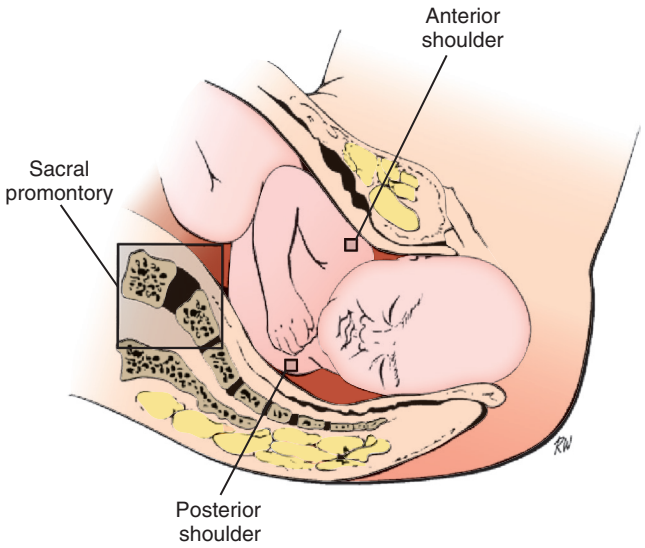
Treatment

No specific treatment is required. However, it is extremely important to document this injury immediately after birth to avoid later unwarranted accusation of parents or other caretakers for suspicion of child abuse.

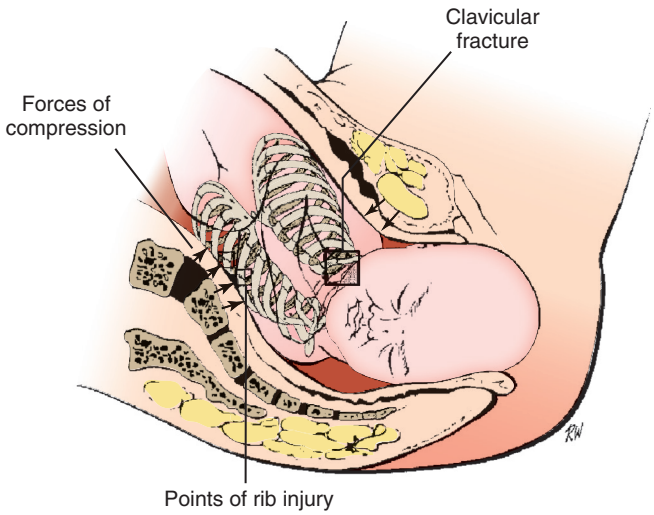
Prognosis

The prognosis is excellent, with spontaneous healing within several months.

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• **Fig. 29.11** Diagram of fetus during delivery, illustrating impaction of anterior (right) shoulder behind the symphysis pubis, with left shoulder attempting to descend into posterior compartment of the pelvis. (From Mangurten HH, et al. Incidental rib fractures in a neonate. *Neonat Intensive Care.* 1999;12:15.)



• **Fig. 29.12** Diagram of fetus, illustrating compression forces on the fetal arms and thorax, which results in spontaneous fractures of right clavicle and left fifth and sixth ribs (*arrows*). (From Mangurten HH, et al. Incidental rib fractures in a neonate. *Neonat Intensive Care.* 1999;12:15.)

Brachial Palsy

See Chapter 99. Brachial palsy is a paralysis involving the muscles of the upper extremity that follows mechanical trauma to the spinal roots of the fifth cervical through the first thoracic nerves (the brachial plexus) during birth. Three main forms occur, depending on the site of injury:

1. Duchenne-Erb or upper arm paralysis results from injury of the fifth and sixth cervical roots and is by far the most common.
2. Klumpke or lower arm paralysis results from injury of the eighth cervical and first thoracic roots and is extremely rare.
3. Paralysis of the entire arm occurs slightly more often than the Klumpke type.

Etiology

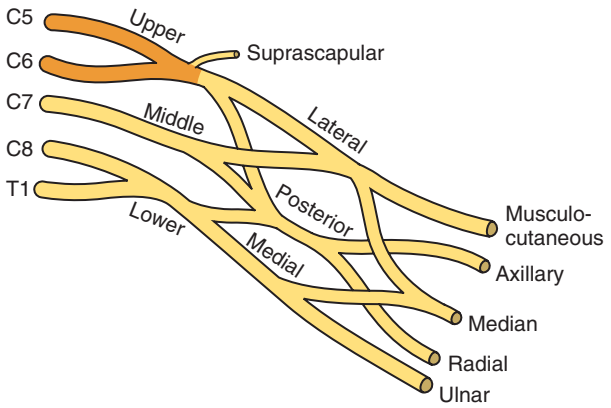
Many cases of brachial palsy follow a prolonged and difficult labor culminating in a traumatic delivery. The affected infant is frequently large, relaxed, and asphyxiated and thereby vulnerable to excessive separation of bony segments, overstretching, and injury to soft tissues. Injury of the fifth and sixth cervical roots may follow a breech presentation with the arms extended over the head; excessive traction on the shoulder in the delivery of the head may result in stretching of the plexus. The same injury may follow lateral traction of the head and neck away from one of the shoulders during an attempt to deliver the shoulders in a vertex presentation, particularly during a vacuum extraction[53] and after shoulder dystocia.[21] More vigorous traction of the same nature results in paralysis of the entire arm. The mechanism for isolated lower arm paralysis is uncertain; it is thought to result from stretching of lower plexus nerves under and against the coracoid process of the scapula during forceful elevation and abduction of the arm. Excessive traction on the trunk during a breech delivery may result in avulsion of the lower roots from the cervical cord. In most patients, the nerve sheath is torn, and the nerve fibers are compressed by the resultant hemorrhage and edema. Less often the nerves are completely ruptured and the ends severed, or the roots are avulsed from the spinal cord with injury to the spinal gray matter.

Some authorities suggest that twisting and extension of the fetal head during the cardinal movements of labor and during delivery contribute to the occurrence of brachial palsy.[62] An increasing number of reports have described "no shoulder" brachial plexus palsy unrelated to excessive traction during delivery.[24] Some experts have suggested an intrauterine insult preceding labor, such as compression by uterine tumors or maternal pelvic bony prominences.[24] One study, which confirmed the well-known association of shoulder dystocia and brachial plexus injury in macrosomic infants, also identified an increased incidence of other malpresentations in low and normal birth weight infants with brachial plexus injury.[25] One report has described an infant with brachial palsy following vaginal delivery with no shoulder dystocia, no delay between delivery of the head and the body, no physician traction during the delivery, and no fundal pressure.[43] A large epidemiologic study revealed that 54% of infants had no identifiable risk factors.[21]

Clinical Manifestations

Clinical manifestations may be understood in relation to depiction of the brachial plexus (Fig. 29.13).[57] The infant with upper arm paralysis holds the affected arm in a characteristic position, reflecting involvement of the shoulder abductors and external rotators, forearm flexors and

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• **Fig. 29.13** Simplified schematic diagram of brachial plexus, indicating spinal nerves of origin, trunks, cords, and major peripheral nerves. *Darker area* signifies the portion of the plexus affected in Erb palsy. (Courtesy of Dr. Joseph H. Piatt Jr., St. Christopher's Hospital for Children, Philadelphia.)

supinators, and wrist extensors. The arm is adducted and internally rotated, with extension at the elbow, pronation of the forearm, and flexion of the wrist. When the arm is passively abducted, it falls limply to the side of the body. Moro, biceps, and radial reflexes are absent on the affected side. There may be some sensory deficit on the radial aspect of the arm, but this is difficult to evaluate in the neonate. The grasp reflex is intact. Any signs of respiratory distress may indicate an accompanying ipsilateral phrenic nerve root injury (see Phrenic Nerve Paralysis).

Lower arm paralysis involves the intrinsic muscles of the hand and the long flexors of the wrist and fingers. The hand is paralyzed, and voluntary movements of the wrist cannot be made. The grasp reflex is absent; the deep tendon reflexes are intact. Sensory impairment may be demonstrated along the ulnar side of the forearm and hand. Frequently dependent edema and cyanosis of the hand and trophic changes in the fingernails develop. After some time, there may be flattening and atrophy of the intrinsic hand muscles. Usually an ipsilateral Horner syndrome (ptosis, miosis, and enophthalmos) also is present because of injury involving the cervical sympathetic fibers of the first thoracic root. Often this is associated with delayed pigmentation of the iris, sometimes of more than 1 year's duration.

When the entire arm is paralyzed, it is usually completely motionless, flaccid, and powerless, hanging limply to the side. All reflexes are absent. The sensory deficit may extend almost to the shoulder.

Differential Diagnosis

The presence of a flail arm in a neonate may be caused by cerebral injury or a number of injuries about the shoulder. Cerebral injury is usually associated with other manifestations of CNS injury. A careful radiographic study of the shoulder, including an examination of the lower cervical spine, clavicle, and upper humerus, should be made to exclude tearing of the joint capsule; fracture of the clavicle; and fracture, dislocation, or upper epiphyseal detachment of the humerus. Posterior dislocation of the humeral head may be difficult to identify with standard radiographs. Torode and Donnan have used CT scans to demonstrate that posterior dislocation is more common than previously believed.[71] Hunter and coworkers[36] reported an infant in whom a posterior dislocation was uncertain with standard radiographs. Ultrasonography clearly revealed a posterior dislocation. Because posterior dislocation will complicate resolution of the palsy, ultrasonographic evaluation should be considered early in the management of these infants.

Treatment

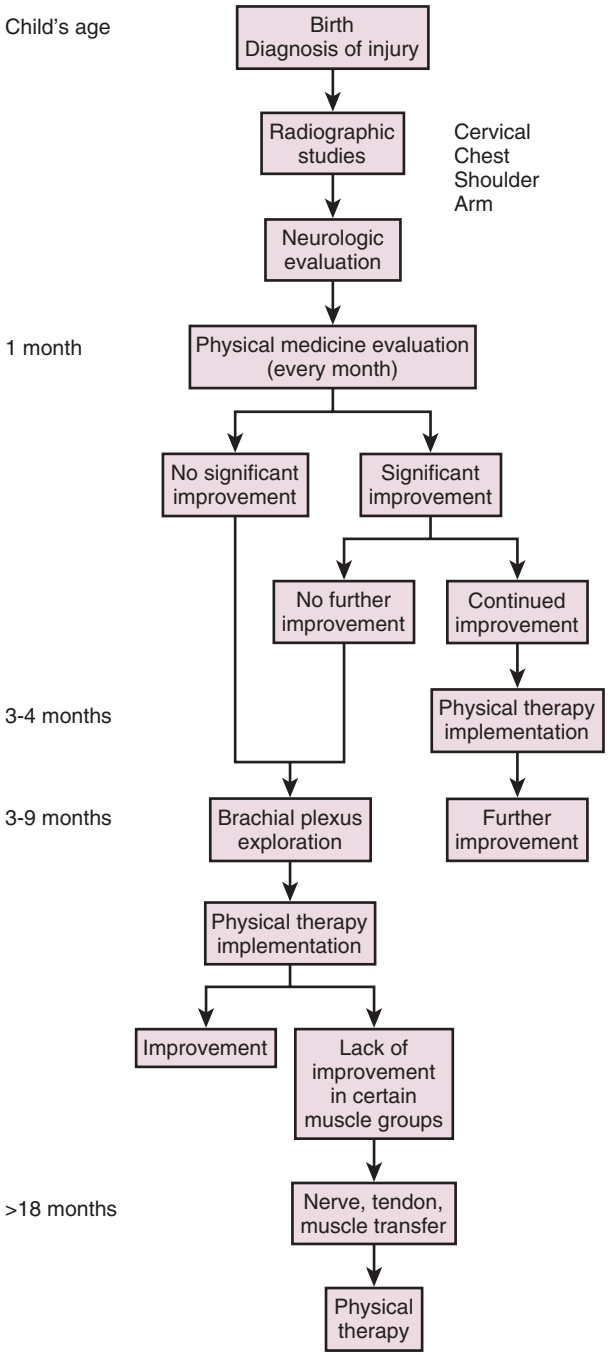
The basic principle of treatment historically has been conservative, with initial emphasis on prevention of contractures while awaiting recovery of the brachial plexus. This approach has been replaced by a more comprehensive program that combines initial conservative management with closer follow-up and an earlier decision regarding surgical intervention. This is best represented by the care plan developed by Shenaq and colleagues (Fig. 29.14).[67] This approach is initiated with a thorough and complete physical examination that includes careful palpation of the sternocleidomastoid muscle for contracture or pseudotumor; inspection for fractures of the clavicle, humerus, or ribs; observation for abdominal asymmetry, which could indicate paralysis of the hemidiaphragm; and assessment for ocular asymmetry, which may indicate associated Horner syndrome.

Ancillary investigations, including CT or myelography and MRI, could be helpful in detecting possible avulsions. Electromyography has been unreliable in predicting the extent of damage.

Some infants may demonstrate discomfort because of a painful traumatic neuritis affecting the brachial plexus. If no discomfort is apparent and other lesions as noted earlier are ruled out, early passive range-of-motion exercises, particularly involving the elbow and wrist, should be instituted. Because of shorter nursery stays, the mother should receive early demonstration and written instructions describing these exercises. She should then begin to work with the infant under the guidance of the therapy staff. Exercises include shoulder rotation; elbow flexion and extension; wrist flexion and extension; finger flexion and extension; and thumb abduction, adduction, and opposition. The infant should be reevaluated every month. If improvement in deltoid, biceps, and triceps function has not occurred by the third month of life, functional outcome without surgery is unlikely. Consequently, a decision for surgery should be made by the end of the third month, followed by primary brachial plexus exploration during the fourth month.

Initial surgical intervention beyond 12 months of age at the level of the cervical root alone has resulted in disappointing outcomes. However, when infants referred at this age have been offered a combined cervical root and infraclavicular exploration with neurolysis, graph reconstruction, and nerve transfer of appropriate elements in both

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• **Fig. 29.14** Treatment protocol for management of obstetric brachial plexus palsy. (From Shenaq SM, et al. Brachial plexus birth injuries and current management. *Clin Plast Surg.* 1998;25:527.)

anatomic compartments, improved outcomes have been noted. Blaauw and Slooff have reported their experience with transfer of pectoral nerves to the musculocutaneous nerve in 25 patients, 22 of whom had upper root avulsions.[9] Seventeen patients, including one who went to surgery at 3 months of age, had excellent outcomes, five had fair outcomes, and two were considered treatment failures.

The initial surgical therapy may include a team of neurosurgeons, plastic surgeons, and physiatrists who collaborate in the exploration, evaluation, and repair of the injury. This aggressive approach has resulted in up to 90% of patients demonstrating useful function of muscle groups above the elbow. Function below the elbow has been characterized by 50%-70% recovery because of the increased distance required for nerve regeneration.

Prognosis

Continued close follow-up includes serial evaluation of shoulder, elbow, forearm, wrist, finger, and thumb function. Based on the child's progress over time, a decision is made regarding further treatment. Physical therapy is continued until there is no further progress or the deficit is debilitating. For the infant who continues to demonstrate lack of improvement in certain muscle groups, secondary surgical reconstruction is available, with a variety of options depending on the individual deficit.

Although most (93%-95%) infants achieve return of function with conservative management, the remainder with persistent deficits may go on to development of long-term severe handicaps of the affected extremity. Early treatment offers significant improvement for about 90% of these children. Referral to centers that have an established rehabilitation program for infants with this condition may be initiated for a timely and successful treatment. In summary, the infant who does not improve spontaneously now has increased hope for recovery owing to advances in microsurgery and nerve transfer techniques.

Phrenic Nerve Paralysis

See Chapter 66. Phrenic nerve paralysis results in diaphragmatic paralysis and rarely occurs as an isolated injury in the neonate. Most injuries are unilateral and are associated with ipsilateral upper brachial plexus palsy.

Etiology

The most common cause is a difficult breech delivery. Lateral hyperextension of the neck results in overstretching or avulsion of the third, fourth, and fifth cervical roots, which supply the phrenic nerve.

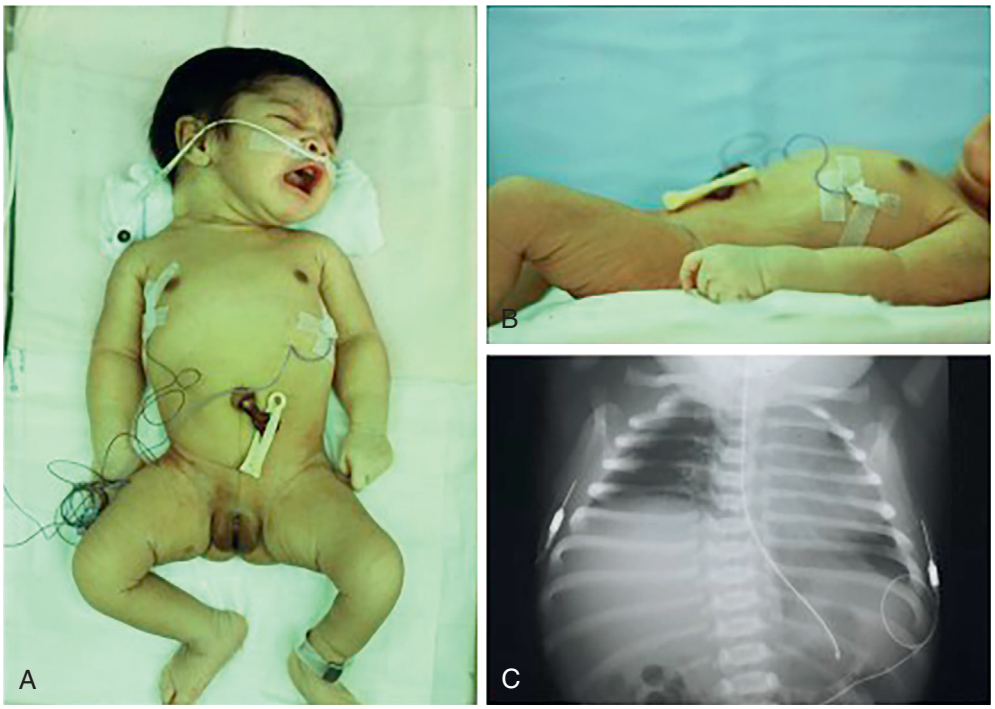
Clinical Manifestations

The first sign may be recurrent episodes of cyanosis, usually accompanied by irregular and labored respirations. The respiratory excursions of the involved side of the diaphragm are largely ineffective, and the breathing is therefore almost completely thoracic, so that no bulging of the abdomen occurs with inspiration (Fig. 29.15*A*, B). The thrust of the diaphragm, which often may be felt just under the costal margin on the normal side, is absent on the affected side. Dullness to percussion and diminished breath sounds are found over the affected side. In a severe injury, tachypnea, weak cry, and apneic spells may occur.

Radiographic Manifestations

Radiographs taken during the first few days may show only slight elevation of the affected diaphragm, occasionally so

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• **Fig. 29.15 A,** Nine-hour-old, 3190-g female infant born after difficult total breech extraction; during delivery, cervix clamped down on head, necessitating extensive tugging and pulling on both arms. Note markedly hyperexpanded chest and classic appearance of both upper extremities in Erb palsy positions. **B,** Lateral view of same infant, demonstrating increased anteroposterior diameter of chest and close-up view of left upper extremity adducted at shoulder, extended at elbow, and pronated and flexed at wrist. **C,** Significant elevation of right hemidiaphragm to level of fifth thoracic vertebra in same infant, compatible with paralysis of right hemidiaphragm. Note significant shifting of heart and mediastinum to the left.

subtle that it may be considered normal. Additional radiographs show the more apparent elevation of the diaphragm, with displacement of the heart and mediastinum to the opposite side (see Fig. 29.15*C*). Frequently, areas of atelectasis appear bilaterally. Early diagnosis can be confirmed by real-time ultrasonographic examination of the diaphragm, which reveals abnormal motion of the affected hemidiaphragm. This procedure provides the added advantage of availability at the bedside. Fluoroscopy should be reserved for equivocal cases. In still questionable cases, diagnosis can be further enhanced by transvenous electrical stimulation of the phrenic nerve.

Differential Diagnosis

Careful physical examination should allow differentiation among CNS, cardiac, and pulmonary causes of neonatal respiratory distress. The diagnosis can be confirmed by fluoroscopy and electrical stimulation of the phrenic nerve.

Treatment

Most infants require only nonspecific medical treatment. The infant should be positioned on the involved side, and oxygen should be administered for cyanosis or hypoxemia. Intravenous fluids may be necessary for the first few days. If the infant begins to show improvement, progressive oral or gavage feedings may be started. Antibiotics are indicated if pneumonia occurs.

Infants with more severe respiratory distress, particularly those with bilateral phrenic nerve palsy, may require assisted ventilation shortly after delivery. de Vries Reilingh and associates have reviewed their experience with 23 infants who incurred phrenic nerve injury as neonates.[18] Infants who had not recovered diaphragmatic function after 30 days of conservative treatment did not demonstrate spontaneous recovery thereafter. Accordingly, these investigators recommend limiting conservative treatment to 1 month, assuming the infant is adequately oxygenated with conventional techniques. The absence of definite improvement after 1 month is considered evidence of disruption of the phrenic nerve, thereby minimizing chances of complete spontaneous recovery. Infants in this category may be considered candidates for plication of the diaphragm or diaphragmatic pacing.

Prognosis

Many infants recover spontaneously. If avulsion of the cervical nerves has occurred, spontaneous recovery is not possible, and in the absence of surgery, the infant is susceptible to pneumonia in the atelectatic lung. Infants treated surgically do well, with no recurrence of pneumonia and no late pulmonary or chest wall complications.

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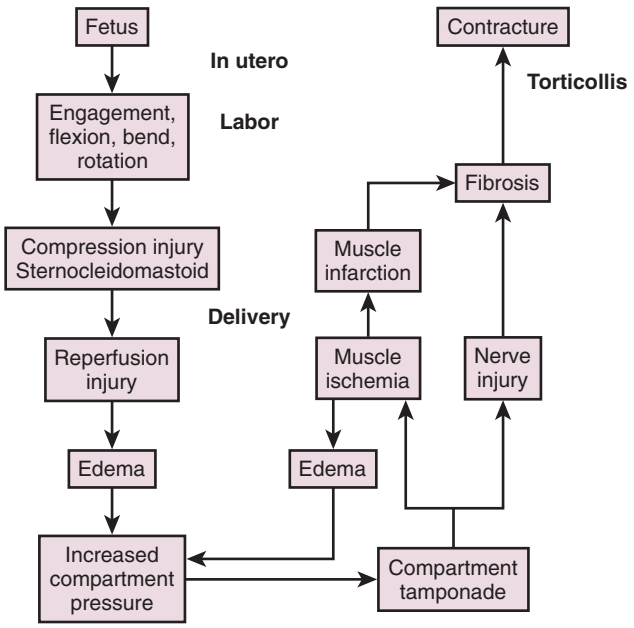
Injury to the Sternocleidomastoid Muscle

Injury to the sternocleidomastoid muscle is designated muscular torticollis, congenital torticollis, or sternocleidomastoid fibroma. Its cause and pathologic features have been controversial.

Etiology

The birth trauma theory suggests that the muscle or fascial sheath is ruptured during a breech or difficult delivery involving hyperextension of the muscle. A hematoma develops and is subsequently invaded by fibrin and fibroblasts with progressive formation of scar tissue and shortening of the muscle. The intrauterine theory postulates abnormal pressure, position, or trauma to the muscle during intrauterine life. Another theory suggests a hereditary defect in the development of the muscle. Others have noted pathologic findings resembling infectious myositis, suggesting an infection in utero or a muscle injured at delivery. Davids and coworkers, based on use of MRI to visualize live infants and cadaver dissections and injection studies, suggest that congenital muscular torticollis results from intrauterine or perinatal compartment syndrome.[16]

In utero or intrapartum positioning of the head and neck in forward flexion, lateral bending, and rotation can result in the ipsilateral sternocleidomastoid muscle kinking on itself. If the kinking continues for a prolonged period in utero, an ischemic injury at the site could develop, followed by subsequent edema and development of a compartment syndrome. Therefore, the mechanism of injury is localized kinking or crush, in contrast to the previously suspected mechanism of stretching or tearing (Fig. 29.16).



• **Fig. 29.16** Algorithm illustrating the Davids study,[16] suggesting that congenital muscular torticollis results from intrauterine or perinatal compartment syndrome.

Clinical Manifestations

A mass in the midportion of the sternocleidomastoid muscle may be evident at birth, although usually it is first noted 10-14 days after birth. It is 1-2 cm in diameter, hard, immobile, fusiform, and well circumscribed; there is no inflammation or overlying discoloration. The mass enlarges during the following 2-4 weeks and then gradually regresses and disappears by age 5-8 months.

A transient torticollis produced by contracture of the involved muscle appears soon after birth. The head tilts toward the involved side, and the chin is somewhat elevated and rotated toward the opposite shoulder. The head cannot be moved passively into normal position. If the deformity persists beyond 3 or 4 years, the skull becomes foreshortened. Flattening of the frontal bone and bulging of the occipital bone occur on the involved side, whereas the contralateral frontal bone bulges and the occiput is flattened. The ipsilateral eyebrow is slanted; the clavicle and shoulder become elevated compared with the opposite normal side, and the ipsilateral mastoid process becomes more prominent. If treatment is not instituted, a lower cervical, upper thoracic scoliosis subsequently develops. Rarely, calcification develops in the affected muscles.

Differential Diagnosis

Careful radiographic examination should be made of the cervical spine and shoulders to rule out Sprengel deformity or Klippel-Feil syndrome, cervical myelodysplasia, and occipitalization of the atlas. In clinically equivocal cases, CT scans may differentiate classic muscular torticollis from other cervical soft tissue lesions that may cause torticollis (e.g., hemangioma, lymphangioma, and teratoma).

Treatment

Treatment should be instituted as early as possible. The involved muscle should be stretched to an overcorrected position by gentle, even, and persistent motion with the infant supine. The head is flexed forward and away from the affected side, and the chin is rotated toward the affected side. The mother can be instructed to repeat this maneuver several times a day. The infant also should be stimulated to turn the head spontaneously toward the affected side; the crib may be positioned so that the infant must turn to the desired position of overcorrection in looking for window light or at a mobile or favorite rattle. During sleep, the infant should be placed on the side of the torticollis; in this position, sandbags should be placed on each side of the infant's body for fixation. An alternative approach involves a helmet that is custom-made for the infant. Rubber straps made of surgical drain tubing attached to the helmet are in turn fixed to the side rails of the crib at night, with appropriate adjustments made to force the infant to sleep on the prominent side of the head. This results in stretching of the shortened sternocleidomastoid muscle.

Ultrasonography may be useful in defining the quantity of normal muscle remnant surrounding the lesion, thereby

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helping to determine whether the infant requires no treatment at all, conservative stretching, or surgery.[14] Conservative therapy may be continued for 6 months. If the deformity has not been fully corrected, surgery may be considered to prevent permanent skull and cervical spine deformities.

Procedures that have been used include distal tenotomy, muscle lengthening, and excision of the affected muscle. All are followed by some problems. After tenotomy, contractures may recur. Lengthening is difficult because of imprecision in estimating how much elongation will be adequate for subsequent growth. Complete excision deforms the outline of the neck. Akazawa and associates reported favorable results after partial resection between 1 and 5 years of age.[2] This was followed postoperatively with massive cotton bandaging of the neck in the neutral position for 3 weeks. Plaster casts, a brace, and physical therapy were not used.

Prognosis

Most infants treated conservatively show complete recovery within 2-3 months. If surgery is necessary and is performed early, the facial asymmetry will disappear almost entirely. Infants treated before their first birthday have a better outcome than those treated later, regardless of the type of treatment. Nonsurgical treatment after 1 year is rarely successful.

Injuries to the Spine and Spinal Cord

Birth injuries to the vertebral spine and spinal cord are rarely diagnosed. The incidence of spinal cord injury in the neonatal period is 0.14 per 1000 live births. It is not certain whether the low incidence is real, reflecting improved obstetric techniques, or represents a tendency for postmortem examination to overlook spine and spinal cord lesions.

Etiology

Spinal cord injury has been usually reported as a result of excessive traction or torsion placed on the spine during traumatic or instrumented delivery or in association with underlying abnormalities of the cord or surrounding tissues. Ligamental laxity, weak muscles, and incomplete mineralization predispose these infants to these types of injury. Other predisposing factors include malpresentations, dystocia (especially shoulder), prematurity, primiparity, and assisted and precipitous delivery. Few cases of spinal cord injury after atraumatic vaginal delivery are also reported in the literature.[26] The injuries are usually caused by stretching of the cord. However, Hankins reported an infant with lower thoracic spinal cord injury after application of maternal fundal pressure to relieve shoulder dystocia.[31] Magnetic resonance imaging revealed focal spinal cord swelling involving T9 through T12, thought to represent ischemia or infarction caused by a compressive injury. The most common mechanism is forceful longitudinal traction on the trunk while the head is still firmly engaged in the pelvis. When combined with flexion and torsion of the vertebral axis, this becomes a more significant problem. Occasionally, a snap is felt by the obstetrician while traction is exerted. Although cesarean delivery has been recommended as optimal for infants in breech presentation with a hyperextended head, Maekawa and colleagues documented spinal cord injury after cesarean section.[47] In fact, the mother had reported weak fetal movements during the third trimester, which suggests that injury occurred before delivery. Difficulty in delivery of the shoulders in cephalic presentations may result in a similar mechanism of injury. The spinal cord is very delicate and inelastic. Its attachments are the cauda equina below and the roots of the brachial plexus and medulla above. Because the ligaments are elastic and the muscles delicate, the infant's vertebral column may be stretched easily. In addition, the dura is more elastic in the infant than in the adult. Consequently, strong longitudinal traction may be expected to cause elongation of the spinal column and to stretch the spinal cord and its membranes. The possible result is vertebral fracture or dislocation, or both, and cord transection. Most often, hemorrhage and edema produce a physiologic transection. The lower cervical and upper thoracic regions are most often involved, but occasionally the entire length of the spinal canal contains a heavy accumulation of blood.

Clinical Manifestations

Affected infants may follow one of four clinical patterns. Those in the first group often manifest a catastrophic presentation and are either stillborn or in poor condition from birth, with respiratory depression, decreased or absent movement, loss of reflexes, lack of response to painful stimulation, shock, and hypothermia. They deteriorate rapidly; death occurs within several hours, often before neurologic signs are obvious. These infants usually have a high cervical or brainstem lesion.

The second group consists of infants who at birth may appear normal or show signs similar to those of the first group; these infants die after several days. Cardiac function is usually relatively strong. Within hours or days, the central type of respiratory depression that is initially present may be complicated by respiratory distress of pulmonary origin, usually pneumonia. The spinal lesion, usually in the upper or midcervical region, frequently is not recognized for several days, when flaccidity and immobility of the legs are noted. Occasionally, urinary retention may be the first symptom. Paralysis of the abdominal wall is manifested by a relaxation of the abdominal wall and bulging at the flanks when the infant is held upright. The intercostal muscles may be affected if the lesion is high enough. Deep tendon reflexes and spontaneous reflex movements are absent. The infant is constipated. The brachial plexus is involved in about 20% of all cases. The spinal column is usually clinically and radiographically normal.

The third group, with lesions at the seventh cervical to first thoracic vertebra or lower, comprises infants who survive for long periods, some for years. Paraplegia noted at

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birth may be transient. The lesion in the cord may be mild and reversible, or it may result in permanent neurologic sequelae with no return of function in the lower cord segments. The skin over the involved part of the body is dry and scaly, predisposing the infant to decubitus ulcers. Muscle atrophy, severe contractures, and bony deformities follow. Bladder distention and constant dribbling persist, and recurring urinary tract infections and pneumonia are common. Within several weeks or months, this clinical picture is replaced by a stage of reflex activity, or paraplegia-in-flexion. This is characterized by return of tone and rigid flexion of the involved extremities, improvement in skin condition with healing of decubitus ulcers, and periodic mass reflex responses consisting of tonic spasms of the extremities, spontaneous micturition, and profuse sweating over the involved part of the body.

Infants in the fourth group have subtle neurologic signs of spasticity thought to represent cerebral palsy. These patients have experienced partial spinal cord injuries and occasional cerebrovascular accidents.

Differential Diagnosis

Differential diagnosis of spinal cord injury in the neonate presenting with flaccid paralysis includes brachial plexopathy, intracranial injury, neuromuscular disease, and a tumor or underlying anomalies of the spinal cord. During the first few weeks of life injuries to the spinal cord may be confused with amyotonia congenita or myelodysplasia associated with spina bifida occulta. The former may be differentiated by the generalized distribution of the weakness and hypotonia and by the presence of normal sensation and sphincter control. The latter is usually associated with some cutaneous lesions over the sacral region such as dimples, angiomas, or abnormal tufts of hair; it is always associated with defects in the spinal lamina. Other conditions less often considered include transverse myelitis and spinal cord tumors, particularly in infants who demonstrate paralysis after an apparently normal labor and delivery. Cerebral hypotonia should be considered in infants who also demonstrate cranial nerve abnormalities, persistent primitive reflexes, and a dull facial appearance, contrasting to the bright, alert facies of the infant with spinal cord trauma. However, the concomitant occurrence of cerebral damage in an infant with spinal cord injury may confound the diagnosis. A final consideration is the infant with bilateral brachial plexus palsy with associated motor and sensory loss, or Horner syndrome; the demonstration of normal lower extremity function should rule out spinal cord injury.

Although somatosensory-evoked potential recording has been used in establishing a diagnosis of spinal cord injury, cervical responses are usually small and can be difficult to detect even in clinically normal infants; in addition, scalp potentials overlying the somatosensory cortex may be absent in normal term neonates. Ultrasonography has been used to evaluate severe spinal cord injury in neonates.[6] The procedure is easily performed at the bedside with no disturbance to the patient. Initial cord edema, hematomyelia, and hemorrhage outside the cord can be assessed. Magnetic resonance imaging provides a direct image of the spinal cord and is the most reliable modality available to evaluate presumptive cervical spinal cord injury in the infant.[52]

Treatment

Treatment is supportive and usually unsatisfactory. The infant affected at birth requires basic resuscitative and supportive measures. Infants who survive present a therapeutic challenge that can be met only by the combined and interested efforts of the pediatrician, neurologist, neurosurgeon, urologist, psychiatrist, orthopedist, nurse, physical therapist, and occupational therapist.

While the infant is reasonably stable, cervical and thoracic spine radiographs should be obtained. In the rare occurrence of vertebral fracture or dislocation or both, immediate neurosurgical consultation is necessary for reduction of the deformity and relief of cord compression, followed by appropriate immobilization. Lumbar puncture in the acute period is of little practical value and may aggravate existing cord damage if the infant is excessively manipulated during the procedure. After several days, however, a persistent spinal fluid block may be demonstrated and may be an indication for exploratory laminectomy at the site of trauma. This possibility should be suspected in an infant with partial paraplegia and negative radiographs.

Prompt and meticulous attention must be given to skin, bladder, and bowel care. The position of paralyzed parts should be changed every 2 hours. Areas of anesthetic skin should be washed, dried, and gently massaged daily. Lambs' wool covers are helpful in preventing pressure necrosis of skin. Benzoin tincture applications help protect the skin in pressure areas. A decubitus ulcer is treated by scrupulous cleansing and complete freedom from weight bearing and friction. An indwelling urethral catheter should be inserted within several hours after severe cord trauma at any level. Repeated instrumentation should be avoided. Cultures of urine should be obtained weekly and as clinically indicated. Antibiotic therapy should be used only in the presence of infection. After several weeks, the infant reaches the stage of paraplegia-in-flexion, and urinary retention usually is replaced by regular episodes of spontaneous voiding. The indwelling catheter may then be removed, and postvoid bladder residuals should be measured. A renal sonogram and a conventional fluoroscopically guided voiding cystourethrogram should be obtained. If there are large postvoid residuals (>10-15 mL) or if the renal sonogram or cystogram shows abnormality, urodynamic studies may be necessary. A high-pressure neurogenic bladder is treated with an anticholinergic agent such as oxybutynin chloride, concurrently with clean intermittent bladder catheterization every 3-4 hours. Treatment of the low-pressure neurogenic bladder requires only clean intermittent catheterization.

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Fecal retention also is a common problem, especially after total cord transection. Appropriate dietary balance should aid in keeping the stools soft. Early use of glycerin suppositories at regular intervals encourages automatic defecation. Digital manipulation may be necessary to relieve fecal impaction.

Physical rehabilitation should be instituted early in an attempt to minimize deformity. After several years, orthopedic procedures may still be necessary to correct contractures and bony deformities.

Prognosis

The prognosis varies with the severity of the injury. Most severe injuries result in death shortly after birth. Infants with cord compression from vertebral fractures or dislocations or both may recover with reasonable return of function if prompt neurosurgical removal of the compression is performed. Infants with mild injuries or partial transections may recover with minimal sequelae. Magnetic resonance imaging evidence of hemorrhage in the cervical spinal cord portends a poor neurologic outcome.[52] If MRI reveals extensive edema in multiple spinal cord segments without concurrent hemorrhage, complete recovery is possible. Infants who exhibit complete physiologic cord transection shortly after birth without vertebral fracture or dislocation have an extremely poor outlook for recovery of function. Many die in infancy of ascending urinary tract infection and sepsis. Long-term survivors have been reported to live into their third decade. They are extremely rare, and although they may have normal intelligence and learn to walk with special appliances, these children face the late complications of pain; spasms; autonomic dysfunction; bony deformities; and genitourinary, psychiatric, and school problems.

MacKinnon and colleagues have published an algorithm for predicting outcome in infants with upper cervical spinal cord injury; the algorithm is based on age at first breath and rate of recovery of breathing and limb movements in the first few weeks and months of life.[46] For infants with rapid recovery, the prognosis was clarified by age 3 weeks. Infants who demonstrated very slow or no recovery of breathing or extremity movements by 3 months of age universally had a poor outcome. Patients with intermediate rates of recovery were thought to have an uncertain long-term prognosis at 3 months of age.

Injuries to Intra-Abdominal Organs

Although birth trauma involving intra-abdominal organs is uncommon, it frequently must be considered by the physician who cares for neonates, because deterioration can be fulminant in an undetected lesion, and therapy can be very effective when a lesion is diagnosed early. Intra-abdominal trauma should be suspected in any newborn with shock and abdominal distention or pallor, anemia, and irritability without evidence of external blood loss.

Rupture of the Liver

The liver is the most frequently injured abdominal organ during the birth process. The autopsy incidence of liver injury varies from 0.9%-9.6%.[66]

Etiology

Birth trauma is the most significant factor contributing to liver injury. The condition usually occurs in large infants, infants with hepatomegaly (e.g., infants with erythroblastosis fetalis and infants of diabetic mothers), and infants who underwent breech delivery. Manual pressure on the liver during delivery of the head in a breech presentation is probably a typical mechanism of injury. Prematurity and postmaturity also are thought to predispose the infant to this injury. Other contributing factors include asphyxia and coagulation disorders. Trauma to the liver more often results in subcapsular hematoma than actual laceration of the liver.

Clinical Manifestations

The infant usually appears normal the first 1-3 days but rarely for as long as 7 days. Nonspecific signs related to loss of blood into the hematoma may appear early; they include poor feeding, listlessness, pallor, jaundice, tachypnea, and tachycardia. A mass may be palpable in the right upper quadrant of the abdomen. The hematocrit and hemoglobin values may be stable early in the course, but serial determinations suggest blood loss. These manifestations are followed by sudden circulatory collapse, usually coincident with rupture of the hematoma through the capsule and extravasation of blood into the peritoneal cavity. The abdomen then may be distended, rigid, and dull to percussion, occasionally with a bluish discoloration of the overlying skin, which may extend over the scrotum in male infants. Abdominal radiographs may suggest the diagnosis by revealing liver enlargement, an abnormal course of a nasogastric tube or umbilical venous catheter, or uniform opacity of the abdomen, indicating free intraperitoneal fluid. Although paracentesis can confirm whether the latter indicates free blood in the peritoneal cavity, ultrasonography offers a noninvasive method of diagnosis.[66] Fresh intrahepatic hemorrhage appears echogenic, with possible enlargement of the involved lobe; with involution of the hemorrhage, the lesion becomes more echolucent and may disappear. Computed tomography scan of the abdomen also may assist in establishing a diagnosis of subcapsular hemorrhage without rupture.

Differential Diagnosis

This lesion is one of several that can result in hemoperitoneum; others include trauma to the adrenal glands, kidneys, gastrointestinal tract, and spleen. The presence of a right upper quadrant mass suggests trauma to the liver, but absence of a mass does not rule it out. Abdominal radiography, ultrasonography, and intravenous pyelography may assist in pinpointing the site of trauma, but ultimately a definitive diagnosis can be made only by laparotomy.

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Treatment

Immediate management consists of transfusion with packed red blood cells, as well as recognition and correction of any coagulation disorder. The role of surgical intervention is controversial. Hemostasis may be difficult to achieve at surgery. Consequently, blood transfusion and the tamponade of intra-abdominal pressure might be adequate therapy in some infants.

Prognosis

In unrecognized liver trauma with formation of a subcapsular hematoma, shock and death may result if the hematoma ruptures through the capsule, reducing the pressure tamponade and resulting in new bleeding from the liver. Recognition of the possibility of liver rupture in infants with a predisposing birth history, followed by early diagnosis and prompt therapy, should improve the prognosis. Early diagnosis and correction of any existing coagulation disorder also improve the prognosis.

Rupture of the Spleen

Rupture of the spleen in the newborn occurs much less often than rupture of the liver. However, recognition of this condition is equally important because of its similar potential for fulminant shock and death if the diagnosis is delayed.

Etiology

The condition is most common in large infants, infants delivered in breech position, and infants with erythroblastosis fetalis or congenital syphilis in whom the spleen is enlarged and more friable and thereby susceptible to rupture either spontaneously or after minor trauma. An underlying clotting defect also has been implicated. Rupture of the spleen has occurred in normal-sized infants with uneventful deliveries and no underlying disease.[35]

Clinical Manifestations

Clinical signs indicating blood loss and hemoperitoneum are similar to those described for hepatic rupture. The hemoglobin and hematocrit values decrease, and abdominal paracentesis may reveal free blood. Several infants have been described in whom the blood was circumscribed within the leaves of the phrenicosplenic ligament and, therefore, was not clinically detectable. Occasionally, a left upper quadrant mass may be palpable, and radiographs of the abdomen may show medial displacement of the gastric air bubble.

Differential Diagnosis

Rupture of the liver and trauma to the adrenal glands, kidneys, and gastrointestinal tract must be distinguished.

Treatment

Packed red blood cells should be transfused promptly, and any coexisting clotting defect should be corrected. This should be followed by immediate exploratory laparotomy. Every attempt should be made to repair and preserve the spleen to prevent the subsequent increased risk for infection. Packing of the wound surface with Gel Foam® and Surgicel® has been used to stop the oozing of blood.[35] The Gel Foam® and Surgicel® may be removed at a follow-up laparotomy within several days, at which time the spleen may be inspected for rebleeding.

Prognosis

With early recognition and emergency surgery, the survival rate should approach 100%.

Adrenal Hemorrhage

Neonatal adrenal hemorrhage is more common than previously suspected; some autopsy studies have revealed a high incidence of subclinical hemorrhage. Massive hemorrhage is much less common, and the incidence is difficult to determine because the diagnosis is often unsuspected and considered retrospectively only years later, when calcified adrenal glands are unexpectedly found on radiographs or at autopsy.

Etiology

The most likely cause is birth trauma; risk factors include macrosomia, diabetes in the mother, breech presentation, congenital syphilis, and dystocia. Placental hemorrhage, anoxia, hemorrhagic disease of the newborn, prematurity, and, more recently, neuroblastoma have been implicated. Pathologic findings vary from unilateral minute areas of bleeding to massive bilateral hemorrhage. The increased size and vascularity of the adrenal gland at birth may predispose it to hemorrhage.

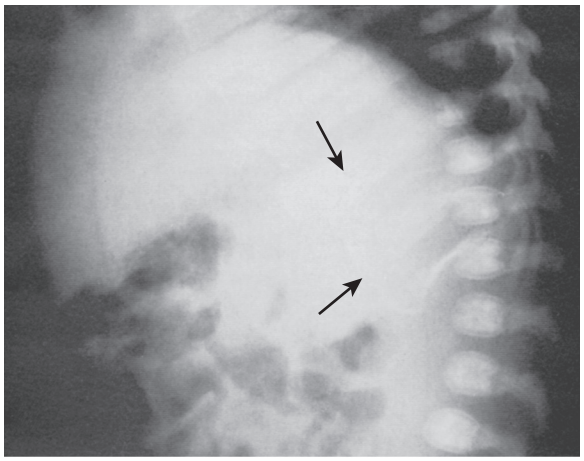
Clinical Manifestations

Signs vary with the degree and extent of hemorrhage. The classic findings are fever, tachypnea out of proportion to the degree of fever, yellowish pallor, cyanosis of the lips and fingertips, a mass in either flank with overlying skin discoloration, and purpura. Findings suggesting adrenal insufficiency include poor feeding, vomiting, diarrhea, obstipation, dehydration, abdominal distention, irritability, hypoglycemia, uremia, rash, listlessness, coma, convulsions, and shock.

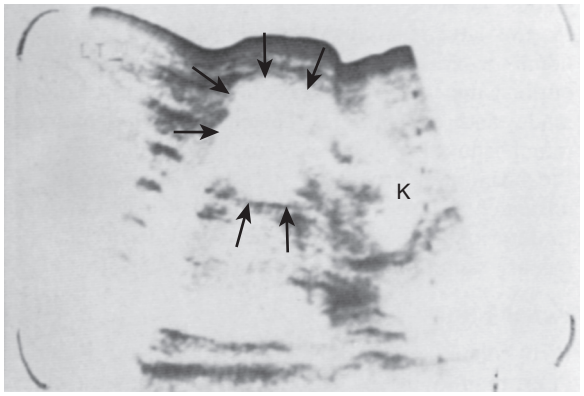
Radiographic Manifestations

Initial radiographic manifestations may be limited to widening of the retroperitoneal space with forward displacement of the stomach and duodenum or downward displacement of the intestines or kidneys. In time, calcification may appear. Typically this is rimlike and has been observed as early as the 12th day of life. After several weeks the calcification becomes denser and retracted and assumes the configuration of the adrenal gland (Fig. 29.17). Ultrasonographic examination of the neonate is an excellent adjunctive method of diagnosis. Abdominal ultrasonography performed during the first several days may reveal a

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• **Fig. 29.17** Lateral abdominal radiographs of a 5312-g male infant delivered vaginally, with difficulty after shoulder dystocia. At 48 hours, fever, icterus, and slow feeding were noted, and a mass was palpable above the left kidney. At 31 days, there was dense, retracted calcification (*arrows*) that assumed the configuration of the adrenal gland.



• **Fig. 29.18** Sagittal gray-scale abdominal ultrasonographic examination of a 4564-g male infant whose mother had gestational diabetes. Problems included fracture of right clavicle, hyperbilirubinemia requiring three exchange transfusions, and abdominal distention with large left flank mass. Ultrasonographic examination at 14 days demonstrated fluid-filled mass (*arrows*) superior to left kidney (*K*), representing adrenal hemorrhage. (Courtesy of Dr. John C. McFadden, Lutheran General Children's Hospital, Park Ridge, IL.)

solid lesion in the location of the adrenal hemorrhage; this is thought to represent either clot fragmentation or diffuse clotted blood throughout the adrenal gland. If adrenal hemorrhage is suspected, ultrasonographic examination should be repeated at 3- to 5-day intervals. If adrenal hemorrhage has occurred, the lesion will change from a solid to a cystic appearance, coincident with liquefaction, degeneration, and lysis of the clot (Fig. 29.18).

Differential Diagnosis

Adrenal hemorrhage must be distinguished from other causes of abdominal hemorrhage. In addition, when a mass is palpable, the differential diagnosis must include the multiple causes of flank masses in the newborn, such as genitourinary anomaly, Wilms tumor, and neuroblastoma. If the infant is large or the delivery is traumatic or breech, an adrenal hemorrhage is most likely. Neuroblastoma may be distinguished by persistent demonstration of a solid lesion on serial ultrasonographic examinations and by increased excretion of vanillylmandelic acid and other urinary catecholamines in 85%-90% of affected infants. Blood pressure measurements and radiographs also may help to evaluate this possibility.

Treatment

Significant blood loss should be replaced with packed red blood cell transfusion. Suspicion of adrenal insufficiency may warrant the use of intravenous fluids and corticosteroids. The decision for surgical intervention is dictated by the location and degree of hemorrhage. If it appears to be retroperitoneal and limited by the perinephric fascia, some recommend blood replacement and careful observation in the hope of spontaneous control by tamponade; often this approach is successful, and surgery is not necessary. If paracentesis reveals blood or if blood loss exceeds replacement, exploratory laparotomy is indicated. Surgery may involve evacuation of hematoma, vessel ligation, and adrenalectomy with or without nephrectomy. When the hemorrhagic process extends to the peritoneal cavity, peritoneal exploration and evacuation of clots are indicated.

Prognosis

Small hemorrhages are probably often asymptomatic and have no associated significant morbidity, judging from the unexpected discovery of calcified adrenal glands on abdominal radiographs taken for other reasons later in infancy and childhood. If hemoperitoneum or adrenal insufficiency or both develop, the outlook depends on the speed with which diagnosis is made and appropriate therapy instituted. Surviving infants should be followed closely after discharge from the hospital. Adrenal function should be tested with adrenocorticotropic hormone stimulation at a later date to determine whether a normal response occurs in the urinary excretion of 17-hydroxycorticosterone.

Renal Injury

Birth-related injury to the kidneys occurs rarely and less often than injury involving the liver, spleen, or adrenal gland.

Etiology

Factors that predispose an infant to any form of intra-abdominal injury also may affect the kidneys. They include macrosomia, malpresentation (especially breech), and precipitous labor or delivery or both. The potential for renal injury is enhanced by a pre-existing anomaly (e.g., hydronephrosis).

Clinical Manifestations

The infant may demonstrate the same signs of blood loss and hemoperitoneum noted in the other intra-abdominal

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lesions. More specific signs include ascites, flank mass, and gross hematuria. Radiographs may confirm the presence of ascites and flank mass. Ultrasonographic examination may further define the mass (e.g., presence of cysts) and reveal ascites and retroperitoneal hematoma. Application of a Doppler probe to the renal hilus and the region of the vessels can assist in assessing renal arterial and venous flow. In ambiguous cases, CT scanning may help to clarify ultrasonographic findings.

Differential Diagnosis

Other lesions that cause hematuria must be considered. They include renal tumor with hemorrhage and renal vein thrombosis with infarction.

Treatment

After providing supportive measures similar to those used in other intra-abdominal injuries, the clinician should consider laparotomy. Possible findings at surgery include kidney rupture or transection, renal pedicle avulsion, and kidney necrosis. Use of an intraoperative Doppler probe can determine the status of renal blood flow. If there is no flow, nephrectomy is indicated.

Prognosis

Early recognition of possible renal vascular injury may lead to earlier intervention, with the potential for kidney salvage.

Injuries to the Extremities

Fracture of the Humerus

After the clavicle, the humerus is the bone most often fractured during the birth process.

Etiology

The most common mechanisms responsible are difficult delivery of extended arms in breech presentations and of the shoulders in vertex presentations. Besides traction with simultaneous rotation of the arm, direct pressure on the humerus also is a factor. This may account for the occurrence of fracture of the humerus in spontaneous vertex deliveries. The fractures are usually in the diaphysis. They are often greenstick fractures, although complete fracture with overriding of the fragments occasionally occurs.

Clinical Manifestations

A greenstick fracture may be overlooked until a callus is noted. A complete fracture with marked displacement of fragments presents an obvious deformity that calls attention to the injury. Often the initial manifestation of the fracture is immobility of the affected arm. Palpation reveals tenderness, crepitation, and hypermobility of the fragments. The ipsilateral Moro response is absent. Radiographs confirm the diagnosis.

Differential Diagnosis

The differential diagnosis includes all the previously noted lesions that cause immobility of the arm. An associated brachial plexus injury occasionally occurs.

Treatment

The affected arm should be immobilized in adduction for 2-4 weeks. This may be accomplished by maintaining the arm in a hand-on-hip position with a triangular splint and a Velpeau bandage, strapping the arm to the chest, or application of a cast.

Prognosis

The prognosis is excellent. Healing is associated with marked formation of callus. Moderate overriding and angulation disappear with time because of the excellent remodeling power of infants. Complete union of the fracture fragments usually occurs by 3 weeks. Fair alignment and shortening of less than 1 inch indicate satisfactory closed reduction. Fractures of the long bones in infants always result in epiphyseal stimulation; the closer the fracture to the epiphyseal cartilage, the greater the degree of subsequent overgrowth.

Fracture of the Radius

Fracture of radius is an extremely rare occurrence, reported in a macrosomic infant born after a shoulder dystocia.[70] There was a concurrent midhumeral shaft fracture of the other arm, with lateral displacement of the distal fragment.

Etiology

This injury, because it was a spiral fracture, was thought to have resulted from rotational maneuvers attempted to alleviate the shoulder dystocia. An alternative explanation is compressive forces related to the shoulder dystocia itself; that is, the affected arm could have incurred an extreme degree of direct compression by the overlying symphysis pubis.

Clinical Manifestations

Physical findings were limited to bruising of the affected forearm. However, as in any long bone fracture, if complete with displacement of fragments, additional findings may include swelling, deformity, tenderness, and crepitation.

Treatment

In the presence of bilateral fractures, casts may need to be placed on both arms. If it occurs as an isolated injury, without displacement, a radial fracture can be treated with simple immobilization.

Prognosis

Radiographs at 2 weeks of age revealed a healed radial fracture and marked callus formation around the humeral fracture.

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Fracture of the Femur

Although a relatively infrequent injury, fracture of the femur is by far the most common fracture of the lower extremity in the newborn.

Etiology

Fracture of the femur usually follows a breech delivery when the leg is pulled down after the breech is already partially fixed in the pelvic inlet or when the infant is improperly held by one thigh during delivery of the shoulders and arms. Femoral fracture even may occur during cesarean delivery.[3] Infants with congenital hypotonia may be more prone to this injury if their underlying disorder (e.g., severe Werdnig-Hoffmann disease) is associated with decreased muscle bulk at birth. Senanayake and associates reported on an infant who sustained a midtrimester fracture of the femur.[65] No apparent maternal trauma was identified during the pregnancy. The infant was otherwise normal, with no other fractures and no evidence of skeletal dysplasia. Follow-up through age 6 years revealed normal growth, with no additional fractures. The authors were unable to identify an etiology, other than possible "unnoticed maternal trauma." It is critical to document such an occurrence to preclude inappropriate focus on the delivery process as a cause of the fracture. In addition, failure to identify and document the timing of the fracture may lead to subsequent suspicion of child abuse.

Clinical Manifestations

Usually an obvious deformity of the thigh is seen (Fig. 29.19); as a rule, the bone breaks transversely in the upper half or third, where it is relatively thin. Less often, the injury may not be appreciated until several days after delivery when swelling of the thigh is noted; this swelling may be caused by hemorrhage into adjacent muscle. The infant refuses to move the affected leg or cries in pain during passive movement or with palpation over the fracture site.



• **Fig. 29.19** Fullness and obvious deformity of left thigh in 4020-g male infant with Werdnig-Hoffmann disease. Muscle wasting of both lower extremities also is apparent. Radiograph confirmed fracture of proximal third of left femur.

Radiographs almost always show overriding of the fracture fragments.

Treatment

Optimal treatment is traction-suspension of both lower extremities, even if the fracture is unilateral. The legs are immobilized in a spica cast; with Bryant traction, the infant is suspended by the legs from an overhead frame, with the buttocks and lower back just raised off the mattress. The legs are extended and the thighs flexed on the abdomen. The weight of the infant's body is enough to overcome the pull of the thigh muscles and thereby reduce the deformity. The infant is maintained in this position for 3-4 weeks until adequate callus has formed and new bone growth has started. During the treatment period, special attention should be given to careful feeding of the infant and to protection of bandages and casts from soiling with urine and feces.

Prognosis

The prognosis is excellent; complete union and restoration without shortening are expected. Extensive calcification may develop in the areas of surrounding hemorrhage but is resorbed subsequently.

Dislocations

Dislocations caused by birth trauma are rare. Often an apparent dislocation is actually a fracture displaced through an epiphyseal plate. Because the epiphyseal plate is radiolucent, a fracture occurring adjacent to an unmineralized epiphysis gives a radiographic picture simulating a dislocation of the neighboring joint. This type of injury has been termed *pseudodislocation*. Because the humeral and proximal femoral epiphyses are usually not visible on radiographs at birth, a pseudodislocation can occur at the shoulder, elbow, or hip.

Of the true dislocations, those involving the hip and knee are probably not caused by the trauma of the birth process. Most likely, they are either intrauterine positional deformities or true congenital malformations. A true dislocation resulting from birth trauma is that involving the radial head. This has been associated with traumatic breech delivery. Recently, radial head dislocation was reported as a late complication years after brachial plexus palsy.[37] Examination reveals adduction and internal rotation of the affected arm, with pronation of the forearm; Moro response is poor, and palpation reveals lateral and posterior displacement of the radial head. This is confirmed by radiographs. With supination and extension, the radial head can be reduced readily. This should be done promptly, followed by immobilization of the arm in this position in a circular cast for 2-3 weeks. Early recognition and treatment should result in normal growth and function of the elbow.

Bayne and associates illustrated the importance of establishing an early diagnosis when they described a term infant with a swollen, tender elbow after breech delivery.[7]

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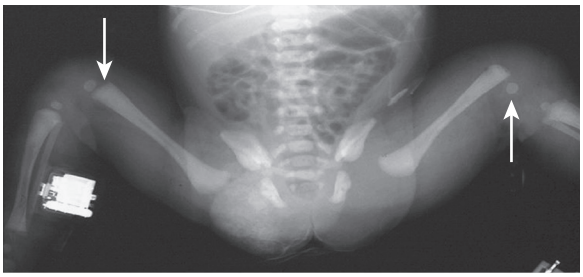
Movement produced obvious pain. Radiographs at that time and again at 8 months of age were misinterpreted as normal. At 1 year, an orthopedist diagnosed anteromedial dislocation. Because of several unsuccessful attempts at closed reduction, future osteotomy was required to treat this now permanent deformity.

Epiphyseal Separations

As with dislocations, epiphyseal separations are rare. They occur mostly in primiparity, dystocic deliveries, and breech presentations, especially those requiring manual extraction or version and extraction. Any delivery associated with vigorous pulling may predispose the infant to this injury. The upper femoral and humeral epiphyses are most often involved. Usually on the second day, the soft tissue over the affected epiphysis develops a firm swelling with reddening, crepitus, and tenderness. Active motion is limited, and passive motion is painful. If the injury is in the upper femoral epiphysis, the infant assumes the frog-leg position with external rotation of the leg.

Early radiographs show only soft tissue swelling, with occasional superolateral displacement of the proximal femoral metaphysis. Because the neonatal femoral capital epiphysis is not ossified, this can be mistakenly interpreted as congenital hip dislocation. However, the presence of pain and tenderness would make dislocation unlikely. Besides plain radiographs of the hips, an infant with a history and physical examination compatible with traumatic epiphysiolysis should also undergo ultrasonography before manipulation is attempted. Magnetic resonance imaging may be a better tool for earlier detection. This examination would demonstrate a normal femoroacetabular relationship, in contrast with the abnormal findings in an infant with septic arthritis and congenital hip dislocation. In addition, in the presence of traumatic epiphysiolysis the femoral head and neck would not be continuous, in contrast with the findings of septic arthritis and congenital hip dislocation. Further differentiation between traumatic epiphysiolysis and septic arthritis can be provided by arthrocentesis; in epiphysiolysis, the joint does not contain excess fluid, and what is obtained may be serosanguineous, whereas in septic arthritis, purulent fluid is obtained. After 1-2 weeks, extensive callus appears, confirming the nature of the injury; during the third week, subperiosteal calcification appears.

If possible, treatment should be conservative. Closed reduction and immobilization are indicated within the first few days before rapidly forming fibrous callus prevents mobilization of the epiphysis. The hip is immobilized in the frog-leg position, as in congenital dislocation. Poorly immobilized fragments of the proximal or distal femur (Fig. 29.20) may require temporary fixation with a Kirschner wire (Fig. 29.21).[49] Union usually occurs within 10-15 days. Untreated or poorly treated epiphyseal injuries may result in subsequent growth distortion and permanent deformities such as coxa vara. Mild injuries carry a good prognosis.



• **Fig. 29.20** Radiograph of lower extremities of a 4205-g male delivered precipitously after complete breech presentation. Radiograph demonstrates displaced distal femoral physeal fracture on left (*arrow*) and nondisplaced distal femoral physeal fracture on right (*arrow*). (From Mangurten HH, et al. Neonatal distal femoral physeal fracture requiring closed reduction and pinning. *J Perinatol.* 2005;25:216.)

Deep Tendon Injuries

Accidental fetal injury is a serious but underreported complication of emergency cesarean deliveries. Although the most commonly documented injury is superficial skin laceration, deeper and more serious injuries have been described, including amputation of the distal digits and tendon injuries requiring surgical intervention.[1] A prospective study at 13 university centers in the United States revealed an incidence of fetal injury of 1.1% during emergency cesarean section, with skin lacerations accounting for 64% of injuries overall.[4] Neonatal tendon injuries during cesarean section have rarely been reported in the literature.[23] Prazad and associates reported a case of severe multiple extensor tendon lacerations with open metacarpophalangeal joints (Fig. 29.22) sustained at the time of an emergency cesarean delivery.[59]

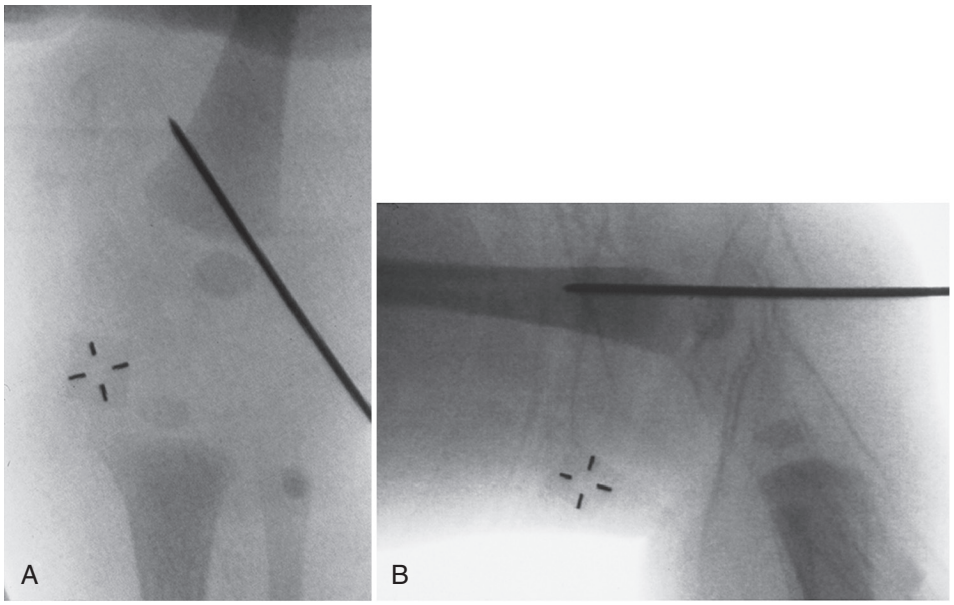
Risk Factors Associated With Deep Tendon Injury

Several factors associated with increased risk for fetal laceration and fetal injury are emergency cesarean delivery, shortened duration between abdominal skin incision and delivery of infant, type of uterine incision, premature rupture of membranes, abnormal fetal presentation, and active labor.[29]

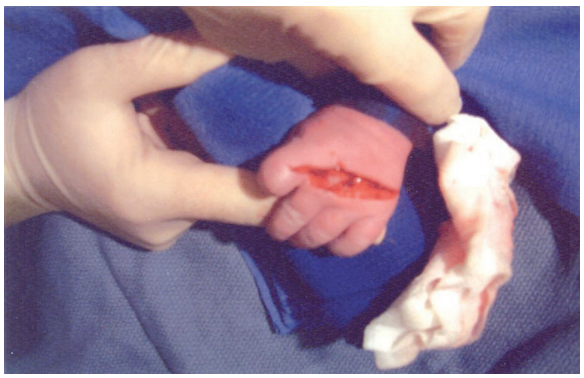
Management

Even though multiple surgical techniques have been described for adults with the same kind of injury, there is no information available regarding a favorable surgical approach in neonates. Fuller and colleagues described two different methods of extensor tendon repair.[23] Laceration in one finger was closed in a single layer using a full-thickness stitch through the skin and extensor mechanism, and laceration in the second finger was repaired in two layers. Excellent clinical outcome of both fingers was noted after surgery. Kavouksorian and coworkers reported a flexor tendon laceration of the hand that occurred during emergency cesarean delivery with excellent functional results despite delayed primary closure.[40] Prazad and colleagues used immediate (within 3 hours of birth) microsurgical repair at the bedside under local field block anesthesia to achieve an excellent functional outcome at 18 months of age.[59]

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• **Fig. 29.21** Because of unsuccessful attempts at closed reduction of left-sided fracture, a Kirschner wire was inserted to provide secure fixation of fracture fragments. Anteroposterior view, **A**, and lateral view, **B**. (From Mangurten HH, et al. Neonatal distal femoral physeal fracture requiring closed reduction and pinning. *J Perinatol.* 2005;25:216.)



• **Fig. 29.22** Laceration extending from index finger to baby finger, with open metacarpophalangeal joints. There were complete extensor tendon lacerations of middle, ring, and baby fingers, with partial laceration of index finger. (From Prazad P, et al. Complication of emergency cesarean section: open metacarpophalangeal disarticulation and complete extensor tendon lacerations of the hand in a neonate. *J Neonat Perinat Med.* 2009;2:131-133.)

Other Peripheral Nerve Injuries

In contrast to the brachial plexus and phrenic and facial nerves, other peripheral nerves are injured less often at birth and usually in association with trauma to the extremity. Radial palsy has occurred after difficult forceps extractions, both from pressure of incorrectly applied forceps and in association with fracture of the arm. Occasionally the palsy occurs later, when the radial nerve is enmeshed within the callus of the healing fracture. Frequently associated subcutaneous fat necrosis overlies the course of the radial nerve along the lateral aspects of the upper arm. The presence of isolated wristdrop with weakness of the wrist, finger, and thumb extensors; skin changes overlying the course of the nerve; and absence of weakness above the elbow distinguish this condition from brachial plexus injury. Palsies of the femoral and sciatic nerves have occurred after breech extractions; sciatic palsy has followed extraction by the foot. Passive range-of-motion exercises are usually the only therapy required. Complete recovery usually occurs within several weeks or months.

Trauma to the Genitalia

Soft tissue injuries involving the external genitalia sometimes occur, especially after breech deliveries and in large infants.

Scrotum and Labia Majora

Edema, ecchymoses, and hematomas can occur in the scrotum and labia majora, especially when they are the presenting parts in a breech presentation. Because the male newborn has a pendulous urethra that is vulnerable to compression or injury, it is possible for significant trauma to occur after a protracted labor in the breech position; the mechanism is believed to be compression of the urethra against a firm structure in the maternal bony pelvis. Rarely, this may cause marked temporary hydronephrosis after delivery. The hydronephrosis usually resolves within 3 days. Because of laxity of the tissues, the degree of swelling and of discoloration occasionally is extreme enough (Fig. 29.23) to evoke considerable concern among the medical and nursing staff, especially regarding deeper involvement (e.g., periurethral hemorrhage and edema), which might hinder

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• **Fig. 29.23** Hematoma of scrotum and penis in a 3895-g male infant delivered vaginally after frank breech presentation. Infant voided at 22 hours and regularly thereafter. Swelling diminished appreciably within 5 hours and was gone by third day. Discoloration was greatly diminished by second day.

normal micturition. However, this has not generally been a problem, and frequently these infants void shortly after arriving in the nursery. Spontaneous resolution of edema occurs within 24-48 hours, and resolution of discoloration occurs within 4-5 days. Treatment is not necessary. Secondary ulceration, necrosis, or eschar formation is rare unless an associated underlying condition such as herpes simplex virus infection is present.

Marked scrotal hematoma may simulate testicular torsion, particularly when accompanied by a solid scrotal mass.[19] Because untreated torsion may result in loss of the testis, it is critical to distinguish the two lesions. This may be done by Doppler ultrasonography. If blood flow to the testes is clearly demonstrated, and if the testes appear symmetric in size and echotexture, torsion may essentially be ruled out.

Deeper Structures

Much less often birth trauma may involve the deeper structures of the genitalia. If the tunica vaginalis testis is injured and blood fills its cavity, a hematocele is formed. Absence of transillumination distinguishes this from a hydrocele. If it appears that the infant is in pain, the scrotum may be elevated and cold packs applied. Spontaneous resolution is the usual course.

The testes may be injured, often in association with injury to the epididymis. Usually the involvement is bilateral. The testes may be enlarged, smoothly rounded, and insensitive. The infant may be irritable, with vomiting and poor feeding. Urologic consultation is indicated; occasionally exploration and evacuation of blood are necessary, especially with increasing size of the testes. Severe trauma may result in atrophy or failure of the testes to grow. The occasional finding in older children of a circumscribed fibrous area within the testicular tissue is thought to represent past birth trauma to the gland.

Injuries Related to Intrapartum Fetal Monitoring

Continuous monitoring of the fetal heart rate and the intermittent sampling of fetal scalp blood for determination of acid-base status often are used to monitor the fetus during labor. Thousands of patients have been monitored by these methods (see Chapter 12). The relative infrequency of complications indicates that in experienced hands, these procedures are generally safe. However, certain specific complications have occurred.

Injuries Related to Direct Fetal Heart Rate Monitoring

Direct monitoring of the fetal heart rate during labor depends on application of an electrode to the fetal scalp or other presenting part. Superficial abrasions, lacerations, and hematomas can occur rarely at the site of application of the electrode. These complications require no specific therapy beyond local treatment.

Rarely, abscesses of the scalp may follow application of scalp electrodes. These abscesses usually have been sterile and have required only local treatment. Systemic signs or symptoms require evaluation for possible septicemia.

Lauer and Rimmer reported a potentially more serious complication related to use of a spiral fetal scalp electrode,[42] as noted earlier in this chapter. At delivery, the electrode was noted to be attached to the infant's eyelid, resulting in a superficial laceration. Marked surrounding edema was considered to have protected the infant from more severe injury.

Injuries Related to Fetal Scalp Blood Sampling

Fetal biochemical monitoring requires puncture of the presenting part, usually the scalp, with a 2-mm blade and the collection of blood under direct visualization in a heparinized tube. Major complications that may occur rarely are excessive bleeding and accidental breakage of the blades. The bleeding can be stopped by pressure, but on occasion this requires sutures. Rarely, blood replacement may be required. It is important to obtain a detailed family history of bleeding disorders before initiation of this procedure.

The second major complication has been breakage of the blade within the fetal scalp. Removal soon after delivery is recommended to prevent secondary infection. This is accomplished by use of a magnet attached to a small forceps that probes the puncture site and elicits a click as the blade is attracted to the magnet. On occasion, radiographic localization followed by a small incision is necessary for withdrawal of the blade.

Injuries Related to Trauma During Pregnancy

Trauma to women during pregnancy continues to be a major cause of maternal, fetal, and neonatal mortality and

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morbidity.[10] The risk of trauma is enhanced by the enlarged size of the gravid uterus, rendering it more exposed to weapons and contact with hard surfaces, putting the developing fetus in close proximity to injury. Trauma unrelated to pregnancy events, which in turn may injure the fetus, may be divided into two major subsets, accidental and intentional. The accidental category most commonly involves automobile accidents in which the woman is the driver, passenger, or pedestrian. In addition, these accidents may result from cycling, falling while horseback riding, or simple falls. The intentional category usually results from criminal intent, resulting in shooting, stabbing, or blunt trauma to the abdomen. Fetal head injuries have been reported after violent insertion of a blunt object through the vagina with an intention to terminate the pregnancy. These may result in skull fractures and intraventricular hemorrhage leading to premature labor and fetal morbidity and mortality. Gunshot wounds, in particular, during pregnancy may result in devastating effects on both mother and fetus throughout gestation. Not only may mother and fetus sustain significant organ damage from gunshot wounds, but also the extent of the physical maternal injury may dictate preterm delivery (Fig. 29.24). Prognosis usually is worse in the fetus than the mother. In a review of 119 cases of gunshot injuries to the uterus, Buchsbaum reported a perinatal mortality rate of 66%.[11] A well-coordinated team of surgeons, obstetricians, and neonatologists providing timely and comprehensive management may improve this outcome.



• **Fig. 29.24** Deep skin wound lateral surface left thigh in 6-hour-old, 845-gm preterm female infant delivered by emergency cesarean birth after mother sustained a gunshot wound to the abdomen.

Key Points

- Birth Injuries may occur despite skilled and competent obstetric care.
- Soft tissue injuries are observed more frequently after instrumental, breech, or precipitous deliveries. Most lesions resolve spontaneously within several days with no specific therapy.
- Subcutaneous fat necrosis is commonly seen in association with perinatal asphyxia and may be associated with hypercalcemia.
- Caput succedaneum may be difficult to distinguish from a cephalhematoma. Careful palpation indicates whether the bleeding is external to the periosteum (caput) or beneath the periosteum (cephalhematoma).
- Subgaleal hemorrhage should be considered in infants who show signs of hypoperfusion and falling hematocrit even in the absence of a detectable fluctuant mass.
- Traumatic facial nerve palsy most often follows compression of the peripheral portion of the nerve by forceps or maternal sacral promontory.
- Fractures of the maxilla, lacrimal bones, and nose may present with respiratory distress and warrant emergent surgical attention.
- It is critical to identify birth-related retinal hemorrhages and to document their presence on the chart to avoid subsequent suspicion of child abuse.
- The clavicle is the most frequently fractured bone during labor and delivery. Greenstick-type clavicular fractures, which occur most frequently, have good outcomes.
- Mechanical trauma to the spinal roots of the fifth cervical through the first thoracic nerves (the brachial plexus) during birth results in brachial palsy. Duchenne-Erb palsy caused by injury of the fifth and sixth cervical roots is by far the most common type.
- Intra-abdominal trauma should be suspected in any newborn with shock and abdominal distention or pallor, anemia, and irritability without evidence of external blood loss.
- Excellent prognosis with complete union and restoration of function is seen after a long bone fracture, which infrequently follows a difficult delivery.

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30
Congenital Anomalies

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Major anomalies are seen in about 2% of newborns, often prompting parental worry and urgent medical intervention soon after birth. In addition, they are a common cause of long-term illness and death. This chapter reviews some of the significant etiologic and epidemiologic aspects of congenital anomalies. It provides an approach to and a framework for the evaluation of the infant with congenital anomalies, with emphasis on conditions that are apparent in the delivery room. More detailed and complete differential diagnoses for each anomaly can be found in other sources.

General Clinical Approach

The neonatologist or perinatologist often is the first person to identify a congenital anomaly and to initiate the necessary medical evaluations. In essence, the clinician observes an abnormal phenotype, which is a term used to describe the identifiable manifestation of a person's genotype, or the genetic constitution of an individual. This observation is followed by the generation of possible causes, which are confirmed or refuted with further testing. Because the underlying defect or genotype is often not known, phenotype in clinical practice refers to a collection of specific traits, physical findings, and the results of medical tests, such as laboratory, pathologic, and radiologic studies.

A congenital anomaly is an internal or external structural defect that is identifiable at birth. Anomalies are deviations from the norm and are classified as major or minor. A major anomaly is a defect that requires significant surgical or cosmetic intervention, such as tetralogy of Fallot or cleft lip and palate, whereas a minor anomaly has no significant surgical or cosmetic importance. The clinician should be aware that minor anomalies often overlap with normal phenotypic variation, so a careful search for specific morphologic patterns is essential. It is important to classify an anomaly as major, minor, or normal because implications differ for both the infant and the family. It is also important to distinguish the concepts of congenital and genetic, terms that are often confused. Congenital merely indicates that the feature is present at birth and can have many genetic and nongenetic causes.

Anomalous external physical features are called dysmorphisms and can be clues to the underlying cause or developmental defect. A useful approach to determining the etiology of a congenital anomaly is to consider whether it represents a malformation, deformation, or disruption of normal development.[65] In a study of 27,145 neonates with congenital anomalies, nearly 98% were caused by an underlying malformation, which is a primary structural defect in tissue formation such as a neural tube defect or a congenital heart defect.[40] A malformation implies an abnormal morphogenesis of the underlying tissue owing to a genetic or teratogenic factor.

In contrast, a deformation results from abnormal mechanical forces acting on otherwise morphologically normal tissues.[1,65] Deformations primarily result from mechanical forces, such as intrauterine constraint, on the growing fetus. A variety of maternal factors can cause fetal constraint, and common examples include breech or other abnormal positioning in utero, oligohydramnios, and uterine anomalies. Clubfoot and altered head shape are frequent anomalies that can result from constraint. Deformations occurring late in gestation often are reversible with changes in position or removal of the force. Observing the position the infant finds most comfortable, along with a careful obstetric history of fetal movement, position, and fluid volume, can be helpful in determining whether an anomaly could have been caused by a deforming force.

A disruption represents the destruction or interruption of intrinsically normal tissue, and it usually affects a body part rather than a specific organ. Vascular occlusion and amniotic bands are common causes of disruptions. Monozygotic twinning and prenatal cocaine exposure are common predisposing factors for disruptions on the basis of vascular interruption.

Malformations may predispose a fetus to additional deformations and multiple anomalies. A neural tube defect, a malformation, causes fetal deformations of hip dislocation and clubfoot, owing to lack of movement below the level of the lesion. If an infant has more than one anomaly, the clinician should then consider whether it is part of a sequence, association, or a known syndrome. Sequence refers to a pattern of multiple anomalies derived from a

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Abstract

Major anomalies are seen in about 2% of newborns, often prompting parental worry and urgent medical intervention soon after birth. In addition, they are a common cause of long-term illness and death. The neonatologist is often involved in the evaluation of newborns with congenital anomalies. This chapter reviews some of the significant etiologic and epidemiologic aspects of congenital anomalies. It provides an approach to and a framework for the evaluation of the infant with congenital anomalies, with emphasis on conditions that are apparent in the delivery room. More detailed and complete differential diagnoses for each anomaly can be found in other sources.

Keywords

birth defects
chromosomal defect
congenital anomalies
dysmorphology
genetic syndrome

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single known or presumed cause. An example is the oligohydramnios sequence, often referred to as Potter syndrome, which consists of limb deformations, pulmonary hypoplasia, and Potter facies of a beaked nose, infraorbital creases, and simple ears. These features are due to a lack of amniotic fluid during gestation, secondary to chronic leakage of amniotic fluid or lack of fetal urine (renal agenesis, a malformation).[35,65] Another constellation of anomalies frequently seen by the neonatologist is the Pierre Robin sequence, consisting of micrognathia, cleft palate, and glossoptosis, in which the disproportionately small, malformed mandible causes the tongue to move backward and upward in the oral cavity during development, resulting in a cleft palate and potential airway obstruction.[19,35] In these instances, the key to understanding the underlying cause of the secondary deformation anomalies lies with the primary malformation.

Multiple congenital anomalies in infants can also be seen as part of an association, which refers to a nonrandom occurrence of multiple malformations for which no specific or common etiology has been identified. An example is the VATER (or VACTERL) association, an acronym for a pattern of anomalies consisting of *v*ertebral abnormalities, *a*nal atresia, *c*ardiac anomalies, *t*racheo*e*sophageal fistula, and *r*enal and *r*adial (*l*imb) dysplasia.[12,61] Although several conditions, such as maternal diabetes, are found in conjunction with VATER, a specific genetic link has not been proved. Over time, the genetic cause for some idiopathic associations has been identified, as in the CHARGE association, now known as CHARGE syndrome. The acronym denotes multiple features of the syndrome (*c*oloboma, *h*eart anomalies, choanal *a*tresia, *r*estriction of growth and development, and *g*enital and *e*ar anomalies), and mutations in the *CHD7* gene were found to be causative in over half of affected children, although the exact mechanism for the multiple malformations is not clear at this time.[27] Further, many new genes have been identified for specific syndromes that have been recognized by dysmorphologists as Mendelian traits for many years. In genetic terms, a syndrome refers to a recognized pattern of anomalies with a specific, usually heritable cause, such as the Holt-Oram syndrome, in which radial dysplasia and cardiac defects occur as a consequence of an autosomal dominant *TBX5* gene mutation.[42,62] The Cornelia de Lange syndrome is another example of this forward progress in genetic understanding of recognized malformation syndromes, in which at least five genetic loci, including the *NIPBL* gene, have been identified in patients with growth failure, microcephaly, limb anomalies, and characteristic facial dysmorphisms.[14] It is expected that the discovery of new genetic defects will continue at a rapid pace, improving the diagnostic capability for infants with congenital anomalies in the future.

Although the underlying causes of congenital anomalies are heterogeneous, disruptions and isolated deformations are usually sporadic, with negligible or low recurrence risks. However, congenital malformations can also have more than one cause, often with different possible associated anomalies and different recurrence risks. Cleft lip and palate, for example, can be isolated or can be part of dozens of different syndromes due to monogenic; multifactorial; or complex, chromosomal, or teratogenic causes.[26] The clinician should remember that the search for the underlying cause of a birth defect can be anxiety provoking for parents of newborns with congenital anomalies, as are the implications for future children and other family members. Evaluating the newborn for a pattern of major and minor anomalies will assist the clinician in more efficiently determining the appropriate tests and procedures for diagnosis and management of a congenital anomaly and determining future recurrence risks for family members.

Epidemiology and Etiology

Major Malformations

About 2% of newborn infants have a serious anomaly[22] that has surgical or cosmetic importance (Table 30.1).[6] Most of these infants have a single anomaly, but this proportion is a minimum estimate, because it is based only on the examination of newborn infants; additional anomalies are detected with increasing age.[41] The most common anomalies are structural heart defects, cleft lip and palate, and neural tube defects, occurring in 5-7 per 1000, 1.5 per 1000, and 0.3 per 1000 live births, respectively.[4,6,50,60] Identifying neonates with a major malformation is medically important, because they have a fivefold increase in morbidity and, if identified in the prenatal setting, have a threefold increased risk for death in utero.[32] From a genetic perspective, the etiology of malformations can be divided into broad categories: genetic (multifactorial, single gene [Mendelian], or chromosomal), environmental or teratogenic, and unknown.

Genetic

Complex or Multifactorial

Most congenital malformations (86%) are isolated and not associated with other anomalies.[31] The most common

TABLE 30.1 Birth Defects Among Hospitalized Newborns, 1997-2001

Defect Category	Rate per 10,000
Central nervous system	4.51-8.34
Ear, eye	2.7-7.9
Orofacial	16.22-18.32
Cardiovascular	106.19-110.77
Gastrointestinal	6.3-6.7
Genitourinary	52.04-55.61
Musculoskeletal	10.28-14.15

Data from Bird TM, et al. National rates of birth defects among hospitalized newborns. *Birth Defects Res Part A*. 2006;76:762.

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and familiar birth defects fall into this category, including congenital heart defects, neural tube defects, cleft lip and palate, clubfoot, and congenital hip dysplasia (see Table 30.1). Most isolated malformations are believed to be the consequence of multifactorial inheritance, sometimes called complex inheritance, occurring when one or more genetic susceptibility factors combine with environmental factors and random developmental events.[37] In most cases, multiple genetic components are involved, some with large effects and some with small contributions, the specifics of which continue to be studied. From a public health standpoint, the nongenetic effects have been harder to identify in most cases, although work has begun to link specific gene sequence variants to environmental factors. For example, epidemiologic studies have demonstrated that neural tube defects are associated with many maternal factors, such as hyperthermia, glucose levels, and folate intake.

Single Gene (Mendelian)

Single genes are responsible for causing 0.4% of newborns to have major malformations. The most common mode of Mendelian inheritance for major malformations is autosomal dominant, with a minority of major malformations resulting from autosomal recessive or, rarely, X-linked genes. Limb anomalies, including postaxial polydactyly, syndactyly, and brachydactyly, constitute the most prevalent major localized malformation, and they are frequently the result of a dominant gene. Any type of malformation, however, may be under the control of a single gene, including multiple anomalies arising in different structures or organ systems. The mechanisms of monogenic malformation disorders are related to the dysfunction of the gene or disruption of the developmental pathway. For example, autosomal recessive Smith-Lemli-Opitz syndrome, characterized by genital abnormalities, syndactyly of the second and third toes, ptosis, wide alveolar ridges, hypotonia, inverted nipples, and abnormal fat distribution, has been found to be caused by a deficiency of the enzyme 7-dehydrocholesterol reductase in the cholesterol biosynthesis pathway.[5,34] Since the genetic cause of this disorder was identified, other single gene disorders of cholesterol biosynthesis have been identified that result in multiple congenital anomalies.[52] Although a biochemical or molecular basis increasingly is being recognized for different malformations, specific diagnosis still relies heavily on the family history and clinical evaluation.

Chromosomal

About 0.2% of newborns have a major malformation as a result of a chromosomal disorder, amounting for 10% of all the major congenital malformations (Table 30.2; see Chapter 10). The most prevalent malformation syndrome caused by an abnormal chromosomal constitution in newborns is Down syndrome, or trisomy 21, which occurs in about 1 in 660 births.[33] The other common trisomies are trisomy 18 and trisomy 13, each occurring in about 1 in 10,000 births. All three autosomal trisomies, and the sex chromosome aneuploidies, 47,XXY and 47,XXX, occur more frequently with increased maternal age.

TABLE 30.2 Etiology of Human Congenital Malformations

Etiology	Malformed Live Births (%)
Environmental	**10**
Maternal conditions *Alcoholism, diabetes, endocrinopathies, phenylketonuria, smoking, nutritional problems*	4
Infectious agents *Rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella, Venezuelan equine encephalitis*	3
Mechanical problems (deformations) *Amniotic band constrictions, umbilical cord constraint, disparity in uterine size and uterine contents*	1-2
Chemicals, Drugs, Radiation, Hyperthermia	<1
Genetic	15-25
Single gene disorders Chromosomal abnormalities	
Unknown	65-75
Polygenic/multifactorial (gene-environment interactions) "Spontaneous" errors of development Other unknowns	

Modified from Brent RL. Addressing environmentally caused human birth defects. *Pediatr Rev*. 2001;22:153.

It is important to note, however, that although about 0.6% of newborns have chromosomal anomalies, the abnormalities are not detectable by physical examination at birth in 66% of these infants.[33] Included among these early phenotypically undetectable chromosomal anomalies are common aneuploidies of the sex chromosomes, such as 47,XXY (Klinefelter syndrome) and 47,XXX. Neonates with these sex chromosome disorders may not have obvious malformations in the newborn period, because the phenotype may develop over time.

In contrast, Turner syndrome (45,X) is present in 1 in 5000 female births, is often detected prenatally, and has a phenotype in a proportion at birth.

Many other types of chromosomal aberrations have been identified using standard karyotype and newer genomic technologies. In addition to detecting the gain or loss of a single chromosome, routine chromosome banding techniques can identify many translocations, inversions, ring chromosomes, marker chromosomes, and deletions.[58] However, not all deletions are detectable by routine or

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even high-resolution (prometaphase) cytogenetic analysis, so that additional methodologies such as fluorescence in situ hybridization (FISH) or comprehensive genomic technologies should be considered. FISH uses fluorescently labeled DNA probes that identify deletions in specific locations on the chromosome metaphase spread, such as those associated with conditions as 22q11 deletion syndrome/ velocardiofacial/ DiGeorge syndrome and Williams syndrome (long arm of chromosome 7).[25]

Newer genomic technologies simultaneously examine the entire structure of the chromosomes.[15] Chromosomal microarray analysis targets known microdeletion syndromes, subtelomeres, and pericentric regions, and is more sensitive than routine karyotype analysis. When the microarray is done with single nucleotide polymorphism (SNP) analysis, regions of the genome that lack heterozygosity can be identified. This may suggest uniparental disomy or consanguinity, which may be contributing to the child's features. In a relatively short period of time, array analysis has revolutionized the diagnosis of neonates and children with multiple anomalies or developmental delay.[15] In an analysis of 1176 cases evaluated by a clinical genetics laboratory, 9.8% had pathogenic chromosomal imbalances identified by comparative genomic hybridization (CGH) array, compared with 2% using routine karyotyping.[51] Other studies have shown that infants with multiple congenital anomalies may have a higher rate of imbalances. Lu et al. showed that 17% of 444 neonates with a variety of malformations had clinically significant aneuploidies found on microarray analysis.[38] Furthermore, new microdeletion syndromes of developmental delay and multiple malformations have been identified, which suggests that whole genome analysis technologies of the future will improve diagnosis and expand our knowledge of clinically significant areas of the genome.[63]

Whole exome sequencing (WES) is a novel technology that allows for evaluation of the entire coding region of the genome, estimated to be 2%-3% of the total genomic material. This testing methodology is estimated to provide a genetic etiology for 24%-47% of fetuses with anomalies.[23,69]

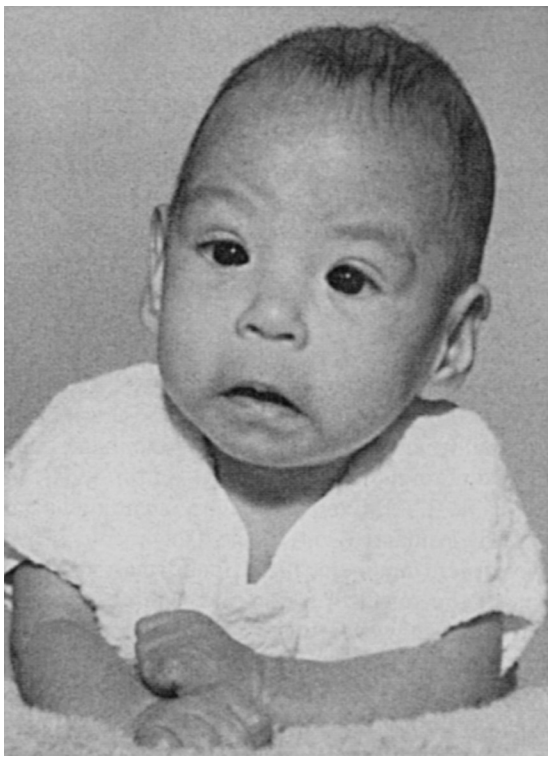
However, karyotype remains the appropriate first-line test for suspected aneuploidy (trisomies 21, 18, and 13, and Turner and Klinefelter syndromes) and in cases of ambiguous genitalia because of the rapid turnaround time and lower cost.

Environmental Exposure and Teratogens

A teratogen is anything external to the fetus that causes a structural or functional disability in prenatal or postnatal life (see Chapter 14). Teratogens can be drugs and chemicals, altered metabolic states in the mother, infectious agents, or mechanical forces. Known teratogenic factors cause only 5%-10% of congenital anomalies despite the ever-expanding list of potential teratogens in our increasingly chemical environment (see Table 30.2).[8] Before one can attribute malformations to a teratogenic agent, there must be one anomaly, only a few specific anomalies, or a recognizable pattern of anomalies found to occur at increased incidence over the background risk in infants exposed at the appropriate developmental stage (usually 2-12 weeks of gestation). With only a few exceptions, teratogenic agents do not affect every exposed infant, which is probably related to genetic susceptibility factors. Dose and timing of exposure also alter the potential of a specific teratogenic agent. To assess for specific drug teratogenic effects, multiple resources are available.[29]

Although beyond the scope of this chapter, pharmaceutical agents and environmental toxins are well documented to alter the development of the fetus.[59] Although many drugs have teratogenic potential, the clinician should be aware of the teratogenic effect of some commonly used drugs and exposures. Alcohol is thought to be the most common teratogen to which a fetus may be exposed. Chronic maternal alcohol use during pregnancy is associated with increased perinatal mortality and intrauterine growth restriction, as well as congenital anomalies such as cardiac defects, microcephaly, short palpebral fissures, and other anomalies (Fig. 30.1). Long-term effects include intellectual disability and behavioral problems. Alcohol carries serious risks when it is used almost at any time during pregnancy in sufficient quantities, because the central nervous system continues to develop throughout pregnancy. For this reason it is recommended that women avoid alcohol, even in small amounts, throughout their pregnancies (see Chapter 46).

Anticonvulsants are a common category of teratogens to which a fetus is likely to be exposed. Although the



• **Fig. 30.1** Fetal alcohol syndrome. Note mild ptosis, epicanthal folds, flat nasal bridge, short nose, smooth philtrum, and thin upper vermilion border. (From Dworkin PH, ed. *Pediatrics*. 2nd ed. Malvern, PA: Lea & Febiger; 1992:168.)

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medical literature is somewhat controversial, clinical geneticists, dysmorphologists, and clinical teratologists generally identify a variable but recognizable pattern of anomalies and developmental defects that occur at a significantly increased frequency among fetuses exposed to older classes of anticonvulsants. Studies have implied that newer classes of antiepileptic medications may not have the same effect on the developing fetus, although the clinician should be cautious in interpreting these studies.[68]

Some altered metabolic states in the mother also are known to have teratogenic potential. One of the most common is maternal diabetes mellitus. Infants of diabetic mothers are at two to three times the risk for congenital heart defects, caudal regression and sacral dysgenesis, and central nervous system abnormalities.[18] In this population, there is about a threefold increase of congenital anomalies over those in the general population. The risk for congenital anomalies appears to be lower in offspring of diabetic mothers with better control of blood glucose, but this is not absolute, and factors other than blood glucose levels are thought to play a role in teratogenesis (see Chapters 18 and 86). Another example is untreated maternal phenylketonuria, in which the elevated levels of phenylalanine cause microcephaly, growth delay, and cardiac and neurologic abnormalities in the developing fetus.

Congenital anomalies also may be associated with certain infections during pregnancy. The most common and best understood infections are represented by the acronym TORCH, which stands for *t*oxoplasmosis, *o*ther agents (including syphilis), *r*ubella, *c*ytomegalovirus, and *h*erpes simplex. Although the sequelae of these infections may not be apparent until later, the clinician should consider these congenital infections in neonates with intrauterine growth restriction, microcephaly, chorioretinitis, intracranial calcification, microphthalmia, cataracts, or hearing loss. Confirmation of the specific diagnosis should be made by antibody studies and other evaluations such as ophthalmic examination and imaging studies.

Unknown

About 66% of major malformations have no recognized etiology, if one includes those of presumed polygenic and multifactorial etiology (see Table 30.2).[8] It is presumed that specific genetic or environmental causes of these congenital anomalies will be identified in the future as medical knowledge about the underlying biology of embryonic development and the technology for identifying gene-environment interaction improves. For example, folic acid supplementation has been recognized to decrease the risk for neural tube defects, thus implicating folic acid deficiency in the etiology of these anomalies.[3]

Anomalies in Aborted Fetuses

Spontaneously aborted fetuses have a higher incidence and severity of malformations than do newborns,[32] which presumably represents a higher lethality of some developmental abnormalities. As in newborns, common anomalies, such as neural tube defects and cleft lip or palate, are also frequent in aborted fetuses, although these may be more severe. Other malformations, such as cloacal exstrophy, are relatively rare in newborns but are comparatively common in aborted fetuses.

In addition to these localized and single anomalies, multiple congenital anomalies commonly occur together in aborted fetuses, including well-recognized syndromes that are caused by single genes and chromosomal abnormalities (Table 30.3).[13] It is estimated that about half of all pregnancy losses before 20 weeks of gestation have an underlying chromosomal abnormality. These losses include unrecognized early pregnancies and fetuses without an obvious structural anomaly. In this context, the most common single chromosomal abnormality is 45,X, followed by triploidy. Both conditions are more common in aborted fetuses than in newborns. The trisomies as a group account for more than

TABLE 30.3 Diagnoses in 375 Consecutive Cases of Pregnancy Loss

Diagnosis	≤20 Weeks (%)	>20 Weeks (%)
Chromosomal abnormalities	19.4	15.7
Trisomy	54	47
Triploidy/tetraploidy	18	5.2
45,X	16	15.8
45,X mosaic	6	0
Deletion/duplication	0	15.8
Other	6	15.8
Placental abnormalities	12	5.8
Infection	7	6.6
Cord problems	7	5
Neural tube defects	6	10
Central nervous system abnormalities	1.2	5
Twins	7.4	3.3
Skeletal dysplasias	2	2.5
Recognizable syndromes	1.2	5.8
Hemoglobinopathies	0	4
Early amnion rupture sequence	3.5	5
Abdominal wall defects	1.2	0
Renal abnormalities	1.2	3.3
Cardiac abnormalities	0.7	4
Other	6.5	9
Total cases with diagnoses	76	85
Diagnoses unknown	24	15

Data from Curry CJR. Pregnancy loss, stillbirth, and neonatal death: a guide for the pediatrician. *Pediatr Clin North Am*. 1992;39:157.

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50% of all chromosomally abnormal pregnancy losses. The most frequent trisomy, accounting for almost one-third of all trisomies, is trisomy 16, which is not found in newborns, because it is lethal to the fetus.[32,70] Trisomy 21, the most common trisomy in newborns, occurs in less than 10% of all recognized trisomic conceptions. Unbalanced translocations account for 2%-4% of all chromosomally abnormal fetuses and are three to six times more frequent in aborted fetuses than in newborns. As with neonates, newer genomic technologies examining the chromosomes for small areas of genomic imbalance have shown an increased number of previously unrecognized deletions or amplifications of genetic material in fetuses with congenital anomalies. Analysis of DNA from the fetus's parents could be helpful in determining whether the chromosomal microarray finding was diagnostic of the congenital anomaly.

Minor Anomalies and Phenotypic Variants

Although major malformations often are easy to identify, minor anomalies are, by nature, more subtle and may not be appreciated unless they are specifically sought. It should be noted that 15%-20% of healthy newborns will have a minor anomaly, so their presence alone is not necessarily indicative of a more serious problem. However, these minor anomalies may be part of a characteristic pattern of malformations and thus may provide clues to a diagnosis. Also, their occurrence may be an indication of the presence of a more serious anomaly. It is estimated that the presence of a single minor anomaly is associated with a 3% risk of having a major malformation, while having three or more minor anomalies is associated with a 20% risk of a major malformation.[2,9]

Minor anomalies are most frequent in areas of complex and variable features, such as the face and distal extremities (Table 30.4).[39] Among the most common features are lack of a helical fold of the pinna and complete or incomplete single transverse palmar crease patterns. Typical single transverse palmar crease occurs in almost 3% of normal newborns, but it appears in 45% of individuals with trisomy 21.[35]

Among the most frequent phenotypic variants, those present in 4% or more of the population, are a folded-over helix of the pinna and cerulean spots in blacks and Asians (Table 30.5).[39] Before attributing medical significance to an apparent minor anomaly or phenotypic variation, it is useful to determine whether the anomaly is present in other family members or whether it is frequent in the patient's ethnic group. It is common for isolated minor anomalies such as syndactyly of the second and third toes to be familial.

Racial and Ethnic Differences

The prevalence of congenital malformations varies among different racial and ethnic groups. This variation is most likely the consequence of differing genetic predispositions and variable environmental factors operating in diverse areas. Table 30.6 shows the prevalence of common major congenital malformations in white Americans, African Americans, and Chinese.[16,50] It is of interest that certain anomalies are especially common in a particular race, such as postaxial polydactyly in African Americans and hypospadias and clubfoot in white Americans. Minor malformations may show an equally striking racial predisposition. Brushfield spots are common in white Americans but are rare in African Americans. Umbilical hernias, however, are common in African-American infants but are relatively infrequent in white American infants. The widely varying frequencies of various traits in different races may make the determination of whether any given characteristic is considered to be a minor anomaly or a phenotypic variant strongly dependent on the race of the patient being studied.

TABLE 30.4 Common Minor Malformations in Newborns (Frequency Greater Than 1:1000)

Minor Malformation	Newborns (%)
Craniofacial	
Borderline micrognathia	0.32
Eye	
Inner epicanthal folds	0.42
Ear	
Lack of helical fold	3.52
Posteriorly rotated pinna	0.25
Preauricular or auricular skin tags	0.23
Small pinna	0.14
Auricular sinus	0.12
Skin	
Capillary hemangioma other than on face or posterior aspect of neck	1.06
Pigmented nevi	0.49
Cerulean spots in white infants	0.21
Hand	
Single palmar creases	2.74
Bridged upper palmar creases	1.04
Bilateral combinations	0.51
Other unusual crease patterns	0.28
Clinodactyly of fifth finger	0.99
Foot	
Partial syndactyly of second and third toes	0.016
Total	12.34

Data from Marden PM, et al. Congenital anomalies in the newborn infant, including minor variations: a study of 4142 babies by surface examination for anomalies and buccal smear for sex chromatin. *J Pediatr*. 1964;64:357.

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One of the best examples is cerulean spots, which occur in almost 50% of African-American or Asian infants but in only 0.2% of white infants.[39] Ethnic differences have also been noted for the Hispanic population, in whom there is a higher prevalence of neural tube defects, gastroschisis, and trisomy 21.[50]

Evaluation

Every infant with a congenital anomaly should have a thorough diagnostic evaluation; without one, accurate information about the natural history of the condition and the recurrence risk for similarly affected future children cannot be provided.[20] In addition, parents usually are intensely interested in why the anomaly occurred and often harbor inappropriate guilt concerning the cause.

When a child is born with one or more anomalies, a number of considerations should guide the physician in the evaluation. The most critical factors to be considered are the detailed prenatal and family histories, the dysmorphic physical examination (including careful observation and measurements of growth parameters and individual features), and the use of appropriate diagnostic tests and evaluations, particularly if there is more than one anomaly. It is important to assess whether the malformation is isolated or part of a constellation of anomalies. It is also essential to identify whether there are other major or minor anomalies, including perhaps unapparent internal malformations, and to recognize well-described patterns of malformations.[10,35] The severity of an anomaly can sometimes be helpful in identifying whether it may be associated with other anomalies and in predicting the prognosis for the infant. Consultation with other specialists, such as a medical geneticist, who have expertise in the evaluation of neonates with congenital anomalies may be required.

Patient and Family History

The evaluation of an infant with congenital anomalies begins with detailed medical, prenatal, and family histories. The important goal is to identify a possible genetic predisposition, environmental factor, or other clue to the cause of the anomalies. It is useful to begin with the pregnancy to document fetal movement and vigor, complications, illnesses, maternal use of any medications, or possible exposure to teratogens, as well as the timing of all complications and exposures (see Chapter 14). In particular, information about previous prenatal ultrasound findings; maternal serum screening; and results of noninvasive prenatal screening (NIPS), amniocentesis, or chorionic villus sampling (if any) should be reviewed. The extent of smoking and alcohol

TABLE 30.5 Common Phenotypic Variants

Phenotypic Variant	Newborns (%)
Craniofacial	
Flat nasal bridge	7.3
Ear	
Folded-over upper helix	43.0
Darwinian tubercle	11.0
Skin	
Capillary hemangioma on face or posterior aspect of neck	14.3
Cerulean spots in African Americans and Asians	45.8
Hand	
Hyperextensibility of thumbs	12.3
Foot	
Mild calcaneovalgus	4.7
Genital	
Hydrocele	4.4

Data from Marden PM et al. Congenital anomalies in the newborn infant, including minor variations: a study of 4142 babies by surface examination for anomalies and buccal smear for sex chromatin. *J Pediatr*. 1964;64:357.

TABLE 30.6 Frequency of Common Congenital Malformations in Various Racial Groups (per 1000)

Malformation	White Americans*	African Americans*	Chinese†
Anencephaly-myelomeningocele-encephalocele	2.4	0.9	1.5
Cleft lip and palate	1.1	0.6	1.3
Cleft palate	0.6	0.4	N/A
Clubfoot (talipes equinovarus)	3.9	2.3	0.1
Polydactyly	1.2	11.0	1.5
Hypospadias	2.4	1.2	0.6

*Data from Erickson JD. Racial variations in the incidence of congenital malformations. *Ann Hum Genet*. 1976;39:315.
†Data from Emanuel I et al. The incidence of congenital malformations in a Chinese population: the Taipei collaborative study. *Teratology*. 1972;5:159.

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consumption should be determined, and every mother should be asked about illicit drug use.

To identify other potentially affected family members and obtain clues to an etiology, a detailed three- to four-generation family history, charted in a concise manner in the form of a pedigree, should be constructed, using squares for male and circles for female members. Horizontal lines indicate genetic union, and vertical lines indicate genetic descent. All abortions and stillbirths should be noted. A question always should be specifically asked about possible parental consanguinity. A simple way to inquire is to ask if the families of the affected child's parents are related in any way. If so, the charting should indicate the exact relationships. The presence of other relatives with congenital anomalies of any type or with growth or developmental abnormalities should be recorded along with other pertinent information, such as the maternal and paternal ages and the nature of the anomaly. Family photographs are often very useful in clarifying questions of possible unusual facial features. The pedigree should, at a minimum, include all siblings and parents of the proband as well as aunts, uncles, cousins, and grandparents. In the case of possible dominant or X-linked disorders, a more extensive pedigree may be needed.[67]

Physical Examination

The goal of the physical examination (see Chapter 28) of an infant with congenital anomalies is to determine whether an anomaly is isolated or to detect a recognizable pattern of malformations so that a specific etiologic determination can be made. In addition, careful attention must be directed not only to an exact description of the major anomalies but also to apparent minor anomalies or variations. Distinctive physical features may become clues in identifying the cause of multiple congenital anomalies; therefore a detailed inspection of various features of external anatomy and measurement of them when appropriate should be performed. The overall body size measurements of length, weight, and head circumference should be compared with gestational norms. Normal measurements of many face and body characteristics can be found in a number of resources.[28,35] Objective description of anomalous features allows for appropriate use of resources or consultants. In this section, an outline of this external examination is presented by region or structure, and certain helpful points, as well as aspects of the differential diagnosis, are discussed. Greater detail in regard to examination and abnormalities of various organ systems is given in other relevant chapters in this book. The reader also is referred to various resources in which the anomalies and syndromes mentioned in this section are discussed at length.[1,30,35,65]

Skin

Normal infant skin, particularly when exposed to cold temperatures, shows a marbling pattern termed cutis marmorata or livedo reticularis (see Chapter 94). In rare instances, this pattern may be unusually prominent and familial, inherited as an autosomal dominant trait. A similar prominent pattern may occur in those with trisomy 21, hypothyroidism, or Cornelia de Lange syndrome.

A variety of lesions with altered pigmentation may provide useful clues to a diagnosis. Café-au-lait spots are characteristic of neurofibromatosis, but they also occur in other conditions and may be isolated, especially in darkly pigmented infants. Hypopigmented macules may be the earliest manifestation of tuberous sclerosis in the young infant. Multiple irregular pigmented lesions arranged in whorls are suggestive of incontinentia pigmenti, but this disorder usually presents initially with a vesicular rash. An angiomatous patch over one side of the face may be an isolated anomaly or part of Sturge-Weber syndrome. More than one skin hemangioma should raise suspicion of internal vascular lesions.

Generalized edema may obscure many minor anomalies, making diagnosis difficult. Turner syndrome, trisomy 21, and Noonan syndrome should be considered in newborns with generalized edema. The texture of the skin also can assist the clinician with a syndromic diagnosis, because thick or coarse skin is characteristic of Costello syndrome, and abnormal distribution of fatty tissue can be seen in congenital disorders of glycosylation.

Hair

The relative sparseness or prominence of body hair should be noted. Sparse hair is characteristic of an ectodermal dysplasia, but it does occur in other syndromes, such as cartilage-hair hypoplasia and oculodentodigital syndrome. Generalized hirsutism is typical of Cornelia de Lange syndrome, fetal hydantoin syndrome, and fetal alcohol syndrome, but it also may occur in those with trisomy 18. It also may be an ethnic (Hispanic, Middle Eastern, American Indian) or familial characteristic.

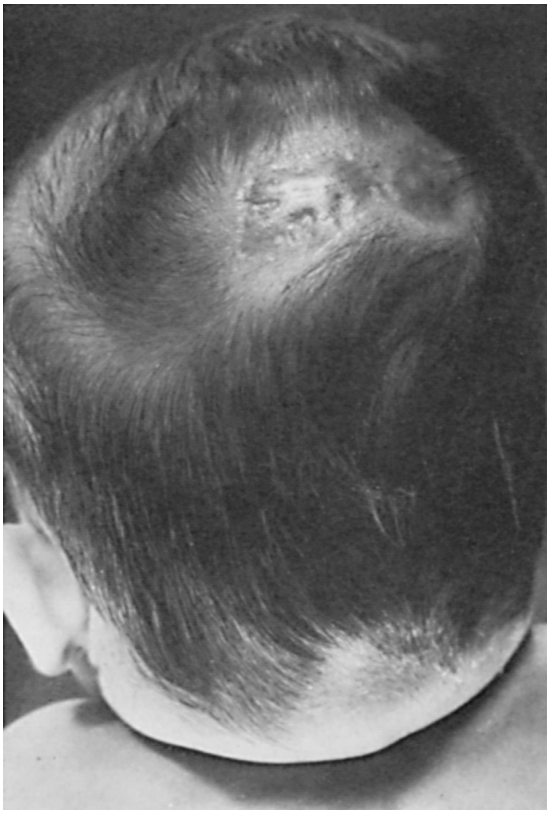
Abnormal scalp hair patterns may reflect underlying brain abnormalities. In microcephaly, there may be a lack of the normal parietal whorl, or the whorl may be displaced more centrally or posteriorly. In addition, the frontal hair may show a prominent upsweep. A low posterior hairline occurs with a short or webbed neck, as in Turner syndrome and Noonan syndrome. Punched-out scalp lesions in the parietal occipital area (aplasia cutis congenita) are typical of trisomy 13 or may be seen in isolation and may be familial (Fig. 30.2).

Head

The size of the head, measured by the maximal head circumference, and the sizes of the anterior and other fontanelles should be compared with those of appropriate standards (see Chapter 57). Head size varies with age, sex, and racial group and correlates with body size. Macrocephaly as an isolated anomaly often is familial and inherited in an autosomal dominant fashion; therefore, determining the head circumferences of the parents is helpful. However, macrocephaly may be a manifestation of several disorders, including

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hydrocephaly and various conditions affecting the skeletal system such as achondroplasia, or overgrowth syndromes such as the PTEN hamartoma tumor syndrome. Microcephaly can also be familial, either autosomal dominant, or recessive, but it is more commonly a manifestation of many syndromes that result in intellectual disability. Large fontanelles occur in hypothyroidism, in trisomies 21, 18, and 13, in peroxisomal disorders like Zellweger syndrome, and in many bone disorders such as hypophosphatasia and cleidocranial dysostosis. A small anterior fontanelle may be a sign of failure of normal brain growth.



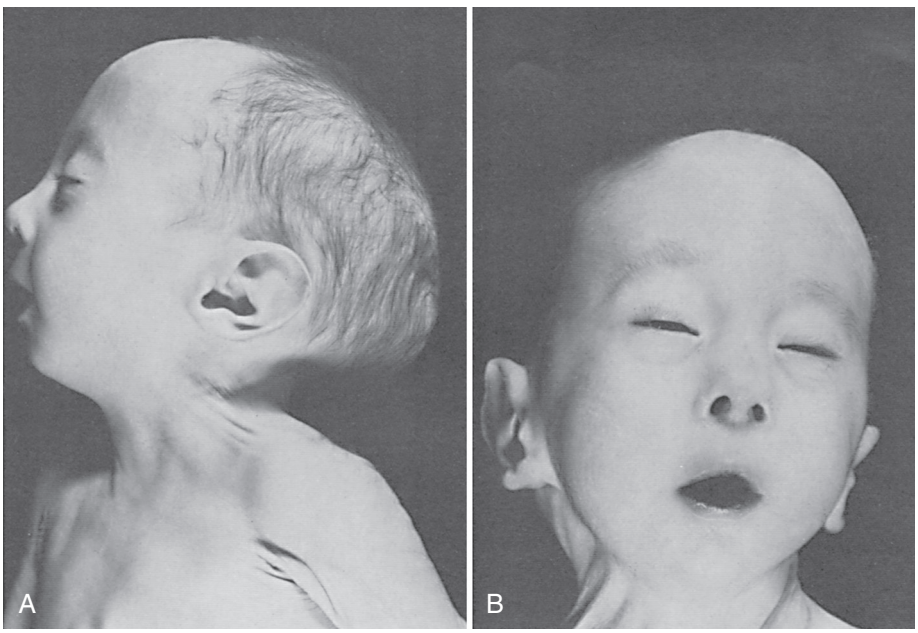
• **Fig. 30.2** Scalp lesions in trisomy 13.

The normal shape of the head may vary from an increase in the anteroposterior diameter (dolichocephaly) to a decrease in this dimension (brachycephaly). Premature infants and those with trisomy 18 characteristically have dolichocephaly (Fig. 30.3), and hypotonic infants often develop dolichocephaly over time, but either type of head shape may be of familial or racial origin. Many Asian and American Indian infants, for example, have strikingly brachycephalic heads.

Premature fusion of cranial sutures (craniosynostosis) results in an abnormal configuration in head shape. Various types occur depending on the sutures involved (see Chapter 57). Torticollis or abnormal mechanical forces in utero can cause asymmetric head shape (plagiocephaly). A common anomaly in head shape is frontal bossing, which is frequent in some skeletal dysplasias such as achondroplasia and in some cases of hydrocephaly.

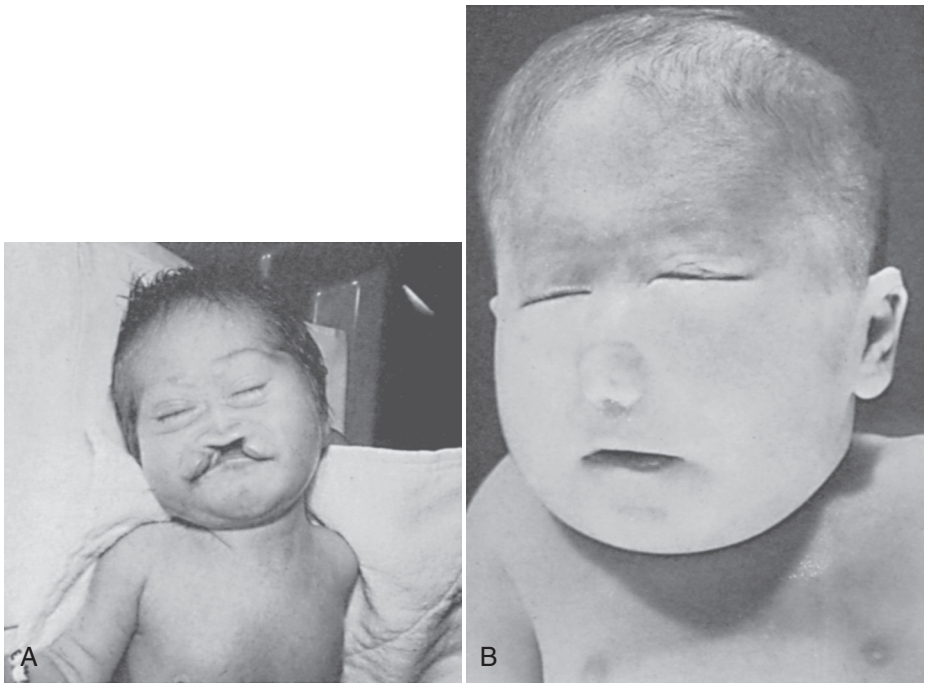
Face

The face is composed of a series of structures, each demonstrating considerable normal variation and providing a distinctive and unique appearance to every human. Because examination of the face is both complex and important to establishing an etiology of anomalies, a systematic approach is necessary. It is never sufficient merely to describe the face as "unusual," nor appropriate to describe the face as "funny looking." Specific abnormalities should be analyzed and quantified, when appropriate, even though an overall gestalt impression may suggest a diagnosis in some cases. Recall that lack of resemblance to other family members may be an indicator of an underlying condition.



• **Fig. 30.3** Trisomy 18. **A,** Note dolichocephaly. **B,** Note small mouth and anomalous ears.

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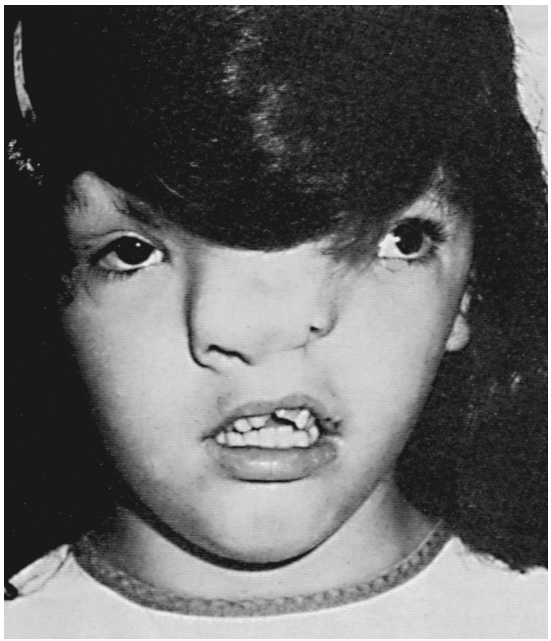


• **Fig. 30.4** Trisomy 13. **A,** Note anomalous midline facial development with hypotelorism, midline cleft lip, and lack of a nose. **B,** Note hypotelorism and abnormal nose.

Eyes

Hypotelorism occurs when the eyes are unusually close together; hypertelorism occurs when the eyes are too far apart. Clinically, hypotelorism and hypertelorism are defined by the interpupillary distance, which may be estimated in a relaxed patient by measuring between the midpoints of the pupils. It is usually impossible to measure the interpupillary distance of a newborn; therefore, two other relevant and useful measurements that are easier to obtain are the inner canthal distance and the outer canthal distance. Telecanthus is an increase in the inner canthal distance, and it may occur in the absence of hypertelorism, such as in Waardenburg syndrome type I. There are other factors that may create an illusion of hypertelorism, such as epicanthal folds and a flat nasal bridge; therefore, a subjective impression should always be confirmed by measurement of all three distances, if possible. From the prognostic and diagnostic points of view, it is important to identify hypotelorism, because often it is associated with holoprosencephaly, a major malformation of the central nervous system that can be associated with severe disturbance of brain function and early death. Holoprosencephaly can be isolated or can be part of trisomy 13 (Fig. 30.4) or occasionally other syndromes. Hypertelorism, however, occurs in a number of syndromes such as frontonasal dysplasia, and even when it is severe, it is less likely to be related to an underlying brain malformation. Comparison with parents' eye distances is important. Figs. 30.5 and 30.6 illustrate hypertelorism with midline facial anomalies.

Epicanthal folds are a feature of normal fetal development, and they may be present in normal infants. They are characteristic in trisomy 21 (Fig. 30.7*A, B*), but they occur in many other malformation syndromes, especially in those that include a flat nasal bridge.



• **Fig. 30.5** Frontonasal dysplasia with hypertelorism and bifid nose.

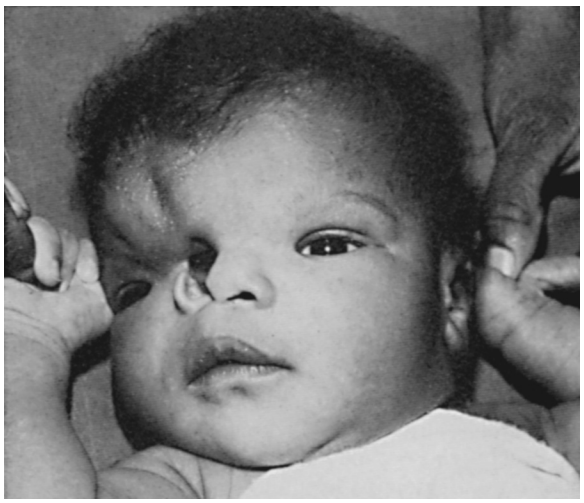
Normally, an imaginary line through the inner and outer canthi should be perpendicular to the sagittal plane of the face. An upward slant to the palpebral fissure is seen in trisomy 21 (see Fig. 30.7*A, B*), and a downward slant is seen in mandibulofacial dysostosis (see Fig. 30.7*C*) and Noonan

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syndrome. Both types of slant can be part of a number of other syndromes.

Palpebral fissure length is measured from the inner canthus to the outer canthus. Short palpebral fissures may occur in association with other ocular anomalies, such as microphthalmia, and they are characteristic of syndromes such as fetal alcohol syndrome (see Fig. 30.1) and trisomy 18 (see Fig. 30.3*B*).

A coloboma is a developmental defect in the normal continuity of a structure, and it often is used in reference to the eye. Colobomas may involve the eyelid margin, as those seen in Treacher Collins syndrome (see Fig. 30.7*C*), or the iris and retina, as those seen in CHARGE syndrome.



• **Fig. 30.6** Frontonasal dysplasia with nasal cleft.

Identification of a coloboma should lead to a formal ophthalmic evaluation.

Synophrys, or fusion of the eyebrows in the midline, is common in hirsute infants, and it may also be familial in some instances. The Cornelia de Lange syndrome is strongly associated with synophrys.

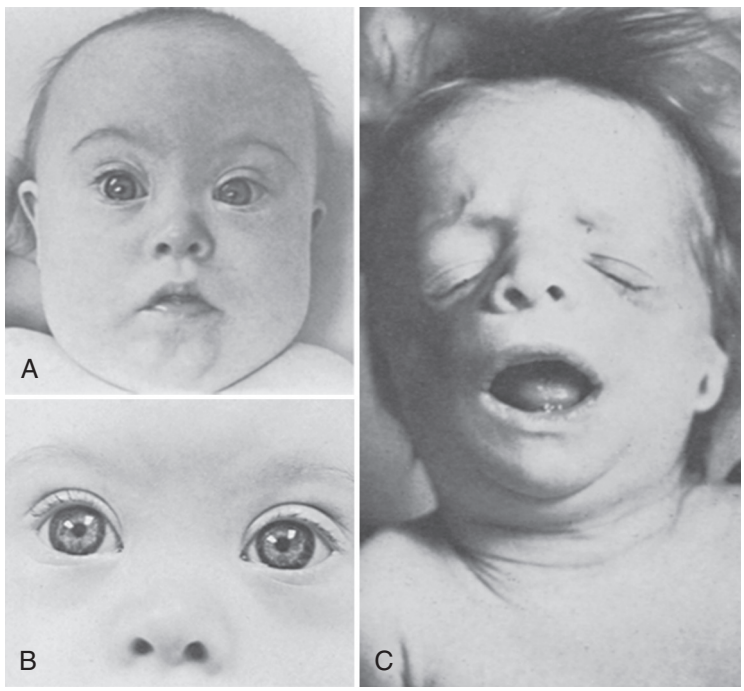
Anomalies of the internal eye structure are discussed in Chapter 95.

Ears

The external ear, or pinna, commonly shows great variation that can be identified by a number of anatomic landmarks. These should be described and measured when evaluating the anomalous ear. These landmarks include the helix, antihelix, tragus, antitragus, external meatus, and lobule (Fig. 30.8). If the ears appear to be large or small, they should be measured by obtaining the maximal length of the pinna from the lobule to the superior margin of the helix. Preauricular tags or pits may be isolated or associated with other abnormalities of the pinna (Fig. 30.9).

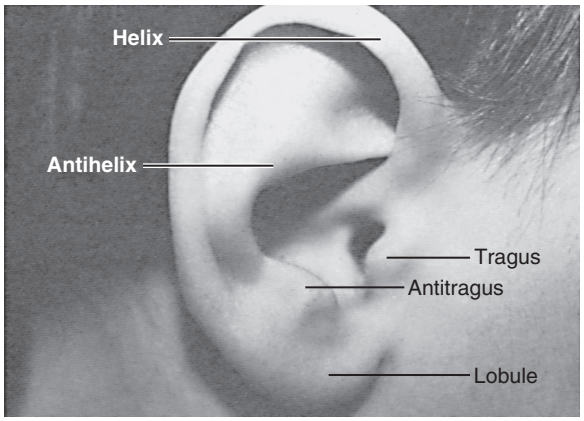
The ears are low set when the helix joins the head below a horizontal plane passing through the outer canthus perpendicular to the vertical axis of the head (Fig. 30.10). It is critical that this condition be assessed with the head in vertical alignment with the body because any posterior rotation of the head can create an illusion of low-set ears. In most instances, the relative placement of the ears is more a function of head shape and jaw size than of an intrinsic anomaly of the ear.

When the vertical axis of the ear deviates more than 10 degrees from the vertical axis of the head, the ears are

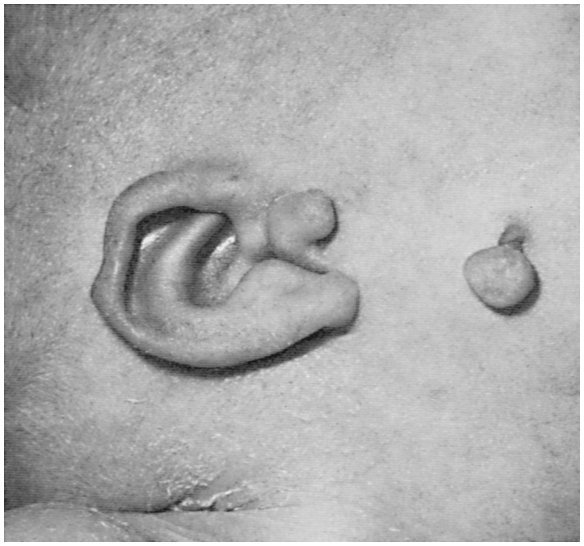


• **Fig. 30.7** **A,** Trisomy 21. Note epicanthal folds and upslant of eyes. **B,** Enlargement of eyes of patient in (**A**). Note Brushfield spots on irides. **C,** Mandibulofacial dysostosis (Treacher Collins syndrome) with down-slanting eyes. Note coloboma, or notch, in left eyelid.

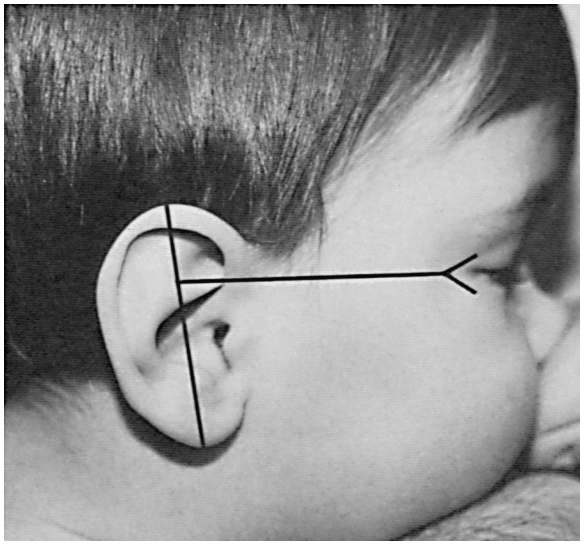
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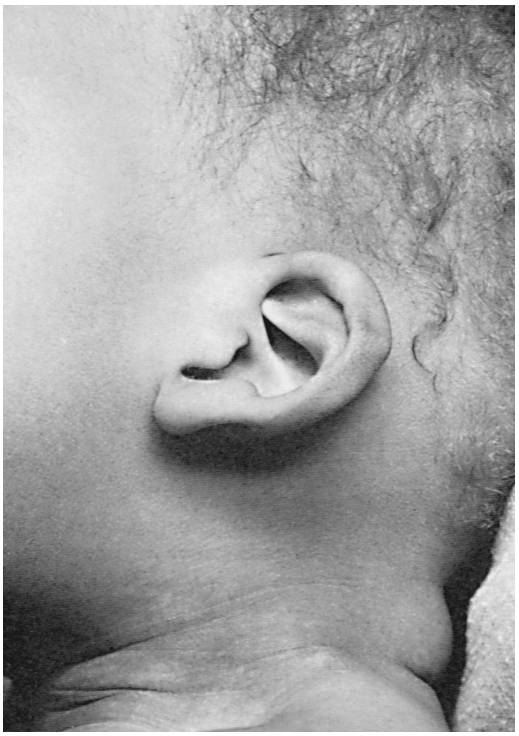
• **Fig. 30.8** Normal pinna and its landmarks.



• **Fig. 30.9** Preauricular tags with malformed pinna.



• **Fig. 30.10** Normal pinna and its orientation with respect to eyes.



• **Fig. 30.11** Abnormal pinna that is low set and posteriorly rotated in patient with Smith-Lemli-Opitz syndrome.

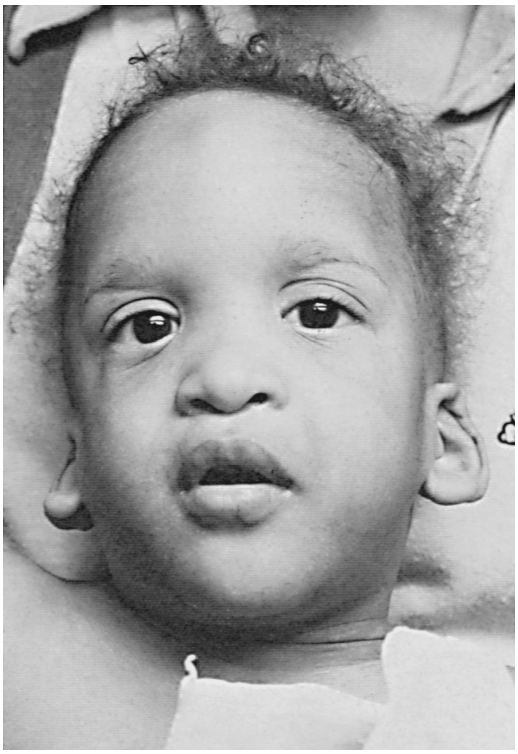
posteriorly rotated. This anomaly often is associated with low-set ears and represents a lag in the normal ascent of the ear during development (Figs. 30.11 and 30.12). Care should be taken when examining neonates in the intensive care unit because tape used to secure intubation or nasogastric tubes can give the false impression of posteriorly rotated ears.

Any significant abnormality of the external ear may be an indication of additional anomalies of the middle or inner ear and may be associated with hearing loss; therefore, an early hearing assessment is indicated in such cases (see Chapter 59). Fig. 30.13 illustrates a patient with hemifacial microsomia, whose findings include a severely malformed pinna and an absent ear canal. This is one condition in which an early hearing assessment is essential because hearing loss is likely.

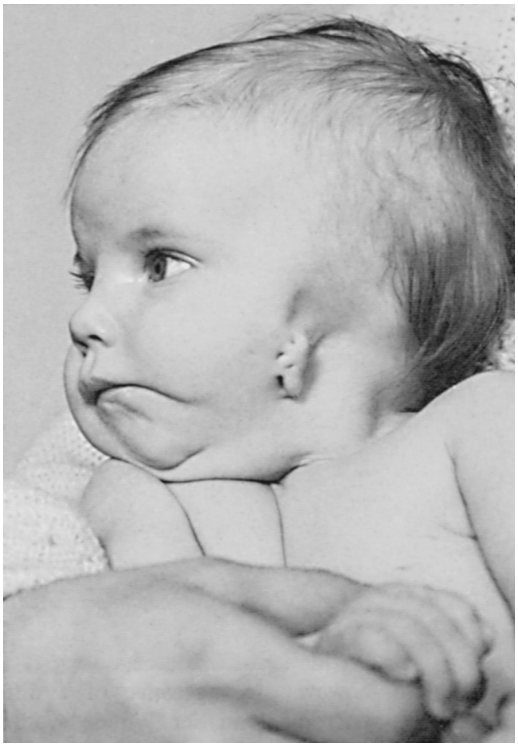
Nose

The nose, like the external ear, shows great individual variation, but certain alterations in shape are frequent in malformation syndromes involving the face. The nose may be unusually thin with hypoplastic alae nasi, as in Hallermann-Streiff syndrome, or it may be unusually broad, as in frontonasal dysplasia (see Fig. 30.5). A depressed nasal bridge with an upturned nose occurs in many skeletal dysplasias, such as achondroplasia. When the depression is severe, the nostrils may appear to be anteverted and the nose may appear to be shortened. A hypoplastic nose is often syndromic, and a nose with a single nostril is highly suggestive of holoprosencephaly (see Fig. 30.4).

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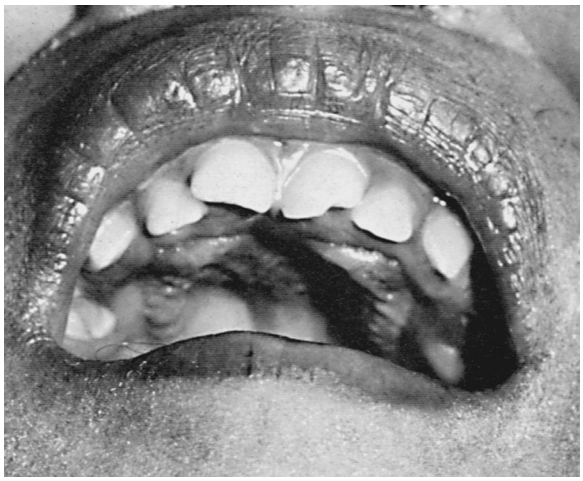
• **Fig. 30.12** Facial view of patient in Fig. 30.11.



• **Fig. 30.13** Hemifacial microsomia showing mandibular hypoplasia, severely malformed pinna, and absent ear canal.

Mouth

The mouth is a complex structure with component parts that require separate evaluation (see Chapter 68). The size and shape of the mouth may be altered. A small mouth, or microstomia, should be noted; it occurs in trisomy 18 (see Fig. 30.3). Macrostomia, a large mouth, should be noted as well; it may be present in such conditions as mandibulofacial dysostosis (see Fig. 30.7*C*). Severe macrostomia may result from a lateral facial cleft. The corners of the mouth may be downturned, as in Prader-Willi syndrome and other conditions with hypotonia. An asymmetric face during crying occurs with congenital deficiency in the depressor anguli oris muscle on one side, and this may be associated with other abnormalities, such as hemifacial microsomia and 22q11deletion/velocardiofacial/DiGeorge syndrome.



• **Fig. 30.14** Prominent alveolar ridges in patient with Smith-Lemli-Opitz syndrome.

Prominent, full lips occur in various syndromes, including Williams syndrome. A thin upper lip may be seen in Cornelia de Lange syndrome and in fetal alcohol syndrome (see Fig. 30.1).

A cleft upper lip is usually lateral, as in the common multifactorial cleft lip (or palate) anomaly, occurring in the position of one of the philtral ridges. The presence of pits in the lower lip associated with a cleft lip or palate, however, is suggestive of Van der Woude syndrome, which is inherited in an autosomal dominant manner. A median cleft lip is very suggestive of holoprosencephaly (see Fig. 30.4*A*). In fact, there are many diverse syndromes with cleft lip or palate that are important to identify, because they may have other associated malformations and relatively high genetic risks for recurrence. Therefore, it is particularly important to evaluate the infant with cleft lip or palate carefully for evidence of other malformations to give accurate recurrence risk and prognostic information to the family.

Isolated cleft palate is different genetically from cleft lip.[53] Mild forms of cleft palate are represented by submucosal clefts, pharyngeal incompetence with nasal speech (velopharyngeal insufficiency), and bifid uvula. A high arched palate may occur normally, but it is also a feature of many syndromes, especially if hypotonia or another long-standing neurologic abnormality is present. Hypertrophied alveolar ridges are apparent in the palate along the inner margin of the teeth, and they are suggestive of Smith-Lemli-Opitz syndrome (Fig. 30.14) if seen in an infant.

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• **Fig. 30.15** Micrognathia in Pierre Robin sequence.

Macroglossia may be relative, as in the Pierre Robin malformation sequence, in which the primary abnormality is mandibular hypoplasia. In other cases, such as hypothyroidism, Beckwith-Wiedemann syndrome, and trisomy 21, the tongue protrudes and is enlarged. A cleft or irregular tongue or oral frenula occurs in various syndromes, such as the orofaciodigital syndromes.

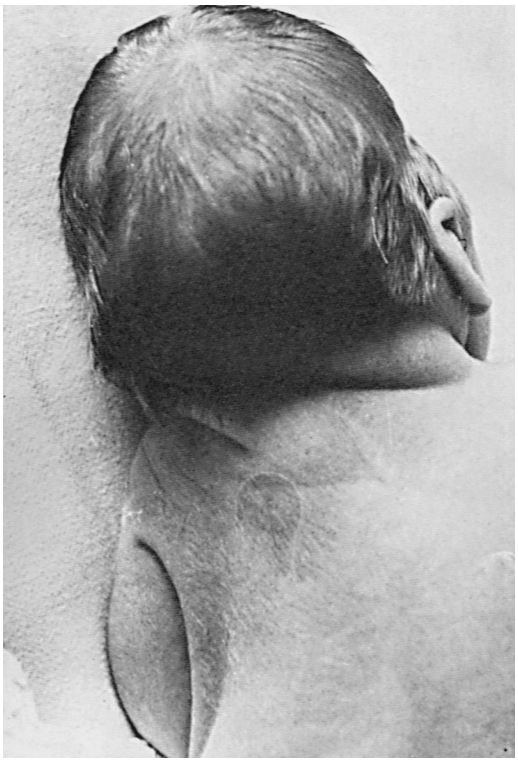
The lower portion of the mouth is formed by the mandible, which in young infants is relatively small. An excessively small mandible is termed *micrognathia*, which is a feature of many syndromes. It is a characteristic of the Pierre Robin sequence, which consists of the triad of micrognathia, glossoptosis, and a U-shaped cleft palate, as opposed to the common V-shaped cleft. A typical patient is shown in Fig. 30.15. The Pierre Robin sequence may be part of a syndrome, such as Stickler syndrome (hereditary arthro-ophthalmopathy), and thus other anomalies and a family history must be sought. In other syndromes, the maxilla likewise may be hypoplastic, decreasing the prominence of the upper cheeks (malar hypoplasia).

Neck

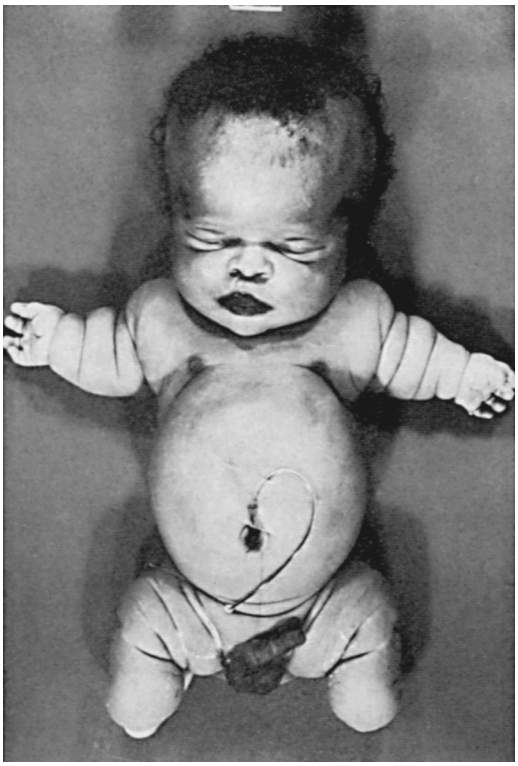
The neck may be short, and limitation of rotation should raise the suspicion of fusion of cervical vertebrae, as in a Klippel-Feil anomaly. Excessive skinfolds are characteristic of Turner syndrome (Fig. 30.16), Noonan syndrome, and trisomy 21. In these examples, the excess nuchal skin often represents resolution of a cystic hygroma that was present prenatally.

Chest

The thoracic cage may be unusually small as part of a skeletal dysplasia, such as thanatophoric dysplasia (Fig. 30.17) or Jeune asphyxiating thoracic dystrophy. The sternum itself may be unusually short, which is typical in trisomy 18, or it may be altered in shape, as is seen in pectus excavatum



• **Fig. 30.16** Excess skinfolds of the neck in patient with Turner syndrome.



• **Fig. 30.17** Thanatophoric dwarfism. Note short limbs and narrow thoracic cage.

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or pectus carinatum. The latter anomalies are commonly seen in a variety of skeletal dysplasias and connective tissue disorders (see Chapter 66).

Abdomen

Hypoplasia of the abdominal musculature may occur in association with intrauterine bladder outlet obstruction and other anomalies of the urogenital system. It results in a characteristic prune-belly appearance in Eagle Barrett syndrome (see Chapter 93). An omphalocele, in which abdominal contents protrude through the umbilical opening, may be part of Beckwith-Wiedemann syndrome (see Chapter 86) or chromosomal abnormalities such as trisomy 13. Gastroschisis, however, is usually an isolated disruption in which the abdominal contents protrude through the periumbilical abdominal wall. Anomalies of a more minor nature, such as inguinal or umbilical hernias, occur in normal infants, but they are more frequent in various syndromes, particularly in connective tissue disorders (see Chapter 84).

Anus

Imperforate or displaced anus may be isolated or may occur as the mildest expression of a caudal regression sequence, in which other anomalies such as sacral dysgenesis are seen. It is most commonly part of a constellation of anomalies, such as the VATER or VACTERL association. It also can be seen in a number of chromosomal abnormalities or as part of diabetic embryopathy (see Chapter 84).

Genitalia

Hypogenitalism can be seen in association with hypotonia in Prader-Willi syndrome or with low-set dysplastic ears, syndactyly of the toes, and thickened alveolar ridges in Smith-Lemli-Opitz syndrome. Genital ambiguity is associated with renal anomalies and an increased risk for Wilms tumor in Denys-Drash syndrome. Virilization may be associated with 21-hydroxylase deficiency, which requires urgent management of adrenal insufficiency (see Chapter 89).

Spine

Among the most common congenital anomalies are the neural tube defects, which involve abnormalities of the central nervous system along with defects in the associated bony structures. Minor external anomalies, particularly of the lower spine, include unusual pigmentary lesions, hair tufts, dimples, and sinuses. Some of these changes, such as hair tufts and sinuses above the gluteal cleft, may be an indication of a more significant deeper anomaly and require further evaluation, such as magnetic resonance imaging (see Chapter 58).

Extremities

Extremities may be relatively long, as occur in Marfan syndrome or homocystinuria, or unusually short, as occur in a diverse group of skeletal dysplasias, the most common being achondroplasia. A simple guide to evaluating relative extremity length is to determine where the fingertips are in relation to the thighs when the upper extremities are adducted alongside the body. In the normal infant, the fingertips fall below the hip joint in the midthigh region. When the upper extremities are short, they align with the hip joint or above (see Fig. 30.17); when they are relatively long, they may reach the knees. A more precise and useful bedside measurement is to determine the ratio of the upper segment to the lower segment. The distance from the pubis to the heel with the leg fully extended constitutes the lower segment. By subtracting the lower segment measurement from the total length, one obtains the upper segment. In normal newborns, the ratio of the upper segment to the lower segment is about 1.7, and the ratio decreases with age to about 1.0 in the adult. A high ratio suggests relative shortening of the extremities, and a low ratio implies either unusually long extremities or a foreshortened trunk, as may occur in spondyloepiphyseal dysplasia.

Paired extremities may be asymmetric in either length or overall size, suggesting either atrophy of one or hypertrophy of the other. The distinction may be difficult to make at times, although it is often evident if an extremity is unusually large or excessively small. Hypertrophy of limbs may be a manifestation of Beckwith-Wiedemann syndrome or Klippel-Trénaunay-Weber syndrome. Isolated hemiatrophy may occur with long-standing corticospinal tract damage as well, as in Russell-Silver syndrome. It is important to identify hemihyperplasia, because individuals with this finding are at increased risk for intra-abdominal tumors, such as Wilms tumor, and thus require close monitoring throughout infancy and childhood.

Foreshortening of long bones leads to various limb abnormalities, depending on the segments involved. A number of terms have been used to describe such anomalies. Rhizomelia denotes proximal shortening of the limbs, such as those in achondroplasia. Mesomelia refers to shortening of the middle segment, and acromelia refers to relative shortening of the hands or feet. A shortened forearm with secondary prominence of skinfolds in a newborn with thanatophoric dysplasia is shown in Fig. 30.18.

The hands and feet have epidermal ridges and creases forming a variety of configurations. Normally, there are two deep transverse palmar creases that do not completely cross the palm. In various conditions, such as trisomy 21, there may instead be a single transverse palmar crease. Single palmar creases may be completely transverse across the palm or may be bridged or incomplete (Fig. 30.19A, B). They may become more apparent when the palm is slightly flexed. A single phalangeal crease on the fifth finger, instead of the normal two, occurs as a consequence of a hypoplastic middle phalanx and results in clinodactyly (incurving of the digit). This is frequently seen in trisomy 21 (see Fig. 30.19*C*) and in a number of other conditions.

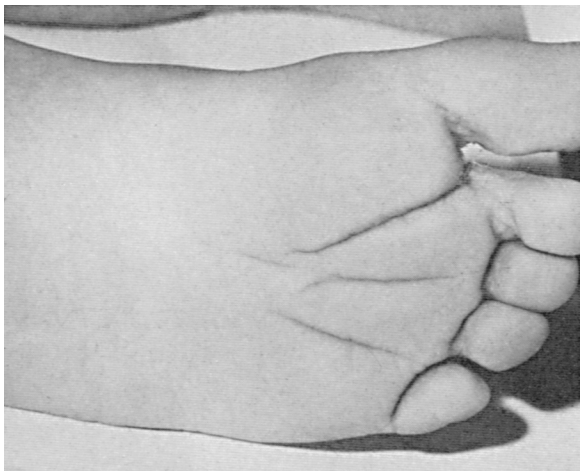
The foot also has ridge patterns. A sandal pattern of deep furrows is typical of mosaic trisomy 8 (Fig. 30.20). Fig. 30.21 illustrates the increased separation of the first and second toes and a prominent interdigital furrow in trisomy 21.

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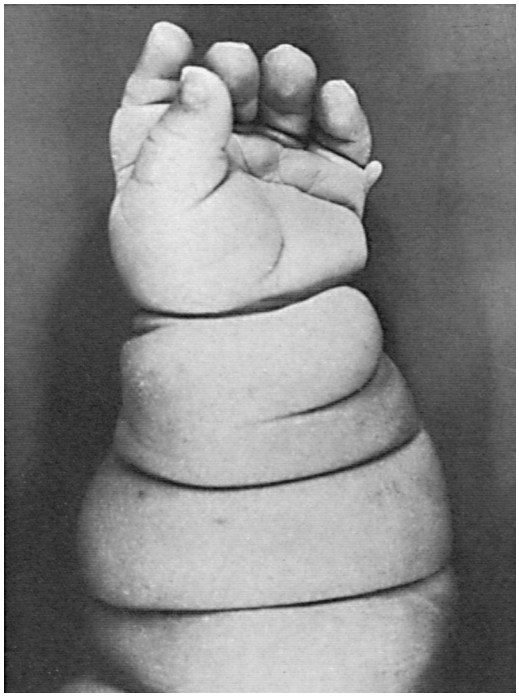
Historically, dermatoglyphics, the study of configurations of the characteristic ridge patterns of the volar surfaces of the skin, was sometimes used to aid in the diagnosis of the newborn with congenital anomalies. The scope of this subject is beyond that of this chapter, and the reader is referred to other sources.[54]

The hands and feet may be enlarged as a result of lymphedema. This is characteristic of infants with Turner or Noonan syndrome, in which the dorsum of the hands and feet may have a puffy appearance (Fig. 30.22). Congenital lymphedema can also be an autosomal dominantly inherited condition with variable expressivity.

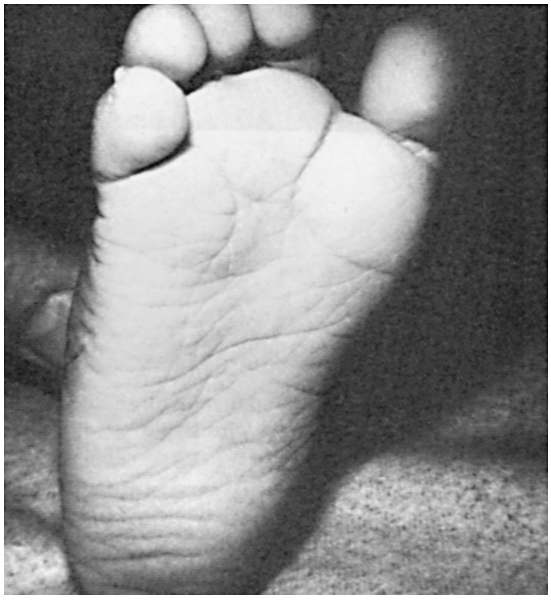
Rocker-bottom feet (Fig. 30.23) is a term used to describe a prominent heel and a loss of the normal concave longitudinal arch of the sole. This feature is common in trisomy 18 and other syndromes.



• **Fig. 30.20** Sandal line furrows in mosaic trisomy 8.



• **Fig. 30.18** Forearm and hand of patient in Fig. 30.17. Note rudimentary postaxial polydactyly.



• **Fig. 30.21** Trisomy 21. Note increased separation of first and second toes.

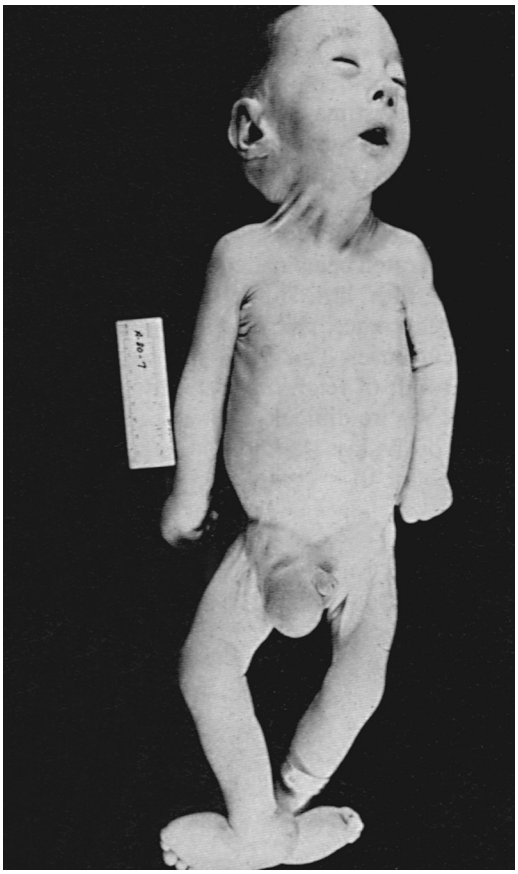


• **Fig. 30.19** **A,** Single transverse palmar crease. **B,** Incomplete bridged single palmar crease. **C,** Hand of patient with trisomy 21 showing single transverse palmar crease, brachydactyly, and clinodactyly of fifth finger with single phalangeal crease.

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• **Fig. 30.22** Dorsal edema of feet in patient with Turner syndrome.



• **Fig. 30.23** Trisomy 18. Note right hydrocele and rocker-bottom feet.

Significant anomalies of the underlying structure produce alterations in the normal form of the hands and feet. Such abnormalities may be classified into the following categories: absence deformities, polydactyly, syndactyly, brachydactyly, arachnodactyly, and contracture deformities (see Chapter 99).

Absence anomalies are of various types, and the etiology and possible associated malformations vary with the type.



• **Fig. 30.24** Postaxial polydactyly.

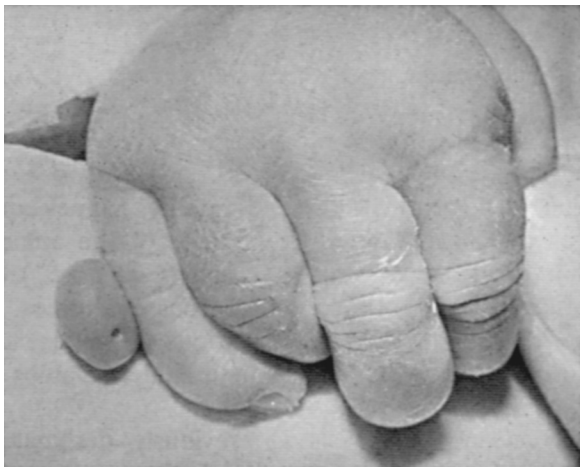
Congenital absence of an entire hand is termed acheiria, and absence of both hands and feet is acheiropodia. Ectrodactyly refers to a partial or total absence of the distal segments of a hand or foot, with the proximal segments of the limbs more or less normal. All such anomalies are examples of terminal transverse defects and may occur sporadically or as part of a syndrome. The term ectrodactyly is frequently misused for the lobster-claw anomaly, which is best described as split hand/split foot. In this anomaly, the central rays are deficient, and there is often fusion of the remaining digits. Split hand/split foot may be seen in isolation, when it is of autosomal dominant origin, or it may be seen with other anomalies.

It is useful to determine whether the defects involve primarily the radial, or preaxial, side of the limb or the ulnar, or postaxial, side. For example, blood dyscrasias such as Fanconi anemia and the thrombocytopenia-absent radius syndrome (TAR) commonly involve radial deficiency (see Chapter 79).

Polydactyly refers to partial or complete supernumerary digits and is one of the most common limb malformations. Postaxial polydactyly is more frequent than preaxial, particularly in African Americans (Fig. 30.24). As an isolated anomaly, polydactyly may be inherited as an autosomal dominant trait. It also may be a manifestation of a multiple malformation syndrome. Postaxial polydactyly may occur in a variety of syndromes, including trisomy 13 (Fig. 30.25), chondroectodermal dysplasia, Meckel-Gruber syndrome, and Bardet-Biedl syndrome. Preaxial polydactyly is characteristic of Carpenter syndrome and Majewski short rib-polydactyly syndrome.

Syndactyly refers to fusion of digits; it is usually cutaneous, but it may involve bone. Minimal syndactyly of the second and third toes is common in normal newborns. More extensive syndactyly is shown in Fig. 30.26 and can be seen in trisomy 21 and Smith-Lemli-Opitz syndrome. As an isolated anomaly, different clinical types may be distinguished, but each of them is inherited as an autosomal dominant trait with variable expressivity and incomplete penetrance.

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• **Fig. 30.25** Postaxial polydactyly in trisomy 13.



• **Fig. 30.26** Syndactyly between second and third toes.

Extensive syndactyly often is part of a syndrome, and typical examples include some of the craniosynostosis conditions, such as Apert and Pfeiffer syndromes.

Brachydactyly refers to shortening of one or more digits owing to anomalous development of any of the phalanges, metacarpals, or metatarsals. Various clinical types may be distinguished, but most isolated forms of brachydactyly are inherited in an autosomal dominant fashion. Brachydactyly is also a component of numerous disorders, including skeletal dysplasias such as achondroplasia and syndromes such as Albright hereditary osteodystrophy and trisomy 21 (see Fig. 30.19*C*).

Arachnodactyly refers to unusually long, spiderlike digits, and it is characteristic but not invariable in Marfan syndrome and homocystinuria. The appearance of brachydactyly and arachnodactyly can be confirmed by measuring and determining the ratio of middle finger to total hand length, which is normally about 0.43 in the newborn.

A variety of congenital joint deformities involving the limbs may occur. Arthrogryposis, multiple congenital contractures, is most often sporadic and may be associated with oligohydramnios or may be the result of some underlying neuromuscular abnormality, such as spinal muscular atrophy. Talipes equinovarus or calcaneovalgus deformities of the ankle are common isolated joint contractures (see Chapter 99). Contractures also may occur in numerous syndromes. Joint hypermobility is frequent in various connective tissue disorders, such as Marfan and Ehlers-Danlos syndromes, and can also be seen in a number of multiple anomaly syndromes such as Kabuki syndrome.



• **Fig. 30.27** Trisomy 18. Note characteristic clinodactyly of second, fourth, and fifth fingers.

Clinodactyly, as discussed previously, designates an incurving of a digit, most commonly of the fifth finger. This condition is frequent in trisomy 21 and other syndromes (see Fig. 30.19*C*). A characteristic clinodactyly involving the fourth and fifth fingers radially and second finger in an ulnar direction occurs in trisomy 18 (Fig. 30.27) or, less often, in trisomy 13.

Camptodactyly is irreducible flexion of the digits. In the hand, it usually involves the fifth finger, but it may affect other fingers as well. Isolated camptodactyly may be inherited as an autosomal dominant trait. Camptodactyly also may be part of a syndrome such as trisomy 8, trisomy 10q, and Freeman-Sheldon syndrome.

Evaluation of the Stillborn

Evaluation of the stillborn is essential to the diagnostic workup and is similar to that of the live-born infant. If this important function is not adequately performed, the family is left with little understanding of the nature and etiology of the anomaly, the recurrence risk, and methods of preventing future occurrences. Further, the grieving process, a natural consequence of fetal loss, can be more difficult without an understanding of the cause of the loss. In addition to the obvious role of the pathologist to learn as much as possible from the examination of the aborted fetus, the clinician is essential in encouraging the family to allow fetal evaluation and to allow the pathologist to conduct it. The clinician also should direct additional testing and meet with the family when the evaluation is complete to ensure that the family receives medical and genetic counseling. These

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evaluations are generally done by the perinatologist or neonatologist, and it is reasonable to assume that before 20 weeks of gestation, responsibility of pregnancy loss evaluation rests with the perinatologist, and after this date, it falls to the neonatologist.

Pregnancy loss before 20 weeks occurs in at least 12%-15% of all pregnancies. When the loss occurs after 20 weeks, it is usually called stillbirth[13,46,55,66] and occurs in 1%-2% of pregnancies. It is optimal for each hospital to develop a protocol for evaluating fetal loss, including which fetuses to study and which evaluations are appropriate.[47] A thorough surface examination by the clinician is useful to identify minor anomalies that may not be apparent to the pathologist as rigor mortis sets in. If indicated, a sample of blood or skin should be obtained as soon as possible under sterile conditions for chromosome analysis and possible chromosomal microarray, because karyotypic abnormalities are seen in 6%-13% of stillbirths.[36,49] Skin can be placed in viral culture media or sterile saline and sent to the laboratory for fibroblast culture. Cells from the fetal side of the placenta may grow when macerated fetal tissue may not. Examination of the stillborn and the placenta by the pathologist may identify internal anomalies that lead to a definitive diagnosis.

Diagnostic Testing and Indications

Once a thorough history has been taken and a physical examination has been performed, the clinician should identify those features that are most unique to the neonate. Sometimes a pattern is readily recognized, such as trisomy 21 in a child with an atrioventricular canal, hypotonia, palpebral fissures that slant upward, small squared ears, and fifth finger clinodactyly. However, a review of reference texts often is required to determine whether the findings represent a previously recognized malformation syndrome.[11,35] A clinical geneticist may be especially helpful at this point.

The following laboratory and imaging studies may be indicated to aid in making an accurate diagnosis. In many cases, a diagnosis does not become apparent until later in life as the physical features change and other structural or functional abnormalities become apparent.[41] Parents should be counseled about this possibility and that even though a diagnosis may not be apparent, the findings may well have a genetic basis and recurrence in future pregnancies is possible.

General Studies

In a newborn with one or more obvious major malformations or with multiple minor anomalies, imaging studies are often indicated to identify other anomalies. Whether or not other significant anomalies are identified, these studies will further describe the phenotype of the affected neonate. Detection of major anomalies involving the brain, heart, and kidneys is particularly important for diagnostic purposes, and it also may allow for more appropriate management and more accurate prognostication. Echocardiography is useful because congenital heart defects are among the most common major malformations with specific indications for genetic testing (Table 30.7). Ultrasonography of the head and abdomen is useful to screen for major structural anomalies of the brain, kidneys, and liver. Head ultrasonography is a crude study for brain abnormalities, and if brain abnormalities are suspected, more definitive procedures such as magnetic resonance imaging are indicated. Newborns with skull abnormalities, short stature, or foreshortened long bones should have a skeletal survey to evaluate for skeletal dysplasias.

Ophthalmology evaluation also can be useful in diagnosing the neonate with congenital anomalies, especially if brain malformations or neurologic abnormalities are present. This evaluation also should be performed if small genitalia are present in a male infant (septo-optic dysplasia) or if features of the CHARGE syndrome are present.

The neonate with ambiguous genitalia requires a battery of tests, including chromosome analysis (see Genetic Laboratory Studies) to determine genotypic sex, pelvic ultrasonography to identify internal genitalia, and endocrine testing (17-OH progesterone, testosterone, luteinizing hormone, follicle-stimulating hormone). It is best to defer assignment of sex until many of these tests have been performed and a urologist has evaluated the newborn. This is an emotional crisis for the family. Every neonatal unit should have a plan in place to treat sex determination as a medical emergency. A psychologist is an essential member of the team to assist the family in dealing with the uncertainty and complexity of decision making (see Chapter 89).

The value of the postmortem examination cannot be overemphasized. A thorough evaluation by an experienced pathologist can yield findings that would not be identified otherwise and that may lead to a definitive diagnosis and thus information about recurrence risk and possible prenatal testing in future pregnancies. The role of the clinician is to educate the family about the importance of such an evaluation. If the family is reluctant to agree to a full autopsy, a partial exam focused on chest and abdomen can be useful.

Genetic Laboratory Studies

Table 30.7 shows typical cytogenetic, molecular, and biochemical tests performed on neonates with congenital anomalies.[24] Genetic analysis is indicated in all newborns with ambiguous genitalia, two or more major anomalies, multiple minor anomalies, or growth restriction in association with anomalies. Such studies should be performed, even if a prenatal chromosome analysis had normal findings, because of improvements in resolution in identifying small deletions or amplifications. Chromosomal microarray (CMA) is considered the first line genetic test in neonates with multiple anomalies.[45] It allows for the detection of deletions and duplications too small to be seen in a high-resolution chromosome analysis. Depending on the study

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TABLE 30.7 Genetic Diagnostic Tests Commonly Used in Newborn Medicine

Indication*	Condition	Approach
Hypotonia	Myotonic dystrophy	Targeted mutation analysis of trinucleotide repeat
	Spinal muscular atrophy	Deletion analysis of exon 7 in *SMN1* gene
	Prader-Willi syndrome	Methylation studies of chromosome 15
	Congenital disorders of glycosylation	Analysis of serum transferrin glycoforms
Multiple anomalies	CHARGE syndrome	Gene sequencing of *CHD7*
	Noonan syndrome	Sequencing of seven genes in the Ras pathway: *PTPN11*, *KRAS*, *RAF1*, *SOS1*, *NRAS*, *BRAF*, and *MAP2K1*
	Microdeletion syndromes	Chromosome microarray
Abnormal genitalia, isolated or with other anomalies	Camptomelic dysplasia	Gene sequencing of *SOX9*
	WAGR or Denys-Drash	Gene sequencing of *LIT1*
Ambiguous genitalia	Congenital adrenal hyperplasia	17-OH progesterone
	Smith-Lemli-Opitz syndrome	7-Dehyrocholesterol
	45,X/46,XY	Karyotype
Small infant or dwarfism	Achondroplasia, hypochondroplasia, thanatophoric dysplasia	Targeted sequencing of *FGFR3*
Pierre Robin sequence	Stickler syndrome	Genetic sequencing of *COL11A1*, *COL11A2*, or *COL2A1*
	22q11 deletion/velocardiofacial/ DiGeorge syndrome	FISH 22q11 deletion probe or microarray
Congenital Heart Disease		
Conotruncal defects	22q11 deletion/velocardiofacial/ DiGeorge syndrome	FISH 22q11 deletion probe
Supravalvular aortic stenosis	Williams syndrome	FISH for *ELN* gene deletion
Coarctation of aorta	Turner syndrome	Karyotype
Pulmonic stenosis	Noonan syndrome	Sequencing of eight genes in the Ras pathway: *PTPN11*, *SOS1*, *RAF1*, *RIT1*, *KRAS*, *NRAS*, *BRAF*, *MAP2K1*

*This list is not exhaustive, and the appropriate genetic test for all these indications is dependent on the phenotype of the neonate. WAGR, Wilms tumor, aniridia, genitourinary anomalies, intellectual disability.
Adapted from Goodin K. Advances in genetic testing and applications in newborn medicine. *NeoReviews* 2008;9:282; and Slavotinek AM. Novel microdeletion syndromes detected by chromosome microarrays. *Hum Genet*. 2008;124:1.

population, CMA is able to identify an additional 5%-10% of cases with genomic imbalance compared with routine karyotyping.[15,38] However, CMA can also identify deletions or duplications known as copy number variants that may or may not be associated with the phenotype of the neonate.[56] Thus, care must be taken when interpreting the CMA results. Parental samples are recommended to determine whether the copy number variant occurred de novo or is inherited from a normal parent and is unlikely to cause the anomaly in question.

Fluorescence in situ hybridization testing can be ordered if there is a high level of suspicion for a known microdeletion syndrome not detectable by routine cytogenetic analysis, such as 22q11 deletion/velocardiofacial/DiGeorge syndrome or Williams syndrome. Testing with FISH has shown that a significant number of neonates with conotruncal heart defects have a 22q11 microdeletion, so this testing is indicated in all patients with truncus arteriosus, interrupted aortic arch, and tetralogy of Fallot. Conditions with known cardiovascular associations are listed in Table 30.8.

When a syndrome or syndromes are suspected in the differential diagnosis, molecular genetic analysis of specific genes should be considered. Molecular gene-based testing has become a useful tool in diagnosing the newborn with congenital anomalies, because the number of genes identified to cause malformation has increased. For example, in those infants with unexplained hypotonia and contractures, DNA testing may identify an expansion in the myotonic dystrophy gene or mutations in the spinal muscular atrophy gene. Fifty percent of infants with Pierre Robin sequence will have an identifiable genetic cause such as mutations in the collagen genes (*COL11A1*, *COL11A2*, or *COL2A1*) causing the autosomal dominant Stickler syndrome, or deletion in 22q11 causing velocardiofacial/DiGeorge syndrome.[19]

The medical sequencing technology should be understood by the ordering clinician because some molecular tests examine the most frequent sequence variants and other methods sequence the entire coding regions of the causative gene. Thus, a targeted test could miss a true causative mutation in a particular patient. Further, sequence variants of unclear pathogenicity have been commonly identified across the genome, so care should be taken when correlating a putative mutation with the phenotype.

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TABLE 30.8 Major Chromosomal and Inherited Syndromes Associated With Heart Defects

Syndrome	Cardiac Defects	Noncardiac Features
Trisomy 13	ASD, PDA, VSD	Microcephaly; cutis aplasia; holoprosencephaly; cleft lip; microphthalmia; low-set ears; micrognathia; hypotonia; polydactyly; rocker bottom feet; cryptorchidism
Trisomy 18	ASD, ECD, PDA, TOF, VSD	Intrauterine growth restriction; microcephaly; prominent occiput; micrognathia; cleft lip/palate; low-set ears; clenched hands with fingers 1 and 4 overlapping 2 and 3; rocker bottom feet; cryptorchidism; short sternum; pectus carinatum
Trisomy 21	ECD, VSD, ASD	Brachycephaly; epicanthal folds; small ears; upslanting palpebral fissures; transverse palmar crease; protruding tongue; excess nuchal skin; hypotonia; duodenal atresia
CHARGE	TOF, ECD aortic arch anomalies	Coloboma; choanal atresia; cranial nerve dysfunction; ear abnormalities; Mondini defect of the cochlea; absent or hypoplastic semicircular canals; developmental delay; growth deficiency; genital hypoplasia
Deletion 22q11 (DiGeorge, velocardiofacial)	IAA, TF, VSD, truncus arteriosus	Hypocalcemia; palatal abnormalities; immune deficiency; significant feeding and swallowing problems; constipation with or without structural gastrointestinal anomalies; renal anomalies; hearing loss (both conductive and sensorineural)
Holt-Oram	ASD, VSD, COA	Upper-extremity malformations involving radial, thenar, or carpal bones; cardiac conduction defects
Kartagener	Dextrocardia	Situs inversus; bronchiectasis; asplenia; conductive hearing loss
Loeys-Dietz	Aortic dilatation and/or rupture, MVP	Hypertelorism; craniosynostosis; cleft palate/bifid uvula; pectus excavatum or pectus carinatum; scoliosis; joint laxity; arachnodactyly; talipes equinovarus; velvety and translucent skin; easy bruising; widened, atrophic scars
Marfan	Aortic dilatation, MVP, TVP, pulmonary artery dilatation (proximal)	Arachnodactyly; pectus deformity; hyperextensible joints; high arched palate; ectopia lentis
Neurofibromatosis	PS, aortic dilatation, MVP, HCM[36]	Café au lait spots; axillary/inguinal freckling; Lisch nodules; cutaneous neurofibromas; anteriolateral tibial bowing
Noonan	PS, HCM[12,33]	Short, broad neck; low hairline; coagulation defects; pectus deformity; scoliosis; cryptorchidism; lymphatic dysplasia; ptosis; low-set, posteriorly rotated ears
Smith-Lemli-Opitz	TAPVC, AV canal	Prenatal and postnatal growth restriction; microcephaly; underdeveloped external genitalia in males/hypospadias; postaxial polydactyly; 2-3 syndactyly of the toes; poor suck, irritability; failure to thrive; temporal narrowing; epicanthal folds; broad nasal bridge; short nasal root; anteverted nares; cleft palate; low-set, posteriorly rotated ears; micrognathia
Thrombocytopenia-absent radius (TAR)	ASD, TOF[16]	Thrombocytopenia; bilateral absent radii with thumbs present; long bone abnormalities
Turner syndrome	AS, COA, HLHS[70]	Broad chest; short, broad neck; lymphedema; hyperconvex nails
Williams syndrome	SVAS, branch pulmonary artery stenosis[10]	Hypercalcemia; feeding difficulties; failure to thrive; fullness of mouth and eyes; hypotonia; hyperextensible joints; hypertension; hypercalciuria

AS, Aortic stenosis; ASD, secundum atrial septal defect; AV, atrioventricular; COA, coarctation of the aorta; ECD, endocardial cushion defect; HCM, hypertrophic cardiomyopathy; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; PS, pulmonary valve stenosis; SVAS, supravalvular aortic stenosis; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TVP, tricuspid valve prolapse; VSD, ventricular septal defect.

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With advances in technology, it is now possible to sequence the entire coding region (exome) or genome of an individual. Whole exome sequencing (WES) is most powerful when DNA samples from both parents are included for analysis, referred to as an exome trio. This testing methodology identified an etiology for the anomalies for 36% of the 140 babies with multiple anomalies who underwent analysis.[21] Other series reporting on results focused on the high-risk NICU population with abnormal neurologic findings have reported identifying a care changing diagnosis in up to 50% of patients.[44,57] As the process of data interpretation improves, the diagnostic yield of WES should continue to increase, making it more informative in the evaluation of the neonate with multiple anomalies.

Biochemical testing for many metabolic malformation syndromes is also possible. Metabolic conditions were traditionally thought of as not being associated with congenital anomalies, but this concept is changing. A definitive diagnosis of multiple malformation Smith-Lemli-Opitz syndrome can be made by obtaining a low serum cholesterol level and an elevated 7-dehydrocholesterol level.[48] Congenital disorders of glycosylation, a group of autosomal recessive disorders with a wide variety of abnormalities, are diagnosed by serum transferrin glycoform analysis.[64] Presumably many other conditions with congenital anomalies will be found to have a biochemical basis, which will allow for more definitive diagnoses and appropriate management strategies (see Table 30.7).

Genetic Counseling

Genetic counseling should be provided at some point to all parents of children with major malformations or multiple anomalies. Genetic counseling is a communication process during which families are informed about the abnormalities present in the affected individual, with medical and genetic knowledge discussed in practical language. It is most often provided by genetic counselors, who typically work with medical geneticists. Genetic counselors are individuals with master's degrees who have been specifically trained to understand genetic disorders and congenital anomalies and to help families with the psychological and emotional adaptation to having a family member with a serious and chronic problem. Medical geneticists are physicians who have received special training in genetic counseling and in the diagnosis and management of genetic disorders and birth defects.

Genetic counseling for congenital anomalies should include a description of the abnormality, the natural history, associated abnormalities, and prognosis for the disorder. The etiology of the abnormality (if known), whether genetic or nongenetic, is explained in such a manner that the family can understand. The family also is given reassurance that the condition in the affected individual is not the fault of any individual, and information about recurrence risk is provided. Analysis of the pedigree can then identify family members who are at increased risk for being affected or having affected offspring. These relatives should also learn about the disorder and receive an explanation of the reproductive options available for the condition, particularly the prenatal and preimplantation technologies, complications, and accuracy. Assistance should be offered in reaching a decision about prenatal or postnatal testing. Information about appropriate community services and family support organizations also is offered.[67]

Educational Resources and Support Organizations

With almost universal access to the Internet, the number of educational resources for clinicians and families about genetic conditions has increased greatly, from clinical description to chromosomal and molecular databases.[7,24] The National Library of Medicine's National Center for Biotechnology Information hosts several gene-specific websites that are particularly relevant for the neonatologist or perinatologist who is evaluating an infant with congenital anomalies.[45a] Gene Reviews provides a detailed description of many single-gene disorders and gives information about clinical genetic testing availability and interpretation, also providing current lists of resources for families.[45b] An excellent reference for all single-gene conditions is the Online Mendelian Inheritance in Man.[43] Because most congenital anomalies and genetic disorders are relatively rare, usually occurring with a frequency of 1 in 1000 or less, family support organizations have been developed to help combat the isolation and grief felt by families who have or have had an affected child. These groups usually offer support and empathy and serve as a clearinghouse for information about the disorder and its management. Often they have a newsletter for members that describes helpful coping mechanisms and keeps families updated on relevant resources and research. With the increased use of social media, many support groups have Facebook pages that allow members another method of communication.

Such organizations often have been started by, and are usually staffed by, parents of affected individuals or by affected individuals themselves. As a result, they vary greatly both in the format and content of what they offer and in the accuracy of the information they distribute. Organizations for more frequent disorders, such as trisomy 21, are usually large and professionally run; offer educational forums, such as an annual conference and lay literature; keep listings of resources locally and nationally; and may even offer grant funding for research on the disorder. Smaller organizations for less common conditions may serve primarily a social and support function. Because of this variability in the knowledge of support organizations and the resultant uncertainty concerning the accuracy of information provided, it is advisable for the physician to become familiar with an organization and its functions before referring a family.

The Genetic Alliance (http://www.geneticalliance.org/, accessed March 17, 2018) provides information services

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for individuals and disease-specific organizations. The alliance supplies contact information and data about the organizations. Another group, the National Organization for Rare Disorders (http://www.rarediseases.org/, accessed March 17, 2018), functions as a clearinghouse for information on genetic disorders; it will send a summary of this information written for lay individuals for a small fee, will match families, and will make medical referrals, if appropriate. The March of Dimes (http://www.marchofdimes.com/, accessed March 17, 2018) provides excellent lay information about specific genetic disorders. Genetics Home Reference (https://ghr.nlm.nih.gov/, accessed March 17, 2018) provides basic information about genes and genetics, as well as information about genetic disorders.

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Key Points

- It is the role of the neonatologist to direct the evaluation of the newborn or stillborn with congenital anomalies.
- Diagnostic testing and evaluations, along with consultation of references and specialists in the field, such as medical geneticists and dysmorphologists, may be helpful.
- The goal is to identify the etiology to improve medical management and to provide accurate information on prognosis and recurrence risk that can be shared with the family.

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31

Overview and Initial Management of Delivery Room Resuscitation

JAY P. GOLDSMITH

The transition from fetus to neonate represents a series of rapid and dramatic physiologic changes during which the placenta is replaced by the lungs as the primary organ of gas exchange. Although this transition goes smoothly most of the time, in approximately 10% of births the active intervention of a skilled individual or team is necessary to ensure that the newborn receives the appropriate assistance to assume independent existence as quickly as possible.[70,72] The need for full resuscitation, including chest compressions and/or medication administration, is relatively rare, occurring in approximately 1-2 per 1000 live births.[48] For these severely depressed newborns and for extremely premature infants, to avoid or minimize injury, the process of resuscitation during the first hour of life requires excellent communication, cognitive knowledge, skilled technical providers, and behaviors that are integral to a collaborative team effort.

Although certain episodes of fetal asphyxia cannot be prevented, there are many circumstances in which, in the immediate neonatal period, a prompt and skilled resuscitation may prevent death or ameliorate lifelong adverse sequelae. Newborns who require medication and/or chest compression in the first few minutes after birth usually have significant fetal acidemia, inadequate ventilation after birth, or both.[48] Because the need for significant intervention cannot always be predicted, the American Heart Association (AHA)/American Academy of Pediatrics (AAP) *Textbook on Neonatal Resuscitation* and the *Guidelines for Perinatal Care* have advised: "At every delivery, there should be at least one individual whose primary responsibility is the infant and who is capable of initiating resuscitation, including positive pressure ventilation."[4,70] The *Guidelines* also suggest that "the identification and resuscitation of a distressed neonate requires an organized plan of action" and that hospitals should assure the competency and periodic credentialing of individuals who perform these tasks.[4]

In the past three decades, neonatal resuscitation has been the subject of extensive research and review. The evidence evaluation process of the International Liaison Committee on Resuscitation (ILCOR) provides rigorously developed evidence-based guidelines based on the available medical science to inform the best approach to neonatal resuscitation.[72] Although many elements of a resuscitation sequence have been agreed upon, debate and discussion regarding certain aspects of the process continue.[14,67] Moreover, the ILCOR guidelines are a Consensus of Science and Treatment Recommendations (CoSTaR) document, and each national resuscitation council may modify the treatment recommendations based on its members' own deliberations of the science and what is deemed appropriate for its country. Thus, despite one international scientific document, there are often significant differences among the recommendations for performing neonatal resuscitation among various countries.[52]

Research continues to search for answers to many difficult questions. The US guidelines (e.g., Neonatal Resuscitation Program), updated every 5-6 years by the AAP and the AHA,[70] are essentially derived from the ILCOR CoSTaR document, which is usually published the preceding year.[72] These recommendations represent the best distillation of the available science at the time of their publication as viewed by the AAP Neonatal Resuscitation Program Steering Committee and should serve as the foundation for any resuscitation program or algorithm in the United States. This chapter presents the current guidelines for neonatal resuscitation and reviews the evolving science in this area to provide an appreciation of common and controversial questions and a basis for understanding conflicting views.

Fetus

In utero, the fetus depends on the placenta for gas exchange. Despite a Pao_2 of 20-30 mm Hg, the normal fetus carries on essential metabolism and is not hypoxic. The tissues receive adequate amounts of oxygen, and anaerobic metabolic pathways are not usually used. Adequate oxygen delivery is accomplished with an adaptive process primarily involving the architecture of the circulatory system, the characteristics of fetal hemoglobin, and the rate of perfusion of fetal organs.

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Abstract

Neonatal resuscitation has been the subject of extensive research over the last three decades, resulting in evidence-based guidelines that are revised every 5-6 years. The transition from fetal to neonatal gas exchange requires many cardiopulmonary physiologic changes, which may be impaired by a variety of intrauterine and/or intrapartum events leading to neonatal depression at birth requiring skillful resuscitation. Someone capable of beginning resuscitation should be at every delivery; in some cases, the need for resuscitation may be anticipated and a team of appropriately trained individuals should be ready to begin the initial steps. The clinical condition of the newly born infant, evolving Apgar scores, and umbilical cord blood gases will inform the resuscitation team of the need for and the extent of resuscitation required. Initial steps should include provisions for the maintenance of normal temperature, clearing the airway, and beginning positive pressure ventilation if adequate breathing does not result from appropriate stimulation.

Keywords

resuscitation
depression at birth
preparation
equipment
personnel

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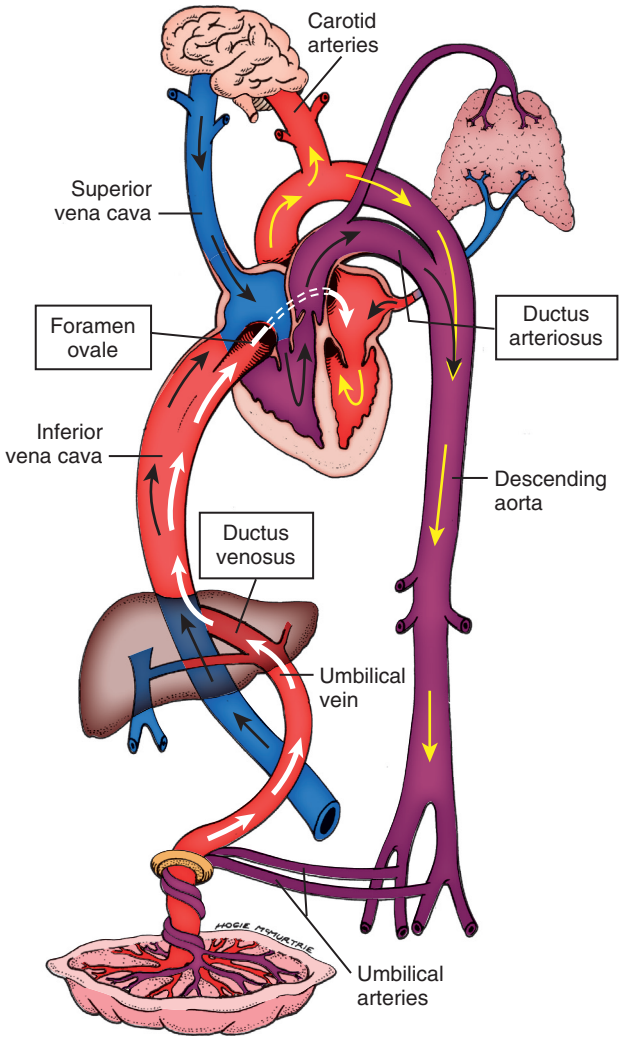
The placenta has the lowest resistance in the circulatory system of the fetus and preferentially receives blood from the systemic circulation. Approximately 40% of the total cardiac output of the fetus flows through the placenta. Blood in the umbilical artery leaving the fetus travelling back to the placenta has a P_{O_2} of 15-25 mm Hg.[37] In humans, umbilical venous blood returning from the placenta to the fetus obtained by percutaneous umbilical vein sampling has a P_{O_2} normally 20-40 mm Hg, but it may range up to 45 mm Hg.[42] When the umbilical venous blood is mixed with venous return from the fetus, the resultant P_{O_2} is lower. Although the arterial oxygen tension of the fetus is low compared with postnatal values, the high affinity of fetal hemoglobin for oxygen shifts the oxyhemoglobin curve to the left, resulting in only mildly diminished oxygen content of the blood.

Several adaptive and anatomic mechanisms help keep fetal tissue well perfused and oxygenated despite low oxygen tension. When the umbilical vein enters the abdomen of the fetus, the stream splits, with slightly more than half of the blood flowing through the ductus venosus into the inferior vena cava. The remaining blood perfuses portions of the liver. The umbilical venous return entering the inferior vena cava tends to stream and does not completely mix with less oxygenated blood entering the inferior vena cava from below. In the right atrium, the crista dividens splits the inferior vena cava stream so that oxygenated blood from the umbilical vein flows through the foramen ovale into the left side of the heart. The less oxygenated blood returning from the fetal body flows into the right ventricle (Fig. 31.1).

In the fetus, blood flow through the lungs is diminished because of the high resistance of the fetal pulmonary circuit, the open ductus arteriosus, and the lower resistance of the systemic and placental circuits. Nearly 90% of the right ventricular output crosses the ductus arteriosus and enters the aorta, bypassing the lungs. With little return from the pulmonary veins, oxygen in the umbilical venous blood crossing the foramen ovale into the left atrium is only slightly diluted. The most highly oxygenated blood perfuses the brain and heart through the carotid and coronary arteries before its oxygen concentration is decreased by blood entering the aorta through the ductus arteriosus.

Another adaptive mechanism keeping the fetal tissues oxygenated is the rate of perfusion. Fetal tissues are perfused with blood at a higher rate than in the adult. The increased delivery of blood compensates for the low oxygen saturation (Sp_{O_2}) in the fetus and the higher oxygen affinity of fetal hemoglobin. Finally, the fetus (except during labor) has less of an oxygen demand than the newborn. Because thermoregulation is unnecessary and respiratory effort is limited, two significant processes that consume oxygen in the newborn are either eliminated or markedly diminished in the fetus.

The P_{CO_2} of the fetus is slightly higher than adult levels. The normal umbilical venous P_{CO_2} is 35-45 mm Hg. Elimination of carbon dioxide from the fetus is enhanced by maternal hyperventilation and relative hypocarbia during pregnancy. Because of the lower P_{CO_2} of maternal blood, a gradient is created favoring the transfer of carbon dioxide across the placenta from fetal to maternal blood (Bohr effect).



• **Fig. 31.1** Fetal circulation.

The low fetal P_{O_2} contributes to the flow characteristics of the fetal circulation by helping to keep the pulmonary vascular resistance (PVR) high. The ductus arteriosus remains patent because of fetal production of prostaglandins and a relatively low P_{O_2}.

The fetus maintains metabolic homeostasis despite low oxygen tensions because of these adaptive and anatomic characteristics. However, any significant compromise of fetal gas exchange before labor (e.g., intrauterine growth restriction, placental abnormalities) or during the intrapartum period or lack of effective transition at birth quickly results in asphyxia, consisting of hypoxia, elevated P_{CO_2}, and metabolic acidosis.

Transition at Birth

The circumstances and process of delivery contribute to the condition of the infant at birth. A cesarean section done

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before the onset of labor has a different physiologic effect on the process of transition than the standard labor process. Delivery of a multiple gestation and anesthesia administered to the mother may also be significant contributing factors. The labor process causes mild hypoxia and acidosis. With each contraction, uterine blood flow decreases, with a resulting decrease in placental perfusion and a temporary impairment of transplacental gas exchange resulting over time in a mild metabolic acidosis; this is accompanied by transient hypoxia and hypercapnia. The intermittent nature of normal labor permits the fetus to "recover" between each contraction; however, the effect is cumulative and may be exacerbated with an abnormal labor contraction pattern. Throughout a normal labor, the fetus undergoes a progressive but slow reduction in P_{O_2}, some increase in P_{CO_2}, a decrease in pH, and the accumulation of a mild metabolic acidosis.[11] The normal fetus enters labor with a base excess of –2 mmol/L; with uncomplicated progression of labor to vaginal delivery, the base excess will be reduced by an additional 3-4 mmol/L.[11,54] In the normal circumstance, these changes are not significant enough to depress the infant and prevent normal transition from intrauterine to postnatal existence.

With birth, the neonate must establish the lungs as the site of gas exchange; the circulation, which in the fetus shunted blood away from the lungs, must now fully perfuse the pulmonary vasculature. Postnatal breathing is on a continuum with in utero breathing movements that are well established but intermittent in the term fetus.[47] Clamping of the cord at birth stimulates peripheral and central chemoreceptors, and in conjunction with tactile and thermal stimulation, results in an increased systemic blood pressure. This combination of events is usually enough stimulation for a noncompromised infant to begin breathing. The American College of Obstetricians and Gynecologists (ACOG) now recommends delayed cord clamping for 30-60 seconds in vigorous term and preterm infants to increase blood volume, decrease need for inotropic support, and reduce several complications of prematurity. However, if the placental circulation is not intact (i.e., abruptio placenta) or the newborn needs immediate resuscitation, immediate cord clamping should be considered or care should be individualized.[15,50]

The clearance of lung fluid after birth is the result of multiple processes and only minimally caused by the "thoracic squeeze" during passage through the birth canal. A few days before a normal term vaginal delivery, the fetal production of lung fluid slows, and alveolar fluid volume decreases.[9] The process of labor is a powerful stimulus for the clearance of lung fluid, and that transfer of fluid from the air spaces is predominantly a process of active transport into the interstitium and drainage through the pulmonary circulation, with some fluid exiting through lymphatic drainage.[28] Although started before labor and influenced by the increasing levels of endogenous catecholamines, the process accelerates immediately after birth.

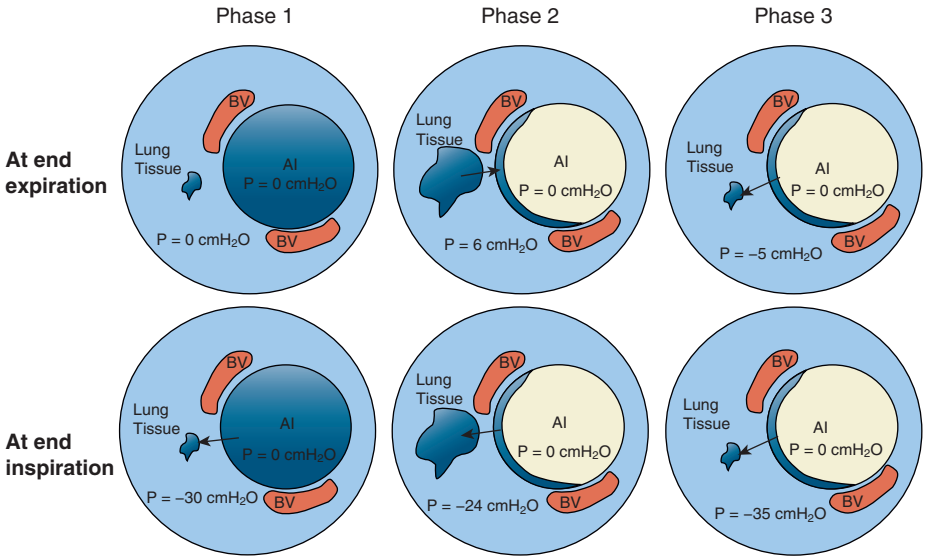
The first few breaths must facilitate clearance of fluid from the lungs and establish a functional residual capacity (FRC).[62,63,69] The first breath of a spontaneously breathing term infant is generally characterized by short inspirations each followed by prolonged expiratory phases. Although the peak inspiratory pressure may be as high as −50 cm H_2O to −100 cm H_2O, the opening pressures are very low. That is, gas begins to enter the lungs at very low pressures, usually less than −5 cm H_2O pressure. Very high expiratory pressures are also generated; these pressures generally exceed the inspiratory pressure. This expiratory pressure, probably generated against a partially closed glottis, drives the liquid in the lung peripherally, increasing the FRC over the first several breaths with multiple inspiratory efforts. In a vigorous, spontaneously breathing, vaginally delivered infant, a significant FRC develops with the first several breaths. However, the depressed neonate may need assistance with establishing an FRC. A three-phase process proposed by Hooper et al. suggests that initial resuscitation of an apneic newly born baby should begin with a sustained inflation to aerate the lung followed by positive end expiratory pressure to maintain the FRC (see Chapter 32) (Fig. 31.2).[26,39] However, sustained inflations at birth are not recommended at this time by the Neonatal Resuscitation Program (NRP).[70]

Expansion of the lungs is a stimulus for surfactant release, which reduces alveolar surface tension, increases compliance, and helps maintain a stable FRC. Simultaneously, the act of ventilation alone reduces PVR. Ventilation leads to a decrease in P_{CO_2} and an increase in pH and P_{O_2}, also causing a decrease in PVR.[13] The administration of oxygen is not necessary to produce this drop in PVR. In a study of lambs, Lakshminrusimha and colleagues showed that PVR decreased nearly as much (72%) in the first 30 minutes after birth with air resuscitation as with 100% oxygen.[31] By 60-90 minutes after birth, the decrease in PVR in the air group had reached the same level as the 100% oxygen group. Fig. 31.3 illustrates the relationships between pH, P_{O_2}, and PVR.[55] Clearance of lung fluid, establishment of FRC, and a decrease in PVR with an increase in pulmonary blood flow facilitate postnatal ventilation and oxygenation.

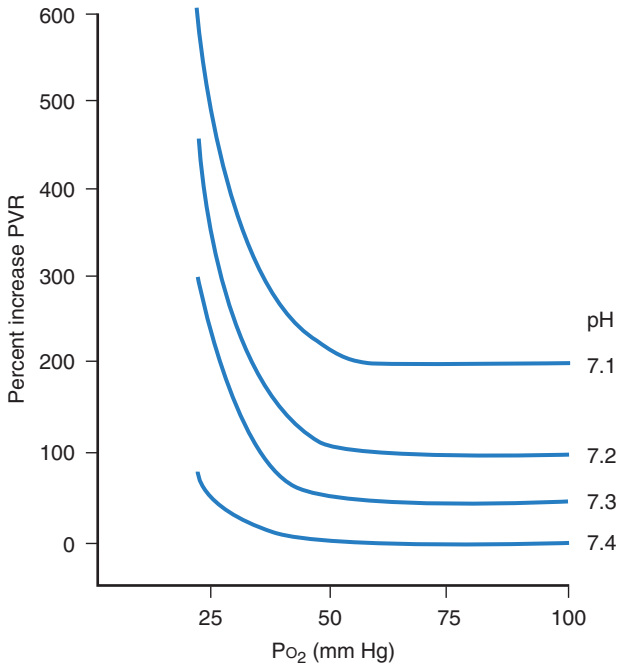
With the onset of ventilation, the fetal circulatory system assumes the adult pattern. Coincident with clamping of the cord, the low-resistance placenta is removed from the systemic circuit, and systemic blood pressure increases. This increase in systemic pressure, coupled with the decrease in PVR and in pulmonary artery pressure, decreases the right-to-left shunt through the ductus arteriosus. The increase in Pa_{O_2} further stimulates functional closure of the ductus arteriosus. With ductal shunting diminished, pulmonary artery blood flow increases, resulting in increased pulmonary venous return to the left atrium and increased pressure in the left atrium. When the left atrial pressure exceeds right atrial pressure, the foramen ovale functionally closes.

An uncomplicated transition from fetal to newborn status is characterized by loss of fetal lung fluid, secretion of surfactant, establishment of FRC, decrease in PVR, increased systemic pressure after removal of the low-resistance placenta from the systemic circuit, functional closure of two shunts (ductus arteriosus and foramen ovale), and increase

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• **Fig. 31.2** Three-phase process of respiratory transition in the newborn. AI, Alveolus; BV, blood vessel; P, pressure. (From Hooper SB, te Pas AB, Kitchen MJ. Respiratory transition in the newborn: a three-phase process. *Arch Dis Child Fetal Neonatal Ed.* 2016;101:F266-F271.)



• **Fig. 31.3** Pulmonary vascular resistance (PVR) in the calf. (Data from Rudolph AM, et al. Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. *J Clin Invest.* 1966;45:339.)

in pulmonary artery blood flow. In most circumstances, the mild metabolic acidosis associated with labor is insufficient to interfere with this process. Regardless of the mode of birth, the transition may be significantly altered by various antepartum or intrapartum events, resulting in cardiorespiratory depression, asphyxia, or both. Infants who are very premature are especially vulnerable to these untoward events.

Causes of Depression and Asphyxia

A newborn may be compromised because of problems initiated in utero with the mother, the placenta, or the fetus itself (Box 31.1). A process initiated in utero may extend into the neonatal period, preventing a normal transition. An asphyxial process also may be neonatal in origin; that is, the infant seems well until required to breathe on his or her own.

Maternal causes of fetal compromise may be related to decreased uterine blood flow, which decreases the amount of oxygen transported to the placenta. Diminished uterine blood flow may result from maternal hypotension (such as hypovolemia, allergic reaction, or as a result of drugs used to treat hypertension), regional anesthesia, eclampsia, or abnormal uterine contractions. Problems with the placenta, such as chronic structural abnormalities, infarcts, premature separation, edema, or inflammatory changes may impair gas exchange. The fetus also may be compromised because of fetal problems related to cord compression, such as nuchal cord, prolapse, or a breech presentation with cord compression by the aftercoming head, or by intrinsic fetal problems such as anemia or congenital abnormalities. In some cases, inflation of the lung occurs normally, but there may be a deficiency in oxygen-carrying capacity, as in severe hypovolemia from acute hemorrhage or fetal-maternal transfusion, or there may be inadequate cardiac output from numerous causes. A neonate may not have adequate ventilation after delivery because of many problems, including asphyxia, drug-induced central nervous system (CNS) depression, CNS anomalies or injury, spinal cord injury, mechanical obstruction of the airways, congenital facial or airway deformities, immaturity, pneumonia, or congenital anomalies.

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• BOX 31.1 Factors Associated with Neonatal Depression and Asphyxia

Antepartum Risk Factors

- Maternal diabetes
- Pregnancy-induced hypertension
- Chronic hypertension
- Chronic maternal illness
- Cardiovascular
- Thyroid
- Neurologic
- Pulmonary
- Renal
- Anemia or isoimmunization
- Previous fetal or neonatal death
- Bleeding in second or third trimester
- Maternal infection
- Polyhydramnios
- Oligohydramnios
- Premature rupture of membranes
- Post-term gestation
- Multiple gestation
- Size-dates discrepancy
- Drug therapy
- Lithium carbonate
- Magnesium
- Adrenergic blocking drugs
- Selective serotonin reuptake inhibitor antidepressants
- Maternal substance abuse
- Fetal malformation
- Diminished fetal activity
- No prenatal care
- Age <16 or >35 years

Intrapartum Risk Factors

- Emergency cesarean section
- Forceps or vacuum-assisted delivery
- Breech or other abnormal presentation
- Premature labor
- Precipitous labor
- Chorioamnionitis
- Prolonged rupture of membranes (>18 hours before delivery)
- Prolonged labor (>24 hours)
- Prolonged second stage of labor (>3 hours)
- Fetal bradycardia
- Nonreassuring fetal heart rate patterns
- Use of general anesthesia
- Uterine tetany
- Narcotics given to mother within 4 hours of delivery
- Meconium-stained amniotic fluid
- Prolapsed cord
- Abruptio placentae
- Placenta previa

Finally, there are some circumstances in which the infant may initiate breathing only to diminish markedly or stop breathing soon after birth. Examples include extreme prematurity with inadequate ventilatory support after birth, drug-induced depression in which the stimuli surrounding birth initially overcome the depression, congenital diaphragmatic hernia (CDH), and spontaneous pneumothorax.

Response to Asphyxia

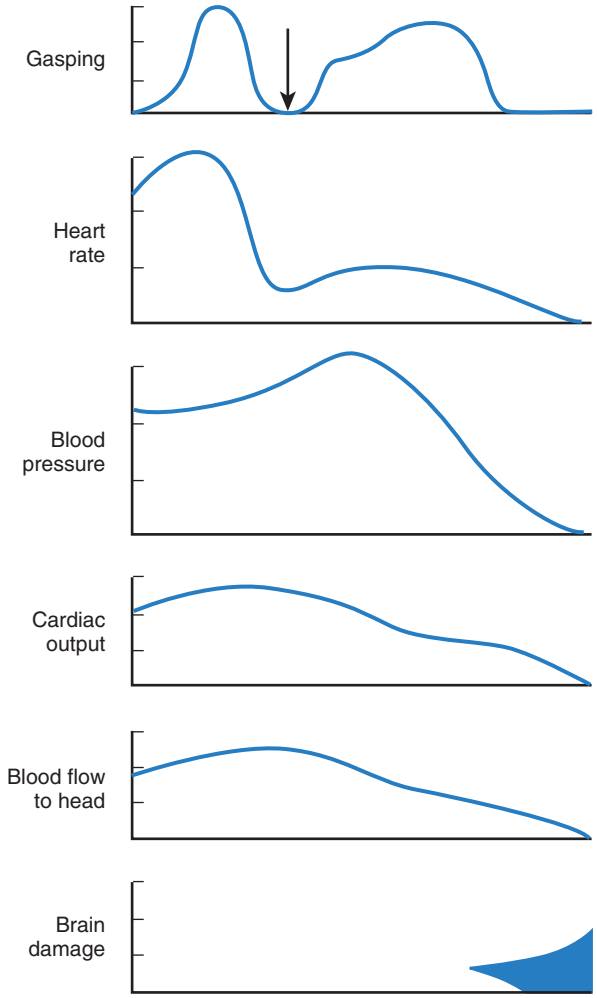
The goal with any depressed or asphyxiated infant, whether the process is initiated in the fetal or the neonatal period, is to reverse the ongoing events as soon as possible and avoid death or permanent injury. An understanding of the response of the fetus or neonate to asphyxia forms the basis of the resuscitative process.

Intrapartum asphyxia can be divided into two major types: acute near-total asphyxia and partial prolonged asphyxia. Acute near-total asphyxia has an abrupt onset, usually lasts 5-30 minutes, and causes complete or near-complete cessation of blood flow to the fetus. Etiologies include maternal cardiac arrest, uterine rupture, complete placental abruption, and severe cord compression. Partial prolonged asphyxia occurs more slowly over one to many hours and usually results from various causes of uteroplacental insufficiency. When a fetus or neonate is subjected to partial prolonged asphyxia, the classic "diving" reflex occurs; this is simply an attempt either to accentuate or restore a fetal type of circulation. Hypoxia and acidosis, regardless of their duration, increase vasoconstriction of the pulmonary vasculature (see Fig. 31.3).[55] The increase in PVR results in a decline in pulmonary blood flow, decreasing left atrial return, which lowers left atrial pressure. The decline in left atrial pressure increases right-to-left shunting across the foramen ovale. In the fetus, this shunting directs the most highly oxygenated blood coming from the placenta to the left side of the heart. In a neonate with no placenta, this shunting merely bypasses the lungs, perpetuating a vicious cycle of hypoxia, more acidosis, and more shunting. In acute near-total asphyxia, there may not be time for the diving reflex to have a physiologic effect; in contrast to partial prolonged asphyxia, there may not be significant multisystem organ damage from shunting of blood away from the kidneys, liver, bones, and other organs not essential to the immediate preservation of life.

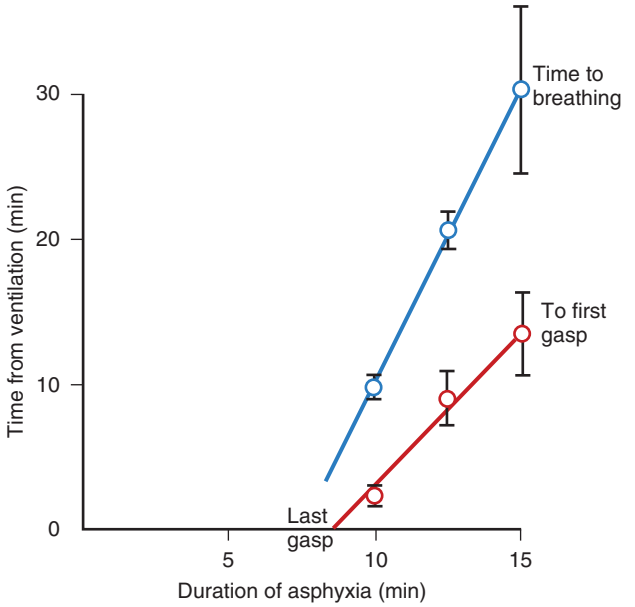
In the fetus and the neonate, the increase in noncerebral peripheral resistance during prolonged asphyxia results in a redistribution of blood flow, with increased flow to the head, heart, and adrenal glands, and decreased flow to organs not vital to immediate survival. Although the oxygen content of the blood is low, during the early stages of asphyxia the amount of oxygen brought to the head and heart is maximized by the maintenance of cardiac output and the increased flow to these organs.[43] The increased peripheral resistance sustains blood pressure early in asphyxia. The blood pressure remains at reasonable levels as long as the myocardium is able to maintain cardiac output. As the asphyxia progresses and hypoxia and acidosis worsen, the myocardium fails, and cardiac output and blood pressure decrease.[20,43]

Hypoxic cardiomyopathy is the intermediary step to significant brain and other organ damage in partial prolonged asphyxia.[51] The asphyxiated newborn will usually be born with little muscle tone, apnea, and a low heart rate. However, most healthy babies are born with a heart rate less

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• **Fig. 31.4** Schematic diagram of changes associated with asphyxia. Arrow indicates point of primary apnea. (Modified from Dawes GS. *Fetal and neonatal physiology*. Chicago: Year Book Medical; 1968:149; Phibbs RH. Delivery room management of the newborn. In: Avery G, ed. *Neonatology.* 3rd ed. Philadelphia: Lippincott; 1987:215.)



• **Fig. 31.5** Time from ventilation to first gasp and to rhythmic breathing in newborn monkeys asphyxiated for 10, 12.5, and 15 minutes at 30°C. (Data from Adamsons K, et al. Resuscitation by positive pressure ventilation and tris-hydroxymethylaminomethane of rhesus monkeys asphyxiated at birth. *J Pediatr.* 1964;65:807.)

than 100 beats/min, and the clinician should use other signs of significant acidosis (i.e., hypotonia, apnea) to determine which baby needs immediate resuscitation. The resuscitation algorithm of children and adults emphasizes interventions to promote the return of spontaneous circulation and does not apply in newborns; the provision of adequate ventilation is the mainstay of neonatal resuscitation with the goals to reverse the bradycardia and restore adequate circulation. Superimposed on these circulatory and hemodynamic changes is a characteristic change in respiratory pattern. Initially, there are gasping respirations (which may occur in utero). With continuing asphyxia, respirations cease in what is known as primary apnea. If the asphyxia is not corrected, the infant again begins to gasp irregularly, and the respirations cease (secondary apnea) unless effective positive pressure ventilation (PPV) and successful resuscitation occur (Fig. 31.4).[17]

Primary apnea usually responds to the cessation of the asphyxiating insult and stimulation. Secondary apnea is usually accompanied by severe metabolic acidemia and requires much more vigorous resuscitation for the newborn to recover. The longer the asphyxia has gone on, the longer it takes for the onset of spontaneous ventilation to occur after PPV is started (Fig. 31.5).[1] Asphyxia may begin before birth, and the infant may pass through any or all of these stages of the asphyxial cascade in utero. It may be difficult to determine at birth how far the asphyxial episode has progressed. With any depressed infant, it is essential to assume that the infant is in secondary apnea, and resuscitation should be initiated without delay. The goal of resuscitation, although not always attainable, is to initiate interventions in a timely and effective manner so that the insults of hypoxia, ischemia, and acidosis are reversed before they cause permanent injury (Box 31.2).

Preparation for Resuscitation

The strategic elements in preparing for resuscitation are anticipation of the problem, provision of adequate equipment, and presence of trained personnel. The turmoil that sometimes occurs with resuscitation of an infant, especially an unexpected resuscitation, is primarily caused by late notification, inadequate or unavailable equipment, or staff members who are unskilled or have difficulty coordinating their activities. In most cases, appropriate preparation and timely notification of a high-risk delivery can ameliorate many of these problems. The training of personnel using simulation has been shown to be an effective preparation for the teamwork and communication needed in the emergent situation of a neonatal resuscitation.[57,66] Some units have designed a scripted protocol of care for each provider at an anticipated difficult resuscitation (i.e., delivery of an

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• BOX 31.2 Consequences of Asphyxia

Central Nervous System

- Cerebral hemorrhage
- Cerebral edema
- Neonatal encephalopathy
- Seizures
- Stroke

Lung

- Delayed onset of respiration
- Acquired surfactant deficiency (respiratory distress syndrome)
- Meconium aspiration syndrome

Cardiovascular System

- Myocardial failure
- Papillary muscle necrosis
- Persistent pulmonary hypertension of the newborn

Renal System

- Cortical/tubular/medullary necrosis

Gastrointestinal Tract

- Necrotizing enterocolitis

Blood

- Disseminated intravascular coagulation

extremely low birth weight infant) to facilitate an orderly response with assigned responsibilities and optimal use of time during the first "golden hour" of life.[5] Periodic training should include cognitive learning and technical and behavioral skills to conduct a resuscitation appropriately. The availability of adequate models to practice technical skills (e.g., intubation, catheter placement) can be a major impediment in the training of personnel for the rare full resuscitation. New high-fidelity manikins now available provide much greater realism and anatomic fidelity to solve this problem in training but are expensive and require a skilled instructor.[40] However, the decreased opportunities for the practice of technical skills on live neonates in both training programs and daily practice make the acquisition and continued mastery of these skills a continuing challenge for all neonatal providers.[19] Moreover, the most recent guidelines suggest that for retention of necessary skills, neonatal resuscitation task training should occur more frequently than every 2 years.[72]

Communication between the obstetric and neonatal teams is essential to the graded response needed for neonatal resuscitation. In some situations, a single competent person is appropriate to the clinical situation. At other times, a full resuscitation team of three or more skilled providers may be necessary. When time allows, a careful review of the antepartum and intrapartum history can identify many problems that put a mother at risk of delivering a depressed or asphyxiated infant (see Box 31.1) and determine the composition of the resuscitation team. Even an emergency call for assistance to the neonatal team should include pertinent information. Using the acronym *HANDS* may be helpful to highlight the most important data: *H* for hemorrhage, *A* for amniotic fluid (clear or meconium-stained), *N* for number of infants expected, *D* for dates (gestational age), and *S* for fetal monitoring strip (category I, II, or III).

Identifying a high-risk situation before delivery of the infant provides time for adequate preparation and gathering the appropriate personnel in the delivery room. Because of modern obstetric techniques and anesthesia, it is no longer necessary to consider a repeat cesarean section as a high-risk delivery because this form of delivery carries no greater risk than a vertex vaginal delivery at term.[33] Only if the cesarean section involves a premature infant, fetal distress, or other complications is there any cause for added concern. It is impossible to identify every infant who may need assistance. At every delivery, equipment and personnel should be available in case of unanticipated neonatal depression.

Adequate Equipment

Whenever an infant is delivered, appropriate equipment must be close at hand and in good working order. An area in or near the delivery room should be designated as the resuscitation area, and provisions should be made for adequate space, heat (radiant warmer), blended oxygen, and suction. Supplies and drugs as specified in the resuscitation guidelines should be placed in a code cart or bag or attached to a wall board for easy access.[70] These supplies should be routinely checked by hospital personnel and rechecked for completeness and good working order (e.g., laryngoscope light works) before an anticipated resuscitation. A delay in effective resuscitation may occur if someone needs to leave the delivery room during the procedure to obtain an essential piece of equipment. When expecting an extremely depressed infant (e.g., terminal bradycardia resulting in an emergency cesarean section), it may be appropriate to prepare the umbilical catheter and draw up epinephrine *before* delivery.

Adequate Personnel

Individuals vested with the responsibility of resuscitating infants should be adequately trained, readily available, and capable of working together as a team. Having trained personnel readily available means having someone present at every delivery who has the skill required to initiate resuscitation, with other available staff close at hand in case they are needed. This person does not have to be a physician but should be able to recognize the need for resuscitation and perform the initial steps, including the initiation of positive pressure ventilation. The hospital is responsible to ensure the competence of these personnel in the same way a surgeon is credentialed to perform certain operations.[4] At least two, if not three, people are needed to carry out a full resuscitation. Adequate training involves more than simply going through a course and receiving a certificate of completion. The neonatal resuscitation program of the

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TABLE 31.1 Apgar Score

Sign	0	1	2
Heart rate	Absent	<100 beats/min	>100 beats/min
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Flaccid	Some flexion of extremities	Active motion
Reflex irritability	No response	Grimace	Vigorous cry
Color	Pale or blue	Acrocyanotic	Completely pink

AHA/AAP and similar courses are simply starting points.[70] These programs do not ensure competence or qualify one to assume independent responsibility.

Finally, the personnel available to the delivery room should be capable of working together as a team. If staff are skilled at carrying out their responsibilities and can anticipate each other's needs, the tension inherent in any resuscitation can be reduced, and the process will go much more smoothly. The use of simulation training using manikins and the holding of mock code drills on an ongoing basis help to maintain skills and develop coordination among staff.[40,57]

Apgar Score

The Apgar score is a tool that can be used objectively to define the state of an infant at given times after birth, traditionally at 1 minute and 5 minutes (Table 31.1).[3,6] The Apgar score should not be used as the primary indicator for resuscitation, because it is not normally assigned until 1 minute of age. As noted, asphyxia may begin in utero and continue into the neonatal period. To minimize the chances of adverse sequelae, one should begin resuscitation as soon as there is evidence that the infant is unable to establish ventilation sufficient to maintain an adequate heart rate. Waiting until a 1-minute Apgar score is assigned before initiating resuscitation only delays potential therapies. An Apgar score at 1 minute of 0-3 often indicates the presence of secondary apnea. Infants who fail to achieve an Apgar score of 7 by 5 minutes of age should have repeated Apgar scores every 5 minutes until the score is at least 7.[3] Steps taken during the resuscitation and the resulting Apgar scores should become part of the medical record (Table 31.2).[3]

Umbilical Cord Blood Gases

Umbilical cord blood analysis for high-risk deliveries (i.e., low 5-minute Apgar score, severe intrauterine growth restriction, fetal heart rate tracing abnormalities, intrapartum fever, multiple gestation pregnancies, and cesarean deliveries for fetal distress) is currently recommended by ACOG.[41] The arterial cord gas can be a valuable representation of the fetal acid-base state prior to delivery.[10,24] Adverse neurologic sequelae have been associated with a low arterial cord pH.[34] Using both the arterial and venous cord values, the clinician may be able to determine the intrapartum events leading to neonatal depression.[10,29] Severe acidosis in a cord blood gas may inform the resuscitation and determine triage of the newborn to the appropriate postresuscitation care.[30] An arterial cord pH less than 7.0 and a base excess greater than −16 have been used as criteria for therapeutic hypothermia in the treatment of intrapartum asphyxia.[27,46,59,60]

If only one cord blood gas is reported, it may be from the umbilical vein, as this vessel is larger and more easily sampled.[24,49] One clue that a single gas sample is of venous origin is the PaO_2 value. If the reported PaO_2 is >31 mm Hg, it is highly likely to be a venous sample.[49]

In the ideal situation, both arterial and venous umbilical cord blood will be sampled for blood gas analysis.[7,71] The umbilical artery pH should be at least 0.02 units lower than the vein.[24] The normal umbilical arterial pCO_2 is usually more than 4 mm Hg greater than the vein.[24] Therefore, if two cord gases are reported and the A-V difference is 0.02 units or less in the pH and <4 mm Hg in the pCO_2, then the two results are likely from the same vessel.[24] Normal umbilical cord blood gases are shown in Table 31.3.[49]

Elements of a Resuscitation

A resuscitation can be viewed as a series of elements. The process is not a linear set of steps in which one marches inexorably from one point to another. Rather, it involves an evaluation of the infant's condition, a decision based on that evaluation, and action.[35] These steps are repeated until the process is concluded. Fig. 31.6 provides an overview of the resuscitation process.[70]

Virtually all infants undergo the initial steps. Most infants requiring active resuscitation respond to appropriately administered PPV.[48] All infants, whether they require only the initial steps or a complete resuscitation, are entitled to a skilled and timely response, regardless of who is performing the resuscitation. Parents may be present while perinatal care is being provided to neonates, including procedures, resuscitation, and stabilization. Parents should be informed about and involved in the care of their infants within the principles of family-centered care.[23]

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TABLE 31.2 Expanded Apgar Score Reporting Form

Sign	Apgar Score 0	1	2	Gestational Age _____ Weeks: 1 minute	5 minute	10 minute	15 minute	20 minute
COLOR	Blue or Pale	Acrocyanotic	Completely Pink					
HEART RATE	Absent	<100 minute	>100 minute					
REFLEX IRRITABILITY	No Response	Grimace	Cry or active withdrawal					
MUSCLE TONE	Limp	Some flexion	Active motion					
RESPIRATION	Absent	Weak cry; hypoventilation	Good, crying					
TOTAL								

Comments:

Resuscitation					
Minutes	1	5	10	15	20
Oxygen					
PPV/NCPAP					
ETT					
Chest compressions					
Epinephrine					

ETT, Endotracheal tube; nCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation.
From American Academy of Pediatrics Committee on Fetus and Newborn; American College of Obstetricians and Gynecologists Committee on Obstetric Practice. The Apgar score. *Pediatrics*. 2015 Oct;136(4):819-22. DOI: 10.1542/peds.2015-2651.

TABLE 31.3 Normal Arterial and Venous Cord Blood Gas Values

	Venous Cord Blood, Normal Range (Mean ± 2SD)	Arterial Cord Blood, Normal Range (Mean ± 2SD)
pH	7.25-7.45	7.18-7.38
pCO_2 (mm Hg)	26.8-49.2	32.2-65.8
pO_2 (mm Hg)	17.2-40.8	5.6-30.8
HCO_3^-	15.8-24.2	17-27
Base excess (BE)	0 to –8	0 to –8

Pomerance JJ. *Interpreting umbilical cord blood gases*. 2nd ed. Glendora, CA: BNMG; 2012.
Data are mean values ±2 standard deviations (SD).
*Base excess, estimated from data.
**1 kPa = 7.50 mmHg; 1 mmHg = 0.133 kPa
Note: "Normal" is arbitrarily defined as the mean ±2 times the standard deviation (approximately 95.4% of a normally distributed population).

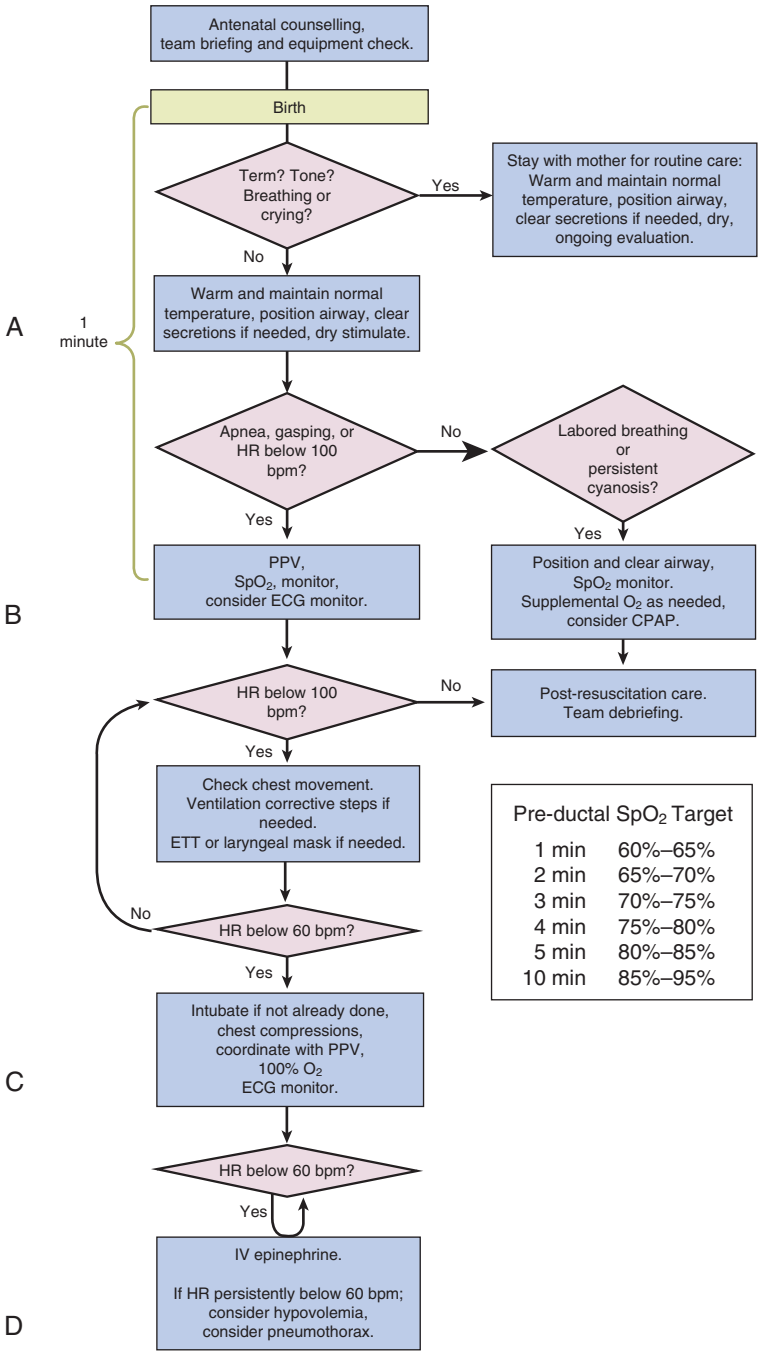
Initial Quick Overview

Most infants are vigorous, cry at birth, and breathe easily thereafter. However, there may be a delay of 30 seconds or more before a healthy baby takes a first breath. Many times, parents prefer that the infant go to the mother immediately after birth rather than be placed on a warmer and put through the "initial steps" in resuscitation. In most circumstances, a healthy and vigorous infant does not require suctioning after delivery. With appropriate triaging and oversight, most newborns can be given directly to the mother for bonding and initiation of breastfeeding immediately after birth without compromising their care.

A rapid initial assessment that provides the information necessary to triage the infant appropriately is required. If the infant has not passed meconium in utero, is term, is breathing easily, has good tone, and appears normal and vigorous, it is appropriate to hand the child to the mother for skin-to-skin contact immediately after birth. As the mother holds the infant, a light blanket may be provided to prevent rapid evaporative heat loss while covering the infant in such a way as to be able to observe the infant for signs of distress. During this process, a trained observer should be able to see the infant's nose and mouth, and the head should be turned to one side.[21] If the infant has passed meconium in utero, is preterm, is not breathing easily, has diminished tone, or does not appear normal and vigorous, the infant should be placed on a radiant warmer until a more thorough assessment of the infant can be done.

Although the following steps apply to any infant who is not term, healthy, and vigorous at birth, there are several caveats. An initial evaluation should be done but may take

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• **Fig. 31.6** Overview of resuscitation in the delivery room. ETT, Endotracheal tube; HR, heart rate; PPV, positive pressure ventilation. (From Weiner GM, ed. *Textbook of neonatal resuscitation*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics, American Heart Association; 2016.)

longer than 30 seconds.[58] The median heart rate in healthy term and preterm infants is <100 bpm and may take up to 2 minutes to rise to 140 bpm.[18] Evaluation of color at birth is usually not helpful in determining the status of a newborn, because it usually takes several minutes for even a healthy term infant to achieve SpO_2 greater than 90% and "become pink" (see Chapter 33).[44,56] Therefore, the clinician must evaluate the newly born infant carefully, looking at all aspects of well-being and recognize the normal processes of transition.

Initial Steps

If resuscitation is deemed necessary, the initial steps are to place the infant in a "sniffing" position, which will facilitate opening the airway. If needed, secretions can be cleared with a bulb syringe and the infant is dried, unless very preterm, in which case a plastic wrap is used to maintain temperature. The infant is then stimulated to breathe and observed before starting the next steps.

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Thermal Management

The fetus maintains a body temperature about 0.5° higher than maternal temperature. Through the accumulation of brown fat late in gestation, the term newborn is able to activate thermogenesis by stimuli of oxygenation, ventilation, and oxidative metabolism via various hormonal intermediaries. The lack of brown fat accumulation in preterm infants and the sequelae of asphyxia in term infants put these newborns at significant disadvantage in thermoregulation postdelivery.[25] Delivery rooms are kept at a level of thermal comfort for the adults working in them. The neonate with a very large surface area-to-mass ratio is susceptible to cold stress; this is especially true for depressed infants with poor perfusion and extremely low birth weight infants. Unintentional hypothermia in neonates has been associated with metabolic acidosis, increased oxygen consumption, and increased mortality, especially in very preterm infants.[36] For very low birth weight infants, one large cohort study revealed a 28% increase in mortality for each 1°C decrease in neonatal intensive care unit admission temperature.[32]

Studies have shown that >30% of infants with extremely low birth weight (<1000 g) become hypothermic with standard warming techniques in the delivery room.[8,36,67] Because this population makes up less than 1% of all deliveries, special preparations should be made for these infants by prewarming the delivery room or an adjacent resuscitation area to 75°F-78°F and using a radiant warmer and food-grade plastic wrap to keep the infant warm after birth.[36,67,68,70] Other strategies may include prewarmed blankets, hats, exothermic mattresses, and using warmed, humidified air/oxygen for ventilation.[61] Care must be taken not to overheat an infant, since animal studies have shown that hyperthermia is synergistic with asphyxia in worsening cerebral injury.[72]

For a term nondistressed newborn, the infant should be placed skin-to-skin with the mother or in the microenvironment of a preheated radiant warmer immediately after birth. Newborns who do not qualify for routine care should be placed in warm blankets and quickly moved to a preheated radiant warmer set at 100% power. The infant should be thoroughly dried, and the wet blankets should be promptly removed to avoid evaporative heat loss. These simple measures can minimize the decrease in core temperature that the term infant experiences at birth.[38] Preventing excessive heat loss can become especially important with a preterm infant or an infant who is asphyxiated and hypoxic. Because hypoxia blunts the normal response to cold, a hypoxic infant undergoes a greater than normal decline in core temperature if not thermally protected.[12] Recovery from acidosis also is delayed by hypothermia (see Chapter 35).[2]

Clearing the Airway

Previously, it was recommended that the airway should be cleared with the use of a bulb syringe or a suction catheter. However, if the newborn is vigorous and born through clear amniotic fluid, this procedure is not necessary,[22] and stimulation of the posterior portion of the pharynx may induce bradycardia.[16] If the infant has excessive secretions, a bulb syringe may be used to clear first the mouth and then the nose ("m" before "n"). An infant exposed to meconium in the amniotic fluid represents a special circumstance (discussed in Chapter 34).

Monitoring

Heart rate may be evaluated by palpation of a peripheral pulse or the umbilical cord. However, studies have shown that these measurements are not reliable.[18] If the resuscitation team is expecting a significantly depressed baby or a very low birth weight infant who probably needs help in transition, attaching ECG leads to monitor heart rate can be done early in the resuscitation process. Use of a pulse oximeter to guide treatment is also suggested by the NRP.[72] There may be a delay of 1-2 minutes after attaching the pulse oximeter until accurate readings of both heart rate and oxygen saturation are obtained. If the baby has poor perfusion or a very low heart rate, the pulse oximeter may not give accurate readings.

Tactile Stimulation and Assessment

Usually the act of drying the infant is enough tactile stimulation to initiate respiration. An infant in primary apnea will generally respond to these gentle measures. All babies will be cyanotic at birth and blow-by oxygen is not indicated. If the infant does not breathe after tactile stimulation, gentle flicking the soles of the feet or rubbing the infant's back may be enough additional stimulation to elicit regular respirations. After initial steps, if assessment fails to elicit a vigorous response, the baby should be assumed to be in secondary apnea, and PPV should be quickly initiated. Positive pressure ventilation may be given initially to term and late-preterm infants with air (21% Fio_2). Continued and more vigorous tactile stimulation is not useful and may be harmful if ineffective maneuvers allow the baby to remain hypoxic and acidotic. The decisions from this point revolve around the response of the infant—primarily heart rate and respirations.

Free-Flow Oxygen

Over the past several years, there has been considerable discussion and research on the use of oxygen in neonatal resuscitation (see Chapter 33).[53,64,65] Previously, the *Textbook of Neonatal Resuscitation* recommended that free-flow oxygen be used if the newborn remained cyanotic after 30 seconds of initial steps (drying, warmth) and evaluation, or if PPV was needed. This recommendation has been revised based on numerous studies. The current recommendation is to use pulse oximetry if resuscitation is anticipated, when positive pressure ventilation is given, and if central cyanosis persists after 5-10 minutes. Resuscitation for full-term infants should begin with room air (21% oxygen at sea level), and oxygen should be given if necessary and titrated according to the interquartile range of healthy term

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TABLE 31.4 Target Preductal Oxygen Saturations for Newborn Infants in the First 10 Minutes of Life

1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-90%

From Weiner GM, ed. *Textbook of neonatal resuscitation*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics, American Heart Association; 2016, 48.

newborns after vaginal birth at sea level (Table 31.4). If chest compressions, medication, or both are needed, 100% oxygen is recommended (see Fig. 31.6).[70,72] Current recommendations advise against the routine use of oxygen for transient cyanosis and the avoidance of high concentrations of oxygen whenever possible.[64,65]

If the infant is spontaneously breathing, and the heart rate is greater than 100 beats/min, but the infant remains cyanotic for >5 minutes after birth, oxygen may be administered through a free-flow system until it can be shown that the oxygen concentration can be reduced (arterial oxygen saturation, SaO_2 >85%) or that lowering the concentration makes no difference (cyanotic heart disease). Studies of normal term newborns have shown that it may take 6 minutes or longer for infants to reach SaO_2 greater than 90%, and many clinicians believe the use of oxygen should be restricted unless the baby remains bradycardic.[56] A high concentration of oxygen can be obtained with an oxygen mask (with escape holes) held firmly over the face or an oxygen tube cupped in the hand. A flow-inflating bag (but not a self-inflating bag) is capable of delivering high concentrations of blow-by oxygen.[70] The use of high concentrations of oxygen is not usually necessary and hyperoxia should be avoided, especially in a preterm infant.

It is best to heat and humidify the oxygen. During an emergency, cold, dry oxygen may be given for a short time; however, if free-flow oxygen is to be continued for any period, it should be heated and humidified and given through wide-bore tubing. An oxygen blender and oximeter are useful in determining the amount of oxygen the infant requires. It is recommended that all hospitals should be capable of blending oxygen in the delivery room and using pulse oximetry in this area.[70] After suctioning and tactile stimulation, if the respirations are gasping or are insufficient to sustain the heart rate at greater than 100 beats/min, PPV must be initiated.

Preterm infants must be resuscitated with modest elevations (30%) of oxygen, as research has shown that resuscitation with 21% oxygen is unlikely to be successful (see Chapter 33).[45]

Key Points

- At birth, the newborn must establish the lung as the organ of gas exchange, and this may require the assistance of a skilled resuscitation team.
- A neonate may not have adequate ventilation after delivery because of many problems, including asphyxia, drug-induced central nervous system (CNS) depression, CNS anomalies or injury, spinal cord injury, mechanical obstruction of the airways, congenital facial or airway deformities, immaturity, pneumonia, systemic infection, or congenital anomalies.
- The strategic elements in preparing for resuscitation are anticipation of the problem, provision of adequate equipment, and presence of trained personnel.
- The need for and the extent of resuscitation required will be determined by the clinical condition of the newly born infant, umbilical cord blood gases, and evolving Apgar scores.
- In most resuscitations, following the algorithm provided by the Neonatal Resuscitation Program will guide the team in the appropriate series of steps to revive a depressed or acidemic newborn.

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32

Role of Positive Pressure Ventilation in Neonatal Resuscitation

LOUISE OWEN AND PETER DAVIS

Newborn babies who do not spontaneously breathe at birth require support to safely make the transition to extra-uterine life. Over the past 20 years, guidelines for those providing care to these infants have been developed.[52] However, the evidence available to guide initial respiratory support remains limited, reflecting the challenges associated with conducting research in the delivery room.

The crucial steps in the adaption to extra-uterine life involve the transition from liquid-filled to air-filled lungs, and the establishment of functional residual capacity (FRC). These changes normally occur in the first minutes after birth and include an increase in pulmonary blood flow and the onset of regular respiration. Lung aeration and the development of an FRC facilitate gas exchange, leading to an increase in heart rate. If an infant does not quickly establish effective respiration, assistance is immediately required. Typically, this is a brief need for basic respiratory support only,[39] unless there is abnormal anatomy, significant fetal acidemia, or if ineffective respiratory support is given. Preterm infants have additional requirements at birth; although most preterm infants breathe and cry,[45] very preterm infants are still likely to need support to effectively establish and maintain FRC. Preterm lungs are delicate, and lung injury can occur with just a few positive pressure inflations.[73] This has led to a shift in emphasis in preterm stabilization toward a gentle, supportive approach to augment rather than override their efforts and to minimize lung injury.

Normal Transition and Initial Spontaneous Breathing

In healthy, newborn term infants, normal transition is characterized by repeated, short, deep inspirations, each followed by a prolonged expiratory phase through a partially closed glottis (crying). The inspiratory efforts generate large negative trans-pulmonary pressures, typically −50 cm H_2O to −100 cm H_2O, such that the high-resistance liquid filling the infant's airways is driven distally, moving the air-liquid interface toward the distal airways.

Detailed imaging of rabbit lungs demonstrates that initial lung aeration depends on the generation of this trans-pulmonary pressure, with consequent stepwise increases in FRC over three to five repeated inspiratory efforts. More volume is inspired than expired with each breath, which overcomes small losses in FRC between inspiratory efforts as lung liquid moves back into airways.[20] The lung liquid then moves into the interstitial tissue and is cleared over the following hours.

Prolonged expiration through a partially closed glottis with simultaneous abdominal muscle contraction pressurizes the chest, further pushing back the air-liquid interface; this is called expiratory braking (Fig. 32.1). Recordings of the first breaths in preterm infants have also shown that they use crying and expiratory braking to facilitate lung recruitment and development of FRC[80] (Fig. 32.2).

Delayed Transition and Need for Respiratory Support

Some infants do not breathe or have ineffective breathing at birth. Guidelines recommend initial steps of umbilical cord clamping, warming, drying and stimulating the baby, and opening, and in some cases clearing, the airway.[52] They stipulate that positive pressure support should be commenced by 60 seconds of age if the baby remains apneic, has irregular or gasping respirations, or has a heart rate less than 100 beats/min (bpm).[52] However, following these recommendations may not always be straightforward.

- Healthy babies may not take their first breath immediately after birth; there may be a delay of 30 seconds or longer.
- In practice, initial evaluation often takes longer than 60 seconds.[64]

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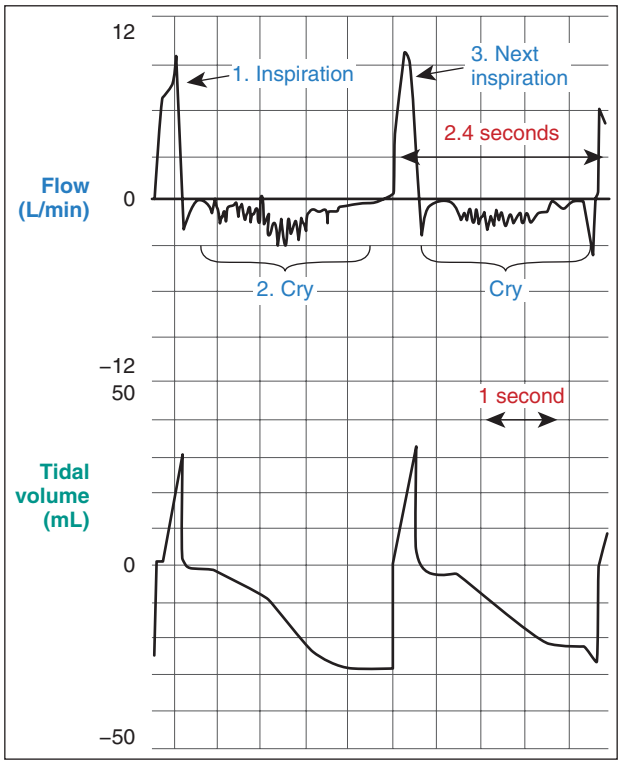
Abstract

Newborn babies who do not spontaneously breathe at birth require immediate support to successfully transition to extra-uterine life. Positive pressure ventilation (PPV) must be applied; this is a critical skill to master, but it is difficult to learn and apply. This chapter covers the indications, techniques and equipment needed to support newborns who do not establish adequate spontaneous breathing. This chapter discusses why transition may be delayed; it identifies the key indicators for assessing the condition of newborns. It explores the basics of PPV, how to generate PPV, and how to choose an interface to deliver it. The chapter discusses assessment of the effectiveness of PPV, how to apply PPV from the first breath, and the practicalities of endotracheal intubation. Most infants breathe at birth and need no support; preterm infants usually breathe, but often need support. Infants who do not establish regular respiration require PPV, typically given using a face-mask and a self-inflating bag. These are the devices of choice in resource limited settings; T-piece resuscitators are the device of choice for stabilizing preterm infants. Effective PPV should result in a rapid increase in heart rate. Ineffective PPV, or poor technique, results in clinical compromise and may cause lung damage. Endotracheal intubation should be considered if resuscitation is prolonged or the infant remains bradycardic. Most newborns do not need assistance at birth. When assistance is required it is needed promptly, applied with appropriate equipment and technique. Acquisition of this skill is critically important.

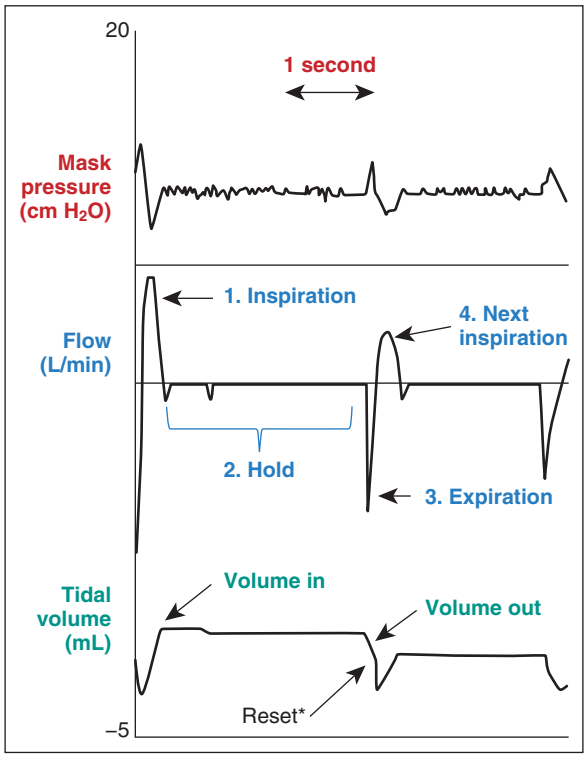
Keywords

resuscitation
failure to breathe at birth
intermittent positive pressure ventilation
infant
newborn

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• **Fig. 32.1** Example of crying in a term infant at birth. There is a large inspiration (*1*), followed by crying, seen as high-frequency interruptions to the expiratory flow wave lasting more than 2 seconds (*2*), followed immediately by the next inspiration (*3*). The software resets the volume trace at end inspiration and end expiration. (Adapted from te Pas AB et al. Breathing patterns in preterm and term infants immediately after birth. *Pediatr Res*. 2009;65:352.)



• **Fig. 32.2** Example of expiratory braking in a preterm infant on continuous positive airway pressure (CPAP), just after birth. There is a short, large inspiration (*1*) followed by a 2-second period without any flow (*2*), then a short, quick expiration (*3*), immediately followed by the next inspiration (*4*), without any postexpiratory pause. The software resets the volume at end expiration. (Adapted from te Pas AB et al. Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. *Pediatr Res*. 2008;64:281.)

- In healthy term and preterm babies, the median heart rate at one minute is <100 bpm, rising to ~140 bpm by 2 minutes of age.[10]
- Clinical assessment of heart rate at birth, either by palpation or auscultation, is intermittent and inaccurate.[26]
- Assessment of a newborn's color is subjective and unreliable.[44] Although assessment of color is not used in the most recent resuscitation guidelines, it remains part of the Apgar assessment.

These factors make assessment at birth, and the decision whether to intervene, more complex. If decisions are made too early, unnecessary interventions may be applied. Whereas, if decisions are delayed, there may be further cardiorespiratory compromise. It may be helpful to be aware that:

- Accurate measurements of oxygen saturation (SpO_2) and heart rate can be obtained by about 90 seconds using pulse oximetry,[9] and heart rate values may be seen within 1 minute using electrocardiography.[28]
- The key sign of an infant's condition in the minutes after birth, and response during stabilization, is the heart rate.
- An infant who has good tone is unlikely to be severely hypoxic.

Basics of Positive Pressure Support

When an infant fails to establish spontaneous breathing after birth, the caregiver must commence positive pressure support. Typically, this is initially applied using a face mask and a pressure-generating device. If the infant is breathing but has not completely established regular, effective breathing, continuous positive airway pressure (CPAP) may aid inflation of the lungs and establishment of FRC. CPAP helps establish and maintain end expiratory lung volume, reduce alveolar collapse, and decrease work of breathing. It aids lung expansion and helps to conserve surfactant. CPAP also improves oxygenation, lung compliance, and ventilation-perfusion mismatch.[1] However, an infant who has no respiratory effort, or who is bradycardic, will require positive pressure ventilation (PPV). Ideally, PPV should be given along with positive end expiratory pressure (PEEP), although not all resuscitation devices are capable of delivering PEEP (Table 32.1). Studies in intubated preterm animals have demonstrated that the addition of PEEP to PPV results in more rapid acquisition of FRC, improved oxygenation and lung compliance, and decreased lung injury.[74] PEEP is recommended for the resuscitation of preterm infants,[52] although clinical trials have failed to show

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TABLE 32.1 Comparison of Attributes Across the Range of Positive Pressure Generating Devices

Attribute	Device			
	Self-Inflating Bag	Flow-Inflating Bag	T-Piece	Ventilator
Operates independent of gas supply	✓	X	X	X
Delivers accurate, consistent peak pressure	X	X	✓	✓
Measures delivered peak pressure	X	X	✓	✓
Ability to deliver a sustained inflation	X	May be possible	✓	X
Delivers PEEP	May be possible	May be possible	✓	✓
Delivers CPAP	X	X	✓	✓
Delivered pressures are independent of gas flow	✓	✓	X	✓
Measures delivered tidal volume	X	X	X	May be possible

✓, Yes; X, no; CPAP, continuous positive airway pressure; PEEP, positive end expiratory pressure.

a significant difference in the proportion of infants requiring intubation in the delivery room,[13] or in SpO_2 at 5 minutes of age[8] when PEEP was added. Use of PEEP during stabilization of preterm infants in the delivery room in major units in the UK and Canada is now reported to be higher than 75%.[12,75]

Endotracheal intubation should be considered for infants who have an ongoing need for PPV and those who remain bradycardic and/or hypoxic in spite of adequate mask PPV. The management of preterm infants who require ongoing respiratory support has evolved over the last decade, moving away from immediate intubation and surfactant administration toward continuing CPAP support with either rescue intubation or surfactant treatment if certain criteria are met, or surfactant administration without endotracheal intubation plus ongoing CPAP. Meta-analysis of trials that compared immediate intubation with CPAP found a reduction in the combined outcome of death or bronchopulmonary dysplasia in the CPAP group, without any difference in pneumothorax risk.[70] Both options may be appropriate, however, international guidelines now recommend initial CPAP for spontaneously breathing preterm infants with respiratory distress rather than routine intubation.[52] As a gentler approach to early respiratory support has become more popular, more preterm infants are likely to be supported by CPAP in the delivery room.

Application of Noninvasive Positive Pressure Support

How to Generate Positive Pressure

Various devices are available for generating positive pressure in the delivery room. The choice of device may be made based on availability of a gas supply, the skills of the resuscitator, the desire to deliver sustained inflations, PEEP and CPAP, and on local preferences. A European survey reported that centers typically use more than one device, with self-inflating bags (SIB) being most commonly used (85%),[59] whereas a recent Japanese survey reported flow-inflating bags (FIB) to be most commonly used (63%).[21]

Self-Inflating Bags (SIB)

Self-inflating bags (Fig. 32.3*A1* and *A2*) re-expand after compression. These are the only devices that can be used without a gas supply; they have been shown to be an effective method for reducing mortality from birth asphyxia in resource-limited areas.[17] Their use is an integral part of the international Helping Babies Breathe program.[42]

Several types and sizes of SIB exist. The smallest sizes, ~240 mL, are most appropriate for newborns. The peak pressure delivered by an SIB depends on how hard and fast the bag is squeezed. SIBs usually incorporate a valve, which limits the maximum deliverable pressure. The valve can be manually overridden to deliver higher pressures but can be inadvertently overridden if the SIB is squeezed very hard or very fast. Pressures greater than 100 cm H_2O have been reported, resulting in very high delivered volumes, >20 mL/kg. The more fingers used to squeeze the bag, the more pressure is generated[2]; for most resuscitations, a gentle squeeze with a finger and thumb is all that is required. Many studies, including Bassani et al., have shown that it is difficult to give consistent peak pressures when using an SIB, particularly if an operator is inexperienced.[61] Manometers attached to the SIB help improve the consistency of peak pressure delivery,[57] and newer "upright" designs of SIB have been shown to provide more consistent volume and pressure delivery,[41] even with novice operators.[86] If a PEEP valve is attached to an SIB, some PEEP can be delivered. However, it is difficult to achieve the desired PEEP, and delivered PEEP is rate dependent.[31] PEEP levels decay quickly between inflations,[40] although newer models are

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• **Fig. 32.3** Neonatal resuscitation devices. **A,** A 320-mL "upright" self-inflating bag (Laerdal Global Health, Stavanger, Norway). **B,** A 240-mL self-inflating bag with an oxygen reservoir attached (Laerdal Medical, Stavanger, Norway). **C,** Fisher & Paykel Healthcare Neopuff™ Infant T-piece Resuscitator (Neopuff Infant Resuscitator; Fisher & Paykel, Auckland, New Zealand).

better.[85] Different brands of SIB have different capacities to deliver a sustained inflation[87]; closing the pressure relief valve improves the ability to perform sustained inflation.[4] It is not possible to deliver CPAP using an SIB, therefore, it may not be the optimal device for stabilizing preterm infants.

Flow-Inflating Bags (FIB)

A flow-inflating bag (see Fig. 32.3*B*) needs a continuous gas supply, something which may not always be readily available. The delivered pressure and tidal volume depend on how hard the bag is squeezed. A pressure-limiting valve can be attached to prevent high pressure being inadvertently delivered. PEEP can be delivered with an FIB by controlling the rate of gas escaping from the back of the bag during expiration. This technique requires experience as it can inadvertently lead to dangerously high PEEP. It is difficult to consistently deliver both the desired PEEP and peak pressures with a flow-inflating bag,[3,7] and many operators find the flow-inflating bag more difficult to use than the SIB. A sustained inflation can be delivered by a skilled operator, but the pressure achieved is more variable than that delivered using a T-piece.[32] It is very difficult to deliver CPAP with an FIB.

T-Piece Devices

T-piece devices (see Fig. 32.3*C*) also require a continuous gas supply, again something that may not be available in resource-limited settings. The gas flow, and an internal valve, generate the set peak pressure and set PEEP. The peak pressure is achieved by occluding the hole in the top/side of the T-piece with a finger. When the hole is open, PEEP or CPAP is delivered. Inflation time depends on how long the hole is occluded.

T-pieces are easy to use and are preferred by both experienced and inexperienced operators.[23] In manikin studies, the T-piece device delivers peak and PEEP pressures more accurately and consistently than other devices, resulting in more stable tidal volume delivery,[60] even with inexperienced operators.[61]

Although facemask leak is common during positive pressure ventilation, leak has less detrimental effect on pressure and volume delivery when using a T-piece, compared with an SIB.[18] Randomized studies of infants requiring PPV at birth have shown less need for intubation,[79,84] less supplemental oxygen, and shorter duration of PPV when using a T-piece compared with an SIB,[84] but no difference in proportion of infants with heart rate >100 bpm at 2 minutes of life[79] or other longer-term outcomes.

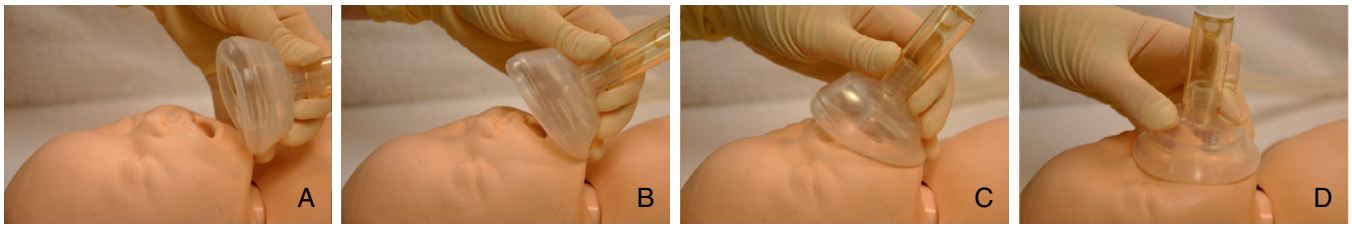
Occlusion of the hole on the T-piece allows delivery of a consistent, sustained inflation of any duration or pressure.[32] Likewise, the T-piece is capable of delivering consistent CPAP,[60] and, therefore, may be the optimal device for providing respiratory support for preterm infants at birth.[23] However, care needs to be taken if gas flow is increased during T-piece PPV as increased flow increases the delivered pressures, particularly PEEP.[81] Additionally, as set PEEP is increased in some T-piece systems, the resistance and imposed work of breathing can increase.[11]

Other Options for Providing Positive Pressure

Positive pressure support can be delivered using a neonatal ventilator; this delivers accurate peak and PEEP pressures, and may allow both synchronization of inflation with the infant's own efforts and tidal volume measurement.[90] CPAP can also be continuously delivered. Other methods of providing respiratory support have been tried and are under investigation, such as use of nasal high flow.[58]

In the resource-limited setting, no devices may be available to generate positive pressure support, so mouth-to-mask[37] and mouth-to-tube[83] ventilation may be used. Both are preferable to mouth-to-mouth resuscitation, but both still carry some risk of infection.

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• **Fig. 32.4** Photographs demonstrating optimal mask placement technique, rolling the mask up the face from the chin. (Photographs courtesy of Fiona Wood and Colin Morley.)

In summary, there are advantages and pitfalls with all these devices (see Table 32.1). With the possible exception of a ventilator, no device provides information on perhaps the most important parameter—the tidal volume being delivered. Novel resuscitation devices and simple delivery room monitors that accurately measure and display delivered tidal volume are currently being developed and tested but are not in general clinical use. Whichever device is used, providers need to be trained in how to set up, use, and troubleshoot the equipment.

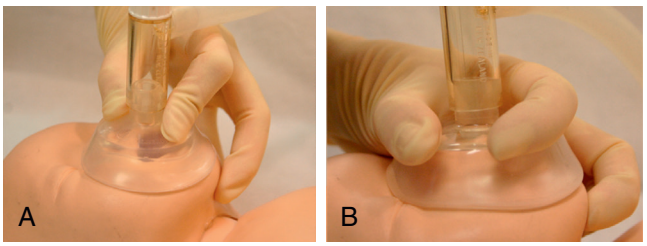
Choosing an Interface to Deliver Positive Pressure

Positive pressure may be delivered via face mask, nasal tube, nasal cannulae, laryngeal masks, and endotracheal tubes.

Face Masks

Use of a face mask requires a good seal between the mask and the infant's face,[96] but this is difficult to achieve and maintain; leak and pressure loss leading to reduced tidal volume delivery is common. Round, cushion-rimmed masks are used more commonly than anatomically shaped, triangular masks,[43] and there is conflicting evidence as to whether leak is greater with one type or the other. Newer masks being tested may help to overcome this.[36] It is, however, clear that mask leak is common in the delivery room and is frequently large and troublesome.[68]

A face mask should seal around the mouth and nose but not cover the eyes or overlap the chin. Several makes and sizes of round face masks are available, but many commonly used brands may be too large for very preterm infants.[49] Accurate positioning and mask hold are required to minimize mask leak. An accurate position can be obtained when the correctly sized mask is rolled upward onto the face from a finger placed on the chin tip (Fig. 32.4); this technique reduces leak.[95] The optimal hold for a mask varies with the brand of mask being used; for example, two commonly used brands shown to have similar leak in the delivery room.[5] With the Laerdal mask (Laerdal Medical, Stavanger, Norway), equal pressure should be applied to the top flat portion of the mask, with the thumb and index finger where the silicone is thickest, to obtain the best seal (Fig. 32.5*A*).[95] The fingers should not encroach onto the skirt of the mask as this causes the rim to kink.[38] In contrast, when using the Fisher & Paykel round masks (Fisher & Paykel Healthcare, Auckland, New Zealand), the thumb and index finger should form a "C" shape (as in the "OK" hand gesture) placed around the top flat portion of the mask, applying an even distribution of pressure to the outer edge of the mask to provide the best seal (see Fig. 32.5*B*).[95] Initial education and regular retraining are important for the maintenance of this important skill.[95]



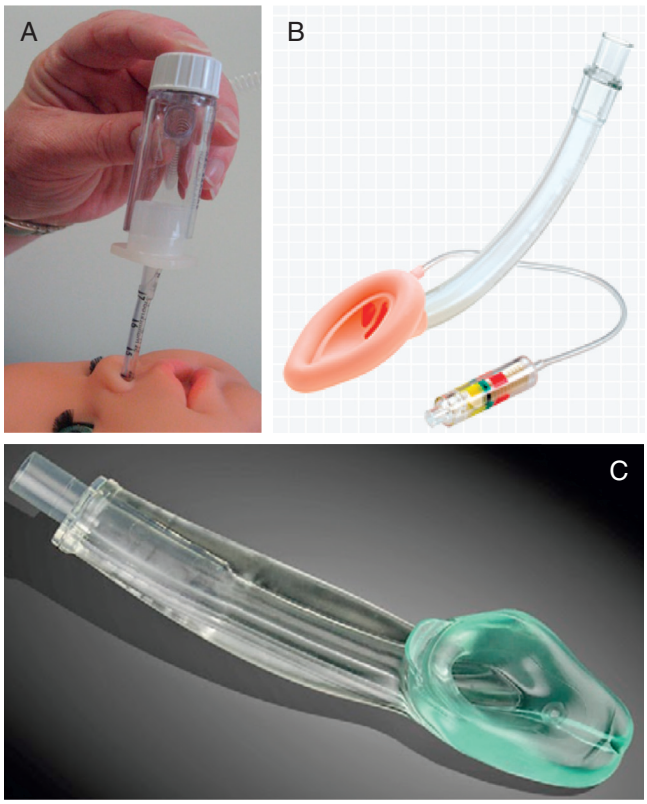
• **Fig. 32.5** **A,** Round Laerdal mask: the "two-point top hold" provides the best mask seal. **B,** Fisher & Paykel round mask: the "OK rim hold" provides the best seal. (Photographs courtesy of Fiona Wood and Colin Morley.)

Typically, operators using a T-piece and face mask with a neonatal manikin have 40%-60% mask leak, although this can be reduced with training[95] and by using a two-handed mask hold technique.[89] Despite large and variable mask leaks, the desired pressure may still be achieved.[18] Unfortunately, neither the delivered pressure nor the amount of chest rise seen correlates well with the delivered tidal volume.[68] Variable leaks may result in some tidal volumes that are too low and others that are dangerously large.[68,77] Concern over large face mask leak may lead the provider to apply excessive pressure to the mask[65] and, therefore, to the face and head of the infant.[92] This pressure may obstruct the airway[14] by distorting the nose and altering the position of the mouth and chin; obstruction occurs in 25%-75 % of preterm mask resuscitations.[14,67] Although inefficient mask ventilation may not achieve adequate pressure and tidal volume, there may still be some benefit due to stimulation of Head's paradoxical reflex. This reflex generates a large inspiratory effort in response to a small inflation. The response may assist with the first effective inspiratory volume during newborn transition, even if mask ventilation fails to adequately inflate the lungs.

Single Nasal Tube and Bi-Nasal Prongs

Alternative interfaces include a single nasal tube (Fig. 32.6*A*), binasal prongs, and nasal cannulae. To ensure minimal leak

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• **Fig. 32.6** **A,** Example of a single nasal tube interface in a neonatal manikin using a cut down endotracheal tube and a T-piece. **B,** An inflatable, laryngeal mask airway showing the rim inflated. (Image courtesy of Teleflex Incorporated. © 2018 Teleflex Incorporated. All rights reserved.) **C,** An i-gel laryngeal mask airway (LMA). (Intersurgical, Wokingham, Berkshire, United Kingdom.)

when the nasal route is used, it may be necessary to close the mouth, and when a single nasal tube is used, it may also be necessary to occlude the contralateral nostril.

A randomized controlled trial comparing a single nasal tube with a round cushion-rimmed face mask showed no difference in measures of effectiveness of resuscitation of preterm infants, including intubation in the delivery room, or in short- or long-term respiratory outcomes.[27] The authors subsequently reported more leak and obstruction with the nasal prong and less overall tidal volume delivery.[91] Therefore, a nasal tube may be a useful alternative to a face mask, but there is no evidence for its superiority. Observational reports exist of nasal prongs[50] and nasal cannulae[58] being used to stabilize preterm infants in the delivery room, but neither have been subjected to randomized trials.

Assessing the Effectiveness of Non-Invasive Positive Pressure Ventilation

It is important to be able to accurately assess whether the support being given is effective. However, clinical assessments of color change[44] and heart rate[26] are imprecise and inaccurate. Pulse oximeters provide rapid, continuous, accurate displays of heart rate and oxygenation and are now recommended for use in babies requiring assistance in the delivery room. Clinicians are poor at assessing mask leak, chest rise, and delivered tidal volume.[68] A respiratory function monitor can assist with assessment of leak and adequate tidal volume delivery.[29,71] However, these monitors are not readily available in the delivery room. A colorimetric carbon dioxide (CO_2) detector or quantitative end-tidal carbon dioxide monitor may help to determine whether there is gas exchange occurring during mask ventilation,[34] but neither have been shown to improve short-term clinical outcomes.[33] Most recently, cerebral oxygenation using near-infrared spectroscopy has been used in the delivery room to give additional information on the effectiveness of resuscitation.[53]

Laryngeal Mask Airway

Laryngeal mask airways are supraglottic airways (SGA) commonly used during anesthesia. SGAs consist of a soft elliptical mask with an inflatable, or gel rim, and a flexible airway tube (see Figs. 32.6*B* and *C*). The mask is inserted into the infant's mouth using the index finger, such that the mask covers the laryngeal opening, and the rim conforms to the contours of the hypopharynx, occluding the esophagus. The inflatable rim can be expanded via a small balloon. The airway tube can be attached to any resuscitation device. Various sizes and reusable and disposable versions are commercially available. An SGA may be helpful for infants with congenital anomalies involving the mouth, lip, palate, or other upper airway anomalies where endotracheal intubation is difficult. It may also be a useful technique where resources, training, and clinical experience are lacking. Almost all SGA insertions are successful at the first attempt and within 10 seconds.[97] Several studies have assessed the effectiveness of PPV delivered by SGA in term and near-term infants, and international guidelines now recommend that an LMA be used in these infants if mask ventilation is unsuccessful and endotracheal intubation is not possible.[52] Most recently, studies have assessed SGA use in more preterm infants for the delivery of surfactant with promising results.[54,62] However, there are currently no SGA devices small enough for infants <1500 g.

Endotracheal Tube

There are no absolute criteria for tracheal intubation after birth. Indications vary depending on gestational age, degree of respiratory effort, response to noninvasive ventilation, and the skill and experience of the resuscitator. International guidelines suggest intubation is considered at several stages:

- if the heart rate is <100 bpm after 30 seconds of effective positive pressure ventilation,[51]
- if non-invasive ventilation does not increase the heart rate, or
- if the infant continues to be apneic despite adequate ventilation.

It is also recommended if mask ventilation is prolonged or ineffective, or there are congenital anomalies affecting transition. Infants without a detectable heartbeat, and who are very hypotonic, should be intubated and ventilated as

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soon as possible. For infants <29 weeks who are spontaneously breathing and who have respiratory distress requiring respiratory support in the delivery room, international guidelines now suggest initial use of CPAP in preference to routine intubation.[52]

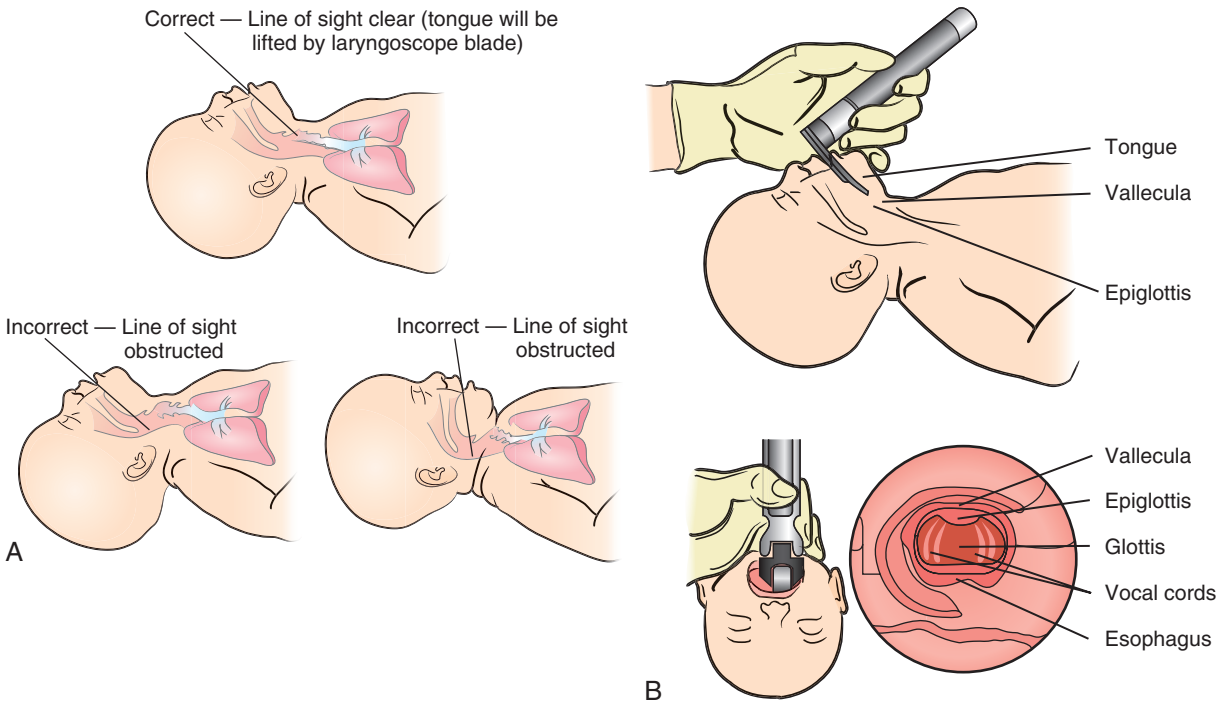
Neonatal intubation is a difficult skill to acquire and maintain. Fewer infants are now intubated and skills are declining. Although experienced operators are successful more than 85% of the time, junior trainees are successful in less than half of attempts.[46] Success can be increased by techniques such as use of videolaryngoscopy,[48] but less experienced operators still take longer to perform intubations. Successful intubations frequently take longer than the recommended 30 seconds, and infants often become bradycardic and deteriorate during intubation attempts.[46] Neonatal endotracheal tubes are uncuffed and usually straight. Some providers use a stylet inside the endotracheal tube, although there is no evidence that this reduces the duration or improves the rate of successful intubation.[47]

Intubation Procedure

Prior to endotracheal intubation, all necessary equipment should be assembled, a team and team leader identified, their roles delineated, and an escalation plan made for the possibility of intubation not initially being successful. The suggested items are outlined in Box 32.1. The infant should be placed supine in a "sniffing position" (Fig. 32.7*A*), avoiding both flexion and hyperextension of the neck, which make the glottis hard to visualize. The tip of the laryngoscope blade should be advanced over the tongue to the vallecula, or over the top of the epiglottis, and elevated gently to reveal the vocal cords (see Fig. 32.7*B*). The laryngoscope should support the tongue toward the left side of the mouth to have adequate space to see the larynx and pass the endotracheal tube (ETT). If the laryngoscope blade is

• BOX 32.1 Equipment Required for Endotracheal Intubation

1. Shoulder roll to facilitate optimal head position
2. Pressure delivery device (T-piece, self-inflating bag, or flow-inflating bag; manometer and PEEP valves optional)
3. Neonatal face masks—preterm and term infant sizes
4. Laryngoscope with blades (straight blade, Miller size number 00, 0 for preterm, and number 1 for term infant)
5. Straight endotracheal tubes (2.5, 3.0, 3.5, 4.0 mm internal diameter); with a standard curve, radio-opaque, and with marks to indicate depth of insertion
6. Endotracheal tube stylet (optional)
7. Magill neonatal forceps (if nasal intubation)
8. Sterile scissors
9. Neonatal stethoscope
10. Exhaled CO_2 detector
11. Air and oxygen supply; oxygen flow meter with air blender
12. Pulse oximeter for measuring heart rate and oxygen saturation
13. Suction apparatus and suction catheters (5, 6, 8, and 10 French sizes)
14. Equipment to secure endotracheal tube; appropriate adhesive tape to attach tube to face

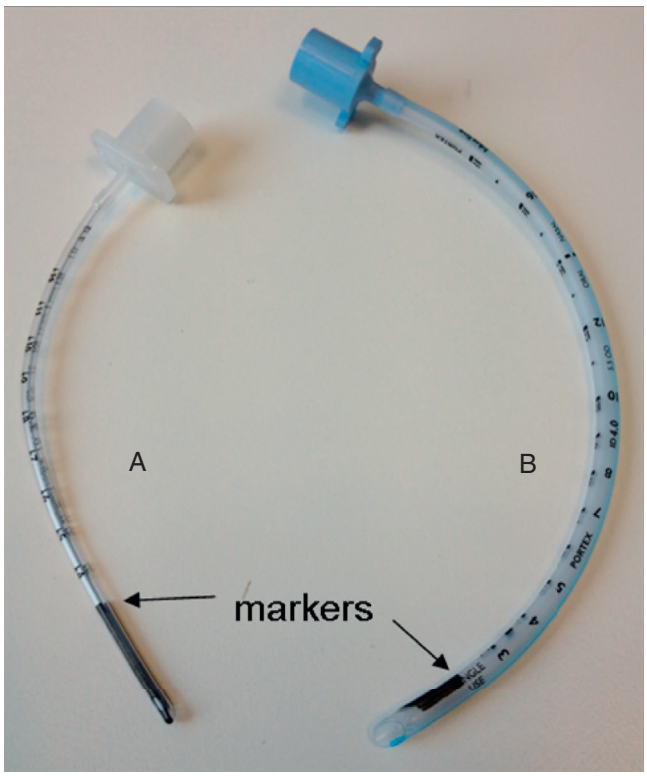


• Fig. 32.7 A, Effects of flexion and hyperextension on ability to visualize the glottis. **B,** Correct view of glottis in preparation for intubation. (Adapted from Kattwinkel J, ed. *Textbook of neonatal resuscitation.* 5th ed. Copyright American Heart Association/American Academy of Pediatrics, 2006. Used with permission of the American Academy of Pediatrics.)

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advanced too far, the tip will be in the lower pharynx, and the larynx will not be visible. Gentle cricoid pressure may be helpful in bringing the larynx into view.

The endotracheal tube should be inserted to the level of the tube marker, so that it is visible just above the larynx (Fig. 32.8). The ETT should be secured with the appropriate centimeter side mark located at the upper lip (Table 32.2). This level is estimated as 6.0 cm plus the infant's weight in kilograms. If a stylet is used to assist with ETT insertion, care must be taken not to allow the stylet to protrude beyond the tip of the ETT and damage the trachea. When removing a stylet from a correctly placed ETT, care must be taken not to dislodge the tube. If a nasal intubation is being performed, McGill forceps may be required to advance the ETT through the vocal cords.



• **Fig. 32.8** Endotracheal tubes showing depth markers at the tip. **A,** Size 2.0 endotracheal tube (Mallinckrodt Medical, Athlone, Ireland). **B,** Size 4.0 endotracheal tube. (Portex endotracheal tube, Smiths Medical, Ohio.)

The position of the endotracheal tube in the trachea must always be verified. The best clinical indicator of correct placement is a prompt increase in heart rate. Correct positioning can be verified by visualizing the tube passing through the vocal cords, listening to both axillae with a stethoscope, observing misting inside the ETT during expiration, and observing chest movements during inflations. However, none of these methods are absolute confirmation. Use of an end-tidal CO_2 detector on the endotracheal tube connector is now recommended to verify correct tube placement quickly.[51] Colorimetric CO_2 detectors can rapidly demonstrate CO_2 in the expired ETT gas more quickly than changes in heart rate and oxygen saturations are seen.[66] However, they can give a false negative result when very low tidal volumes are being delivered[15] and false positive results when contaminated by adrenaline and surfactant.[22] Respiratory function monitors can provide a quicker indication of correct ETT placement than clinical assessment and expired CO_2 detectors.[72] When insertion is verified, correct depth of ETT insertion should be assessed by checking the measurement on the tube at the lips and by assessing symmetric chest movement and with chest radiography.

Applying Positive Pressure Support

When delivering positive pressure ventilation the clinician aims to provide effective ventilation for adequate gas exchange, without causing lung injury. It has been well documented that lung injury can be caused by lung overdistention (volutrauma),[24] excessive pressure (barotrauma), and by repeated alveolar collapse and re-expansion (atelectrauma). Studies in preterm animals have shown that lung injury can occur within the first few positive pressure inflations, resulting in an inflammatory response within a few minutes.[19] Therefore, knowledge about the causes and prevention of lung injury during ventilation of preterm

TABLE 32.2 Guidelines for Endotracheal Tube Sizes and Depth of Insertion

Weight (g)	Gestation (wk)	Endotracheal Tube Size (mm ID)	Orotracheal Tube Length (cm) from Upper Lip	Nasotracheal Tube Length (cm) from Nasal Flare
500-750	<26	2.5	6.5	7.5
750-1000	<28	2.5	6.5-7.0	7.5-8.0
1000-2000	28-34	3.0	7.0-8.0	8.0-9.0
2000-3000	34-38	3.0 / 3.5	8.0-9.0	9.0-10.0
>3000	>38	3.5 / 4.0	>9.0	>10.0

Depth can be calculated as weight (in kg) +6 cm for oral intubation, or weight (in kg) +7 cm for nasal intubation.

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infants should be applied from birth. Actions to prevent lung injury include facilitating formation and maintenance of FRC, avoiding large tidal volumes that can easily and inadvertently be delivered with currently available resuscitation equipment,[77] and avoiding repeated lung collapse and re-expansion.

Very premature infants are especially vulnerable to the interventions applied in the first minutes after birth.[93] Therefore, as most preterm infants spontaneously breathe soon after birth, they may manage with CPAP alone, which is likely to cause less lung damage than routinely intubating them and applying positive pressure ventilation.[25] For infants who do not breathe or who require more than CPAP support, a gentle ventilatory strategy needs to be applied.

The First Breaths

The long initial inspirations, followed by prolonged expirations through a partially closed glottis that are seen in spontaneously breathing infants at birth, led researchers to question whether longer initial positive pressure inflations would be beneficial in infants without adequate spontaneous breathing. In anesthetized, intubated, preterm animal models, sustained inflation at modest pressure leads to rapid lung aeration without overexpansion, immediate development of appropriate FRC, and uniformly aerated lungs[82] without serious side effects.[76] Alternative strategies such as serial increases in applied PEEP may also have similar benefits.[88]

The optimal pressure and duration of a sustained inflation in preterm infants is unknown, and the effects of variable face mask leak, intermittent spontaneous breathing, and potential closure of the glottis make the standardization of applying a sustained inflation difficult. Randomized trials of sustained inflation for resuscitation in preterm infants have produced mixed results; meta-analysis showed less need for intubation in the delivery room but no effect on longer-term outcomes when sustained inflation was compared with standard PPV.[69] The current recommendation is for sustained inflation not to be used routinely and to limit its use to within randomized clinical trials.[52]

Peak Inflation Pressures and Tidal Volumes

Tidal volumes are not usually measured in the delivery room; therefore, clinicians must use peak pressure and clinical judgment of chest rise as a proxy for volume delivery. Neither of these provide reliable guidance regarding volume delivery.[56,68] However, they remain the most practical methods of targeting delivered volume given the equipment currently available. The actual delivered volume depends on multiple factors—the infant's spontaneous breathing effort, lung compliance, mask leak, obstruction at the mouth and nose, and the resuscitation device used. This means that tidal volumes delivered during PPV are variable and usually much higher than those generated during spontaneous breathing.[30] Animal studies have shown that high tidal volumes given soon after birth result in reduced oxygenation, increased need for ventilatory support, and instability of cerebral blood flow that increases the risk of brain injury.[55] The ideal target volumes for ventilation of term and preterm infants remain uncertain. Avoidance of tidal volumes greater than 8 mL/kg appears reasonable.[78] Development and testing of inexpensive, reliable, and accurate techniques to measure and display tidal volume is an important priority in neonatal resuscitation.

In the absence of tidal volume monitoring devices, clinicians rely on set peak pressure and clinical signs to deliver safe and effective ventilation. Typically, pressures in the range of 20-30 cm H_2O are suggested as initial settings[51,94] and have been shown to produce reasonable tidal volumes. Infants who make no respiratory effort may require higher pressures initially. As the lungs aerate and become more compliant, pressure may need to be reduced.[35] A rising heart rate is a good sign that effective ventilation is being delivered.[51]

Positive End Expiratory Pressure

The lungs of preterm infants are immature, surfactant-deficient, partially liquid-filled, and prone to collapse at end expiration. The beneficial effects of a continuous distending pressure include:

- splinting the airways open
- facilitating lung fluid clearance
- increased lung expansion and promoting the formation and retention of a residual lung volume at end expiration, preventing alveolar collapse
- conserving surfactant
- reducing ventilation-perfusion mismatch and right-to-left shunting
- improving oxygenation
- improving lung compliance
- reducing airway resistance by dilating the larynx and airways
- reducing upper airway occlusion by decreasing upper airway resistance and increasing the pharyngeal cross-sectional area
- reducing the work of breathing
- stabilizing the respiratory pattern
- stabilizing the chest wall and counteracting paradoxical movements

PEEP protects against lung injury and distal airway collapse at end expiration, while improving lung compliance, oxygenation, and accumulation of FRC. Whether or not an initial sustained inflation is given, animal studies have shown that without PEEP, no FRC is established[74] or maintained.[82] After an inflation without PEEP, lung volume is lost, airways collapse, and the infant becomes at risk of atelectrauma during the following inflations.[6]

There are few randomized studies in premature infants examining the use of PEEP at birth. Those that have been published failed to show a significant benefit over PPV without PEEP in terms of short-term respiratory

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outcomes.[8,13] International guidelines suggest that PEEP is likely to be beneficial during positive pressure support of preterm infants, and if it is available it should be used.[51]

It is not possible to predict a single optimal PEEP level for all infants; however, infants with the highest oxygen requirements usually have the smallest FRC and may benefit from higher PEEP. Guidelines recommend the use of PEEP of 5 cm H_2O in the delivery room.[52] Trials of different levels of PEEP during resuscitation of human infants at birth are required.

Inflation Rate and Duration

There is little evidence on which to base the optimal inflation rate. Rates of 40-60 per minute are recommended and match the typical respiratory rates of healthy newborns. In an infant who has some respiratory effort, it is likely that manual inflations will sometimes be asynchronous with spontaneous breaths. This may lead to ineffective resuscitation, inadvertent high pressures, and increased risk of injury such as pneumothorax.[16] The duration of each inflation may, following the initial inflations, be best timed to reflect spontaneous inspiratory times of newborn infants to last approximately 0.3 seconds.

Gas Flow

It is rarely necessary to change the gas flow above the standard 8-10 L/minute during a resuscitation. Alteration of gas flow may not affect pressure or volume delivery when using a self-inflating or flow-inflating bag. Increasing gas flow above recommended rates during T-piece ventilation increases leak; it also increases the PEEP without increasing the peak pressure, resulting in lower delivered tidal volumes.[63,81]

Key Points

- Most full-term and late preterm infants breathe at birth and need no assistance to transition to extrauterine life.
- Infants who do not establish regular respiration require prompt respiratory support.
- Effective mask ventilation should result in a rapid increase in heart rate.
- Excessive tidal volume may cause lung damage especially to preterm infants.
- Endotracheal intubation should be considered if resuscitation is prolonged or the infant remains bradycardic.

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33

Oxygen Therapy in Neonatal Resuscitation

MAXIMO VENTO

Use of Oxygen in Perinatal Asphyxia and Resuscitation

Oxidative Stress: Pathophysiologic Background

Perinatal asphyxia is a devastating disorder that affects roughly 2% of newborn babies in industrialized countries, but constitutes one of the leading causes of early neonatal death in nonindustrialized countries.[26] Both ischemia and hypoxia reduce oxygen and glucose supply to neurons leading to ATP depletion and inactivation of ATP-depending ion pumps, causing intracellular accumulation of Na^{+} (cell swelling), of ionic Ca^{++} (increased free radical formation and oxidative stress/damage), and inhibition of neurotransmitters' recaptation at the synaptic cleft causing hyperexcitability. Altogether these pathophysiologic circumstances will not only lead to cell necrosis but will collectively predispose tissue to reoxygenation injury.[12] During hypoxia, limited oxygen availability decreases oxidative phosphorylation, resulting in a failure to resynthesize energy-rich phosphates, including adenosine 5′-triphosphate (ATP) and phosphocreatine, resulting in an accumulation of purine derivatives, especially hypoxanthine. The tissue concentration of these metabolites is directly dependent on the intensity and prolongation of hypoxia[22] (Fig. 33.1). Upon resuscitation, restoration of oxygen and glucose supply may salvage neurons, but it will also activate the transformation of xanthine dehydrogenase in xanthine oxidase leading to the generation of a burst of oxygen and nitrogen free radicals that will trigger apoptotic and proinflammatory pathways, thus expanding the initial neuronal damage.[39] Moreover, in the endothelium, ischemia promotes expression of certain proinflammatory gene products (e.g., leukocyte adhesion molecules, cytokines) and bioactive agents (e.g., endothelin, thromboxane A_2) while repressing other "protective" gene products (e.g., prostacyclin, nitric oxide). Ischemia induces a proinflammatory state that increases tissue vulnerability to further injury on reperfusion.[16]

Reperfusion and reoxygenation of ischemic tissues result in the formation of toxic reactive oxygen species, including superoxide anions ($\bullet O_2^-$), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and nitrogen reactive species, especially peroxynitrite (•ONOO-). Under physiologic conditions, hypoxanthine accumulated during the ischemia is further oxidized by xanthine dehydrogenase to uric acid in the cells containing this enzyme. However, during prolonged ischemia, xanthine dehydrogenase is converted to xanthine oxidase by specific proteases. Of note, xanthine oxidase uses oxygen as a substrate and during hypoxia-ischemia is unable to catalyze the conversion of hypoxanthine (resulting in the buildup of excess tissue levels of hypoxanthine). When oxygen is reintroduced during resuscitation, conversion of the excess hypoxanthine by xanthine oxidase results in the formation of reactive oxygen species, especially anion superoxide. Moreover, in the presence of nitric oxide, both superoxide and nitric oxide will combine in the formation of reactive nitrogen species, especially peroxynitrite. In tissues rich in ferrous iron such as the brain, Fenton chemistry will ensue, leading to the formation of the highly reactive hydroxyl radical. Interestingly, xanthine oxidase in humans is mainly restricted to the liver and intestine. It has been shown, however, that xanthine oxidase leaks out into the blood after hypoxia and hypotension, and the hypoxanthine-xanthine oxidase system may be detrimental in all parts of the body. Many other oxygen radical–generating systems are presently well described.[48]

Reactive oxygen species and reactive nitrogen species are potent oxidizing and reducing agents that directly damage cellular structures. They are able to peroxidize membranes, structural proteins and enzymes, and nucleic acids. In addition, they are known to be extremely important regulators of intracellular signaling pathways that modulate DNA and RNA synthesis, protein synthesis, and enzyme activation, and directly influence the cell.[19] Increasingly, the concept of redox code has acquired more relevance. The redox code defines the positioning of nicotinamide adenine dinucleotide (NAD, NADP), thiol/disulfide (GSH/GSSG; CysSH/

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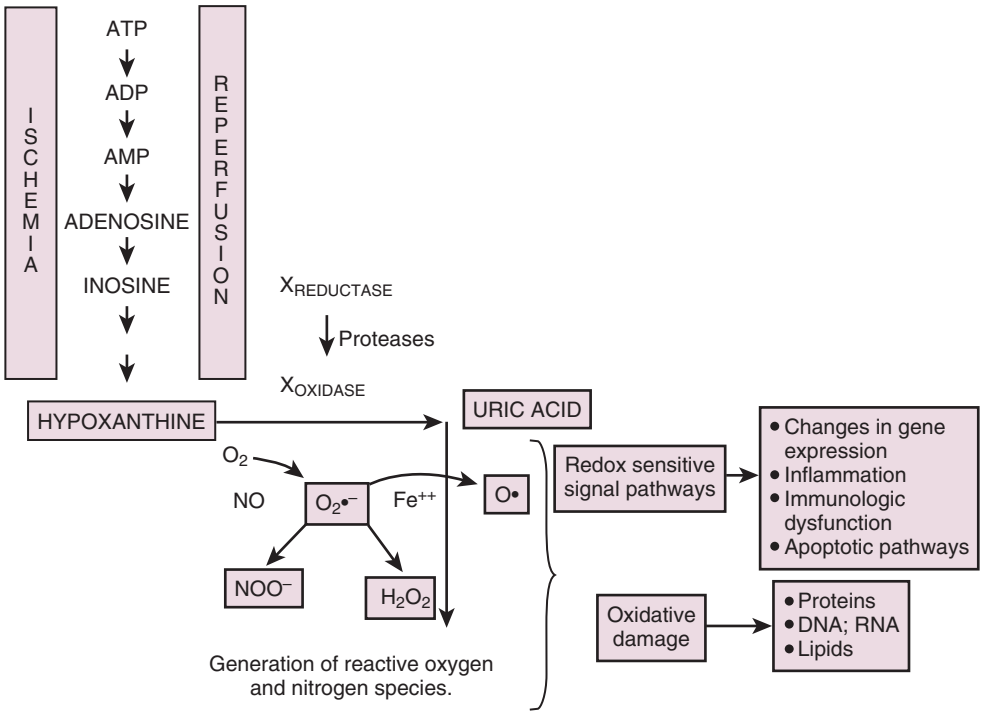
Abstract

Fetal to neonatal transition causes an increased supply of oxygen to tissue, a burst of oxygen free radicals, and subsequently a physiologic oxidative stress. Healthy term newborn babies are readily prepared to overcome this circumstance. However, in asphyxiated babies, prolonged hypoxia and ischemia lead to a pathologic oxidative stress that overcoming newborn infants' defenses may cause damage to brain, myocardium, and other organs. Therefore, it is recommended that resuscitation is started with room air, and oxygen supplementation when needed should be under strict pulse oximeter control. Preterm babies are especially vulnerable to oxygen-derived damage because of the immaturity of the antioxidant system. Therefore, it has been recommended in the recent 2015 ILCOR guidelines that the initial inspired fraction of oxygen (FIO_2) for these babies should be 0.3 and titrated according to evolving pulse oximetry and heart rate, trying to adjust saturation to the American Heart Association (AHA) recommended ranges. However, recent studies have shown that babies that are supplemented with lower initial FIO_2 and do not achieve saturations of 85% or are kept with heart rates <100 bpm at 5 minutes after birth are more prone to develop intraventricular hemorrhage or have increased mortality. It is not known if these babies are already born with some in utero handicap, or it is because they are not supplied with enough oxygen. Adequately powered and designed randomized controlled trials are necessary to find an answer to this conundrum.

Keywords

oxygen
oxidative stress
pulse oximetry
inspired fraction of oxygen
asphyxia
prematurity

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• **Fig. 33.1** During hypoxia, adenosine triphosphate (ATP) is exhausted, and complete rebuilding is not achieved. Purine derivatives (e.g., hypoxanthine) accumulate. During reoxygenation, specific proteases transform xanthine reductase ($X_{REDUCTASE}$) into xanthine oxidase ($X_{OXIDASE}$), which uses oxygen as a substrate, generating a burst of reactive oxygen species such as superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical (O·). In the presence of ferrous iron (Fe^{++}), Fenton chemistry generates great amounts of superoxide anion. Superoxide anion easily combines with abundant nitric oxide (NO), generating peroxynitrite (NOO·), an extremely aggressive nitrogen free radical. Free radicals are capable of damaging nearby molecules and organelles but also act as signaling molecules causing changes in gene expression, promoting inflammation, altering immune response, and inducing apoptosis.

CysS-S), and other redox systems as well as the thiol redox proteome as common elements for biologic processes. These control elements are functionally organized in redox circuits, which are controlled by central nodes constituted by sulfur/disulfide couples. These circuits function independently and are highly responsive for redox conditions, thus signaling and regulating biologic processes. The code is present in an oxygen-dependent life. Activation and deactivation cycles involving oxygen and hydrogen peroxide contribute to spatiotemporal organization for differentiation, development, and adaptation to the environment.[18]

A vast array of enzymatic and nonenzymatic antioxidants has evolved in biologic systems to protect cellular structures against the deleterious action of free radicals. Antioxidant enzymes catalytically remove reactive oxygen species (ROS), thereby decreasing ROS reactivity, and protect proteins through the use of chaperones, transition metal-containing proteins (transferrin, ferritin, ceruloplasmin), and low molecular weight compounds that purposely function as oxidizing or reducing agents to maintain intracellular redox stability.[19]

Clinically, antioxidant enzymes that have been most widely studied are the superoxide dismutases, catalases, and glutathione peroxidase. The most relevant nonenzymatic cytoplasmic antioxidant is reduced glutathione (GSH), a tripeptide (γ-glutamyl-cysteinyl-glycine). Hence, two molecules of GSH establishing a disulfide bond form oxidized glutathione and release one electron that is accepted by a free radical to stabilize the outer atomic shell. Thiol-disulfide strategy is extremely important in maintaining the reducing state in the cytoplasm and the cell redox status, essential for cell reproduction and maturation. Other systems to detoxify hydrogen peroxide in mitochondria and other organelles include glutaredoxin, thioredoxin, thioredoxin reductase, and the peroxiredoxins. Other enzymes with antioxidant and signaling functions are heme oxygenases (HO-1 and HO-2). HO-1 removes heme, a pro-oxidant, and generates biliverdin, an antioxidant, releasing iron and carbon monoxide. Finally, nonenzymatic antioxidants such as reduced glutathione, vitamin C, vitamin E, and β-carotene also function to protect cells from damaging effects of ROS.[54]

Oxidative stress in a biologic system is defined as the imbalance of pro-oxidants and antioxidants in favor of pro-oxidants.[15] Different biomarkers of oxidative stress have been used in biology and medicine. An indirect way of measuring oxidative stress is the detection of increased activity of antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, or glutathione redox cycle enzymes. Another measure is to analyze the oxidized form

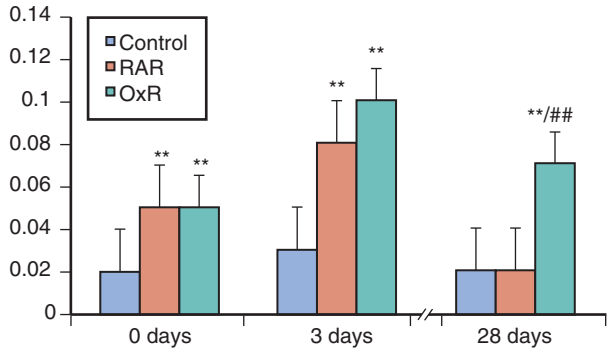
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of a nonenzymatic molecule such as oxidized glutathione. An increased concentration of oxidized glutathione or a decreased ratio of reduced to oxidized glutathione may indirectly reflect a pro-oxidant status.[43]

For clinical purposes, the most widely employed markers of oxidative stress are those derived from the oxidant alteration of biologic molecules that convey the following characteristics: being chemically stable, reproducible, and easily measurable in biologic fluids. Urinary markers of oxidative stress are extremely valuable in neonatology, because urine sampling is readily available, allowing serial measurements without the need of supplementary blood sampling. In recent studies, reliable high performance liquid chromatography coupled to tandem mass spectrometry methods has been validated in the urine of newborn infants.[7] Hence, protein oxidation can be readily measured, analyzing phenylalanine oxidation by the action of hydroxyl radicals that leads to the formation of ortho-tyrosine (O-tyr) and meta-tyrosine. In addition, the action of hypochlorous acid and peroxynitrite upon phenylalanine produces byproducts such as chlor-tyrosine and nitro-tyrosine that reflect inflammatory processes and nitrosative stress respectively.[47] Hydroxyl radical aggression upon DNA can be assessed analyzing urinary concentration of oxidized guanidine bases.[21] The byproducts 8-hydroxyguanine (8-oxo-Gua) and its 2′-deoxynucleoside equivalent 7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) are highly mutagenic. Urinary elimination of 8-oxo-Gua and 8-oxo-dG perfectly reflects nuclear attack by hydroxyl radicals.[8] In experiments performed in a piglet model of hypoxia and reoxygenation, urinary elimination of metabolites O-tyr and 8-oxo-dG correlated significantly with the amount of oxygen used on reoxygenation.[44] Lipid oxidation, especially arachidonic (isoprostanes, isofurans), docosahexanoic (neuroprostanes, neurofurans), and adrenic (di-homo isoprostanes) acids perfectly reflect damage to neuronal membranes and lipid components in gray and white matter respectively. Hence, F2-isoprostanes and isofurans, which are non-cyclooxygenase oxidative derivatives of arachidonic acid, are considered at present the most reliable markers of lipid peroxidation. These compounds are chemically stable, formed *in vivo*, present in all organic fluids and tissues, and are not affected by dietary content of lipids. Isofurans reflect oxidation in a high oxygen atmosphere and isoprostanes in a normoxic environment. In addition, byproducts derived from the oxidation of docosahexanoic acid such as neuroprostanes and neurofurans have also been considered very valuable biomarkers, especially related to oxidative damage of neuronal membranes, and adrenic acid reflects white matter damage by oxygen free radicals.[2,6,45]

Oxidative Stress: Differences Between Resuscitation With 100% Oxygen and Room Air

In the absence of severe lung disease or cyanotic congenital heart disease, resuscitation with 100% oxygen has been shown to cause supra-physiologic arterial partial pressures of oxygen in the newly born infant. By contrast, resuscitation with room air increases the Pao_2 to physiologic levels only (i.e., approximately 70-80 mm Hg). Biomarkers of oxidative stress such as oxidized glutathione or antioxidant enzyme activity are significantly increased in patients receiving excessive oxygen. Thus, newborn infants resuscitated with pure oxygen exhibit higher oxidative stress after resuscitation than infants recovered with room air.[50] Conspicuously, oxidative stress derived from resuscitation with pure oxygen may cause a long-lasting pro-oxidant status. Hence, in newborn babies resuscitated with 100% oxygen, oxidative stress was detected 4 weeks after birth. These infants had a decreased ratio of total blood reduced (GSH) to oxidized (GSSG) glutathione and oxidized DNA bases in urine at 1 month of life. No such effect has been observed in infants resuscitated with room air (Fig. 33.2).[49]



• **Fig. 33.2** Ratio of oxidized glutathione to reduced glutathione in asphyxiated newborns resuscitated with room air (RAR) or 100% oxygen (OxR) determined at 0 (birth), 3, and 28 days of life. ** $p < .01$ versus control; $p < .01$ versus RAR.

Hyperoxemia has also been associated with a series of negative side effects, including increased oxygen consumption and metabolic rate, increased activation of leukocytes and endothelial cells, and increased formation of reactive oxygen species and reactive nitrogen species.[16] Prolonged vasoconstriction of cerebral arteries has also been shown. In a study involving premature infants younger than 33 weeks' gestational age at 24 hours, cerebral blood flow was reduced by 20% in infants given 80% oxygen compared with infants for whom room air was used. This finding is in line with studies in newborn rats showing that the use of 100% oxygen for resuscitation reduces cerebral blood flow compared with room air resuscitation.[14]

Room Air versus Pure Oxygen for Resuscitation of the Newborn

Traditionally, postnatal resuscitation in the delivery room had been performed with 100% oxygen.[1] However, in 1998, the Resair 2 trial showed that it was feasible to resuscitate depressed newborn infants with room air.[36] Thereafter, a series of clinical studies summarized in an updated

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review and meta-analysis has shown not only the suitability of room air for the resuscitation of the depressed term neonate but also a series of advantages, among which the most relevant is a decrease in mortality.[38,39]

Animal Studies

Animal studies have shown that after a period of severe hypoxia, physiologic functions such as blood pressure and blood flow to various organs, including the brain, are restored equally efficiently with 21% and 100% oxygen. Evoked potentials and biochemical indicators such as base deficit and hypoxanthine are restored efficiently using room air for resuscitation. Furthermore, experimental studies have also clearly shown that using 21% instead of 100% oxygen offers significant additional advantages. Hence, the use of high oxygen concentrations is not only toxic for the lungs but also for several other organs such as the heart, liver, and brain. In a review, the most relevant findings in animal models of hypoxia and reoxygenation with 21% versus 100% have been detailed.[40] Thus, extracellular glycerol concentration from the striatum was significantly higher in hypoxic piglets resuscitated with pure oxygen as compared with those resuscitated with air. Moreover, in a mouse model, hyperoxia after hypoxic-ischemic brain injury increased secondary neuronal injury and interfered with myelination. Matrix metalloproteinases, which reflect tissue damage and repair, were measured in lung, liver, heart, and brain of hypoxic piglets recovered with 100% versus 21% oxygen. Remarkably, the use of elevated oxygen concentration caused a significant increase of metalloproteinases in all analyzed tissues.[14] The H_2O_2 concentration in leukocytes from the sagittal sinus increased significantly in newborn hypoxic piglets resuscitated with 100% oxygen, in contrast to piglets given 21% oxygen. The nitric oxide concentration in the brain also tended to become higher if pure oxygen was used compared with ambient air for resuscitation of piglets. The stage might be set for a higher production of reactive nitrogen species and peroxynitrite if 100% oxygen is used.[20,23,24]

There are also clear indications that resuscitation with 100% oxygen augments inflammatory processes in the myocardium and the brain more than 21% oxygen. In a study using cord occlusion of fetal lambs, resuscitation with room air restored blood pressure as fast as when using 21% oxygen. In the cortex and subcortical area, significantly higher levels of proinflammatory cytokines and activities of Toll-like receptors 2 and 4 were found in animals given 100% oxygen.[28]

Some animal studies have shown that cerebral brain microflow is reestablished faster with 100% oxygen. One study in newborn mice found that 100% versus 21% oxygen gave faster cerebral blood flow restoration and poorer short-term and improved long-term recovery.[34] In another study, the slower normalization of cerebral blood flow in animals resuscitated with room air versus animals resuscitated with 100% oxygen almost disappeared, however, if moderate hypercapnia was present. In birth asphyxia, hypercapnia always coincides with hypoxia. Hypercapnia might seem to be an important factor in reestablishing brain blood flow after asphyxia. As mentioned earlier, other studies have shown that 100% oxygen during normocapnia, in contrast to the use of 21% oxygen, reduces cerebral blood flow.[14]

Oxygen is a pulmonary vasodilator, but studies performed in animal models of hypoxia reoxygenation have shown that hyperoxia blunts vasodilator activity of oxygen probably mediated by the generation of reactive oxygen species, especially H_2O_2 in the mitochondrial matrix. H_2O_2 diffuses to the cytoplasm, activating phosphodiesterase 5 (PDE5), which, acting upon the vascular smooth muscle cells, degrades cGMP thus inhibiting nitric oxide–mediated vasorelaxation and favoring persistent vasoconstriction. Remarkably, resuscitation with 100% oxygen of term fetal lambs asphyxiated by cord occlusion initially induced a decrease in pulmonary vascular resistance (PVR) and subsequent increase in pulmonary blood flow. Nonetheless, subsequent values (between 2 and 30 min) for PVR did not differ between lambs resuscitated with air or 100% oxygen. Interestingly, the increased pulmonary artery contractility induced by 100% oxygen was reversed when superoxide anions were scavenged. Hence, the use of 100% oxygen increases partial pressure of oxygen in the pulmonary artery, yet it does not enhance oxygen uptake by lung tissue, does not decrease pulmonary vascular resistance, and does not increase systemic oxygen extraction ratios. Furthermore, 100% oxygen also induces oxidative stress and increases pulmonary artery contractility, thus favoring pulmonary hypertension.[25,26] Animal studies have also shown that even in meconium aspiration, resuscitation with room air is as efficient as resuscitation with 100% oxygen, provided that a sufficient tidal volume is given.[46]

The results from animal studies quite overwhelmingly indicate that room air resuscitation is, in most cases, beneficial when compared with the use of 100% oxygen. Still there might be clinical conditions such as prematurity with primary lung disease when limited initial supplemental oxygen should be added.

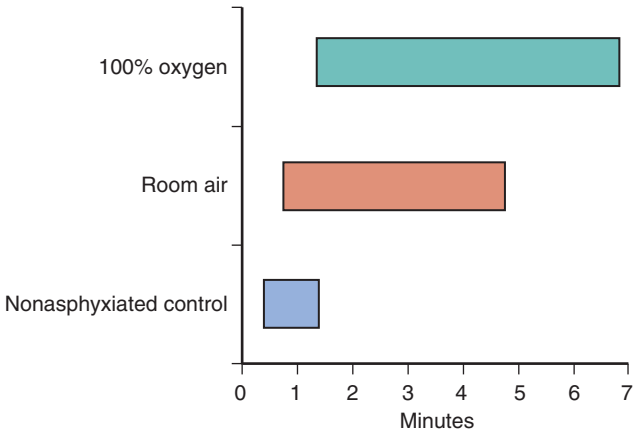
Clinical Data

Several clinical studies have been conducted, aiming to evaluate the efficacy of resuscitation with ambient air compared with pure oxygen. Ten studies including 2133 newborns have been included in randomized or pseudo-randomized studies investigating any differences between infants resuscitated with 21% oxygen and 100% oxygen.[38] Results of these studies indicate that Apgar scores are more depressed, at least at 5 minutes of age, in newborns resuscitated with 100% oxygen compared with 21% oxygen; this is probably because newborns given oxygen take their first breath and cry significantly later than newborns given room air. As shown in a newborn rat model, initiation of diaphragmatic contractility and spontaneous respiration after hypoxia

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is directly influenced by the oxygen concentration used upon reoxygenation.[3] Normal, nonasphyxiated newborns delivered vaginally or by cesarean section initiate the first cry almost immediately after birth and attain a sustained pattern of respiration within the first 30 seconds of life. Hypoxic and acidotic-asphyxiated infants do not initiate breathing spontaneously, however, and may require positive pressure ventilation. The duration of the resuscitation period directly correlates with the severity of asphyxia and the efficiency of the resuscitation procedure. Furthermore, onset of respiration was delayed in infants given 100% oxygen compared with infants given room air. Hence, time to first cry in infants resuscitated with room air ranged from 0.6-4.5 minutes, whereas infants resuscitated with 100% oxygen took 1.2-7 minutes to the first cry (Fig. 33.3). Another study of the duration of resuscitation until asphyxiated infants were able to sustain a spontaneous and regular pattern of breathing revealed that infants resuscitated with room air also needed less time (5.3 ± 1.5 minutes) than infants resuscitated with 100% oxygen (6.8 ± 1.2 minutes) to establish a regular respiration.[49,50,51]

An updated review and meta-analysis indicate that neonatal mortality is reduced 30% in the room air group. If we translate this data to the worldwide incidence of severe neonatal depression, this intervention could potentially save approximately 250,000 lives annually.[38,39] Remarkably, systematic review showed neonatal mortality of 12.8% in the 100% oxygen group versus 8.2% in the room air group, giving a relative risk (RR) of 0.69 (95% confidence interval [CI] 0.54-0.88) for neonatal mortality in infants given 21% oxygen. Number needed to treat is 25. These dramatic results raise several questions, first about the quality of the studies included and second, regarding what was the cause of death in these infants. The studies represent a mixture of blinded and unblinded, multicenter and single-center studies from many countries. Most of the infants were recruited from countries with poor resources. When analyzing separately the children from industrialized countries enrolled in six strictly randomized trials, a significant reduction of 2.8% (from 3.9%-1.1%) in neonatal mortality rate was still found (RR 0.32, 95% CI 0.12-0.84) in favor of the infants resuscitated with ambient air.[38]



• **Fig. 33.3** Time to first cry in asphyxiated newborns resuscitated with room air or 100% oxygen.

The causes of death can be mainly, but not exclusively, attributed to asphyxia. If oxidative stress is induced in infants resuscitated with pure oxygen, this may lead to alterations of cell function and physiology that place the infant at increased risk. This situation is illustrated in one study finding significantly higher troponin and *N*-acetylglucosaminidase in infants resuscitated with 100% oxygen compared with 21% oxygen, indicating more damage to the myocardium and kidney in the infants exposed to pure oxygen.[51] There was also a trend toward a reduction of severe hypoxic-ischemic encephalopathy stage 2 and 3 in the room air–resuscitated infants compared with 100% oxygen–resuscitated infants (RR 0.88, 95% CI 0.72-1.08).[38]

In newborns needing intervention at birth, with an Apgar score of less than 6 at 1 minute and given room air by bag and mask, the median SpO_2 at 1 minute of age was 65%, with 10th-90th percentiles ranging from 43%-80%. At 3 and 5 minutes, the corresponding figures are 85% (60%-90%) and 90% (73%-95%). The infants randomly assigned to pure oxygen did not have higher SaO_2 values over the first 10 minutes of life.[37]

Follow-up of 414 children aged 12-24 months and resuscitated with 21% versus 100% O_2 after birth were analyzed. Of note, none of these studies were designed to perform long-term follow-up as an outcome; nonetheless, final results indicated that no significant difference was found between groups regarding neurodevelopmental outcome. However, given the heterogeneous design of these studies, estimates are imprecise and warrant further study to draw conclusions.[41]

Oxygen Supplementation in the Delivery Room in Extremely Low Gestational Age Neonates

Mortality of neonates of extremely low gestational age (≤28 weeks' gestation) has substantially decreased in recent decades; however, morbidity, especially in the lower gestational age segment, remains high. Among neonates of extremely low gestational age, 70% may need some type of positive pressure ventilation in the delivery room.[55] In animal experiments, ventilation with high tidal volumes in the first minutes of life cause structural changes in the lung, predisposing to chronic lung disease.[17] Moreover, oxygen in excess upon resuscitation causes oxidative damage, especially in patients with an immature antioxidant defense system predisposing to chronic lung disease.[48,52] The feasibility of resuscitating extremely preterm infants with low initial FIO_2 has been approached in different studies. The use of room air was unsuccessful in achieving target saturations and heart rate in a significant number of very preterm infants who needed to be switched to 100% oxygen.[56] Contrarily, resuscitation with an initial FIO_2 of 0.3 was significantly more successful in achieving postnatal stabilization with less

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oxygen exposure.[13,52] In both studies, very preterm infants achieved Spo_2 of 75% at 5 minutes after birth, and Spo_2 of 85% at 8-10 minutes. In 2014, a meta-analysis by Saugstad et al., including randomized trials (RCT) comparing higher (60%-100%) versus lower (21%-30%) initial oxygen in 677 preterm infants ≤32 weeks' gestation showed no differences in morbidity but a trend toward lower mortality in the lower oxygen group. It was concluded that preterm infants could be initially stabilized with Fio_2 of 0.21-0.3.[42] A survey among neonatologists from 25 countries in 2016 showed that only a small minority would resuscitate with an initial high supplemental oxygen.[29] However, Oei et al. published results of the largest RCT, comparing the effects of resuscitation with room air versus 100% oxygen in 289 preterm infants <32 weeks' gestation, targeting an SpO_2 65%-95% by 5 minutes and 85%-95% until admission. Mortality in the subgroup of babies <29 weeks' gestation was 16.2% in the room air group and 6% in the 100% oxygen group. Although statistically marginal, results emphasized the urgent need for larger RCTs.[30] In addition, the Canadian Neonatal Network published a retrospective cohort study comparing infants ≤27 weeks' gestation before and after 2006 when the policy regarding initial Fio_2 for preterm infants in the delivery room was changed from 100% to <100% oxygen and titration according to SpO_2. Adjusted OR (AOR) for the primary outcome of severe neurologic injury or death was higher in the lower oxygen group (AOR 1.36; 95% CI 1.11-1.66) and in those resuscitated with room air (AOR 1.33; 95% CI 1.04-1.69), when compared with 100% oxygen. The investigators cautioned about the consequences of a policy of initial stabilization with lower oxygen in very preterm infants compared to starting with 100% oxygen.[35] However, since both of these studies were simultaneously published with the 2015 ILCOR treatment recommendations, they were not included in the 2015 ILCOR final statements. In 2016, in a systematic review and meta-analysis of outcomes of randomized controlled trials in infants ≤28 6/7 weeks' gestation randomized to resuscitation with low (≤0.3) versus high (≥0.6) fraction of inspired oxygen (Fio_2) at delivery, main outcomes were death in hospital, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) (>grade 2), intraventricular hemorrhage (IVH) (>grade 2), patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC) (>stage 2 of Bell). No differences in BPD, ROP, PDA, and NEC, and overall mortality were found.[31] Furthermore, a study in 2017 has analyzed the association of SpO_2 at 5 min after birth and clinical outcomes in preterm infants ≤32 weeks' gestation.[32] Data from 768 infants ≤32 weeks' gestation from 8 randomized control trials of lower (≤0.3) versus higher (≥0.6) initial Fio_2 were analyzed. The study aimed to establish a relationship between SpO_2 at 5 minutes, death, and IVH >grade 3. Interestingly, only 23% of the 706 patients met the SpO_2 targets at 5 minutes, and 46% did not reach SpO_2 80%. Pooled data showed decreased likelihood of reaching SpO_2 80% if resuscitation was initiated with Fio_2 <0.3 ($p<0.05$); moreover, SpO_2 <80% was associated with lower heart rates and with IVH ($p<0.05$). Of note, bradycardia (HR <100 bpm) at 5 minutes increased the risk of death ($p<0.05$). Taken altogether, and after accounting for confounders including gestation, birth weight, and bradycardia at 5 minutes, risk of death was significantly increased with time taken to reach SpO_2 80%. These findings could be explained because insufficient oxygen was provided or because inability of infants to respond to resuscitation is a reflection of the infant's *in utero* status.[32]

Boronat et al. have published in 2016 the only follow-up study from preterm infants randomized to an initial FIO_2 of 0.3 versus 0.6.[4] A total of 206 infants <32 weeks' gestation representing 81.4% of the total recruited in two studies completed follow-up at 24 months. No differences in perinatal characteristics, oxidative stress, or morbidities during the neonatal period were found. Moreover, no differences of mortality at hospital discharge or when follow-up was completed were found between groups. Remarkably, no differences regarding Bayley III scale scores (motor, cognitive, and language composites), neurosensorial handicaps, cerebral palsy, or language skills between groups were found.[4]

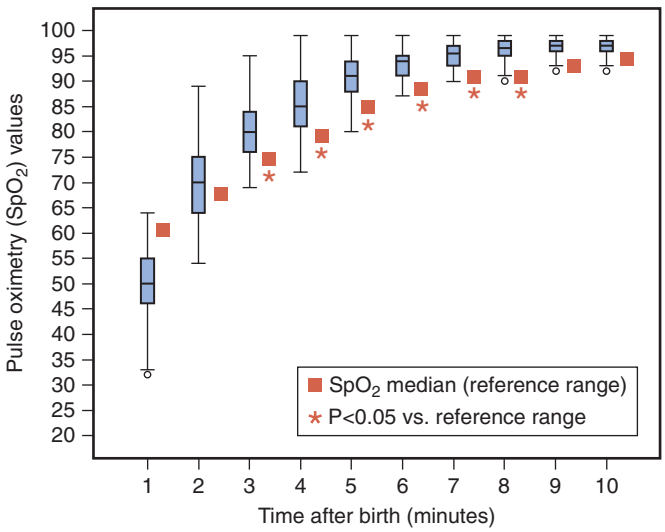
Oxygen Saturation Nomogram

Dawson, Kamlin, and Vento separately enrolled in three prospective observational studies 468 healthy newly born infants with gestational ages ranging from 25-42 weeks not needing any type of intervention in the delivery room after birth and until stabilization. SpO_2 was measured using preductal pulse oximetry and retrieved from the first minute after birth using state-of-the-art monitors set at maximum sensitivity attached to the right wrist. Thereafter, the three data sets were assembled into a graph that represents a reference range for SpO_2 for normal babies <42 weeks' gestation in the first 10 minutes after birth. Interestingly, it was shown that enrolled babies needed a median of 7.9 (interquartile range [IQR]: 5.0-10.0) minutes to reach SpO_2 >90% (Fig. 33.4).[9] Moreover, preterm infants needed significantly more time to reach this saturation. Hence, time needed to achieve SpO_2 stabilization was inversely proportional to gestational age.[9] In addition, a nomogram for heart rate also revealed different timing for stabilization in term and preterm infants.[10] At present, Dawson's oxygen saturation nomogram represents the best estimate of the most appropriate SpO_2 targets for term, but especially for preterm infants, during the first minutes of life.[11] Interestingly, preterm infants on continuous positive airway pressure and room air achieved targeted saturations reflected in the nomogram significantly earlier than those breathing spontaneously (see Fig. 33.4).[53]

Room Air versus 100% Oxygen—or Something Else

In 2010, the ILCOR guidelines clearly established the use of air as initial gas admixture to resuscitate depressed

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• **Fig. 33.4** *Red squares* represent oxygen saturation as measured by preductal pulse oximetry (SpO_2) in neonates with a gestational age ranging from 25-42 weeks' gestation who did not receive active resuscitation after birth. *Blue squares* represent SpO_2 of preterm babies (<32 weeks' gestation) who received respiratory support with continuous positive airway pressure and air immediately after birth. (Data from Dawson JA, et al[9] and Vento M, et al.[53])

newly born term infants. Moreover, if recovery is not successful, increased oxygen concentrations should always be used guided by pulse oximetry.[33] However, there is a discrepancy between the American Heart Association's (AHA) algorithm and the European Resuscitation Council (ERC) regarding SpO_2 targets for term infants. Hence, while the AHA recommends SpO_2 ranges at 1, 2, 3, 4, 5, and 10 minutes after birth of 60%-65%, 65%-70%, 70%-75%, 75%-80%, 80%-85%, and 85%-90%, respectively, the ERC recommends starting oxygen at an SpO_2 of 60%, 70%, 80%, 85%, and 90%, respectively, at 2, 3, 4, 5, and 10 minutes after birth. The differences between recommendations are based on the percentiles chosen as safety references to avoid hyperoxia and hypoxia, which have not yet been determined in randomized controlled trials.[11]

The use of supplemental oxygen to stabilize very preterm infants is still a matter of debate among neonatologists. In the last few years, a series of studies have shown that it is preterm infants ≤28 weeks' gestation who are at the center of the debate. Prolongation for more than 5 minutes of hypoxemia (SpO_2 <80%), and especially bradycardia (HR <100 bpm), seems to increase the probability of death and/or IVH. However, it is not clear if preterm infants do not reach these saturation and heart rate targets because they are already compromised *in utero* or because they are not adequately ventilated or oxygen supplementation is too low. The only means to solve this conundrum is to launch adequately designed and powered studies addressing this relevant issue. However, until more data are available, starting with 30% oxygen and trying to achieve SaO_2 of 85% within 5 minutes is recommended. In those cases, where there is no response in the first 3-4 minutes, titration should be performed, increasing more rapidly with higher oxygen increments.

Key Points

- Cellular injury results from biochemical pathways activated by both hypoxia and reoxygenation with oxidative stress determined by prooxidant/antioxidant imbalance.
- Both animal and human studies have documented detrimental physiologic and biochemical consequences of 100% versus 21% oxygen resuscitation. In extremely low gestation infants, initial low supplemental oxygen (e.g., 30%) is frequently needed.
- Available oxygen saturation nomograms provide a useful guide to titrate supplemental oxygen against SpO_2 targets obtained via pulse oximetry, especially in preterm infants.

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34

Chest Compression, Medications, and Special Problems in Neonatal Resuscitation

VISHAL KAPADIA AND MYRA WYCKOFF

Advanced resuscitation in the delivery room is rarely needed as long as effective ventilation is quickly established. When compressions are needed, it is critical to minimize pauses, use the most effective two-thumb method from the head of the bed position, and coordinate with breaths that inflate the lung. In rare cases of profound asphyxia, intravenous epinephrine may be needed to reestablish adequate coronary perfusion pressure. Medical personnel who attend deliveries should practice these rare but vital steps so that when a crisis delivery occurs, they can mobilize additional help rapidly and perform the needed steps with skill without hesitation.

Accurate recording of the events in the delivery room and deliberate team debriefing should be employed to drive constant improvement in management of complex resuscitations.

Importance of Effective Ventilation

Effective positive pressure ventilation (PPV) is the most critical action needed to stabilize a newborn infant that is compromised at delivery. This is because the most likely cause of cardiovascular collapse of a newborn is asphyxia (inadequate gas exchange).[94] When effective ventilation is the primary focus of a newborn resuscitation team, chest compressions and medications are rarely needed. Data from a busy intercity delivery service with a highly trained resuscitation team suggests that chest compressions are provided for 0.1% of all deliveries[67] and chest compressions plus medications in 0.05%.[31] Premature newborns have higher rates of receiving chest compressions than their term counterparts.[1,32]

The most recent Neonatal Resuscitation Program (NRP) guidelines from the American Heart Association and the American Academy of Pediatrics suggest that chest compressions be performed if the heart rate remains less than 60 beats per minute after ventilation that inflates the lungs, as evidenced by chest rise with ventilation breaths.[97] Specific steps to improve ventilation before starting chest compressions should be initiated using the mnemonic algorithm MRSOPA (Table 34.1), which includes checking for a good *m*ask seal, *r*epositioning the infant in the open airway position, *s*uctioning the oropharynx for possible obstructing secretions, *o*pening the mouth so that ventilation attempts are not just through the higher resistance nasal passages, increasing the peak inspiratory *p*ressure of the PPV device, and placing an advanced *a*irway such as a laryngeal mask airway or endotracheal intubation.[94] Thus, if at all possible, the airway should be secured and ventilation provided via an advanced airway before initiation of chest compressions. The increased focus on achieving effective ventilation means that some extra time is allowed to work on the MRSOPA steps before proceeding to chest compressions. Common sense must prevail in the uncommon circumstance when neither a laryngeal mask airway nor endotracheal tube can be placed successfully. In this situation, chest compressions may have to be started while continuing to focus on optimization of mask ventilation. This can be accomplished by observation of adequate chest rise, bilateral auscultation of the lungs, and use of an end-tidal CO_2 ($ETCO_2$) detector. A neonatal pig study of asphyxia-induced asystole found no difference in rates of return of spontaneous circulation when the initial steps of resuscitation (dry, position, suction if needed, and stimulation) were followed by 30 versus 60 seconds of ventilation before compressions were started; however, 90 seconds of ventilation before supporting the circulation with compressions decreased rates of return of spontaneous circulation.[83] There is no evidence regarding optimal length of ventilation before compressions in the situation of severe bradycardia rather than asystole.

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Abstract

Advanced resuscitation in the delivery room is rarely needed as long as effective ventilation is quickly established. When compressions are needed, it is critical to minimize pauses, use the most effective two-thumb method from the head of the bed position, and coordinate with breaths that inflate the lung. In rare cases of profound asphyxia, intravenous epinephrine may be needed to reestablish adequate coronary perfusion pressure. Medical personnel who attend deliveries should practice these rare but vital steps so that when a crisis delivery occurs, they can mobilize additional help rapidly and perform the needed steps with skill without hesitation. Accurate recording of the events in the delivery room and deliberate team debriefing should be employed to drive constant improvement in management of complex resuscitations.

Keywords

resuscitation
delivery room
asphyxia
ventilation
compressions
oxygenation
simulation

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TABLE 34.1 Steps to Improve Ventilation Before Starting Chest Compressions (MRSOPA)

M	Mask	Check mask seal
R	Reposition	Position in open airway "sniffing" position
S	Suction	Suction to remove obstructing secretions
O	Open the mouth	Open the mouth to decrease resistance
P	Pressure increase	Increase the peak inspiratory pressure
A	Advanced airway	Place a laryngeal mask airway or intubate

There is no clinical evidence to offer guidance in either circumstance.

Current resuscitation guidelines[68] recommend that initial PPV be provided with 21%-30% oxygen in preterm infants <35 weeks of gestation[65] and with 21% oxygen in the remaining older preterm and term infants.[75] Oxygen supplementation should be guided by pulse oximetry and oxygen saturation per minute-of-life norms; however, when chest compressions are initiated, it is recommended that 100% O_2 be used until the heart rate is stabilized.[97] This recommendation remains controversial, and clinical data for guidance are lacking. Animal studies of profound cardiovascular collapse caused by asphyxia provide mixed results, with some suggesting a protective effect when 100% O_2 is avoided.[45,86] Other studies suggest that 100% O_2 and 21% O_2 are equivalent,[57,82] and still others suggest benefits when 100% O_2 is used.[56,70] Two clinical reports suggest that following asphyxia and resuscitation, newborns who demonstrate early hyperoxia in the neonatal intensive care unit (NICU) have worse neurologic outcomes.[40,72] There are no randomized studies to determine whether hyperoxia is causal for neurologic injury or merely a marker of a more severe asphyxial insult that needed more oxygen for stabilization. The best compromise for the clinician at the present time continues to be to resuscitate with supplemental oxygen when chest compressions are necessary (as ventilation with room air will have already been tried by this point), with weaning of the oxygen as soon as possible once the heart rate is stabilized to limit exposure to hyperoxia.

Chest Compressions

The most common reason for why a newborn fails to successfully transition at birth is lack of gas exchange resulting in simultaneous hypoxia and mixed metabolic and respiratory acidosis, otherwise known as asphyxia.[39] Combined profound hypoxia and acidosis depresses myocardial function and promotes maximal vasodilation. The goal of chest compressions is to mechanically pump the blood through the heart until the myocardium is sufficiently oxygenated to recover spontaneous function. Due to preferential perfusion of the heart and brain during cardiac compressions, greater than 50% of normal cardiac and cerebral blood flow can be achieved through optimized cardiac compressions.[8,9] Improved myocardial perfusion increases the likelihood of faster return of spontaneous circulation, while improved cerebral perfusion positively impacts neurologic outcome.

Chest compressions should be centered over the lower one-third of the sternum to compress most directly over the heart.[27,50,66,69] Compression of the sternum directly over the heart squeezes it against the spine. This increases intrathoracic pressure, which causes blood to be pumped from the heart into the arteries. When the pressure on the sternum is released, venous blood refills the heart and blood flows into the coronary arteries.[94] Chest radiograph studies demonstrate that the center of the infant heart is positioned under the lower third of the sternum the majority of the time.[27,69] Ten pediatric patients (between 1 month and 3 years of age) who sustained cardiac arrest and had arterial pressure monitoring lines in place were monitored during external chest compressions performed by medical providers who were blinded to the blood pressure monitoring.[66] Compressions were provided in random order either at the level of the patient's nipples (midsternum) or over the lower one-third of the sternum above the xiphoid. Each patient served as his or her own control with compressions performed at both locations in random sequence. The performance of compressions over the lower one-third of the sternum resulted in significantly better systolic and mean arterial blood pressures.[66] A more recent study of 63 infants confirmed that location of the left ventricle in 90% of cases was under the lower 1/3 of the sternum using infant CT scan measurements.[50] Although there is one report of CT scan measurements for 75 infants with a mean age of 4.4 ± 3.6 months, which found the heart to be located under the lower 1/4 of the sternum,[102] care must be taken to not be too low on the sternum to avoid dislocation of the xiphoid process, which could lead to liver laceration.[18] Similarly, placement of the compressing thumbs must be centered over the sternal bone so as to not cause rib fractures, which could inhibit critical ventilation via pneumothoraces or a flail chest.

The two-thumb technique in which the hands encircle the chest while the thumbs compress the sternum should be used for neonatal chest compressions.[24] The older, less effective two-finger method is no longer recommended.[68] Evidence from animal models of asphyxia-induced asystole demonstrate that the two-thumb technique generates higher blood pressures than the two-finger technique.[36] This has also been shown in a manikin model with a customized artificial arterial system.[23] Manikin studies demonstrate that the two-thumb technique improves depth of compression, lessens fatigue of the compressor, and results in more consistently accurate thumb placement on the sternum than the two-finger technique.[17,73] Clinical data are limited to a few case reports but also suggest that the two-thumb

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technique generates better perfusion pressures than the two-finger technique in newborns.[20,88] In the past, the two-finger technique was used primarily as a means of keeping the compressor's arms out of the way while emergent umbilical venous line placement was obtained. With the implementation of the MRSOPA algorithm and securing an advanced airway before initiation of compressions, the compressor can move to the head of the bed once the tube or laryngeal mask is secured and continue the more effective two-thumb technique even while emergent intravenous access is obtained. It is crucial that compressions from the head of the bed never interfere with adequate ventilation and establishment of an advanced airway.

Optimal compression depth for the newborn is believed to be one-third the anterior-posterior (AP) diameter of the chest and thus varies with the size of the baby. Computed tomography images of the chest of neonates and young infants estimate that a compression depth of half the AP diameter might result in internal organ damage but that one-third the AP diameter would lessen this risk while still resulting in enough compression of the heart to generate blood flow.[12,63] Clinical data are limited to a report of six infants who had arterial lines in place after cardiac surgery and subsequent cardiac arrest.[59] Chest compressions were given to a depth of one-third the AP diameter and subsequently one-half the AP diameter. Although a compression depth of one-half the AP diameter resulted in higher mean arterial pressures, this was mainly owing to an effect on systolic blood pressure. Diastolic pressures between the two groups were similar. This is an important distinction, because coronary perfusion pressure is determined by aortic diastolic blood pressure minus the right atrial diastolic blood pressure, so it is the diastolic blood pressure that is most critical.[39] It has also been noted that a compression-to-relaxation ratio with a slightly shorter compression than relaxation phase offers theoretical advantages for blood flow in the very young infant.[21,39] The chest must be allowed to fully recoil before the next compression so that the heart can refill with blood.[52,100]

The best ratio of compressions to ventilations to optimize perfusion and ventilation during neonatal resuscitation is unknown. It is clear from animal models that ventilations in combination with chest compressions result in better outcomes than if resuscitation proceeds with ventilations or compressions alone,[6,7] especially during prolonged resuscitation.[22] Physiologic mathematical modeling suggests that higher compression-to-ventilation ratios would result in underventilation of asphyxiated infants.[3] Such models predict that three to five compressions to one ventilation should be most efficient for newborns. The current NRP guidelines recommend a ratio of three compressions to one ventilation breath such that 90 compressions and 30 breaths per minute are achieved. The medical providers performing the compressions and ventilations should communicate by having the compressor count the cadence out loud as "one and two and three and breathe and."[94] Studies have compared 3:1 to 9:3 compression-to-ventilation ratios[83] and 3:1 to 15:2 ratios[84] in newborn pig models of asystole caused by asphyxia. Although the 15:2 ratio provided more compressions per minute without compromising ventilation as measured by arterial blood gas and generated statistically higher diastolic blood pressures, the diastolic blood pressure was still inadequate until epinephrine was given, and thus there was no difference in the time to stabilize the heart rate. A manikin study of 3:1, 5:1, and 15:2 compression-to-ventilation ratios using the two-thumb technique compared depth of compressions, decay of compression depth over time, compression rates, and breaths delivered over a 2-minute interval.[34] Providers using the 3:1 versus 15:2 ratio achieved a greater depth of compressions as well as more consistent depth over time. The 3:1 ratio delivered the most breaths and fewest compressions, as would be expected. Thus, there is no evidence from human, animal, manikin, or mathematical modeling studies to warrant a change from the current compression-to-ventilation ratio of 3:1. Rescuers may consider using higher ratios (15:2) if the arrest is believed to be of cardiac origin.

Concern that simultaneous compressions and ventilation breaths might impede effective ventilation has led to continued emphasis that compressions and ventilations should be coordinated during neonatal cardiopulmonary resuscitation (CPR), so that they do not interfere with each other. Although studies of asynchronous chest compressions and ventilation (CCaV) show improved minute ventilation, there was no improvement in return of spontaneous circulation (ROSC).[77] CCaV is associated with increased rescuer fatigue and poor quality chest compressions as well as increased left ventricular lactate levels, possibly from trauma or anaerobic metabolism.[10,11,52,85,86] Recently, neonatal animal model studies[54,78] and a randomized feasibility study in a small number of neonates showed shorter time to ROSC with continuous chest compressions during sustained inflation.[76] A larger clinical trial is underway to determine if continuous chest compressions during a sustained inflation results in increased ROSC in neonates receiving CPR.

Strategies for optimizing the quality of the compressions and ventilations with as few interruptions as possible should be considered. NRP currently recommends that the interval between auscultation pauses be at least 1 minute in an effort to decrease interruptions in perfusion.[94] Once compressions are initiated, cardiac monitoring leads should be placed so that pauses for auscultation of heart rate can be minimized.[97] It can take a team 17 seconds to complete the auscultation process during delivery room resuscitation when using a stethoscope.[93] When the cardiac monitor heart rate is greater than 60 beats per minute, it is important to confirm by auscultation that the displayed heart rate is not just pulseless electrical activity.

Quantitative $ETCO_2$ monitoring can serve as a noninvasive tool to eliminate frequent auscultation pauses during CPR. Changes in $ETCO_2$ primarily reflect changes in cardiac

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output during CPR. A piglet model of asphyxia-induced asystole demonstrated that once effective PPV is provided, $ETCO_2$ plummets to near zero with loss of pulmonary blood flow and then increases slightly with initiation of chest compressions, reflecting some blood being pumped through the lungs by the chest compressions. ROSC correlates with a sudden rise in $ETCO_2$ as the re-established perfusion brings CO_2-laden blood back to the lungs. An $ETCO_2$ greater than 15 mm Hg correlates well with return of an audible heart rate greater than 60 beats per minute in a newborn pig model.[13] A single case report of CPR in a very preterm infant at birth noted ROSC just after $ETCO_2$ reached 12 mm Hg during the resuscitation.[53] Clinical correlate studies are currently underway.

Medications

Epinephrine

When asphyxia is severe enough to cause asystole or agonal bradycardia despite initiation of CPR, the newborn heart is depleted of energy substrate (adenosine triphosphate [ATP]) and can no longer beat effectively. Oxygenated blood must be restored to the coronary circulation, or ROSC with a heart rate greater than 60 beats per minute will not be achieved. During CPR, coronary blood flow occurs exclusively during diastole, presumably because of increased intramyocardial resistance and increased right atrial pressure during chest compressions[44]; therefore, coronary perfusion pressure is determined by the aortic diastolic blood pressure minus the right atrial diastolic blood pressure. Given the profound acidemia and resultant vasodilation induced by severe asphyxia, a vasoconstricting pressor agent such as epinephrine is frequently required to attain sufficient aortic diastolic pressure to improve coronary perfusion during newborn CPR. Consequently, if the heart rate remains less than 60 beats per minute despite 30 seconds of effective positive pressure ventilation (with chest rise), followed by coordinated chest compressions and ventilation, then 0.1-0.3 mL/kg of 1 mg/10 mL epinephrine solution should be given rapidly via the intravenous (IV) route followed by 0.5-1.0 mL of normal saline flush.[97]

Data regarding optimal dosing for intravenous epinephrine during newborn CPR are lacking. Intravenous rather than endotracheal delivery of epinephrine is preferred and mandates that delivery room resuscitation providers be well trained in rapid preparation and placement of umbilical venous catheters.[94] In a newborn lamb model of asphyxia, endotracheal (ET) epinephrine was absorbed slowly compared to IV epinephrine, which resulted in lower plasma concentration and less effectiveness.[91] In addition, the absorption of ET epinephrine was delayed, which increases chances of very high epinephrine levels after multiple doses of ET epinephrine in animals who achieved ROSC. Similarly, a recent retrospective cohort study in newborns who required CPR in the delivery room also noted that only 20% of newborns responded to ETT epinephrine alone even though the recommended ET dose was increased compared to a decade earlier.[4,31] The total dose of epinephrine delivered was higher when any ET epinephrine was given.[31] This might increase risk of arrhythmia or other adverse outcomes due to higher plasma epinephrine levels.

Newborn transitional physiology limits the success of the endotracheal route, because the decreased pulmonary blood flow may be insufficient to transport the drug from the alveoli to the central circulation, pulmonary vasoconstriction from acidosis may impede drug absorption, unresorbed alveolar fluid may dilute the epinephrine, and potential right-to-left intracardiac shunts could bypass the pulmonary circulation altogether. Based on current evidence, once the airway is secured and CPR initiated, immediate attention should be on establishing IV access so that IV epinephrine can be given. The endotracheal route should be used only until IV access is available.[41] However, if the endotracheal route must be tried because of inability to obtain intravenous access, a higher dose (0.5-1.0 mL/kg) of 1 mg/10 mL epinephrine solution may be used in hopes of improving efficacy.[97] Loading endotracheal epinephrine doses in a larger 3- to 5-mL syringe to alert the resuscitation team as for which route the dose is intended can help avoid accidentally giving the higher endotracheal dose through the umbilical line. Successful resuscitation of newborns using the intraosseous route for epinephrine delivery has been reported.[26] A neonatal simulation study found that health care providers could quickly obtain the intraosseous route for delivery of epinephrine.[71] Neonatal resuscitation teams should routinely practice emergent placement of whatever kind of line is used most often at their institution.

At this time, the only other vasopressor that has been studied for use during neonatal CPR is vasopressin. In a newborn piglet asphyxia model, vasopressin improved survival and resulted in lower postresuscitation troponin levels and less hemodynamic compromise compared to epinephrine.[62] This epinephrine alternative needs to be evaluated further before any recommendation can be made.

Volume

Although an asphyxiated infant may be in shock, this is not usually caused by hypovolemia but rather by decreased myocardial function and decreased cardiac output from asphyxia. Most infants who have undergone intrauterine asphyxia and delivery room CPR are not hypovolemic.[28,99] In some circumstances, however, hypovolemic shock is a real possibility (Box 34.1). Shock at birth may be caused by asphyxia, hypovolemia, or sepsis. In addition, most causes of hypovolemic and septic shock result in neonatal asphyxia. Although most severely hypovolemic and septic infants are asphyxiated, most septic or asphyxiated infants are not hypovolemic. Some studies have shown that antepartum asphyxia is associated with increased transfer of blood from the placenta to the fetus before birth, resulting in normal

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• BOX 34.1 Causes of Hypovolemia

- Decreased blood return from placenta
- Cord compression resulting in venous, but not arterial, occlusion
- Placental separation compromising placental blood return to the fetus
- Hemorrhage from the fetal side of the placenta
- Fetal-maternal hemorrhage
- Fetal-fetal transfusion
- Incision of the placenta during cesarean delivery
- Velamentous insertion of umbilical cord with fetal arterial rupture

or increased circulating blood volume.[55,101] The difficulty is in distinguishing hypovolemic and septic shock from asphyxial shock that does not involve hypovolemia.

A history of bright red vaginal bleeding just before delivery, a cesarean delivery where the uterine incision had to be made through an anterior placenta, or the finding of a velamentous insertion of the umbilical cord can raise suspicion for acute fetal blood loss. Placental abruption is a major cause of asphyxia but rarely is associated with fetal blood loss unless caused by trauma such as a high-speed motor vehicle accident. The painful bleeding of abruption is almost always maternal blood loss. Maternal fever, fetal tachycardia, and other signs of chorioamnionitis may indicate neonatal sepsis and shock. Volume expanders may be detrimental in an infant who is not hypovolemic, especially one who has experienced hypoxia-induced myocardial dysfunction.[96] Volume expanders should be given in the acute circumstance when, after adequate ventilation and oxygenation have been established, poor capillary filling persists, and there is evidence or suspicion of blood loss with signs of hypovolemia. In an infant in whom the pulse cannot be normalized despite adequate resuscitation, measures including epinephrine and volume expansion should be considered.

In an acute situation, the volume expander of choice is normal saline; although 5% albumin was used in the past, it has no advantage over crystalloid solutions, and there is some evidence of increased risk for subsequent pulmonary edema and, thus, it is no longer included in neonatal resuscitation guidelines.[28] Lactated Ringer's has never been studied in neonatal resuscitation and for simplification of stocking delivery room neonatal resuscitation supplies has been removed from the NRP recommendations.[94] The best volume expander, although rarely immediately available, is whole O-negative blood; this provides volume, oxygen-carrying capacity, and colloid. Infusion of volume expanders should consist of a volume of 10 mL/kg given over 5-10 minutes. In true acute hypovolemia, it is often necessary to repeat this infusion a second or third time. In acute hypovolemia, hematocrit may be misleading since not enough time has passed for equilibration to occur. Therefore, with a history of acute blood loss (i.e., ruptured velamentous cord insertion), volume should be given even in the face of a normal early hematocrit.

Other Drugs

Other drugs such as sodium bicarbonate, naloxone, and pressor agents other than epinephrine are no longer considered resuscitation drugs for the delivery room. They are discussed briefly in the section Immediate Care after Establishing Adequate Ventilation and Circulation.

Intravenous Access

Medications should preferentially be given through an umbilical venous catheter. When an umbilical catheter is used, it should be inserted into the umbilical vein just beneath the skin, approximately 2-4 cm until free flow of blood is obtained when the stopcock is opened to the syringe and the syringe gently aspirated. If the catheter is inserted too high and becomes wedged in the liver, solutions can be infused into the liver, which may cause liver necrosis. The depth of insertion of the catheter is much less in premature infants depending on their weight, and care should be taken not to insert the catheter too far. If a catheter is not prepared and ready, endotracheal administration of epinephrine may occur through the endotracheal tube while the catheter is being prepared, but only as a temporizing measure while IV access is established. It is prudent, however, that when preparing for a "crash" delivery, the catheter should be prepared in advance to minimize the delay in giving epinephrine by the most effective route. Table 34.2 presents an overview of the medications used in delivery room resuscitation, including concentration, dosage, route, and precautions.

When to Discontinue Resuscitation Efforts

If an infant still has no heart rate after 10 minutes of what otherwise appears to be effective resuscitation, resuscitation providers may consider discontinuing their efforts.[97] This does not mean that the resuscitation team must stop at 10 minutes after birth, but rather that after 10 minutes of well-coordinated resuscitation efforts if the newborn is still asystolic, it is appropriate to consider discontinuation. The majority of available data indicate that after 10 minutes of asystole, there are few survivors[33,80,87] and those who do survive frequently have severe disability.[33] Infants with 10-minute Apgar scores of zero but who survived to be admitted to the NICU and entered into a hypothermia clinical trial had better outcomes than those reported in the systematic review by Harrington; however, there was significant selection bias.[42,48] Recent cohort studies of infants with 10-minute Apgar scores of zero who were subsequently treated with hypothermia had ~20%-30% survival with normal development on early assessments.[80] Decisions regarding whether to continue or discontinue resuscitative efforts must be individualized. Variables to be considered

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TABLE 34.2 Medications for Neonatal Resuscitation in the Delivery Room

Medication to Administer	Concentration	Syringe for Preparation	Dosage; Route	Weight of Newborn (kg)	Total Dose (mL)	Precautions
Epinephrine	1 mg/10 mL	1 mL	0.1-0.3 mL/kg; IV	1	0.1-0.3	Preferred route; give rapidly
				2	0.2-0.6	
				3	0.3-0.9	
				4	0.4-1.2	
		3 or 5 mL	0.5-1.0 mL/kg; ET	1	0.5-1	5-10 times IV dose; give directly into the ET tube
				2	1-2	
				3	1.5-3	
				4	2-4	
Volume expanders	Normal saline, whole blood	30 mL	10 mL/kg; IV	1	10	Give over 5-10 min
				2	20	
				3	30	
				4	40	

ET, Endotracheal.

may include whether the resuscitation was considered optimal; the availability of advanced neonatal care such as therapeutic hypothermia; the specific circumstances before delivery (e.g., known timing of the insult); and the wishes expressed by the family.[97]

Documentation and Debriefing

A critical member of the neonatal resuscitation team is the recorder, who should document in real time the steps of resuscitation that the team makes and the infant's response. It is not acceptable to write a summary from memory after the fact when the accuracy of the details may be lost. The resuscitation record should be used to debrief the team after every advanced resuscitation to look for opportunities to improve in communication, documentation, resuscitation skills, and knowledge of the algorithm. Some institutions choose to video record delivery room resuscitations for this purpose.

Immediate Care After Establishing Adequate Ventilation and Circulation

Induced Therapeutic Hypothermia

Any newborn who undergoes significant resuscitation efforts in the delivery room should have an umbilical artery cord blood gas to check for fetal acidemia and have a careful neurologic exam. Infants born at ≥36 weeks' gestation with evidence of an acute perinatal event and moderate to severe hypoxic-ischemic encephalopathy should be offered therapeutic hypothermia. Therapeutic hypothermia initiated within 6 hours of birth with cooling to 33.5°C has been shown to reduce mortality and neurologic impairment at 18-month follow-up. The hypothermia treatment should be implemented according to the studied and published protocols, which currently include initiation of cooling within 6 hours following birth, continuation for 72 hours, and slow rewarming over at least 4 hours.[97] Because the goal is initiation of cooling within 6 hours of birth, it is important that all delivery hospitals have such protocols in place or have access to a referral center to which such infants can be sent quickly. Passive cooling before transport has not been studied, and clinical judgment should prevail until further data are available. Hypothermia initiated after 6 hours of birth is not as effective as early hypothermia but appears to confer some benefit for those infants that cannot get to the cooling center in time or for whom moderate/severe encephalopathy was not obvious until after 6 hours of age.[49] The risks and benefits of hypothermia treatment for late preterm infants (33-35 weeks' gestation) with moderate to severe neuroencephalopathy are not clear and trials are currently underway.

Sodium Bicarbonate

There is no evidence either from experimental neonatal animal studies or clinical trials regarding the risks or benefits of sodium bicarbonate on achieving ROSC in the situation of severe bradycardia or asystole. The only randomized trial of sodium bicarbonate infusion in neonates requiring positive-pressure ventilation in the delivery room failed to show any benefit on neurologic outcome or survival.[58] Adult animal models and clinical studies have demonstrated

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deleterious effects on physiologic end points after administration of sodium bicarbonate during CPR, effects that include depression of myocardial function from the osmolar load with severe acidosis, paradoxic intracellular acidosis, and reduced cerebral blood flow.[2,51] Thus, use of sodium bicarbonate should be discouraged during CPR. Its use in the newborn should be moved to post-resuscitation care in the NICU and guided by arterial blood gas levels or serum chemistries, although even in the NICU there is not clear benefit.[19,43] It should never be given unless there is assurance that adequate ventilation has been achieved or it will paradoxically worsen acidemia because of increased respiratory acidosis. To avoid a sudden increase in osmolality with the risk of intracerebral hemorrhage, the concentration of bicarbonate should be 0.5 mEq/mL and infused slowly.

Naloxone

The most common reason for a newborn to have respiratory depression is asphyxia. Respiratory depression caused by the mother receiving narcotics during labor is quite rare. The appropriate response to respiratory depression, no matter what the cause, is to initiate effective PPV. Rather than give an opiate antagonist such as naloxone in the delivery room, the apneic newborn's respirations should be supported as needed, including placement of an advanced airway if necessary and the infant taken to the NICU. In the NICU, more information can be gathered to rule out other causes of respiratory depression such as shock, sepsis, elevated magnesium levels, or fetal acidemia. If ultimately it is decided that the infant's poor respiratory effort is caused by narcotic depression, then naloxone can be given to the infant with an appropriate intravenous line established and continuous monitoring within the NICU.

Dopamine

Sometimes an infant has experienced enough myocardial compromise that, despite all resuscitative measures, poor cardiac output and hypotension remain. If the infant is not hypovolemic, inotropic support is indicated rather than continued volume expansion in the face of hypoxic cardiomyopathy. In such circumstances, dopamine may be used. At dosages of 10 μg/kg per minute, dopamine has inotropic and alpha-adrenergic effects. At this dose, the increased cardiac output antagonizes the alpha-adrenergic effect, resulting in increased cardiac output with only mild peripheral vasoconstriction. In higher doses, the alpha-adrenergic effect predominates with generalized peripheral vasoconstriction. In low doses of 5 μg/kg per minute, dopamine binds to dopaminergic receptors in the renal, mesenteric, and cerebral arteries, producing vasodilation. Traditionally, dopamine is started at 5 μg/kg per minute, and the dosage is increased as necessary. If the dosage reaches 20 μg/kg per minute without adequate response, it is unlikely that increasing the dose further would make a difference and other vasopressors can be considered.

Prolonged Assisted Ventilation

Some infants need a ventilator after immediate resuscitation. In a severely asphyxiated infant, central nervous system depression may inhibit spontaneous ventilation. The longer the asphyxia lasts, the longer it takes for resumption of spontaneous ventilation. Most infants in this category also have some degree of pulmonary compromise related to asphyxia. Some infants with primary lung disease initially breathe spontaneously; however, these infants subsequently may need assisted ventilation to attain adequate gas exchange. Asphyxia may also affect the type 2 cells of the lung and result in acquired surfactant deficiency. Meconium or blood aspiration or sepsis may also inactivate surfactant, resulting in the need for continued ventilatory support. Whenever an infant is in need of ventilation for more than the immediate resuscitative period, evaluation of blood gases should guide the ventilatory support. Prolonged ventilation by hand is often overzealous, with resultant hypocapnia, or inadequate, leading to respiratory acidosis. Continued ventilation by machine or a T-piece resuscitator gives more uniform ventilation.

Glucose

As soon as possible after stabilization from an asphyxia event, an infusion of glucose at approximately 4-8 mg/kg per minute should be started. Adjustment of the glucose infusion rate depends on repeated measurements of blood glucose levels. The purpose of the glucose is twofold: (1) to provide fuel and (2) to help eliminate the metabolic acidosis. A steady infusion of glucose provides fuel to an infant who has depleted much of his or her glycogen, especially myocardial glycogen, during the asphyxial episode. This infusion helps prevent the hypoglycemia that frequently accompanies asphyxia. Glucose should not be started until the infant is adequately oxygenated and ventilated. Anaerobic metabolism of carbohydrate leads to the formation of additional lactic acid, worsening the acidosis. Hypoglycemia is synergistic with asphyxia in producing brain damage, and failure to provide glucose and monitor levels may result in additional brain injury.[5,74]

Fluids

The urine output of any infant who undergoes an asphyxial episode should be carefully monitored. Acute kidney injury resulting in oliguria is a common complication of asphyxia, and an infant can easily be overloaded with fluid. Fluid should be restricted until there is evidence of adequate urine output. The need to restrict fluid and yet give adequate glucose emphasizes the importance of considering glucose infusion in terms of milligrams of glucose per kilogram of body weight per minute, rather than the amount of 10% glucose to be given. The concentration of infused glucose depends on how much fluid can be given to the infant (see Chapter 92). In addition, potentially

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nephrotoxic antibiotics and diuretics should be administered with caution, because poor renal clearance may result in toxic levels.

Feeding

During asphyxia, ischemia of the intestine occurs as a result of vasoconstriction of the mesenteric vessels. Because of the suggested relationship between ischemia of the intestine and necrotizing enterocolitis, it may be prudent to delay enteral feedings in an asphyxiated infant, especially one who is premature (see Chapters 41 and 85).

Other Problems

Other complications of asphyxia that are of concern include hypocalcemia, disseminated intravascular coagulation, seizures, cerebral edema, and intracerebral hemorrhage. These are discussed elsewhere in this text.

Special Problems During Resuscitation

Infants With Very Low Birth Weight and Extremely Premature Infants

Infants born at less than 32 weeks' gestation or less than 1500 g birth weight require special considerations in the delivery room. Most facilities do not have an adjacent NICU to provide a warm and monitored environment immediately for these very fragile infants, so provisions must be made in the delivery room. It has been suggested that simulating the intensive care environment in the delivery room from the moment of birth helps to improve survival and reduce morbidity in this population.[92] The provision of a well-trained and complete resuscitation team at delivery is of critical importance. Unless significant preventative efforts are made, preterm newborns will quickly lose heat in the delivery room by evaporation of amniotic fluid from the baby's body, conduction of heat from the body touching cooler surfaces, convection to cooler surrounding air, and radiation to cooler objects in the vicinity.[98] It is important to prevent hypothermia because for every 1°C below 36°C on admission temperature, mortality increases significantly.[46,47] An important initial preventative step is to increase the ambient temperature of the delivery environment to 73°F-77°F (23-25°C) before delivery occurs. Several randomized trials demonstrate that warming the delivery environment to this level can decrease rates of moderate hypothermia upon NICU admission in preterm infants.[25,38] Polyethylene plastic bags and wraps that prevent evaporative heat loss improve NICU admission temperatures in preterm newborns.[68] Plastic bags do not prevent all hypothermia; thus, additional strategies may be required in the delivery room. Chemically activated thermal mattresses improve temperature stabilization as well.[81] The use of plastic wrap and thermal mattresses in combination can further reduce hypothermia, but caution must be taken to prevent hyperthermia.[60] Covering the preterm newborn head with a plastic[79,89] or wool hat[15] may help as well. Warmed, humidified gases for use during ventilation in the delivery room can also reduce hypothermia in the preterm population[61] (see also Chapter 35).

In preterm infants, delayed cord clamping reduces mortality[29] and is now recommended for at least 30-60 seconds for most preterm infants showing some signs of vigor.[97] Animal studies suggest that inflation of the lung prior to cord clamping may have significant benefits.[35] Randomized trials are underway to compare the impact of initiating resuscitation and positive pressure ventilation before versus after clamping the umbilical cord. Other investigations to examine the risks and benefits of cord milking compared to delayed cord clamping are underway.

The NRP recommends the use of pulse oximetry and blending oxygen in the delivery room to avoid hyperoxia.[97] The avoidance of barovolutrauma during initial ventilatory support may be facilitated by the use of a T-piece resuscitator, the use of an end-tidal CO_2 detector, and the measurement of tidal volumes. Many preterm infants can be placed directly on nasal CPAP and avoid intubation.[30] Less invasive techniques for surfactant administration without intubation are under investigation.[37] For infants who require intubation for stabilization, early administration of surfactant may reduce long-term respiratory morbidity. Many such infants may be managed with an *INSURE* protocol (*IN*tubation, *SUR*factant, *E*xtubation).[30,37]

Meconium Aspiration

If meconium is present in the amniotic fluid, there is a chance that meconium may enter the mouth of the fetus and be aspirated into the lungs. Aspiration of meconium can result in a ball-valve obstruction of the airways, causing gas trapping and pneumothorax. It can also cause a reactive inflammatory process. Because meconium-stained amniotic fluid (MSAF) is frequently associated with asphyxia in newborns, the inability to achieve adequate ventilation combined with the initial asphyxia may result in enough hypoxia and acidosis to maintain the increased resistance of the pulmonary vasculature, resulting in persistent pulmonary hypertension of the newborn.

For many years, in an effort to prevent meconium aspiration syndrome (MAS), a combined obstetrical (suctioning of the oropharynx prior to delivery of the chest) and pediatric (intubation and suctioning of selected infants born through MSAF) procedure was routine practice in the delivery room. As new evidence became available, recommendations changed. Vain and colleagues showed that suctioning the hypopharynx after delivery of the head and before delivery of the shoulders has no effect on the development of MAS.[90] A multicenter randomized study looked at vigorous infants with a gestational age of more than 37 weeks who were born through MSAF of any consistency. In these vigorous infants, intubation and tracheal suctioning did not offer any advantage over expectant management.[95]

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More recently, routine suctioning of the trachea in nonvigorous infants born through MSAF has been called into question. Indirect and low quality evidence from multiple observational studies was inconclusive regarding benefits of tracheal suction in nonvigorous infants born through MSAF.[68] In 2015 and 2016, two small randomized trials performed in the setting of high incidence of MSAF and MAS found no difference in the incidence of MAS, need for mechanical ventilation and mortality whether or not tracheal suctioning was performed on nonvigorous infants.[16,64]

Routine suctioning of nonvigorous infants may delay initiation of critical ventilation in nonbreathing infants. In addition, intubation can cause harm such as trauma or vagal responses resulting in bradycardia. In the face of any unknown benefit of routine suctioning of nonvigorous infants born through MSAF, and in hopes of avoidance of harm, the International Liaison Committee on Resuscitation recommended to stop routine tracheal suction after the birth of these infants. Instead, emphasis should be placed on initiating ventilation within the first minute if the infant is not breathing or the heart rate is <100/min after the initial steps are completed. Because the presence of MSAF may indicate fetal distress and is associated with increased risk that the infant will need resuscitation, an individual skilled in tracheal intubation should be part of the team present at delivery. If during positive pressure ventilation, even after ventilation corrective measures the chest is not rising and obstruction is suspected, tracheal suction should be performed. If intubation is to be done and meconium removed from the trachea, the best method is to attach an adapter to the endotracheal tube so that suction can be directly applied using regulated wall suction at approximately 100 mm Hg as the tube is withdrawn. The trachea can be reintubated and suctioned again if necessary (see also Chapter 66).

Pneumothorax

A pneumothorax may occur spontaneously and may be the cause of the need for resuscitation. More commonly, pneumothorax is a complication of PPV. Pneumothorax should be suspected in any infant who is improving during a resuscitative effort and then suddenly decompensates. Listening to the infant, one may hear unequal breath sounds and distant heart sounds, which may be shifted from the normal position in the left side of the chest. The affected side of the chest may appear hyperinflated compared with the nonaffected side and move less during ventilation. If the pneumothorax is large enough to obstruct venous return, cardiac output decreases, and the infant becomes hypotensive and eventually bradycardic. When these events occur in an infant who is otherwise stable, pneumothorax is easy to suspect. When pneumothorax occurs early during resuscitation of a severely compromised infant, the signs and symptoms are not as obvious. When immediate intervention in the delivery room is needed, it may be necessary to insert a needle into the thorax before radiographic confirmation, especially if transillumination is not available. The NRP suggests using an 18- or 20-gauge percutaneous catheter and inserting it in the fourth intercostal space in the anterior axillary line or the second intercostal space at the midclavicular line.[94]

Congenital Diaphragmatic Hernia

With the increasing availability of prenatal ultrasound, most infants with congenital diaphragmatic hernia (CDH) are anticipated and can be delivered in a level III or IV center where the appropriate team can attend the delivery. An infant with an undiagnosed CDH is usually in significant respiratory distress at birth, although the diagnosis may not be immediately obvious. The diagnosis may be suspected when there is a scaphoid abdomen and decreased breath sounds, usually on the left side (85%). The situation may be worsened by the use of mask ventilation, which inflates the bowel in the chest and compromises ventilation further.

An infant with CDH may appear similar to an infant with a pneumothorax. To prevent gas from entering the intestines, one should always use an endotracheal tube when ventilating the lungs of an infant with a suspected CDH. An orogastric tube should be inserted as soon as possible to remove air before it passes into the portion of intestine located in the chest. The main focus of management includes gentle ventilation, hemodynamic monitoring, and treatment of pulmonary hypertension followed by surgery[14] (see Chapters 13 and 66).

Erythroblastosis and Hydrops Fetalis

Successful resuscitation of an infant with hydrops fetalis demands preparation of a coordinated team with preassigned responsibilities. The team should be prepared at delivery to perform a partial (or, rarely, complete) exchange transfusion with O-negative packed red blood cells crossmatched against the mother. In addition, team members should be prepared to perform a thoracentesis, paracentesis, and complete resuscitation, including intubation and CPR if needed. In recent years, most infants with hydrops have nonimmune causes. With advanced ultrasound technology, most of these infants are diagnosed in utero, and the delivery and resuscitation can be carefully planned. An infant with hydrops may not only be severely anemic but also is likely to have ascites, pleural effusions, and pulmonary edema. Such infants frequently have had chronic intrauterine and intrapartum asphyxia. Because they are usually premature, respiratory distress syndrome may be an underlying confounding complication.

On delivery, the infant should immediately undergo intubation because of poor lung compliance and the risk of pulmonary edema. High ventilator pressures are often needed, and the use of high-frequency ventilation may be necessary to minimize lung injury. If adequate ventilation cannot be attained (as judged by inability to stabilize the

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heart rate), and if there is evidence of fluid in the abdomen or pleural space, paracentesis and/or thoracentesis may be needed. Ultrasonography performed before delivery can help determine in which spaces the fluid resides (pleural, ascitic, or pericardial) and the amount of fluid present. If the abdomen is markedly distended, the paracentesis should be performed first to relieve pressure on the diaphragm; this may need to be followed with a thoracentesis. Although most of these infants initially have a normal blood volume, after a large amount of ascitic and pleural fluid has been removed, some of this fluid may reaccumulate, reducing intravascular volume. Careful attention should be paid to maintain intravascular volume and prevent shock after resuscitation.

A hematocrit obtained immediately at birth determines the need for an exchange transfusion (usually partial) in the delivery room. If the infant is extremely anemic and in need of oxygen-carrying capacity, catheters should be inserted into the umbilical vein and artery to permit a slow isovolemic exchange with packed red blood cells, which results in minimal impact on the already borderline hemodynamic status of the infant. These lines also can be used to monitor central venous pressure and aortic pressure to determine the volume needs of the infant. This is especially important when large amounts of fluid are removed from the thorax or abdomen. Given the complexity of the resuscitation in these cases, the resuscitation team must be of sufficient number and skill to perform these procedures expeditiously and skillfully to achieve optimal outcome (see Chapters 23 and 24).

Screening for Congenital Defects

Two to three percent of infants are born with a congenital anomaly, some of which will require intervention soon after birth (see Chapter 30). If undetected, some of the anomalies may result in life-threatening problems. Immediately after birth, choanal atresia, severe micrognathia, or CDH may result in respiratory distress. Other problems may appear later, such as aspiration caused by esophageal atresia (with esophageal fistula) or a high intestinal obstruction. A rapid screening exam for congenital defects can easily be performed by delivery room staff to help identify many of these defects, along with others that are not life threatening but require prompt recognition and intervention.

Before examining the infant, the team should inquire about the amniotic fluid, placenta, and umbilical cord. Oligohydramnios may be a marker for oligohydramnios sequence (Potter sequence) with pulmonary hypoplasia. These infants also have growth deficiency, Potter facies, and limb positional defects. A significantly short umbilical cord at term (<40 cm) is a sign of fetal akinesia sequence and usually indicates a muscle or central nervous system etiology for the infant's respiratory insufficiency, or may be associated with pulmonary hypoplasia (Pena-Shokeir syndrome). If antenatal sonograms suggest significant postnatal airway obstruction is likely, an EXIT (ex utero intrapartum treatment) procedure may be a consideration for delivery (see Chapter 13).

Physical Examination

A rapid external physical examination identifies obvious abnormalities, such as abnormal facies and limb, abdominal wall, or spinal column defects (see Chapter 28). A close look at the abdomen may reveal a scaphoid abdomen, which is a clue to a CDH. If an umbilical vessel count reveals only two vessels, there is a possibility of other defects, especially involving the genitourinary tract. Because infants are preferential nasal breathers, bilateral choanal atresia results in respiratory difficulty and need for airway stabilization after birth (see Chapter 68). Bilateral choanal atresia can be ruled out quickly if the infant is able to breathe while the mouth is held closed. Some infants with unilateral choanal obstruction appear normal until an examiner closes the mouth and then sequentially obstructs each nostril with a finger. When the patent nostril is obstructed, such infants have difficulty breathing. Choanal atresia is confirmed by the insertion of a soft nasogastric tube into each nostril. If an obstruction is reached within 3-4 cm, choanal atresia is a possibility.

An examination of the mouth may identify a cleft palate. Inserting a nasogastric tube through the mouth may help identify an esophageal atresia or a high intestinal obstruction. If the tube does not reach the stomach, an esophageal atresia, most often associated with a tracheoesophageal fistula, is likely. A few cubic centimeters of air forced through the tube, while listening over the stomach, confirms that the tube is in the stomach. A minute or so spent screening for congenital defects in this way may help to avert many future problems.

Key Points

- Make sure the lungs of the newborn are truly inflated prior to initiation of chest compressions (place advanced airway if possible).
- When compressions are needed, use the two-thumb technique and coordinate with ventilations in a three-compression to one-breath ratio using 100% oxygen.
- Use a cardiac monitor when compressions are needed to help avoid pauses in circulation.
- Use intravenous epinephrine rather than endotracheal if possible.
- Practice advanced resuscitation skills on a frequent basis via simulation.
- Record in real time what is being done during delivery room resuscitation so that you and your team can debrief and look for opportunities for improvement with every delivery.

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35

Thermal Environment of the Intensive Care Nursery

JOHAN ÅGREN

Thermal management of the newborn infant is a cornerstone of neonatal care: The field accommodates important advances in care provision spanning from pioneering studies on chronic cold stress[58] and neonatal incubation to kangaroo mother care,[46] prevention of low admission temperatures,[43] and therapeutic hypothermia. Globally, cold stress remains a contributor to neonatal mortality and morbidity, and the potential impact of optimal thermal care provision on infant health is huge.[38] A basic understanding of the physics and physiology of heat exchange enables the undertaking of adequate measures to reduce heat loss and monitor body temperature, measures that often are simple and easy to apply. Without thermal care, a term 5-kg newborn may quickly and easily become hypothermic, increasing its need for endogenous heat production and posing a risk for cardiorespiratory instability and failure to feed properly, states that may be detrimental to an otherwise healthy or only slightly depressed infant. On the other hand, with adequate preparation, equipment, and training, the body temperature of a 500-g extremely preterm infant can be kept within the normal range, aiding a smooth transition to extrauterine life. In general, adequate thermal management depends at least as much on sound knowledge as on the use of high-tech devices such as incubators and radiant warmers.

Heat Exchange Physics

The Four Modes of Heat Exchange

Direct heat exchange between the infant and its environment occurs through the skin and through the respiratory tract. With use of different techniques, this heat exchange may be calculated and estimated with reasonable accuracy.[26,60] The four modes of heat exchange—convection, radiation, evaporation, and conduction (Box 35.1)—all influence thermal balance, and the relative contribution of each mode changes with maturity, postnatal age, disease state, and care environment. Analysis of the contribution from the different modes of heat exchange makes it straightforward to reduce heat loss in any given situation, minimizing the need for delivery of heat through another route. Together with proper temperature monitoring, such an approach simplifies thermal management and renders individual estimates of heat loss unnecessary.

Heat Exchange at Term Birth

The wet newborn infant will be exposed to moving air and surfaces that have a much lower temperature than that in utero. Unless the infant is wiped dry and covered by a blanket, heat loss through evaporation and radiation to surrounding surfaces of the delivery room will be high and lead to rapid cooling.[22] Heat loss through convection is also significant unless airflow velocity is reduced (e.g., by covering, clothing). As soon as the term or moderately preterm infant is dry, radiant heat loss will dominate.[22]

Evaporative Heat Loss Is Related to Infant Maturity and Ambient Humidity

As loss of fluid also implies loss of heat, evaporative fluid loss is an important component of heat exchange, particularly in extremely preterm infants. A functionally competent skin barrier develops gradually during fetal life.[17] Consequently, the magnitude of water loss through the skin is related to maturity at birth,[55] and the tiniest infants may have evaporative heat losses that are many times higher than those of a term infant under similar environmental conditions (Fig. 35.1).[21] In the preterm infant relatively rapid postnatal skin maturation occurs, leading to decreased evaporative loss over the first postnatal days and weeks (Fig. 35.2).[3,22] This maturation explains the gradual reduction in the environmental temperature needed to obtain thermal balance, even though evaporative heat loss still exceeds radiant heat loss for about a week in the most immature infants (see Fig. 35.2).

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Abstract

To establish an adequate thermal environment and maintain normal body temperature is a cornerstone of neonatal care. This chapter reviews key routes of heat exchange, neonatal thermal physiology, modes of care, and treatment recommendations in the area of neonatal thermal management.

Keywords

newborn
hypothermia
heat exchange
evaporation
incubator
radiant warmer
skin-to-skin care

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• BOX 35.1 The Modes of Heat Exchange

Convection

- Air movement causes warm air close to the skin to move away, resulting in heat loss.
- The relative magnitude of heat loss through convection is similar in term and preterm infants.
- Convective heat loss is much increased when air velocity is high (forced convection).
- Convective heating is the mode by which modern intensive care incubators operate.
- Convective heat exchange is reduced by any measure that will minimize air movement close to the skin (e.g., limiting incubator porthole opening to one side at a time, providing clothing and/or blankets).

Radiation

- Radiant heat transfer occurs *from* the infant to surrounding cooler surfaces and *to* the infant from radiant heaters and warm-light phototherapy devices.
- The magnitude of heat exchange depends on the temperatures of the surfaces facing the infant and on the body surface area exposed.
- Heat radiation is reduced by clothes, blankets, double incubator walls, heat shields, flexible plastic wrap, and bags.

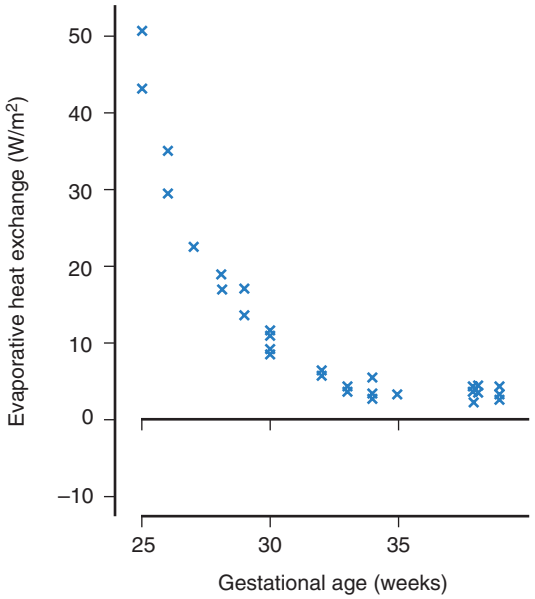
Evaporation

- Evaporation of fluid from the skin surface implies loss of heat (approximately 2.4 kJ/g water).
- Evaporation is the dominant route for heat loss from the wet neonate in the delivery room but is substantially reduced by immediately wiping the infant dry at birth.
- Very immature infants have poor skin barrier function, leading to large ongoing losses of water and heat for several days to weeks after birth.
- Evaporation is reduced in a high vapor pressure environment.

Conduction

- Inadvertent conductive heat loss is negligible in most care situations, because mattresses used in incubators and cots are made of insulating material.
- Care must be taken when using equipment with an active warming function. If switched off, a gel mattress such as those used in some radiant warmer beds and/or an unheated water-filled mattress will be a very effective conductive cooler for any size neonate.
- Conductive cooling is the method by which all systems for hypothermia treatment operate.
- Conductive heat delivery (e.g., heated mattress or skin-to-skin care) is a simple and effective way to rewarm infants and stabilize body temperature.

Evaporative heat losses are inversely related to ambient humidity (Fig. 35.3),[21] and measures to increase the vapor pressure close to the skin thus simplify fluid and thermal management.[54] Note that the impact of postnatal age and ambient humidity on evaporative loss is less clinically important in newborn infants with a gestational age of more than 28-30 weeks[22] and in the extremely preterm infant beyond the first postnatal week.[3]



• **Fig. 35.1** Heat exchange through evaporation in relation to gestational age. Measurements from the first day of life during incubator care at an ambient humidity of 50%. (Data from Hammarlund K, et al. Transepidermal water loss in newborn infants. VI. Heat exchange with the environment in relation to gestational age. *Acta Paediatr Scand.* 1982;71(2):191-196.)

Respiratory Loss of Heat

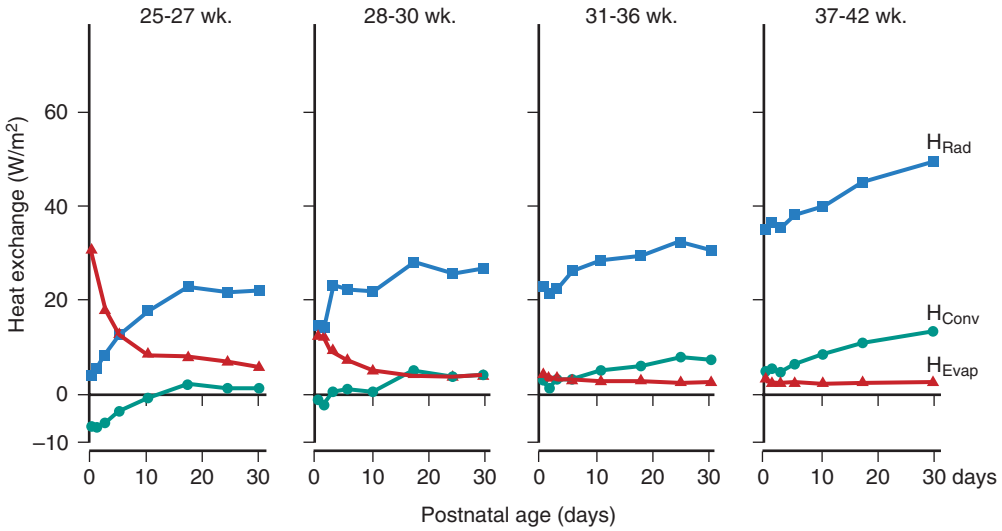
Respiratory water and heat exchange take place by the combined processes of evaporation and convection. These processes occur as the temperature and vapor pressure of the inspired air rapidly equilibrates in the airway. Consequently, the losses are related to air temperature and humidity and directly proportional to the rate of breathing.[53] Provision of a warm and humid environment (e.g., humidified incubator) and/or assisted ventilation with use of adequately warmed and humidified (saturated at ≥37.0°C) gas will reduce respiratory loss of water and heat to a minimum[60] and aid temperature stability.[61] Only in situations in which cold (pressurized) gas is delivered or when ambient temperature and humidity are low, such as during transport in a cold climate, will the heat loss through the airway be of clinical significance.

Thermal Physiology

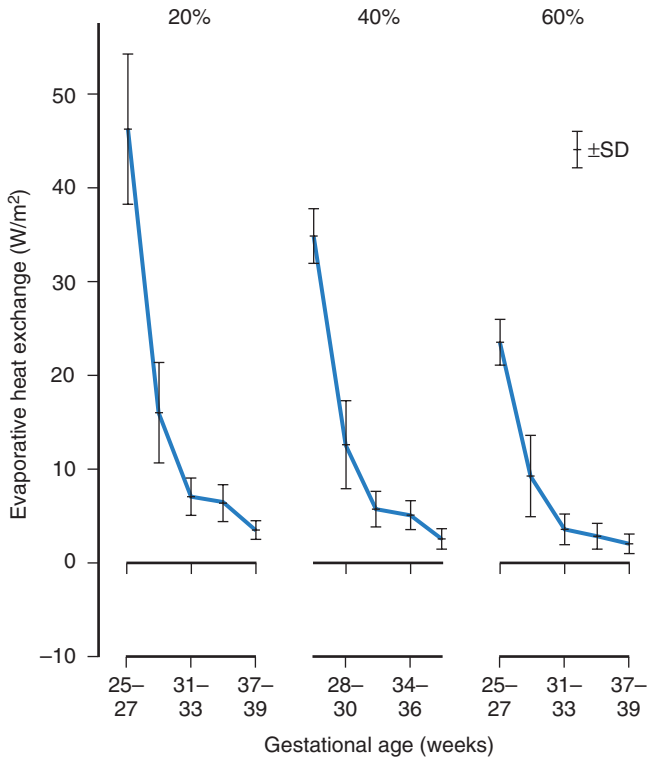
The Fetal Thermal Equilibrium

The fetus generates heat in the processes of tissue proliferation, metabolism, maintenance of physiologic functions, and muscular movement. From experimental studies, fetal (and neonatal) heat production per unit weight has been demonstrated to be considerably higher than in the adult. Together with heat generated by the uterus and placenta,[51] this results in a temperature gradient between the fetus and the mother of about 0.5°C, with the heat being dissipated mainly via the placental circulation.[51]

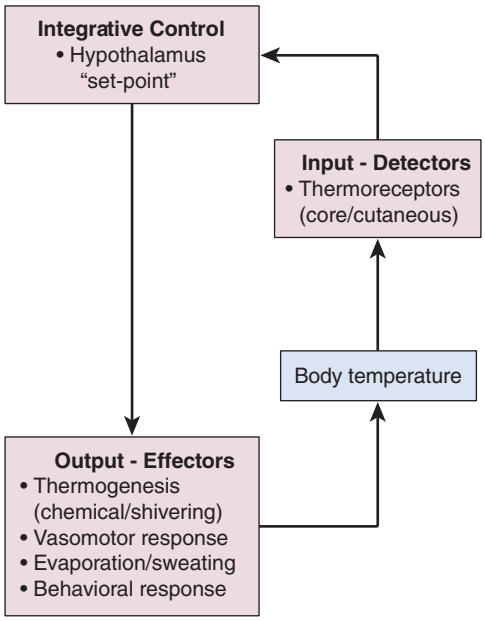
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• **Fig. 35.2** Heat exchange in relation to postnatal age in different gestational age groups. (Data from Hammarlund K, et al. Heat loss from the skin of preterm and full-term newborn infants during the first weeks after birth. *Biol Neonate.* 1986;50(1):1-10.)



• **Fig. 35.3** Heat exchange through evaporation in relation to gestational age at different ambient relative humidity. (Data from Hammarlund K, et al. Transepidermal water loss in newborn infants. VI. Heat exchange with the environment in relation to gestational age. *Acta Paediatr Scand.* 1982;71(2):191-196.)



• **Fig. 35.4** The main components of the homeostatic thermoregulatory system.

Neonatal Thermoregulation

The exposure to cold, clamping of the umbilical cord, and the general "stress of being born" induce a thermal response. This response is part of a homeostatic system with input (detectors) and output (effectors) that is aimed at preserving body temperature. The main components are schematically depicted in Fig. 35.4.

In the neonate, shivering thermogenesis is nonoperative in the normal to near-normal body temperature range, and a cold-exposed infant thus depends primarily on chemical thermogenesis to avoid hypothermia.[12] Exposure to cold induces a sympathetic surge that acts on receptors in brown fat stores stimulating lipolysis.[12] The presence of the protein thermogenin in brown fat uncouples β-oxidation, resulting in metabolic production of heat instead of adenosine triphosphate. The metabolic rate of a newborn has been observed to increase up to threefold when maximally

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stimulated by cold,[30] but preterm infants have a limited thermogenic capacity due to scarce fat stores and often suboptimal nutritional provision.

The cost of heat production implies that even a slight long-term exposure to cold will increase thermogenesis, consume oxygen and substrate stores, and impact negatively on growth.[63]

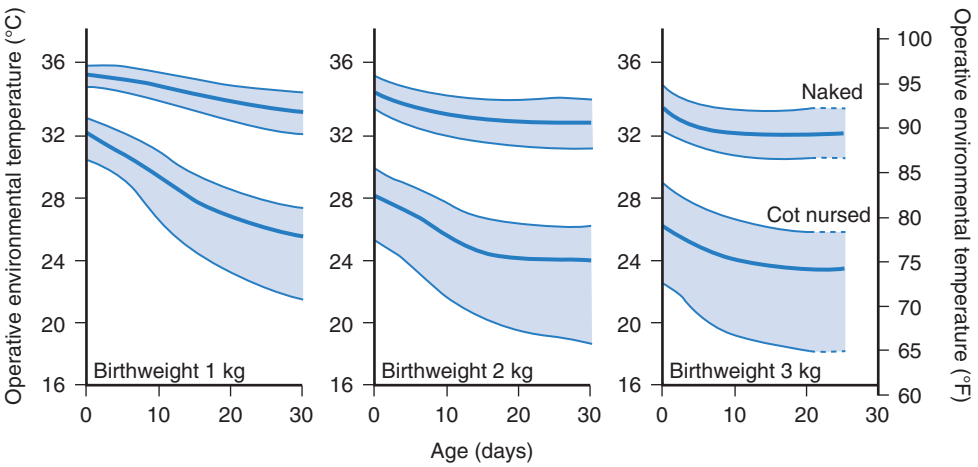
Thermoneutrality

The concept of an optimum thermal environment for newborn infants evolved during the 1960s.[28] This "thermoneutral zone" (Fig. 35.5) is defined as the range of temperature within which the infant can maintain a normal body temperature at minimal metabolic rate with use of non-evaporative processes (vasoconstriction, vasodilation, and/or changes in posture) only.[25] Body size has a large impact on the range in which infants can maintain body temperature. Compared with an adult, the newborn infant has both a several times higher body surface per mass ratio and a poorly insulated body shell.[27] Several factors related to the care environment will, to a varying extent, influence the boundaries of the thermoneutral zone (Table 35.1). Outside this range, body temperature might still be maintained at the cost of an increased metabolism, but if the temperature deviates further, inevitable cooling (or warming) will take place. The temperature ranges for each care modality and individual infant may be crudely estimated, and together with proper infant monitoring, such estimates will suffice as a starting point for routine care.

TABLE 35.1 Infant and Environmental Factors and Their Impact on the Heat and/or Temperature Setting Needed to Obtain Thermoneutrality

	Heat/Temperature Setting to Maintain Thermoneutrality
Infant Factor	
Smaller/more immature	Increase
Postnatal age	Decrease
SGA*	Decrease, but to a lesser degree
Environmental Factor	
Radiant Warmer	
with plastic shield	Decrease, but to a lesser degree
with plastic wrap	Decrease
with "warm" phototherapy	Decrease, but to a lesser degree
Incubator	
with single wall	Increase
with humidification	Decrease
with "warm" phototherapy	Decrease, but to a lesser degree
frequent interventions	Increase
Clothes/blanket	Decrease
"Cold" phototherapy	—

SGA, Small for gestational age.
*Effect versus non-SGA infant of same weight.



• **Fig. 35.5** The ranges of environmental temperatures needed to provide warmth for infants weighing 1 to 3 kg at birth in draft-free, uniform-temperature surroundings at 50% relative humidity. *Upper curves* represent naked infants, and *lower curves* represent swaddled, "cot-nursed" babies. *Thick lines* represent "thermoneutral" temperature, and *shaded areas* represent the range within which the infant can maintain normal temperature without increasing heat production or evaporative heat loss by more than 25%. (From Hey EN. The care of babies in incubators. In: Gairdner D, et al, eds. *Recent Advances in Paediatrics.* 4th ed. London: Churchill Livingstone; 1971.)

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Overwarming Versus Fever

Overheating activates heat-losing mechanisms such as skin vasodilation (redness/flushing/peripheral warmth) and behavioral changes (the infant assumes spread-eagle posture). Evaporative heat loss increases and overt sweating can be noted in a term infant. The gradient between central and peripheral temperature decreases. With severe heat stress, the infant may become hyperactive and irritable.

In contrast, an infant with fever due to an increase in endogenous heat production presents differently. The febrile infant, at least during the phase of rising temperature, is vasoconstricted as displayed by an increased central-to-peripheral temperature gradient[45] and pale-blue–appearing extremities.

Hypothermia

Different thresholds of the effector response for nonshivering and shivering thermogenesis explain the differences observed between hypothermic adults and neonates. In the range of normal to near-normal body temperature (≥36°C), shivering thermogenesis will be nonoperative in the neonate, and chemical thermogenesis dominates.[12] However, as core temperature is further lowered, shivering may occur. Thus, shivering is exclusively (and not always) seen in the severely cold-stressed (e.g., hypothermia-treated) infant. Therapeutic hypothermia treatment for neuroprotection in neonatal encephalopathy is discussed elsewhere (see Chapter 54), but the methods used are based on conductive heat loss from either the head (cooling cap), or the whole body (cooling mattress). During therapeutic hypothermia, core temperature has to be monitored, because surface temperatures will not adequately reflect core temperature. During cooling, significant set point displacement may occur, explaining why some infants are difficult to warm with the risk of temperature overshoot during rewarming. Therefore, the infant's body temperature needs to be carefully monitored and controlled for several days after termination of the hypothermia treatment. Data obtained from the cooling trials support the notion that it is better to slowly (maximal rate 0.5°C/h) increase core temperature in a hypothermic infant. It seems reasonable to apply similar caution also when rewarming infants who have become hypothermic from other causes, although the optimal speed of rewarming has not been identified.

Temperature Monitoring

Temperature measurements as such do not provide much information on whether the infant is in thermal balance, and there are no methods suitable for routine bedside monitoring of metabolic rate. Therefore, thermal management needs to be based on several sources of information. They include (but are not limited to) trends of continuous or intermittent measurements of central and peripheral body temperature, ambient temperature and humidity, as well as the general appearance and behavioral state of the infant.

Central ("Core") Body Temperature

Several measurement sites serve as estimates of core body temperature. *Direct temperature measurements* make use of a probe inserted into a body cavity (e.g., rectum, esophagus) that is central enough to measure zero temperature gradient versus the body core. Esophageal temperature measurements are technically feasible, represent true core temperature, and are well tolerated by the infant.[59] Esophageal temperature monitoring is recommended when very strict thermal monitoring is needed and body surface measurements are unreliable (i.e., during therapeutic hypothermia). Rectal temperature measurements do not reliably reflect core temperature, pose unnecessary risks of repeated trauma to the rectal mucosa, and their use should be limited.[44]

Core temperature can also be estimated from *indirect temperature measurements* at the body surface by artificial creation of zero temperature gradient, or "zero-heat-flux." By insulation of the measurement probe from the environment, zero-heat-flux will be created between the body core and the probe. Trunk skin temperature measurements (back to mattress, abdomen to mattress, abdomen to insulated pad) rely on this principle and give readings that are very similar to esophageal temperature. Axillary temperature also makes use of zero-heat-flux (insulated by the arm and shoulder) and can be used as a proxy for core temperature when intermittent measurement is deemed sufficient but may be associated with infant discomfort and occasionally differ from esophageal temperature.

What Temperature Should Be Aimed for?

The concept of an easily defined hypothalamic set point for core temperature is relative. Because not only core, but also peripheral sensory input, influences the action of thermoregulation, the optimal core body temperature may indeed vary with maturity/age, care environment, and disease state. Deflections in the set point occur with pyrogen exposure but may also result from exposure to cold and/or warm environment, even for a relatively limited time. Normal human central body temperature is considered to be 37.0 ± 0.5°C, and this is probably also true for the newborn infant.[42,47,48] However, it is evident that seemingly well babies with central temperature kept within this range may still be subjected to cold stress (i.e., display increased metabolic rate due to thermogenesis). Thus, aiming for such a "normal" body temperature might at times be suboptimal in neonatal care. In the preterm infant, the fetal thermal equilibrium has been suggested as also optimal after birth.[8] In fact, to minimize the risk of cold stress when caring for infants with limited thermoregulatory capacity, it has been shown to be adequate to aim for slightly higher core temperatures.

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TABLE 35.2 Thermoneutral Central-to-Peripheral Temperature Differences (ΔT) in Low Birth Weight Infants in Relation to Postnatal Age

Infant Group	Postnatal Age (Days)	ΔT (°C)
<750 g	0-5	<0.5*
	6-14	<1*
	>14	1-2*
750 g-1000 g	0-2	<0.5
	3-5	<1
	>6	1-2
1000 g-1500 g	0-2	0-1
	>3	1-2

*Estimated values.

Peripheral Temperature and Central-Peripheral Temperature Difference

Although not considered integral to routine thermal care, peripheral temperature measurements from the sole of the foot might provide additional and valuable information about the thermal state of the infant, particularly if graphed together with core temperature.[40] Cold exposure induces vasoconstriction and a decrease in skin temperature, resulting in an increased central-to-peripheral temperature difference (ΔT), well before a drop in central temperature occurs. Likewise, other causes of vasoconstriction (hypovolemia, sepsis, catecholamine administration) and low cardiac output (hypovolemia, large ductal shunting, and some congenital heart defects) increase ΔT, which could potentially be of value as an early warning sign.[45] However, the optimal ΔT depends on infant maturity, postnatal age, and care environment and is, therefore, not easily defined. Recommended ΔT for very low birth weight and extremely low birth weight infants nursed in incubators are available[39,40] (Table 35.2).

Thermal Aspects of the Care Environment

Convective Thermal Support—Incubator Care

In a modern convectively heated incubator, the warm air is directed so that the walls of the incubator are also kept warm. With a low airflow velocity (<0.1 m/s), the convective heat transfer will depend on the gradient between the skin and the air temperature, and the vapor pressure gradient close to the skin will be maintained, avoiding an increased evaporative heat loss.[9,37] The feature of double wall design reduces the radiant heat loss to the inner walls of the incubator. In a single wall incubator, the "working" temperature in the incubator will be lower than the set air temperature because of the higher radiant loss of heat and thus will require a higher temperature setting, depending on the room temperature. The incubator is controlled thermostatically by air or infant temperature, two modes with distinct advantages and disadvantages.[62]

Infant skin temperature servo control has the advantage of providing a more stable body temperature under changing care conditions. However, if the probe becomes detached, this may lead to overwarming, although usually this is not severe. Also, when using skin servo control, the use of body temperature as a possible signal of disease (hypovolemia, sepsis) has to be replaced by monitoring incubator temperature, which might not be as intuitive. An anterior abdominal skin temperature of 36.5°C has been widely used for servo control of incubator air temperature[18] but may be too low to ensure thermoneutrality in the tiniest and most immature infants.[40] An abdominal skin (or back to mattress) temperature setting of 37.0°C may then be preferable.

Air temperature servo control does not require a probe to be attached but makes it necessary to frequently determine infant temperature, thus adding further to the load of procedures disturbing the infants. For both modes, it is essential that procedures such as intravenous line insertion and/or intubation are performed through the portholes and not through the large front access panel.

Incubator Humidification

Because evaporative loss is related to ambient relative humidity, adding humidification will decrease heat loss; the higher the humidity, the lower the evaporation. However, in most situations, a higher evaporative loss can be compensated for by a higher air temperature (convective gain), and a "too low" incubator humidity will only increase metabolic demand if the infant is nursed below thermoneutral temperature. Thus, a high incubator ambient humidity (70%-90%) is only vital in situations wherein high insensible water loss *per se* complicates fluid management (i.e., in extremely preterm infants during the first postnatal week).[54] In this situation, a high ambient humidity is often needed to maintain normal body temperature even at maximal incubator temperature.[10] An increased risk of pseudomonas infections has been demonstrated with the use of incubator humidification[24] when condensation of vapor on the inner incubator walls occurs, which therefore should be avoided. Also, experimental studies demonstrate that transepidermal water transport is an important signal for stratum corneum formation,[23] and results obtained in extremely preterm infants nursed in incubators at two levels of ambient humidity after the first postnatal week indicate a more rapid barrier formation in infants nursed at a lower relative humidity.[2] However, running incubators entirely without humidification will often result in very low humidity (<15%-20%), promoting large insensible water losses.[16] Although reserving high ambient humidification (70%-90%) for the first postnatal week in the extremely preterm (<28 weeks) infant, a medium level of 40%-50% can be recommended for general incubator care.

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Radiant Thermal Support—Radiant Warmers

Radiant warmers provide excellent accessibility for the care of the newborn infant and have, therefore, become widely used in neonatal intensive care. The high power output of the device explains the effectiveness and speed with which a hypothermic infant can be warmed. However, harmful overheating can rapidly occur unless careful monitoring (preferably continuous) of infant temperature is instituted.[6] Because ambient humidity is low and air velocity at times relatively high, heat loss through evaporation and convection may be extensive but can be compensated for by radiant heat gain.[7,8] An anterior abdominal temperature of 37.0°C is generally recommended for servo control of radiant heat output,[7] at least as a starting point. Unless the warmer is equipped with a warming mattress, the back-to-mattress (zero-heat-flux) temperature can also be used for servo control.

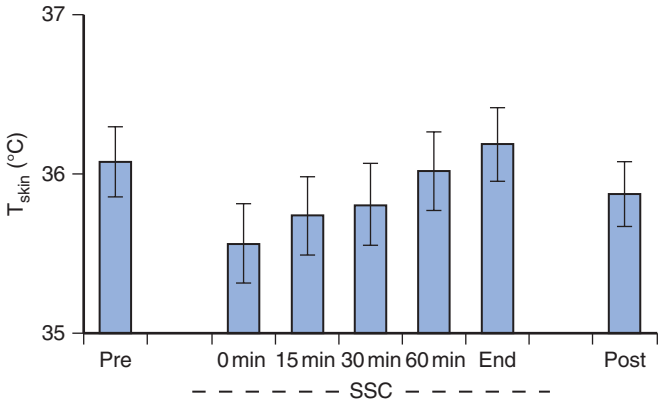
A transparent heat shield positioned over the infant may influence the heat exchange (occurring through convection, evaporation, and radiation) and result in reduced losses of heat.[5] However, such a shield will also disrupt the servo-control mechanism and thus may intervene with thermal control. An alternative is the placement of flexible plastic wrap as a blanket loosely over the infant. This method has proved to result in a more homogenous environment and to reduce insensible water loss and metabolic rate[8] and is used in many institutions. Incubators that can interchangeably be used both as radiant warmers and incubators might at times add flexibility of use and improve thermal management of very preterm infants.[32]

Conductive Thermal Support—Skin-to-Skin Care

Skin-to-skin care (SSC) has been practiced for as long as humanity, long before the concept of kangaroo mother care for preterm infants was introduced. Studies mainly performed in countries with limited resources demonstrate important benefits.[14] In the moderately preterm and low birth weight infant, SSC has proven to enhance physiologic stability[1,11,64] and is recommended.[13] Limited guidelines are also available for use in a high-tech setting.[50] In SSC, the kangaroo position is optimal to enable conductive heat gain through skin-to-skin contact between infant and parent (see also Chapter 36).

Studies in more immature infants have shown that SSC can be safely applied, and without an increase in metabolic rate, as early as during the first week after birth in stable 28- to 30-week infants and from the second week in infants born at a gestational age of 25-27 weeks.[4,41]

In another report,[31] mechanically ventilated extremely preterm (<26 weeks) infants were studied during early SSC (first week of life), demonstrating that ambient air temperature and humidity are lower during SSC compared with incubator care, thus increasing heat loss through convection, radiation, and evaporation. Transfer from the incubator to SSC results in a drop in temperature, but the conductive heat gain during SSC is sufficient to result in a gradual recovery of the infant's temperature (Fig. 35.6).



• **Fig. 35.6** Skin temperatures (T_{skin}) in a group of extremely (22-26 week) preterm infants during early (1st week) skin-to-skin care (SSC). T_{skin} was measured in the incubator before SSC (Pre), during SSC, and after return to the incubator (Post). (Data from Karlsson V, et al. Early skin-to-skin care in extremely preterm infants: thermal balance and care environment. *J Pediatr*. 2012;161(3):422-426.)

Heated Mattresses and Cot Nursing

Conductive thermal support may also be provided by use of a heated mattress. It has been demonstrated that infants as small as 1 kg can be rewarmed and kept warm by placing them on a heated (water-filled) mattress.[63] Heated mattresses are most often used in cots for stable, growing preterm infants and are convenient to use interchangeably with SSC. A heated pad can also be used inside incubators or with radiant warmers. Such a mattress should always be prewarmed and the temperature never set lower than the desired body temperature since this will lead to significant conductive heat loss and may impact negatively on weight gain.[19,29]

Clothing

After the immediate postpartum thermal adaptation (30-60 min), a room temperature of ≥24°C provides a neutral thermal environment for a dressed (clothes, cap, and blanket) term neonate.[35] Indeed, clothing can be expected to reduce all modes of heat exchange and in the relatively stable preterm infant, the use of clothes or a blanket will improve thermal stability during both incubator and radiant warmer care.[33]

Phototherapy

Open phototherapy increases insensible water loss from the skin of the newborn infant.[15] This is mostly an effect of a decrease in relative humidity caused by the increase in ambient temperature, but minute effects have also been

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demonstrated with cold-light phototherapy.[20] Accordingly, the effect is not observed if the infant is treated in an incubator with controlled environment,[34] and neither fluid nor thermal management should be significantly impacted. In recent years, flexible and portable "phototherapy blankets" have been made available. Such devices work well with most modes of neonatal care, including incubator, radiant warmer, cot nursing, and skin-to-skin care.

Recommendations for Practice

Thermal care benefits from a protocol-driven approach based on guidelines that minimize variation in practice. Such guidelines should specify ranges for normal body and skin temperatures and thermal environment recommendations. They should specify in which situations incubators, radiant warmers, heated mattresses, and skin-to-skin care are applicable, and when to use continuous temperature measurement and infant servo or air control. As incubator settings and operation will differ between types of incubators, it is beneficial if the most vulnerable population can be cared for under uniform environmental conditions (same room and incubator type, for instance) within each neonatal unit, and extra caution should be applied when switching to a different mode of care (e.g., from incubator to SSC). The different modes of care each have their advantages and disadvantages, and a combination of incubation, radiant warmer, and SSC is needed to ensure physiologic stability and early detection of disease and to promote parental involvement. It is not a matter of high- versus low-tech care delivery but rather of finding the best compromise and getting the most out of each mode of care.

Before Birth

The space used for resuscitation should always be ready for instant use. With a prewarmed radiant warmer (and mattress), adequate thermal management of an ill moderately preterm or term neonate is uncomplicated. When needed, the radiant heat output can be instantaneously increased. When available, the heated mattress should be set at 37.0°C. When an extremely preterm infant is awaited, further measures must be undertaken (see Very [28–31 weeks] and Extremely [<28 weeks] Preterm Infants). It is, for many reasons, valuable to meet the parents prior to delivery, time permitting. Specifically, information about thermal care is relatively easy to grasp even in a stressful situation and can as such contribute to a sense of recognition, involvement, and meaningfulness for the parents.

Term and Moderate to Late Preterm (>32 Weeks) Infants

The vigorous term and near-term infant should be carefully wiped, placed on the mother's chest, and covered by a cap and blanket. As long as the delivery room temperature is ≥24°C, these measures will usually suffice to provide thermoneutrality. The term infant may then be continuously cared for skin-to-skin and when not, dressed and placed in a cot. If the infant is low birth weight and/or in the lower range of gestational age, uninterrupted conductive heat support, preferably through skin-to-skin care, is required to maintain thermal balance. If skin-to-skin care cannot be arranged, the low-birth-weight infant must be dressed and placed on a heated mattress or in an incubator. If resuscitation is required, it should be performed under a radiant warmer and the infant placed skin-to-skin with the mother after stabilization.

Globally, most infants will be born in a low-resource setting without access to neonatal care facilities (see Chapter 8). Specifically, thermal care will often have to be provided without high-tech equipment and/or electricity. The principle of wiping the infant dry and establishing continuous skin-to-skin contact with the mother (or other family member) is solid and could, if uniformly applied, be expected to reduce infant mortality.[35,36] If resuscitation is needed, this might be performed without interrupting the skin-to-skin contact or at least by rapidly returning the infant to its natural conductive heat source (i.e., mother) after stabilization.[52]

Very (28-31 Weeks) and Extremely (<28 Weeks) Preterm Infants

At birth, very preterm infants must be cared for under a radiant warmer, preferably equipped with a heated mattress, to ensure adequate thermal balance. The infant should be wiped and placed on dry linen under the radiant warmer for resuscitation and stabilization. In the extremely preterm infant, transepidermal water loss will keep the skin constantly wet. As a consequence, it is not meaningful to dry the infant. This situation is better handled by placing the infant in a transparent plastic bag. This will effectively limit convective heat loss and create a high humidity microclimate close to the skin that will reduce evaporative heat loss.[43] Radiant heat will still be transferred from the warmer to the infant's skin through the plastic bag. This measure has proved to improve thermal care during resuscitation and result in higher NICU admission temperatures.[43] In this vulnerable population, ventilator support should always be provided using humidified gas saturated at body temperature.[56,61] If stabilization takes more than approximately 10 minutes, it is advisable to monitor infant temperature to avoid overwarming. After stabilization, the preterm infant may either be nursed in an incubator or under a radiant warmer. For extremely preterm infants, measures to reduce insensible water and heat loss through the skin are recommended throughout the first week of life. In the incubator, this is accomplished by use of high ambient relative humidity, and under the radiant warmer, by use of a plastic wrap.[57] Skin-to-skin care can provide even the tiniest infant with an excellent care environment but needs to be carefully conducted and should be postponed until the end of the first week in the smallest infants. For these infants, the room

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TABLE 35.3 Suggested Modes of Care in Infants of Different Gestational and Postnatal Ages

Infant Group	At Birth	Week 1	Weeks 2-4
<28 weeks	Radiant warmer	Incubator with ≥70% RH	Incubator with 50% RH
	Plastic bag Warm/humid gas	Radiant warmer with plastic wrap	Radiant warmer SSC
		SSC (end of first week)	
28-31 weeks	Radiant warmer	Radiant warmer	Radiant warmer
		Incubator	SSC
		SSC	Heated mattress
32-35 weeks	SSC	SSC	SSC
	Radiant warmer	Heated mattress	Cot
≥36 weeks	SSC	SSC	
	Radiant warmer	Cot	

RH, Relative humidity; SSC, skin-to-skin care.

temperature needs to be elevated, preferably to ≥26°C during skin-to-skin care. The parent should wear an open-front shirt, and the infant a diaper and a cap and be wrapped during the transfer. The infant is placed skin-to-skin in the kangaroo position on the parent's chest, monitoring is attached (including thermistor for back skin temperature), and the infant covered by blankets. To minimize cold stress, the sessions of SSC should be at least 1-2 hours, preferably longer, to allow the attainment of a stable microenvironment around the infant and stabilize body temperature. As monitoring of back skin temperature under a blanket will not render zero-heat-flux, a back skin temperature of ≥36.5°C during SSC may be considered thermally neutral (author's unpublished observations). Suggested modes of care and their timing are given in Table 35.3.

During the first 12-24 hours after birth, perturbation of the care environment occurs very frequently. Careful planning and prioritizing among procedures such as weighing, umbilical line insertion, intubation, obtaining chest radiographs, manipulating intravenous lines, repositioning, and suctioning is often helpful, and precautions should be undertaken to prevent heat loss during these procedures.

With increasing postnatal age and body weight, the temperature requirements of the care environment decrease and as infant stability improves, there is less need for constant monitoring of the infant. The infant may eventually be dressed and/or covered and transferred from the incubator (or radiant warmer) to a cot with heated mattress.[19] Weaning from the mattress is usually possible at a body weight of approximately 1600 g.[49] Thermal stability is an important criterion for discharge, and parents should be advised on how to proceed with thermal care at home.

Key Points

- Cold stress and/or hypothermia negatively impacts on vital neonatal outcomes such as survival and growth.
- Heat exchange between the infant and the care environment occurs through convection, radiation, evaporation, and conduction. Their relative contribution and the direction of heat transfer depend on infant maturity, postnatal age, and mode of care.
- Thermal (and fluid) management of the extremely preterm infant is simplified by use of a high humidity micro-environment during the first week(s) of life. This can be accomplished in a highly humidified incubator by use of plastic dressings under a radiant warmer, or by appropriately conducted skin-to-skin care.
- Thermal care benefits from a protocol-driven approach using guidelines that minimize variation in practice. They should specify in which situations incubators, radiant warmers, heated mattresses, and skin-to-skin care should be used, and how to monitor body temperature and what temperature to aim for.

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36

Optimization of the NICU Environment

LIISA LEHTONEN AND ROBERT WHITE

Neurobehavioral Maturation

The expected physiologic environment for a preterm infant would be in utero, floating and moving in warm amniotic fluid, mostly in a flexed position, tasting the amniotic fluid, sensing their mother's movements and circadian rhythm, hearing her voice and sounds from her body but being protected from loud noises, receiving rich amounts of nutrients for optimal growth, and performing gas exchange through the placenta. Full-term newborns demonstrate capabilities they have developed and learned during their fetal life: they recognize their mother's smell and voice and they are ready to crawl to the breast of the mother and start sucking from the breast during the first hour of life. From this time point onwards, the development continues in the physical and emotional closeness with the caregivers and the larger social environment, optimally by getting breast milk directly from the breast for the first months of life.

The neurobehavioral maturation of a preterm infant is based on the genetically programmed development occurring in utero, including highly active axonal and dendritic growth, myelination, synaptogenesis, and proliferation of microglia and astrocytes. This development is modified by environmental influences from a completely different environment, the neonatal intensive care unit, usually for several weeks or months. The experiences provided for the developing brain can either strengthen or weaken the development of specific neural connections, or they can modify the reading of the genetic information by epigenetic mechanisms.[19] The time window during prematurity and early infancy is also the time for unique plasticity, allowing therapeutic interventions to compensate for structural brain injuries. Therefore, the quality of the hospital care has a large potential to affect the long-term developmental outcome of preterm infants. Medical treatments and procedures, medications and nutrition, physical and social environment, and routine infant care can be either nurturing or directly toxic to the brain. Experiences in the NICU environment should be designed to mimic the physiologic, age-appropriate in utero environment.

Depending on their gestational age at birth, preterm infants are born at different developmental stages with a large variation in the degree of immaturity of the central and autonomous nervous systems and sensory functions. Whereas a full-term newborn infant has a well-developed sleep-wake cycle; is capable of reciprocal social interaction, meaningful behaviors and responses to the stimuli from the environment; and has abilities to breastfeed, a preterm infant has an attenuated capacity to regulate his/her behavioral/sleep states and has problems processing or even tolerating a high amount of sensory information. Preterm infants have immature feeding competencies and undifferentiated and/or weak signals about their needs or stress. Their skills for social interaction are immature, especially visual interaction, emphasizing the role of the senses that develop in earlier phases of fetal life.

A preterm infant has especially poor compensatory capacities in response to stressful stimuli, which cannot be completely avoided due to the many inevitable invasive procedures in the neonatal intensive care environment. Therefore, focusing on a developmentally supportive physical and social environment is especially important during prematurity when infants are still developing their capacities to reach a balanced state, i.e., to achieve neurobehavioral organization and to be able to interact with the caregivers. Reciprocity has been shown to be a very strong factor supporting learning in fetal experiments in animal models.

There is extensive animal research and clinical observation over decades by Rene Spitz, James Robertson, Konrad Lorenz, Harry Harlow, and John Bowlby, among others (as reviewed by Sullivan et al.[70]), showing that newborn infants (or offspring in animal models) are biologically preprogrammed to attach to their mother/caregiver, and this attachment process is a prerequisite for normal emotional and cognitive development of the child. The mediating elements for attachment include sensory stimuli provided by the mother and hormonal and metabolic changes both in the mother and infant, making them susceptible for bidirectional bonding.[59] Because mother/caregiver–infant

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Abstract

The neurobehavioral development of a preterm infant is modified by environmental influences from the neonatal intensive care unit for several weeks or months. This chapter summarizes research on (1) the development of the behavioral/sleep states and the significance of protecting sleep in preterm infants, (2) the development of the sensory functions and circadian rhythm and their implications on the neonatal care environment, (3) the developing muscle tone and feeding skills, and the prevention of infections from the perspective of NICU environment, (4) the parent–infant interaction in the NICU environment, (5) the assessment methods of the neurobehavioral maturation of preterm infants, and (6) NICU design including research on the single-family room design. This chapter aims to describe how the NICU environment can support neurobehavioral maturation of a preterm infant and the development of parent-premature infant relationship. The goal should be to provide the infant with nurturing stimuli and an opportunity to form a healthy attachment relationship with his/her parents. Single-family rooms bring family members together and provide privacy, individuality, a sense of closeness, peacefulness, and protection, which have been shown to benefit all family members.

Keywords

neurobehavioral development
sleep states
skin-to-skin care
parent–infant interaction
NICU design
single-family room

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bonding has been shown to be essential to neurobehavioral organization and the long-term outcome in a preterm infant, neonatal care should support parents to be physically and emotionally close to their infant and to enhance sensitive, reciprocal parent–infant interaction. The following paragraphs will describe how the NICU environment can support neurobehavioral maturation of a preterm infant and the development of parent–premature infant relationship.

Behavioral/Sleep States and NICU Environment

The behavioral states of a newborn are commonly classified into six categories, from sleep to crying. The behavioral states of a preterm infant are summarized in Table 36.1. In preterm infants with still immature sleep states, criteria for non–rapid eye movement (NREM) and rapid eye movement (REM) sleep are not always met. Then sleep is classified as indeterminate, which can also occur as a transition between sleep states. Drowsiness can be seen as a transition between sleep and wakefulness, but it can be justified as a behavioral state in preterm infants who spend long time periods in drowsiness. Fussing can be considered as a transition from active wakefulness to crying.

Preterm infants sleep most of the time. When polysomnography is available, electroencephalography (EEG) patterns together with REMs represent the established practice to classify sleep states in preterm infants. From 28 weeks of gestation onward, the concordance between EEG and REMs begins to emerge, defining NREM and REM sleep in preterm infants.[4] In fetuses, because EEG is not available, REMs and body movements are used instead and similarly show the concordance from 28 weeks of gestation onward.[15] A strong biologic basis can be assumed behind the maturation of sleep states, because fetuses and neonates have identical proportions of sleep states at corresponding gestational ages (Fig. 36.1).

By term, the sleep states have developed such that indeterminate sleep has disappeared and it has given space to NREM sleep, which comes ontogenically later than REM sleep. REM sleep is related to more fetal respiratory patterns such as susceptibility to apnea, suggesting that REM sleep is physiologically more immature than NREM sleep. At term, infant sleep has nearly similar proportions of NREM and REM sleep. Sleep states alternate so that one cycle of sleep states lasts for about an hour at term age and becomes longer during childhood. Fig. 36.2 shows the development of the proportions of behavioral states before and after term age.

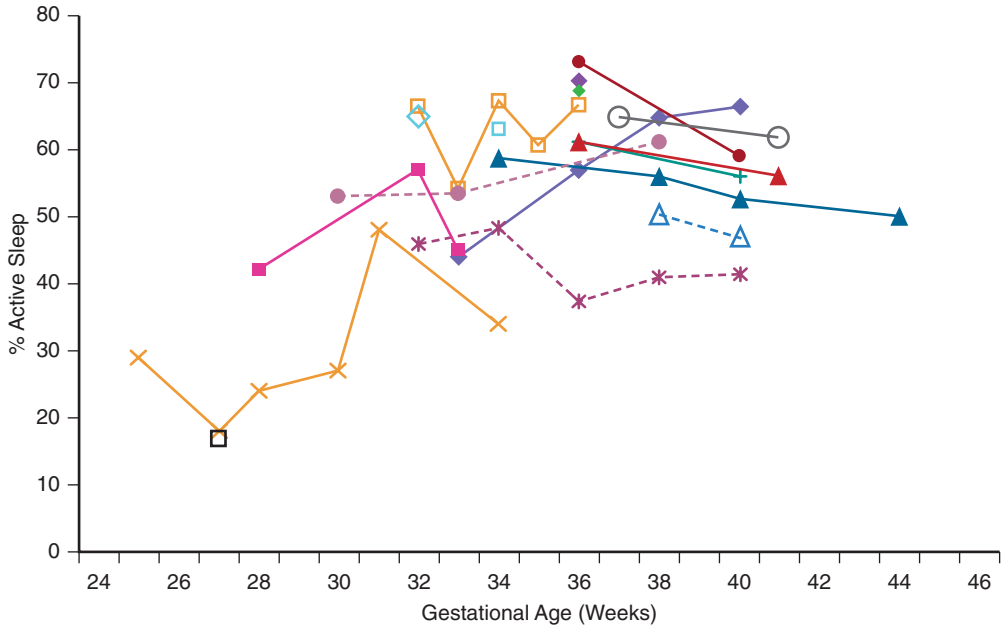
Sleep, especially REM sleep, is important for normal brain development.[41] Animal experiments have shown that REM sleep deprivation during early development leads to permanent deviations in behavior, to alterations in neurotransmitter responses, and to reduced brain volumes. In addition, REM sleep deprivation abolished the effects of environmental enrichment seen in nondeprived animals, suggesting that REM sleep deprivation might have detrimental effects on the later capacity for learning. In a fetus, endogenous neural cell activity of retinal ganglion cells happens during REM sleep. Cortical processing of auditory stimuli also happens during REM sleep, but not in NREM sleep,[71] supporting the role of REM sleep in auditory learning as well. Furthermore, oxygenation in ventilated extremely preterm infants is most stable during REM and NREM sleep while indeterminate sleep or arousals are associated with more time in hypoxemia.[35]

TABLE 36.1 The Behavioral States of a Preterm Infant

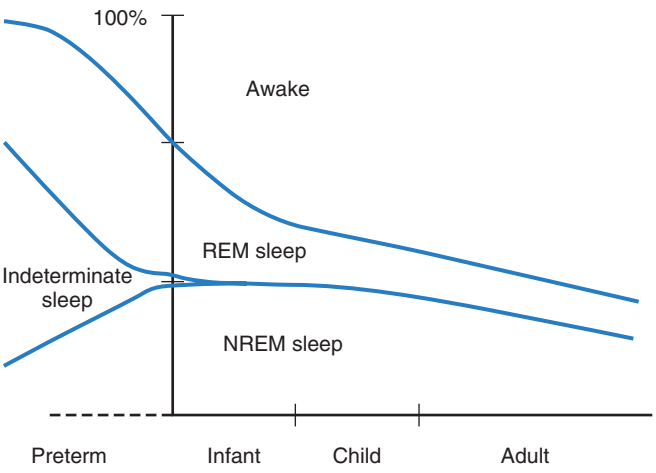
Behavioral State	Characteristics
I. Non–rapid eye movement (NREM) = Quiet sleep = Deep sleep	Eyes closed, no eye movements Regular breathing EEG discontinuous up to 36 weeks of gestation, tracé alternant from 37 weeks of gestation onward High muscle tone, no movements (occasional startles may occur)
II. Rapid eye movement (REM) = Active sleep = Light sleep	Eyes closed (may open briefly), REMs Irregular breathing (variation >20 cycles/minute), sighs EEG continuous Low muscle tone, slow or jerky movements occur (in body/limbs/digits, facial movements, sucking, startles) Brief vocalizations may occur
III. Drowsy	Eyes half open, eyes may be open but not fully alert
IV. Quiet awake	Wide open, bright eyes Breathing usually regular High muscle tone, few movements
V. Active awake	Eyes open and moving, eyes opening and closing Irregular breathing High muscle tone, active gross body movements Vocalization may be present, not crying
VI. Crying	Eyes open or tightly closed Regular, intense cry vocalization during expirations; grimacing face Very high muscle tone, gross body movements

Adapted from Anders T, Emde R, Parmelee A. *A manual of standardized terminology, techniques and criteria for scoring of states of sleep and wakefulness in newborn infants*. Los Angeles: Brain Information Service, Neurological Information Network; 1971; Brazelton TB, Nugent JK. *Neonatal behavioral assessment scale*. 3rd ed. London: Mac Keith Press; 1995; Curzi-Dascalova L, et al. Manual of methods for recording and analyzing sleep-wakefulness states in preterm and full-term infants. Paris: *INSERM*; 1996; and Andre M, Lamblin MD, d'Allest AM, et al. Electroencephalography in premature and full-term infants: developmental features and glossary. *Neurophysiol Clin*. 2010;40(2):59-124.

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• **Fig. 36.1** The development of the proportion of active sleep in preterm infants (*solid lines*) and in fetuses (*broken lines*), according to the corrected gestational age. Each line represents data from an individual study. The definitions are comparable within each study. (Adapted from Lehtonen L, Martin R. Ontogeny of sleep and awake states in relation to breathing in preterm infants. *Semin Neonatol.* 2004;9(3): 229-238.)



• **Fig. 36.2** The development of the proportion of behavioral states by age.

Based on the research knowledge on the importance of sleep on brain development of a preterm infant, all efforts should be made to develop neonatal care environments and care cultures so that they minimize sleep disturbances. A lot can be done to make the space calmer (Table 36.2). Optimally, families have their own rooms so that alarms and care of other infants do not disturb the infant close by. Infant care can be delivered based on the behavioral states and cues of the infant, not based on a routine time schedule. Invasive procedures should be minimized and noninvasive monitoring prioritized (e.g., transcutaneous CO_2 monitoring instead of blood gases). Medications such as opioids should be minimized as they affect REM sleep.[6] We discuss below the ways to decrease sleep disturbances caused by noise and ambient light.

Awake states can be classified according to behavioral criteria in a full-term infant, but it can be difficult to define wakefulness in very preterm infants. The time spent in a quiet awake state is also short in very preterm infants, but it increases with development. The emergence of an attentive quiet awake state changes the quality of social interaction, as quiet awake state provides a window of opportunity for verbal and visual parent–infant interaction and related learning, and for feeding practices. Multiple internal and external stimuli may disturb preterm infants and may prevent them from reaching an attentive awake state. Therefore, attention is needed to control environmental stimuli and to facilitate infants' self-soothing.

Infants at very early gestational ages cry little despite stressful and even painful intensive care. In one study, ventilator-treated very preterm infants presented crying facies for less than 1% of observation time.[35] Crying in neurologic assessment situations increases after 31 weeks of gestation. The attenuated capacity of preterm infants to produce reactions seen in relation to pain in older infants needs to be remembered when evaluating pain responses in preterm infants. Crying increases in preterm infants after term age, reaching the peak at the average age of 6 weeks of corrected age,[8] when the amount of crying peaks also in full-term infants. Excessive crying has been seen as a sign of poor behavioral regulation, and its role has been studied in predicting later development.[46] Many neurobehavioral assessment tools include infant crying or irritability.

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TABLE 36.2 How to Promote Sleep in the NICU Environment

Goal	Methods
Avoid noise	Single-family rooms; technology with no/few auditory alarms at bedside; decibel meters
Avoid bright lights	Indirect, dimmed lighting; protect eyes during procedures
Ensure thermoneutral environment	High enough ambient temperature in the room
Cluster caretaking and procedures to the times when the infant is awake	Infant-centered, individualized care
Minimize heel sticks and other painful/stressful procedures	Consider each heel stick carefully: Is it likely that the infant benefits more from not being disturbed than from the information of the blood test? Use noninvasive monitoring when possible
Minimize the use of opioids	Routine use of nonpharmacologic pain management such as skin-to-skin contact

Sensory Functions and NICU Environment

The developing sensory functions form a basis for interaction between preterm infants, caregivers, and the environment. The age-specific sensory functions determine which modes of interaction are relevant at each age. The onset of sensory functions occurs in the same sequence in all mammals: the first one to occur is tactile function, followed by gustatory and olfactory, vestibular, auditory, and visual functions, suggesting a fundamental importance of this sequence for the development.[59] However, it is also known from animal studies that normal development requires balanced multimodal stimulation.

Tactile Function and Skin-to-Skin Contact

The role of touch is central in very early developmental phases. Although preterm infants need to be carefully protected from unnecessary painful and stressful tactile stimulation, not always completely avoidable in intensive care, there is a vast literature about the benefits of parent–infant skin-to-skin contact (also called kangaroo care). Skin-to-skin contact is a natural interaction mode between the caregiver and a preterm infant when other senses are even more immature. Through skin-to-skin contact the caregiver coregulates infant physiology and behavior. It was shown in a meta-analysis of 124 controlled studies that preterm infants have a lower breathing rate and higher oxygen saturation, less pain symptoms, and better temperature and glucose balance in skin-to-skin contact compared to care in an incubator.[12] Furthermore, the meta-analysis showed that skin-to-skin contact decreases mortality and infections and improves breastfeeding rates and the head growth of preterm infants. Furthermore, skin-to-skin care has been shown to increase vagal tone and to enhance neurobehavioral maturation in preterm infants.[39] Consistently, very preterm infants had more optimal neurobehavioral performance at term age if the neonatal units allowed parents unlimited access and practiced daily skin-to-skin contact compared with the units with less infant-centered care.[43]

Many hormonal mechanisms mediate the neurobehavioral effects and the psychological processes related to skin-to-skin contact. Oxytocin is one of the key hormones facilitating parent–infant relationships. Seven of eight human studies showed a strong association between oxytocin levels and the mother–infant relationship as summarized by Galbally et al.[24] Furthermore, the fundamental biologic role of oxytocin is supported by extensive animal literature, reviewed by Rilling.[58] Breastfeeding, skin-to-skin contact, and infants' social signals stimulate oxytocin secretion in mothers. Oxytocin may promote early interaction by several mechanisms, such as improved face and affect recognition and increased caregiving motivation by activation of the dopaminergic system, the "reward pathway." Maternal behavior is increased by estrogen, which increases the number of oxytocin receptors.

Consistent with reports showing that massage, a type of tactile stimulation, increases growth in preterm infants, an Italian group showed in a randomized study that infant massage 15 minutes three times a day increased blood levels of insulin-like growth factor 1 (IGF-1).[25] In addition, the group receiving massage had accelerated maturation of visual function and EEG. In rat pups, the beneficial effects on vision were blocked by antagonizing IGF-1.

The effects of skin-to-skin care on improved growth might partially be mediated by cholecystokinin (CCK), which enhances digestion and has a calming effect. Preterm infants in skin-to-skin care had a CCK response to tube feeding while tube feeding without skin-to-skin care did not increase CCK levels.[73] Skin-to-skin contact and breastfeeding also decrease cortisol levels in mothers. A care setting supporting parental presence in a NICU improved cortisol synchrony between the mother and the infant.[45]

Most commonly, parent–infant skin-to-skin contact has been implemented during neonatal intensive care and practiced for a few hours daily. Although skin-to-skin contact

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• **Fig. 36.3** Four-day-old infant born at 25 weeks' gestation is skin-to-skin with her mother while on the ventilator, receiving tube feedings and parenteral nutrition via a PICC line. Daily skin-to-skin care was started on the second day of life and continued throughout the hospital stay.

has been shown to be safe, even in extremely low gestational age infants from the first week of life[12,28,40] (Fig. 36.3), the beginning is commonly delayed and the average daily duration of skin-to-skin contact in preterm infants remains low in most neonatal units. In a study done in 11 European neonatal units, the duration of skin-to-skin contact was longer in the neonatal units providing an opportunity for the parents to stay overnight in the neonatal unit.[54] Comfortable, reclining chairs or adult beds at the infant bedside can be provided even without family rooms to facilitate longer periods of parent–infant skin-to-skin contact. Flacking and Dykes explored the role of space in neonatal units from the perspective of mother–infant attunement at feeding interaction.[22] The researchers concluded that the bed or chair at bedside signaled the importance of the parents and what was expected of them. When a bed was at bedside, parents were signaled that they were expected to lie in it and that a bed was needed for parent–infant closeness. A chair at bedside conveyed a message that parents were expected to come and stay close to the infant, possibly holding him/her for as long as they could.

The value of early contact in the formation of the mother–infant bond was shown in full-term infants in the landmark study by Klaus et al.[29] in 1972 and has been confirmed later by them and others.[44] There is evidence that early physical contact between a preterm infant and the mother in the delivery room is associated with fewer later behavioral problems at 5 years of age.[33] However, it remains challenging to apply continuous skin-to-skin care for preterm infants right after birth in the delivery room. Poor implementation of early skin-to-skin contact in preterm populations might be defended by safety concerns, but it is more likely that the obstacles are related rather to the care culture and attitudes, which do not sufficiently appreciate the value of mother–infant closeness. The preterm infant is optimally transported to intensive care on the parent's chest, and the mother and her preterm infant are cared for together in the same room throughout the hospital stay (couplet care). Flacking and Dykes concluded in their observational study of four neonatal units that the earlier and the longer a mother can stay with her baby in close proximity, the more she will be attuned to the signals of the baby and assume the role as the primary caregiver.[22]

In addition to tactile stimuli, skin-to-skin contact with a parent provides the infant with other stimuli, including kinesthetic, olfactory, and auditory stimuli, and an interactive dimension associated with the parents' immediate responses to their infant's cues. Some of these elements can be achieved by holding the infant (with clothes on). All caring and gentle touch should be encouraged in all units, even in those that have not yet developed competencies for early and prolonged skin-to-skin contact.

Taste and Smell Functions and Environmental Experiences

Full-term newborn infants show a preference for their own mothers' smell, suggesting learning in utero as maternal dietary flavors are transmitted to the amniotic fluid and recognized as both flavors and odors by the term newborn. Fetuses show behavioral responses to taste as early as 16 weeks of gestation. Olfactory stimuli leading to behavioral responses or cortical blood flow changes have been documented from 28-35 weeks of gestation.[9]

Familiar taste and smell can be used in NICU environment to calm the preterm infant. During tube feeding, drops of maternal breast milk to the tip of the tongue of the infant familiarizes her/him to the taste of maternal breast milk. Smell has been used as a calming method by bringing the mother's smell to the baby in a fabric if the mother herself is not available.[76] Smell might be one beneficial component of mother–infant skin-to-skin contact and is available even without skin-to-skin contact when the infant is held.

Vestibular/Proprioceptive Functions

Newborn babies are carried around by their caregivers for most of the day in many traditional cultures. Better motor development is shown in the infants who are carried in an upright position, facing the caregiver and legs flexed. Rocking is also a common experience provided to young infants. Fetuses are exposed to acceleratory environment when the mother moves, usually for most of the day. The care provided for very preterm infants in incubators is far from these physiologic situations in fetuses and full-term infants. Lying in one flat position easily molds the skull of a preterm infant. It can be hypothesized that the lack of upright position and lack of experiences of acceleratory movements during early development partly explain later problems in motor coordination commonly seen in very preterm infants.[63]

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Auditory Functions and Environmental Experiences

Fetal auditory learning is suggested by newborn infants' preference for the voices of their own mothers and to music their mothers have listened to during pregnancy. Auditory function in fetuses develops during pregnancy in an environment in which amniotic fluid and maternal tissues protect the fetus from high-frequency noise. All axon layers of the auditory cortex are found histologically by 25 weeks of gestation, but the density of the axons increases up to 9 months of corrected age, suggesting increasing cortical capacity in processing sounds.

Very preterm infants from 23 weeks of gestation react behaviorally and electrophysiologically to intense auditory signals. Fetuses have been shown to have magnetoelectrographic responses to auditory stimuli from 28 weeks of gestation. Very preterm infants born below 30 weeks of gestation show different auditory evoked potentials compared with older preterm infants when tested at 35 weeks of gestation, suggesting that the development of auditory functions is affected by the neonatal care environment as compared to the intrauterine environment.[10a]

When skin-to-skin contact is practiced, the infant is exposed to the heartbeat and breathing sounds of the parent and also to the parent's voice, which are normal stimuli during fetal life. Parental voice seems, indeed, to be one important stimulus for infant development. A study showed that preterm infants vocalized more actively already at 32 weeks of gestation when the parents were present compared to when the staff were present.[13] Later language development correlated to the amount of adult words these very preterm born infants had heard at 32 weeks of gestation.[14] Consistently, very preterm infants had better language development if their mothers were actively involved in their care compared to low involvement mothers.[37] The infants cared for in a single-family room unit supporting parents' presence had better language development compared to those cared for in an open bay model.[75] Consistently, if preterm infants were cared for in private patient rooms without parents' beds, their language development was more delayed than those cared for in an open unit model.[53]

All these studies support NICU environments where parents are engaged in the care of their infants and where they have a natural (calm, quiet, private) environment to talk (and maybe sing) to and with their infants. The environment should be calm and quiet for the comfort of both the infant and the parents. The parent's voice may have many benefits compared to the unfamiliar voices of the staff members: the parent's voice is familiar to the newborn from the intrauterine environment, and its familiarity strengthens during postnatal time; the parent's voice might include more emotional components; and the parent's talk is likely to be more sensitively tuned to the infant's cues and responses.

It is important and possible to control noise in the neonatal environment. Noise disturbs the developing auditory system and is a source of stress. The noise level of any equipment should be taken into account when making decisions on purchases. Technologies should also be developed better; there are, for example, no incubators with less than 55 dB noise (compared to the hotel room standard of 40 dB). Technologies transmitting alarms to the staff member responsible for the patient can be used to avoid disturbing the patient and parent. In the patient room, visual alarms instead of auditory ones can be prioritized. Single-family rooms prevent infants from being exposed to the noise from alarms and care of other patients. Technologies should also be improved to increase the reliability of signals, and thereby decreasing false alarms, which would be a benefit from both infant and staff perspectives.

Visual Functions and Environmental Experiences

The visual system matures in utero anatomically and functionally, even if fetuses are not exposed to discrete visual stimuli. Endogenous neural cell activity of retinal ganglion cells is an important part of visual system development. Together with sleep cycle organization, the endogenous neural activity concentrates in REM sleep periods. Stimuli disturbing the immature retina or REM sleep might interfere with the development of the visual system. Therefore, exposure to bright lights is one potentially toxic but avoidable environmental stimulus. Extremely preterm infants can already react to bright light. The capability to follow an object emerges at 29-30 weeks of gestation. Although preterm infants have been reported to be ahead of full-term infants in visual tracking at term, delays have been reported in preterm infants compared with full-term infants in many dimensions of visual functioning such as smoothly pursuing eye movements and cortical vision.[38] These delays suggest that the development of visual function is affected by the neonatal care environment as compared to the intrauterine environment. Maturation in vision, eye movements, and cortical vision will continue after term age.

One implication of the research on the development of vision on NICU design is that ambient light should be gentle. The rooms should be designed with indirect ambient lighting with levels adjustable through a range of 10-600 lux. When needed for procedures, the light should be a spotlight directed only to the area in attention, and the eyes of the patient should be covered.

Circadian Rhythm and NICU Environment

Circadian rhythmicity has developed during evolution to adjust life to the rotation of earth. Specific genes have been identified that regulate circadian rhythmicity, yet it is profoundly affected by the sensory environment, especially light. In newborn infants, the shorter (about 3-hour) cycles regulated by feedings dominate and circadian rhythm is not yet established. Wakefulness starts to cluster to daytime during the second month of life, and clear rhythm following the 24-hour day is normally developed by 1 year of age.

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During fetal life, circadian rhythmicity operates quite differently than during the rest of life. The fetus has a well-developed circadian rhythm by the end of the second trimester,[62] probably influenced by multiple maternal stimuli, including physical (movement, body temperature) and hormonal (transplacental melatonin, cortisol) *zeitgebers* (timekeepers). In preterm infants, a circadian rhythm cannot be detected, even though the neural mechanisms to respond to a circadian light stimulus are intact by early in the third trimester. In exploring this phenomenon, one is struck by the absence in the NICU of the circadian stimuli that would be available to the fetus. Body temperature is rigidly servo controlled, touch and kinesthetic stimuli are as likely to occur in the middle of the night as during the day, and access to maternal rhythms of melatonin and cortisol, present in breast milk, is often prevented by administration of breast milk without regard for the time it was expressed or by the use of artificial formula. Even skin-to-skin contact with the mother for several hours a day may not be sufficient to impart circadian information to the preterm infant. Preterm infants may develop a circadian rhythm sooner if exposed to cycled lighting.[26]

Sensory Functions and Pain

Very preterm infants have not yet developed clear behavioral pain responses. The robustness of pain responses (crying, arousal, and facial grimace) increases with development. Even if poorly capable of displaying clear behavioral responses, preterm infants are sensitive to pain. Blood flow changes in the contralateral somatosensory cortex have been shown to be related to a heel stick as early as 25 weeks of gestation, and the blood flow responses are stronger at lower gestational ages compared with more mature preterm infants.[65] Recurrent pain exposure in preterm infants is suggested to delay their growth, alter their brain maturation and the performance in neurobehavioral assessments, and impair their motor and cognitive development.[74]

As both pain and pain medications are potentially harmful for brain development, the optimal solution is to avoid both of them. The care of preterm infants has become less invasive and more gentle, which has been reflected in decreasing rates of neurologic impairments in preterm infants shown in both European and Australian register studies.[61,66] Interestingly, Lester et al. showed in their study about single-family rooms that the infants cared for in a single-family room were exposed to fewer procedures.[36]

Skin-to-skin contact in different forms has been used to alleviate pain and stress in preterm infants.[16] Parents can effectively alleviate the stress/pain behavior of their preterm infant by holding the infant by their warm hands in a flexed position during a painful or stressful procedure.[7]

Muscle Tone, Movements, and Reflexes

Preterm infants typically have lower muscle tone and less coordinated movements than full-term infants. A flexed position maintained most of the time in utero supports infants' self-soothing abilities such as bringing the hand to the mouth (Box 36.1). To provide similar opportunities for preterm infants, special attention in nursing care needs to be paid to supporting a flexed position in a preterm infant both during rest and during handling. Although healthy preterm infants by term can reach the same level in muscle tone, tone distribution, spontaneous movements, and reflex functions as full-term infants, preterm infants present a larger variation in their performance, especially in muscle tone. This variation makes it more difficult to define neurologic normality in preterm infants at term equivalent age than in full-term infants. Preterm infants at term tend to have less flexor limb tone, less head control, and increased hyperexcitability seen in brisk reflexes, strong grasp, startles, and tremors. More tremors are seen in preterm infants born in the lowest gestational weeks.[57]

The flexed position of a preterm infant should be supported in their environment whether it is in an incubator or on a parent's chest, or during rest and handling. It is an open question how much movement (vestibular stimulation) the care environment should offer for a preterm infant and whether a more physiologic upright position could be feasible.

• BOX 36.1 Examples of Behavioral Signs of a Preterm Infant Indicating Stress/Avoidance and Self-Soothing/Approach Behavior

Stress Signs/Avoidance

Abnormal cry (high-pitched, monotonous, weak), irritability
Abrupt behavioral state changes, unable to reach quiet awake state
Gaze aversion, abnormal eye movements
Labored breathing
Yawning, sneezing, hiccoughing
Burping, gagging
Pale, mottled, cyanosis
Startles, tremors
Hypertonia, back arching, fisting

Self-Soothing Behaviors/Approach

Visual fixation
Hand-to-mouth
Sucking on the fist/thumb/fingers
Stroking the face
Crossing arms/legs
Grasping cords/tubes/blanket
Bracing leg(s)
Moving to a flexed posture

Adapted from Boukydis CF, Bigsby R, and Lester BM[11]

Sucking and Swallowing

A fetus swallows amniotic fluid from 12 weeks of gestation in increasing amounts as sucking movements develop as an integral part of age-appropriate neurobehavioral

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development. Immature sucking patterns with short bursts and long pauses develop into long, rhythmic sucking bursts of 10-30 sucks per burst. To be able to feed orally, a preterm infant must be able to synchronize sucking and swallowing with breathing. Both respiratory stability and sufficient neurobehavioral organization are required for safe and efficient oral feeding. Nonnutritive sucking has been used as an indicator for readiness for oral feeding, but there are no proven feeding readiness instruments to predict the time to full oral feedings. Breastfeeding seems to be easier for preterm infants to coordinate with breathing compared with bottle feeding.[10] Even if respiratory stability requires ventilator support, the first feeding experiences, such as licking/sucking the breast or small drops of milk from a syringe, can be initiated for the infant's pleasure and learning. Occasional infants are capable of starting breastfeeding at 28 weeks of gestation and are able to reach full breastfeeding at 32-33 weeks of gestation.[27] Full oral feeding is reached at an earlier postmenstrual age by infants born at lower gestational age, suggesting that exposure to (breast) feeding enhances learning. Controlled studies have demonstrated that nonnutritive sucking, sensory stimulation, and early initiation of oral feedings enhance the learning of nutritive sucking.[23] In some studies, however, it might be that the experimental settings allow the infants with readiness for feeding to feed earlier than is allowed in many clinical practices at which feeding may be rigidly based on weeks of gestation instead of the infant's individual capacities. Full oral feeding can be achieved by most infants at 34-36 weeks of gestation, and almost all preterm infants are capable of full oral feedings at 38 weeks of gestation, even if the efficacy of feeding increases after infants reach term. The key is to sensitively observe the behavioral state and cues of the infant to see the readiness of the infant to feed.

Environment Supporting Growth

During the period of rapid brain growth, it remains challenging to provide a preterm infant with nutrition comparable to the nutrition provided through the placenta to a fetus during normal pregnancy. The initiation and maintenance of sufficient lactation to enable breastfeeding, when the infant is ready for it, is also a challenge for the mothers of preterm infants. In full-term infants, breastfeeding relates to higher IQ scores as shown in a cluster randomized study design.[31] Both nutrients and the mother–infant closeness and interaction component of breastfeeding are likely to contribute to this effect. Better developmental outcome was found in very preterm infants who were breastfed at discharge despite lower weight gain before term age compared with formula-fed controls.[60] Both the duration of breastfeeding and the amount of breast milk intake during neonatal care have been shown to correlate in a dose-response relationship with developmental outcome in very preterm infants so that 100 mL/kg/day increase in maternal breast milk volume at 4 weeks of age was shown to increase Bayley test language and cognitive scores by 3 points.[75]

The neonatal unit care culture and environment can support breast milk pumping and breastfeeding in many ways. It is important to value breastfeeding as an important moment for mother–infant interaction regardless of the volume of milk produced/ingested. Providing privacy for pumping and breastfeeding is important to many mothers. Breast milk pumps, comfortable chairs and refrigerators in the patient rooms, and easy milk logistics are essential parts of NICU design. Maternal breast milk volumes were shown to be higher in a single-family room neonatal unit compared to earlier open-bay units among mothers of very preterm infants.[75]

Environment Protecting From Infections

If a preterm infant acquires sepsis during the hospital stay, the risk for clinically significant developmental problems doubles as shown in two large follow-up studies.[42,69] Therefore, care routines and design protecting preterm infants from nosocomial infections are important also from the perspective of infant neurodevelopment. Several studies have shown that single-family room design decreases the risk of infections.[17,36] It may be due to better location/availability for hand disinfectants and sinks for handwashing, longer distances between patients, or parents' surveillance and control on staff hand hygiene. Ideally, one patient should stay in the same room throughout the stay as patient logistics affects spreading of bacteria.

Environment Supporting Parent–Infant Interaction

As supported by animal research, the mother/parent is an important regulator of infant physiology, behavior, and development. Separation from the parent produces dysregulation in the offspring's brain functioning and behavior. A controlled study was carried out to reduce mother–preterm infant separation in the era when separation was the hospital routine. The mother's early participation in infant care was shown to improve mother–infant interaction and later cognitive development of the child in a study by Klaus and Kennell in 1982.[30] In a later NICU care context, when it had become routine for parents to visit daily, those infants whose mothers visited less than daily were at higher risk for behavioral problems at 7 years of age.[34] Parents' visitations, as well as the time the parent cuddled their preterm infant, correlated with better neurobehavioral organization during the neonatal period, even in a neonatal environment with low median amounts of parent–infant closeness.[56] Despite the evidence, neonatal care is still often organized in such a way that separation occurs to a significant extent and reducing the obstacles of parent–infant closeness is not prioritized in quality improvement efforts.

Intervention programs have been designed to guide parents and staff more systematically to use the knowledge of infant neurobehavior and infant cues in neonatal care

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environments. The main principles of preterm infant behavior, such as the capacity of an infant to show stress signs or avoidance behaviors when overwhelmed or to use self-soothing behaviors and to show approach behaviors (see Box 36.1), can be used by the staff and by the parents. As the staff and parents understand how to adjust the amount of stimulation and interaction to the immediate capacity of their infant, they can help the infant to reach and sustain a quiet awake state, or they can support the infant's sleep. Parents and staff can plan the everyday care of the infants so that it is guided by the individual neurobehavioral signs of the preterm infant to synchronize the care better with the infant's needs. There will be consistency in the style of care when the parents are the primary caregivers and continue to be such after hospital stay at home.

A famous study randomized a group of orphans located in the orphanages in Romania to those who continued their (low-quality) care in the orphanages and those who were provided a foster home. This study showed that essential elements of care supporting later growth and development included sensitivity (child-centered, contingent responses) and positive regard for the child (acceptance, respect, and warmth, including expressions of physical affection).[47,80] Low birth weight infants were shown to be especially sensitive to the quality of care. In the preterm infant, the basis of the parent–infant relationship is formed during neonatal hospital care. Thereby, the engagement of the parents during hospital time modifies the neurobehavioral development of the preterm infant during neonatal care and also throughout childhood by modifying the psychological growth environment of the child.

A Norwegian study using a modified Mother Infant Transaction Program, developed by Achenbach et al.,[1] demonstrated possible mechanisms mediating the long-term neurodevelopmental benefits of parenting programs in NICUs and also the time span needed to judge impact of the program. The Norwegian intervention consisted of 12 sessions provided by a nurse, most of them just prior to discharge, teaching the parents to recognize infants' behavioral cues and to respond sensitively. In addition, one session was designed to reflect the experience during the hospital stay. The intervention influenced parent–infant interaction in the long term: the children in the intervention group showed more joint attention in examiner–child interaction at 12 months of age, the parents showed more nurturing child-rearing attitudes when the child was 12 and 24 months old, and parents' stress related to parenting decreased progressively over years.[32] The children in the intervention group had better cognitive outcome at 5 years of age[49] and fewer behavioral problems reported by the parents (although not by the teachers).[50] The benefits were still seen at 9 years of age. This study suggests that parenting interventions can start a positive trajectory early on and that the effects accumulate over years and are mediated through different dimensions of parent–infant interaction. It is noteworthy that the differences in neurodevelopment were not yet measurable at 2 years of corrected age, similar to Achenbach et al.,[1] showing that the intervention effect on cognition progresses after 24 months of age. Although evidence is accumulating regarding interventions focused on parent–infant relationship (supporting parent participation and more sensitive parenting), conflicting results have been reported. The benefits may not be seen if interventions are carried out in isolation so that the care culture in the neonatal unit counteracts the intervention. The intervention might also be too short-lasting or the follow-up too short to show the possible effects on cognitive development.

A meta-analysis of early interventions showed that the interventions focusing on the parent–infant relationship had a greater impact on cognitive outcome of the children compared with those that focused on infant development.[67]

One mechanism behind the beneficial effects of parenting interventions may be decreased postpartum depression. Parenting interventions in neonatal units have been shown to decrease maternal depression by as much as 75%–80% compared to controls.[2] Depression is known to be associated with less optimal mother–preterm infant interaction. The high incidence of postpartum depression in the mothers of preterm infants might be partly a result of separation and an undervalued parenting role. Parents' participation in infant care and in decision-making about infant care and skin-to-skin contact during intensive care continued with breastfeeding during convalescent care are safe ways to decrease caregiver–infant separation and to provide the mother a unique role in caregiving.

Several new protocols focusing on supporting parenting in neonatal care units have been published. They include different aspects of developmentally supportive care and different levels of neurobehavioral observations and interpretation of infants' cues with parents. It is important to support parent–child interaction and infant neurobehavioral development from the beginning to make the intervention preventive instead of treating and correcting abnormal development. It will be important to learn which type of intervention, at which time point, and for how long will be needed to effectively support infant neurobehavioral development.

The NICU design can support parents' participation and optimal long-term neurodevelopmental outcomes of preterm infants (see NICU design below). Single-family room units providing the families with better facilities increased mothers' participation in the United States,[36] and the hospital stay shortened by 15 days in the high maternal involvement group.[37] The neurodevelopmental outcome of preterm infants cared for in the single-family room unit were better than those cared for in the traditional open bay unit.[75]

Neurobehavioral Assessment Tools

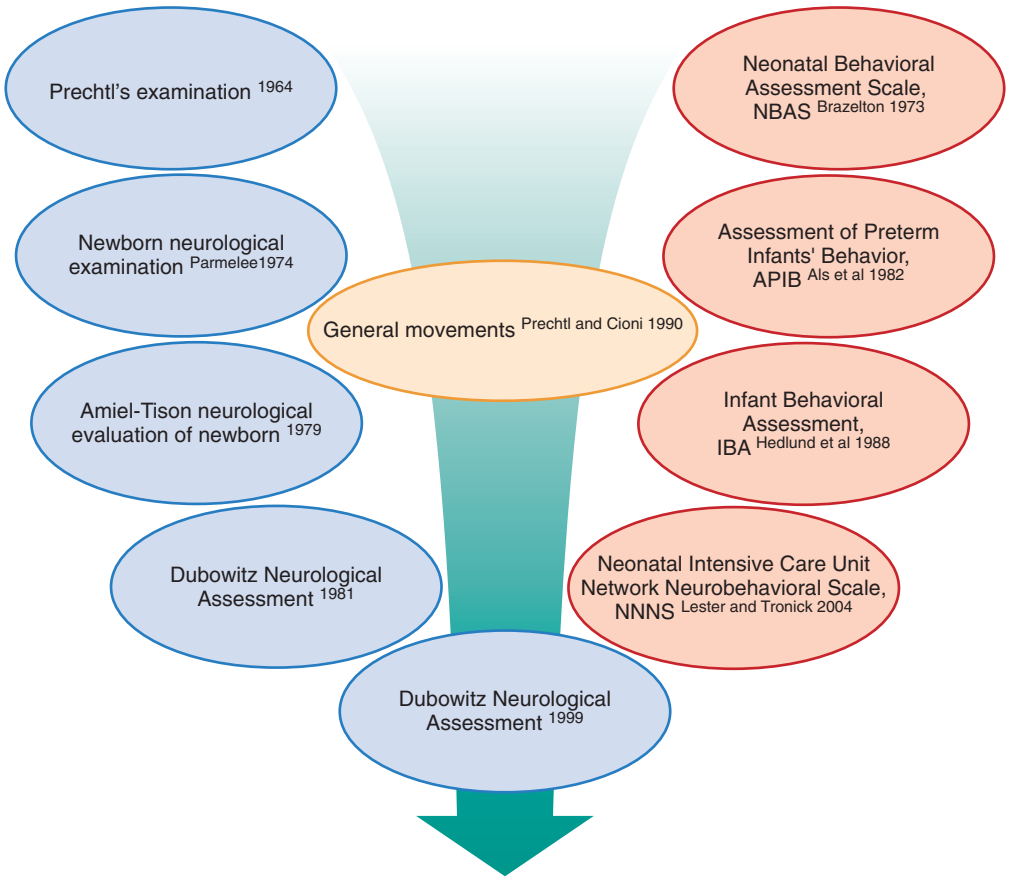
The assessment of neurobehavioral performance and development is an essential part of the clinical assessment of a preterm infant in neonatal care but can also be used to demonstrate the impact of a change in the NICU design

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or care culture, or differences between neonatal units. The assessment tools have evolved over decades, reflecting the increase in understanding of the complex, multidimensional neurobehavior of an infant. The assessment methods were developed first for full-term infants and later further adjusted specifically for preterm infants. The history of the development of standardized assessment methods for preterm infants includes, among others, André-Thomas defining active and passive muscle tone and reflexes in newborn infants and Saint-Anne Dargassies showing the maturation of these neurologic functions in preterm infants. This formed the basis for Amiel-Tison's assessment method for newborn infants (1979, 1980). Prechtl (1969), Brazelton (1973), and Parmelee (1976) studied behavioral states, and Prechtl and Cioni (1990) studied general movements of a newborn. Dubowitz and Dubowitz (1981) developed an evaluation method for the neurobehavioral performance of newborn infants based on neurologic functions of the newborn but integrating behavioral measures and spontaneous movements derived from the framework of assessing general movements.

Most methods used today combine neurologic, sensory, and behavioral items with differences in emphasis. The most widely used assessment methods are schematically presented in Fig. 36.4 to emphasize their origin and focus. However, the similarities in their content are greater than the differences. Because behavioral states influence motor and reflex performance, sensory functions, and their interaction, behavioral states need to be taken into account when assessing neurobehavioral development in a preterm infant using any method.

Assessment methods focusing on behavioral performance examine the full range of behavioral states and provide a global view of higher neurologic functions. These methods are well suited to follow recovery of an at-risk infant in neonatal care or to adjust the care of an individual infant based on a differentiated understanding of his/her neurobehavioral maturation and vulnerabilities. When applied systematically, the neurobehavioral assessment of the preterm infant population in a unit can serve as a tool to monitor the effects of quality improvement efforts. Lester et al. showed that preterm infants had better performance in the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) when cared for in a single-family room unit compared to open bay unit.[36] In Italy, an association between the level of infant-centered care in the unit and neurobehavioral performance of preterm infants was also shown by using the NNNS.[43]



• **Fig. 36.4** The main methods for the assessment of the neurobehavioral development of newborn infants are schematically presented. Those with emphasis on neurologic items are in blue, those with emphasis on behavioral items are in red, and assessment of general movements is in orange.

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On the other hand, if the goal is in diagnostics or in defining the infants at risk for long-term neurodevelopmental problems and, therefore, in need of additional support, the structured methods with more specific neurologic items, such as the Dubowitz Scale, or general movements seem to give better predictive value. More important than the method chosen is the systematic application of a standardized assessment. To screen for neurologic diagnoses of a preterm infant in neonatal care, any method is expected to discriminate normal maturational progress of the infant. The strengths and weaknesses of the assessment methods are important to understand, and they differ in the amount of training needed to use them reliably as reviewed by Spittle et al. (2008),[68] El-Dib et al, (2011),[18] and Noble and Boyd (2011).[48] The length of time needed for assessment is also important from a practical point of view. Preterm infants do not tolerate much handling, so it is beneficial if the test is noninvasive. The methods with clear written/illustrated manuals, easily definable variables, and a relatively short time to perform may better suit the realities of everyday clinical settings, whereas those requiring long training, extensive lists of variables, and longer time to perform may better suit research purposes.

If the expected age-appropriate progress in neurobehavioral development is not seen, a concern for underlying neurologic disease or pathology related to prematurity should be raised. The precise prediction of outcome based on the neurobehavioral status of a preterm infant cannot, however, be expected, because preterm infants benefit from their unique brain plasticity, compensating for deficits during the neonatal period. Early information about deviations in neurobehavioral status should be used to optimize care, and the neonatal environment to support neuronal growth and synaptogenesis and to support inherent compensating plasticity.

NICU Design

A renovation or building a new space allows major changes in the neonatal care environment. The planning process can progress according to the phases described in Box 36.2. The key factors to be taken into account in designing the NICU are listed in Box 36.3. Single-family rooms with facilities for the parents to stay throughout the day and night in the patient room of their infant have become more common in different countries. Several benefits related to single-family room NICUs have been discussed above. Controlled studies on single-family room NICUs are summarized in Table 36.3. There are, however, large differences in how this concept is implemented. Particularly, the degree of privacy provided to the families is different in different units: some units rely on technology to monitor the patient while others have transparent walls to the rooms, compromising privacy to maintain visual access to the room. The differences in design should be reported in detail when reporting the outcomes.

Although the benefits of single-family rooms, for example, fewer infections and shorter length of stay,[51] may generate economic savings for the hospital and society, the greatest advantages are likely to be seen in the improved well-being of the infants and satisfaction of the parents and other family members. The benefits for the developing parent–infant relationship and for parents' psychological well-being are likely to mediate the improvement shown in the long-term outcomes of the infants.

Health Care Team Perspectives

New NICU designs and related changes in family-centered care culture are both challenges and opportunities for the health care team of the unit. The challenge for staff is how to adopt a professional role focusing more on facilitation of parenting and to let parents perform infant care routines. The whole health care team needs new skills to negotiate and collaborate with parents as equal partners and to support parenting.[3] In one study, the nurse–parent interaction time per nursing shift increased from 35 minutes to 117 minutes after moving to a single-family room unit.[72] New care culture, together with parents, is likely to bring more meaning and satisfaction to the work of the staff when the child is seen as a part of a larger family context.[5,36] Family members are also in a better position to improve the quality of care. The health care team needs to openly embrace their input.

The health care team members also appreciate the opportunity to collaborate and socialize with their colleagues throughout the workday. A "nursing station" is a space away from the bedside, but within the patient care area, for the health care team to meet and collaborate in a setting that encourages interaction with their colleagues while keeping them informed of the status of their patients through electronic monitoring and communication devices. Charting stations immediately outside the patient rooms do not replace this additional gathering area. Many units have found that a total of 8-12 beds are required for one "nursing station" to have enough persons for a team, as significant time is spent inside the patient rooms. The staff lounge should be attractive and comfortable, and it should be located separate from parents' lounges to allow the staff time off from the close contact with the parents. The staff lounge has its role during pauses, and it does not replace the "nursing station" area facilitating team work.

The layout of the unit significantly dictates distances the staff has to cover. However, the distances are likely longer between the patients in single-family room NICUs. Many hospitals have still succeeded to move from open bay units to single-family room NICUs without increasing the number of staff members.[17]

The optimal physical NICU environment may also be different from staff and infant perspectives. Preterm infants require high ambient temperatures and dimmed lights. The staff might feel more energetic in lower temperature and brighter light. Most night-shift workers are nocturnal while working but diurnal on their days off, leading to stress and sleep deprivation.[21] Although even moderate levels of light at night can suppress melatonin-induced sleepiness and

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• BOX 36.2 The Planning Process of a Neonatal Intensive Care Unit

Dream

- Assemble the team. Who are equal partners—and who are not? Disciplines that are not included from the beginning are often given the message that they are not on an equal level in the decision-making process. Most notable in this respect are parents, who are often not included until the "user group" stage.
- Determine the vision. How will the new unit change the culture, attitudes, processes, and lives of the people who are cared for and caregivers there? Recognize that this is a life-defining place for many people who pass through. How can the unit design facilitate the best outcomes for all constituencies?
- Review what you appreciate about your existing unit (e.g., collegiality, visibility, easy communication). Too often, a new unit is built to address the glaring inadequacies of the existing unit but creates new problems of its own, because the benefits of working in close, open quarters are overlooked and, therefore, are not preserved with new strategies.
- Educate your team on change strategies. Building a new unit requires major changes for everyone, and achieving buy-in will be necessary at many points along the way.

Design

- Select an architectural firm, as well as any additional design collaborators (e.g., acoustical engineer, lighting engineer, interior designer).
- Review the advantages and challenges a new location will give you. Typical constraints include financial and space limitations. Finding out about these after the design process is well advanced can be the source of much frustration!
- Develop the functional program together with the multidisciplinary team involved in the whole care process and the representatives of families. Use, for example, Value Stream Mapping to identify the bottle necks and lean fundamentals to optimize the care processes.[55] Identify all discrete areas needed, the amount of space needed for each, and desirable adjacencies and traffic patterns. Make sure you do not leave out areas that you may not have now but should include in a new unit, such as family support spaces, recycling area, and sufficient staff support space. All change is incremental, so spaces that do not exist or are grossly inadequate currently are often the hardest to get right. The tendency is to make the space larger but still inadequate.
- Design the patient room mock-up concurrently with the floor plan. Do not let the geography and space available dictate the ideal room size/layout any more than absolutely necessary.
- Additional activities that are important to initiate early in the design process:
  - Methods for communicating the progress of the design process to all staff for their input and buy-in
  - Planning for the move, especially if interim space will be used during the construction process or if the relationship of the neonatal intensive care unit to the labor, delivery, and recovery area will change
  - Planning for sustainable design/operation. Many of these decisions will need to be made very early in the design process and would be very expensive to introduce later. This will lead to decisions about HVAC systems; floor, wall, cabinetry, and ceiling finishes; power supply and use; and more.
  - New communication systems/strategies for a larger, more private unit (e.g., patient [monitor] to nurse, nurse to nurse)
  - New health care team collaboration/training opportunities/challenges/strategies. Collaboration with parents needs to be in focus (Ahlqvist-Björkroth et al. 2017).
  - New supply access/storage/removal opportunities/challenges/strategies
  - New infection control opportunities/challenges
  - HIPAA/privacy considerations
  - Site visits—a very important component to "get right." Choosing at least a couple of units to visit that have a similar size, acuity, and philosophy is important, but much can be learned from innovative units even if they are much different from your own and even if they are in other parts of the hospital, such as pediatric or adult ICUs or noncritical care facilities.
  - Equipment planning

Build

- Once the design is finalized and the unit is under construction, many months remain to prepare for the dramatic changes in culture and practice that can occur in a new unit. Teams that are already at this stage are advised to review the items in the design stage and focus on any of those that still remain in an early stage or may even have been overlooked until now.

Modified from the work developed for use in the Vermont Oxford Network NICQ 2009 Improvement Collaborative.

improve alertness while reducing the normal night-time temperature decline,[21] attempts to keep the infant's environment dark may make supplemental lighting difficult to provide for caregivers. In addition, with evidence that night-shift workers are at increased risk for cancer[21] and that melatonin may be beneficial in reducing tumor growth, it is impossible to know at present what the ideal lighting environment is for night-shift workers, at least with respect to providing them an optimal work environment while causing the least harm.

Natural daylight and a view to nature have been suggested to improve staff well-being and recovery of adult patients.[64] Similarly, the parents in the unit would benefit from natural daylight and a view to nature. The design of the unit should find a solution to provide those elements for the staff and parents without compromising the infant's environment.

Conclusion

The management of a preterm infant calls for a delicate counterbalance between necessary and sufficient support for the infant's physiology and avoidance of any unnecessary interference with parent–infant interaction. During

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• BOX 36.3 Key Factors in Designing the Neonatal Intensive Care Unit[78]

Location
- Close proximity or controlled access to delivery and transport areas
- Controlled access and egress for patient and staff safety

Space Allocation
- Minimum of 120 square feet per bed space, excluding sinks and aisles (165 square feet minimum for single-patient rooms)
- Adequate and easily accessible storage (30 square feet per bed) for supplies and equipment

Access
- At least 4-foot aisles in multibed rooms
- At least 8-foot corridors outside private rooms

Privacy
- Minimum of 8 feet between beds, with provisions for family and speech privacy
- A comfortable reclining chair and/or a hospital bed (head to be adjusted) for the parent for skin-to-skin contact and breastfeeding

Nutrition
- A breastmilk pump for each mother, a comfortable reclining chair for breastmilk pumping, and refrigerator for breastmilk storage

Headwall
- Twenty simultaneously accessible electrical outlets, divided between normal and emergency power circuits
- Three each of compressed air, oxygen, and vacuum outlets, all simultaneously accessible
- Data transmission port

Hand Hygiene
- Hand disinfectant at each patient bed
- Large sinks with hands-free controls within 20 feet of every bed
- Sinks designed to accommodate children and persons in wheelchairs
- Appropriate provision for soap, towel dispensers, and receptacles for trash, recyclables, and biohazardous waste

Surfaces
- Floors[77]—easily cleanable, durable, glare free, and cushioned in patient care areas
- Walls—easily cleanable and durable; sound-absorbent materials can be used where they can be protected from damage; interior design signaling warmth, comfort, and normality
- Ceilings—washable, highly sound-absorbent acoustical tile wherever feasible

Lighting[20]
- Ambient lighting levels adjustable through a range of 10-600 lux
- No direct ambient lighting in patient care areas
- Light sources with suitable spectrum to permit accurate color rendering[17]
- Procedure lighting capable of providing at least 2000 lux at the bed surface and adjustable in both location and intensity
- Daylighting for adult work areas, with appropriate shading and insulation

Acoustics
- Noise control measures to maintain the combination of background and operation sound below a mean level of 45 dB[52]

Heating, Ventilation, and Air Conditioning
- Ambient temperature of 22°-26° C (72°-78° F)
- Relative humidity of 30%-60%
- Minimum of six air exchanges per hour with appropriate filtering; two changes should be with outside air
- Exhaust vents situated to minimize drafts near patient beds and appropriately sized and constructed to minimize noise from airflow

Family Support
- Adequate and welcoming directional and informational signage and parking space
- Lounge, refreshments, restrooms, showers, storage, Wi-Fi
- Overnight rooms if rooming-in is not possible
- Private, quiet space for consultations/grieving
- Lactation area (if sufficient privacy is not available at the bedside)
- Dedicated area at the bedside for infant care, work, and rest

Staff Support
- Lockers, lounge, restrooms, on-call rooms
- Adequate and comfortable charting/work area at each bedside
- Clerical/work areas away from, but easily accessible to, each bedside
- Office/desk space for all disciplines that routinely provide care

Sustainable Design
- Use of materials that are free of substances known to be teratogenic, mutagenic, carcinogenic, or otherwise harmful to human health
- Designs and materials that reduce consumption of energy, cleaning fluids, and nonrenewable resources[79]

the long care process, countless decisions are made and encounters occur in the complex system of neonatal care. Within this care process, all treatment and care practices, and the physical and psychological environment are important in optimizing the neurobehavioral development of a preterm infant. The goal should be to provide the infant nurturing stimuli and an opportunity to form a healthy attachment relationship with his/her parents. Single-family rooms bring family members together and provide privacy, individuality, a sense of closeness, peacefulness, and protection, which have been shown to benefit all family members.

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TABLE 36.3 Studies on the Impact of Single-Family Room Design in Neonatal Intensive Care Units on the Infant, Parent, and Staff Outcomes

Author; Year of Publication	Design	Population	Outcome	Finding
Örtenstrand et al.; 2010	RCT	<37 weeks' GA; n = 183 in SFR vs. n = 182 controls	LoS, infant outcomes up to discharge, maternal, and infant salivary cortisol levels	SFR: 5.3 days shorter LoS in infants <37 weeks' GA; 10.1 days shorter if <30 weeks' GA, less BPD (1.6% vs. 6.0%); better mother–infant cortisol synchrony
Domanico et al.; 2011	Prepost	Pair matched NICU infants, mean 34 weeks' GA; n = 75 in SFR after 2008 vs. n = 75 controls	Medical progress, growth, breastfeeding, ambient sound, and light measurements	SFR: Earlier enteral feeds; less apnea; no change in growth; more sustained lactation and discharge with maternal breastmilk
Flacking and Dykes; 2013	Ethnography in 4 neonatal units	2 units in Sweden, 2 units in England	Attuned parent–infant relationship and feeding	Parents' feeling of "ownership" of place and space, at-homeness, privacy, and possibility to follow infant's cues improved parent experience and parent–infant attunement
Lester et al.; 2014	Prepost	<30 weeks' GA; n = 252 in SFR in 2010-2012 vs. n = 151 controls in 2008-2009	Infant, parent, and staff outcomes up to discharge	In SFR: Better weight gain; less procedures; earlier full enteral nutrition; less infections; better neurobehavioral performance at discharge; less maternal stress; better work satisfaction
Lester et al.; 2016	Prepost	<30 weeks' GA; n = 93 in SFR in 2010-2012 vs. n = 123 controls in 2008-2009	Bayley III at 18 months	Nonsignificant developmental difference by unit design, but more maternal involvement improved outcomes in both types of NICUs. SFR did not have adverse effects in low maternal involvement group.
Vohr et al.; 2017	Prepost	<1250 g; n = 297 in SFR in 2010-2011 vs. n = 394 controls in 2007-2009	Breastmilk provision and Bayley III at 18-24 months	SFR: Higher cognitive and language scores; higher rates of human milk provision at 1 and 4 weeks; higher human milk volume at 4 weeks
Toivonen et al.; 2017	Prepost observation study	20 nurses observed both in SFR in 2014-2015 vs. in 2013-2014	Nurse–family interaction time per work shift	SFR: Nurse–family interaction time doubled, nurse–parent interaction time tripled; the increase in nurse–infant interaction time was not statistically significant

These data are based on single-family room design that provides space, facilities, and privacy for parents to stay throughout the day and night close to their infant.
LoS, Length of stay; RCT, randomized controlled trial; SFR, single-family room unit; BPD, bronchopulmonary dysplasia.

Key Points

- The neurobehavioral development of a preterm infant is modified by environmental influences from the neonatal intensive care unit.
- The physiologic sensory environment of a preterm infant that would be in utero includes multimodal sensory inputs and intimate interaction with the mother's activities and physiology.
- Parent–preterm infant closeness and interaction can compensate for many environmental elements that would have been present in utero.
- Undisturbed sleep is shown to be important for brain development.
- Single-family rooms protect preterm infants from noxious stimuli and provide more nurturing stimuli. Single-family rooms also support an opportunity to form a healthy parent–infant attachment relationship by bringing family members together and by providing privacy, individuality, closeness, peacefulness, and protection.

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37

Biomedical Engineering Aspects of Neonatal Cardiorespiratory Monitoring

JULIANN M. DI FIORE

Preterm infants are exceptionally unstable in terms of respiratory control due to both immaturity of the central nervous system and susceptibility to disease and infection. As a result, they exhibit a high incidence of apnea, bradycardia, and desaturation events during the first few months of life.[17,55] Respiratory support including supplemental oxygen, continuous positive airway pressure (CPAP), and mechanical ventilation are ubiquitous in the neonatal intensive care unit (NICU) but with a goal of decreasing duration and level of support to minimize the incidence of chronic lung disease.[71] These treatment decisions are most often based on nursing documentation of apnea, heart rate, and desaturation alarms[8] making bedside cardiorespiratory monitoring an integral part of NICU clinical care.

Because of their small stature and fragile skin, extremely low birth weight (ELBW) infants continue to be a challenge in monitor design with a focus on continuous, accurate, artifact-free recordings obtained in a safe and noninvasive manner. More often than not, monitors are developed for adult patients or older children followed by application in newborns with minimal data demonstrating accuracy and safety. Nevertheless, even a well-designed monitor is only as good as the end user. Therefore, a thorough understanding of bedside monitor functionality is also needed to maintain optimal settings to reduce both nuisance alarms and signal distortion of real events. This chapter includes a description of the principles of operation of cardiorespiratory monitoring modalities, including current and future directions of hemodynamic, blood gas, and respiratory waveform acquisition in the NICU setting.

Hemodynamic Monitoring

Electrocardiogram

Principle of Operation

During each heartbeat, an electrical impulse originates in the sinoatrial node, and is propagated among the muscles of the atrium, through the atrioventricular node, followed by dispersion throughout the ventricles. In summary, the heart can be viewed as a dipole, as excited myocardium is negatively charged with respect to the myocardium at rest. The small alterations in voltage generated by the heart can be measured at the body surface with electrodes placed on the chest. The most common type of electrode used in the NICU is the silver-silver chloride, foil-based, recessed, or floating electrode. Each electrode contains a highly conductive electrolyte gel with a composition that varies by manufacturer. Electrode location is important in acquiring a signal of adequate resolution, especially in neonates with a limited surface area.[3] Multiple probe applications should be avoided to optimize adhesiveness of the electrodes and ECG signal integrity and decrease the chance of skin damage, including high transepidermal water losses,[10] in extremely preterm infants with fragile skin.

The ability of the electrodes to detect small electrical changes with each heartbeat requires the application of a current to the chest wall. The recommendations of acceptable current limits by the American Heart Association (AHA) cover two aspects of electrical safety. The first entails the amount of current allowable in a patient-connected lead that can flow through the myocardium without inducing ventricular fibrillation. The second aspect pertains to the allowable chassis leakage current that flows through the patient to ground. The AHA recommends that currents be limited to 10 μA through patient leads and less than 100 μA, with an optimal level of 10 μA for chassis leakage current.

The initial goal of simple heart rate measurements has expanded to include identification of specific arrhythmias and more complex algorithms of heart rate variability. For example, alterations in spectral indices and prolongation of QT interval have been shown to be associated with prematurity[79] and sudden infant death.[26] In addition, longitudinal regression-based models of abnormal heart rate characteristics associated with systemic infection and inflammation have been shown to reduce infant mortality in VLBW

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Abstract

Preterm infants exhibit a high incidence of apnea, bradycardia, and intermittent hypoxemia during early postnatal life. As a result, many preterm infants require respiratory support, including pressure to maintain airway patency and supplemental oxygen to provide adequate gas exchange. With current aggressive weaning protocols, cardiorespiratory monitoring plays a crucial role in documentation of fluctuations in respiration and oxygenation as well as identifying periods of hyperoxemia. Due to the small stature and fragility of very low birth weight infants and accompanying ventilatory instability, the technologies available in the NICU must include noninvasive continuous modes of monitoring heart rate, respiration, and oxygen. This chapter summarizes the strengths and limitations of current modalities used for both acute and longitudinal measures of cardiorespiratory monitoring in the NICU setting.

Keywords

pulse oximetry
transcutaneous monitoring
near-infrared spectroscopy hemodynamic monitoring
blood pressure
end-tidal carbon dioxide
respiratory airflow

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infants.[46] Although sophisticated mathematical analyses have been predominantly limited to the research arena, development of the ability to detect alterations in heart rate variability in an automated fashion may play a role in future clinical care.

Cardiac Output

Principle of Operation

Application of the Fick principle is considered the gold standard of cardiac output monitoring in a research setting. This method states

$$CO = VO_2/(Ca\text{-}Cv)$$

where VO_2 = oxygen consumption, Ca = oxygen concentration of arterial blood, and Cv = oxygen concentration of mixed venous blood. Although the Fick principle may be accurate, especially in low flow states, precision may be limited by air leakage, cardiopulmonary disease, and enhanced pulmonary oxygen consumption.[15]

Noninvasive methods that are validated in neonates include transcutaneous Doppler, transthoracic echocardiography (TTE), and thoracic electrical impedance. Doppler ultrasound uses an ultrasound beam to measure blood flow velocity. A velocity-time waveform is then produced from spectral analysis of Doppler shifts, caused by moving erythrocytes. The stroke distance can be calculated by the area under the velocity-time waveform. If the cross-sectional area of the vessel is known, cardiac output can be calculated by:

$$\text{Cardiac output} = \text{stroke distance} \times \text{cross-sectional area of the vessel} \times \text{heart rate}$$

Doppler-based cardiac output measurements can vary widely and should be limited to trend monitoring.[15]

During TTE, measures of left ventricular output, right ventricular output, or superior vena cava flow can be obtained. Validation data with TTE have been limited to transthoracic left ventricular output measures, which have been shown to be comparable with pulmonary artery thermodilution and O_2-Fich methods.[15] A variation of thoracic electrical impedance, electrical velocimetry, includes surface ECG electrodes placed on the forehead, left side of the neck, left mid-axillary line at the level of xiphoid process, and left thigh. During application of a small alternating electrical current through the thorax, changes in voltage are measured during periods of systole and diastole. Stroke volume (SV) is then determined using the following equation:

$$SV = V_{ept} \times \nu_{LVET} \times LVET$$

where V_{ept} (mL) = volume of electrically participating tissue derived from body mass and height, ν_{LVET} (s^{-1}) I = ohmic equivalent of mean aortic blood velocity during left ventricular ejection, and LVET (s) = left ventricular ejection time. Data have shown electrical velocimetry as a comparable mode of measuring left ventricular output in neonates when compared with echocardiography,[48] although variation among individuals was seen using both techniques.

Blood Pressure

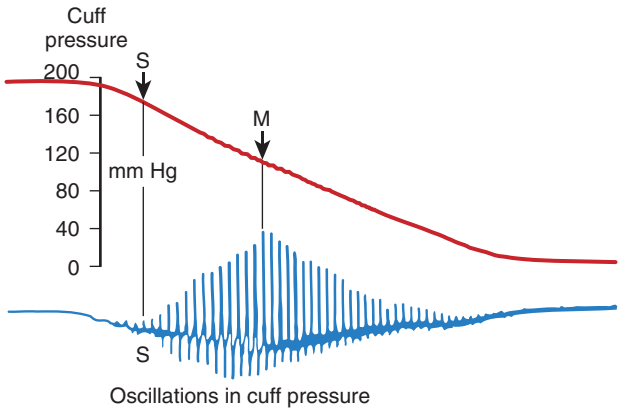
Principle of Operation

Direct continuous readings from an indwelling arterial line are considered the gold standard for blood pressure monitoring in the neonate. Arterial and venous pressures are usually accessed by a catheter placed in the umbilical vessels. The catheter is then attached to a transducer. The transducer works on the principle that fluid exerts a force on the diaphragm. This force can be converted to a change in voltage and calibrated to a given pressure. The dome must be flushed, making sure there are no bubbles in the circuit; the transducer must be placed at the level of the distal tip of the catheter; and a zero pressure should be established before patient data are acquired.

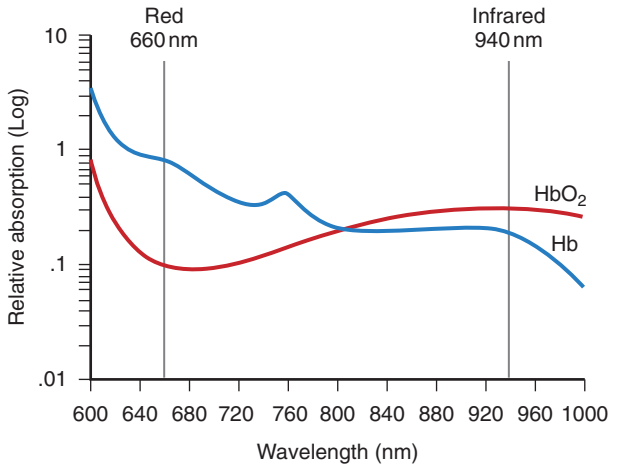
Indirect blood pressure readings can be acquired through a cuff or inflatable bladder placed around the upper arm or calf. The cuff is inflated to a pressure adequate to cause occlusion of the arterial flow. During deflation of the cuff, measurements of diastolic and systolic blood pressure can be obtained. Mean blood pressure is then defined as the integrated area under the arterial pressure waveform.

The size and placement of the cuff can affect accurate measurements of blood pressure. A cuff that is too narrow or applied loosely may result in falsely high readings. The American Heart Association recommends a cuff width of approximately 40% of the limb circumference. The two modes of indirect blood pressure monitoring include the auscultatory and oscillometry methods. The auscultatory method entails rapid inflation of the cuff, followed by slow deflation while listening for distal Korotkoff sounds with a stethoscope. This method, most commonly used in adults, is limited by the inaudible frequency range of arterial sounds in neonates, intra-observer variability, and disturbance to the patient. The oscillometry method is more often used in newborn intensive care units. In this method, cuff pressure is rapidly inflated to above systolic pressure. As the pressure is slowly released, small pulsations can be detected as the cuff approaches systolic pressure. When the cuff pressure decreases to below systolic pressure the oscillations increase in magnitude because of blood flowing into the artery. Ultimately a maximum oscillation point will be reached, corresponding to mean arterial pressure, followed by a decline as the cuff pressure decreases to baseline (Fig. 37.1). In critically ill premature infants, oscillometric blood pressure measurements have been shown to have good agreement with arterial catheter values, although accuracy is greatly diminished in infants with a mean arterial pressure less than or equal to 30 mm Hg.[72] Although the use of a cuff does not allow for continuous monitoring of blood

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• **Fig. 37.1** Blood pressure measurement using the oscillometric method. M, mean pressure; S, systolic pressure. (From Geddes LA. *Cardiovascular devices and their applications.* New York: John Wiley & Sons; 1984. Reprinted by permission of John Wiley & Sons, Inc.)



• **Fig. 37.2** Relative light absorption by hemoglobin (Hb) and oxyhemoglobin (HbO_2).

pressure, many systems have the ability to provide automated transient readings.

Blood Gas Monitoring

Arterial blood gas sample measurements provide the most accurate estimate of arterial oxygen and carbon dioxide status. However, blood gases are limited by painful and time-consuming procedures, inherent risks including infection and vascular events, and intermittent short-term monitoring of PaO_2 and $Paco_2$. Continuous monitoring of oxygenation and carbon dioxide modalities offer an improved alternative by providing noninvasive, easy-to-use, portable, high-resolution, and fast-response options to alert the clinician to rapid decompensations that often occur in this high-risk infant cohort. Ideally, implementation of these devices in the NICU setting would lead to the ultimate goal of ventilation of the neonate—to stabilize respiration and minimize the use of supplemental oxygen and invasive respiratory support.

Oxygenation

The multitude of diseases associated with prematurity frequently necessitates oxygen therapy as a component of clinical care. Even during periods of supplemental oxygen, severity of illness compounded with immature respiratory control quite often leads to respiratory instability presenting as rapid intermittent hypoxemia events.[20] Therefore, blood gas measurements are useful for estimating baseline levels of oxygenation but cannot quantify short desaturation events that commonly occur in this patient population.[17] As a result, intermittent blood gas sampling is often accompanied by noninvasive continuous pulse oximetry or transcutaneous monitoring.

Pulse Oximetry

"One man's noise is another man's signal."

—SEVERINGHAUS

Principle of Operation

The principle of pulse oximetry is based on the Beer-Lambert law, which states that the concentration of an absorbing substance in solution can be determined by the intensity of the light transmitted through the solution.[68] Applying this concept, pulse oximetry relies on the light absorption characteristics of deoxygenated and oxygenated hemoglobin in the red (600-750 nm wavelength) and infrared (850-1000 nm wavelength) light spectrum ranges, respectively (Fig. 37.2). The oximeter probe comprises two LEDs, each emitting light of a specified wavelength (660 and 940 nm) through the capillary bed of the infant's extremity. A photodiode detector on the opposing side of the electrode measures the intensity of the light passing through the extremity at each wavelength, which is equivalent to the amount absorbed by tissue, and venous and arterial blood. Oxygen saturation values can be extrapolated from this measurement by exploiting the relatively small arterial pulsatile changes, also known as the plethysmogram waveform, with each heartbeat. This is accomplished by measuring the ratio of the transmitted light owing to the arterial pulsatile component (pulsatile) to the transmitted light owing to the constant component of the signal (constant); that is, tissue and baseline blood in tissue (Fig. 37.3). This ratio is calculated separately for both the red and infrared waveform signals. The ratio of the red (pulsatile/constant component at 660 nm) to the infrared signal (pulsatile/constant component at 940 nm) can then be converted to a measure of oxygen saturation.

The advantages of pulse oximetry are ease of use, fast response time, and continuous measures of oxygen saturation. The probe requires no heating or calibration by the user and is routinely placed on the palm of the hand or sole of the foot. In sick infants with intravenous lines or heparin locks precluding access to these extremities, the wrist or ankle have been suggested as an adequate alternate site.[51] Rapid response time and continuous measurement capabilities make oximetry the ideal modality for detection of intermittent hypoxemia, especially in preterm infants.[17]

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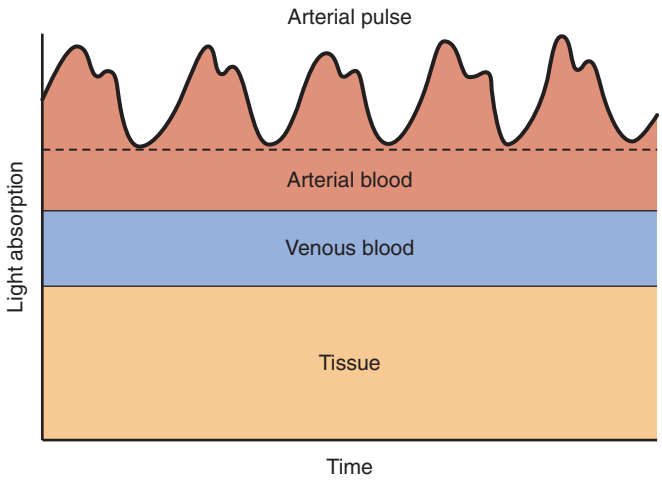
Accuracy of pulse oximetry is dependent on multiple factors, including range of oxygenation, probe position, motion and ambient light interference, low perfusion, skin pigmentation, variations in hemoglobin, and calibration algorithms. Many manufacturers report accuracy of ±2% full scale, but error increases with decreasing SpO_2.[23,60,65] For example, in a study of 1664 preterm infants, overall mean differences between SaO_2 and SpO_2 were −1.84 ± 2.93%, but less than 40% of infants were within 3% of the corresponding SaO_2 when SpO_2 fell below 88%.[60] Improper probe placement and ambient light interference can result in either falsely high or low values of SpO_2.[54,75] Under conditions of excessive ambient light interference, the SpO_2 will trend toward a value of 85%, the SpO_2 value at which the ratio of red to infrared light absorption equals 1, or complete failure to detect SpO_2 with a value of 0%. Direct opposition of the emitter and detector and covering of the extremity can minimize an optical shunt and reduce ambient light interference. Display values of 0% can also occur because of motion artifact, a common occurrence in early model pulse oximeters. Improved filtering algorithms have been shown to minimize loss of signal and accompanying nuisance alarms,[40] the most successful being developed by Masimo Corporation (Irvine, CA).[31,63] The procedure begins with detection of all optical density ratios that correspond to oxygen saturations of 1%-100% and computation of the reference signal for each optical density ratio (Fig. 37.4). The output power of the adaptive noise canceler is measured for each reference signal followed by identification of the appropriate peak in the Discrete Saturation Transformation Algorithm that corresponds to the largest SpO_2 value. The saturation algorithm is independent of recognition of a clean pulse, giving it a distinct advantage over pulse oximetry systems using these criteria as a prerequisite for calculation of arterial oxygen saturation. Additional factors affecting SpO_2 accuracy include dark skin pigmentation and low perfusion (i.e., periods of hypothermia, low cardiac output, or vasoconstriction), which may result in delayed waveform recognition and underestimation of oxygen saturation levels.[54,75]

Differences in SpO_2 values between manufacturers can be attributed to multiple factors. The manufacturer should state whether the instrument is displaying functional or fractional SpO_2[73] where:

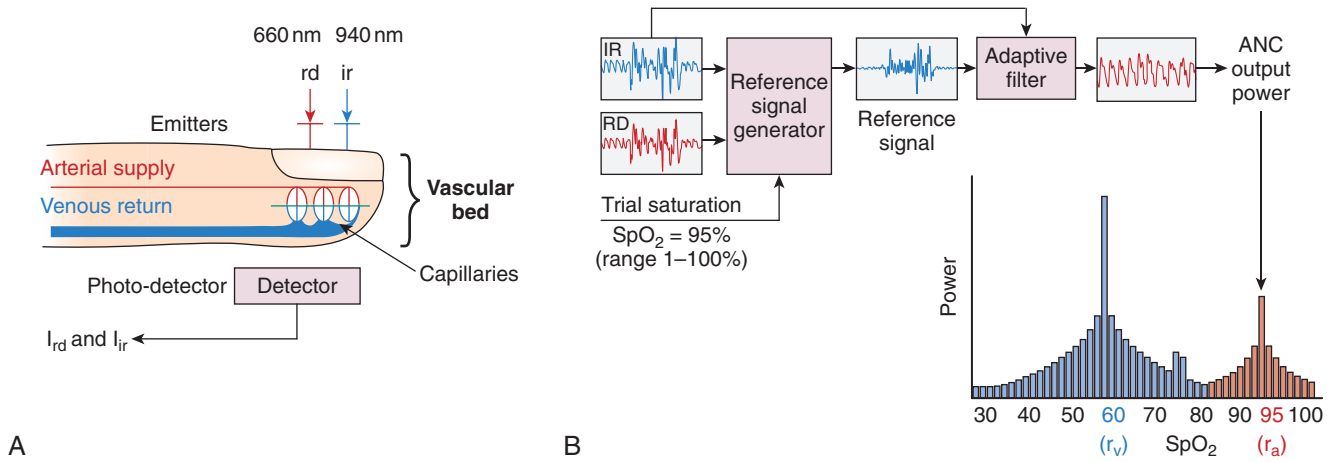
$$\text{Functional } SpO_2 = [HbO_2/HbO_2 + RHb)] \times 100$$

$$\text{Fractional } SpO_2 = [HbO_2/(HbO_2 + RHb + MetHb + COHb)] \times 100$$

These values typically differ by 2%, the value equivalent to the levels of COHb, MetHb, and other dysfunctional hemoglobins in healthy, nonsmoking adults. The type of hemoglobin can also contribute to deviations in both



• **Fig. 37.3** An illustration of the light absorption due to dynamic arterial pulsations and static nonpulsatile absorption in arterial blood, tissue, and venous and capillary blood.



• **Fig. 37.4** **A,** The optical density of red (I_{rd}) and infrared (I_{ir}) light transmitted through the vascular bed of the finger. **B,** The noise cancellation process (discrete saturation transformation algorithm) developed by Masimo Corp. In this example the reference signal, shown in blue, is considered the noise component, and the true physiologic signal is shown in red. ANC, Active noise cancellation; IR, infrared; Ra, arterial; RD, red; Rv, venous. (Courtesy of Masimo Corp., Irvine, CA.)

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displayed value of SpO_2 and clinical interpretation of oxygen content delivery. In the presence of fetal hemoglobin, because of its high affinity to oxygen, a normally clinically acceptable level of SpO_2 may not translate to adequate oxygen delivery to the tissue. This effect is noted by a left shift in the oxygen dissociation curve.[67] Blood transfusions during the first week of life will reduce the proportion of fetal hemoglobin and should be taken into consideration when oxygen therapy is being regulated.[16] Finally, calibration procedures, including motion artifact algorithms, software versions, and mathematical extrapolations at low ranges of SpO_2 can vary by manufacturer and affect the displayed SpO_2 value. Trials randomizing infants to low oxygen saturation to decrease the incidence of retinopathy of prematurity revealed a flawed calibration artifact in the Masimo SET Radical, resulting in an artificial reduction in saturations of 87%-90% and an increase in higher values of oxygen saturation.[37,70] Revised software implemented in 2009 corrected this bias. Encompassing all of the factors that can affect accuracy, it is not surprising that measures of bias, precision,[66] and event detection[31] have been shown to vary widely among manufacturers.

There are three pulse oximeter settings that directly affect patterns of oxygenation and clinical management—alarm threshold, alarm delay, and waveform averaging time. A high alarm setting of 95% for infants receiving supplemental oxygen is generally accepted to avoid excessive oxygen exposure, although standards for ideal oxygen saturation targets,[69,70] and thus corresponding alarm thresholds, do not yet exist. Low alarm thresholds are much less clear and are based on the individual NICU target focusing on avoidance of both sustained and intermittent periods of hypoxemia. Alarm delays currently range from 0-15 sec depending on the manufacturer. Implementation of a long alarm delay can reduce nuisance alarms, but there is wide variation between clinical practices in both their use and availability. Averaging time is probably the most misunderstood parameter on the pulse oximeter display. Conceptually, a longer averaging time will minimize oscillations in the SpO_2 waveform and reduce nuisance alarms by averaging the current data point with previous values within a specified window (2-16 seconds). However, longer averaging times can erroneously under-report the incidence of short events (<10 seconds) and event severity[24] and falsely over-report the occurrence of prolonged desaturation events (>20 seconds),[76] which is concerning as longer intermittent hypoxemia is more likely to be treated with supplemental oxygen. Therefore, in theory, ideal monitor settings should include a short averaging time to accurately detect the incidence and severity of true desaturation events and a long monitor alarm delay, if needed, to minimize nuisance alarms.

Transcutaneous Monitoring of Oxygen

Principle of Operation

Transcutaneous oxygen tension measurements are based on the principle of oxygen diffusion through the skin. The electrode consists of a platinum cathode and silver reference anode encased in an electrolyte solution that is then separated from the skin by a membrane permeable to oxygen. The electrode is heated, which arterializes the blood in the capillaries underneath the skin and breaks down the stratum corneum barrier, allowing diffusion across the skin surface. The oxygen from the skin sensor reacts with the platinum-silver chloride sensor to create an electrical current, which is converted to partial pressure measurements of oxygen.

Agreement between arterial PaO_2 and PO_2 measured at the skin surface is influenced by multiple factors, including decreased solubility of oxygen in blood owing to heating of the skin, oxygen consumption in the heated skin and inside the electrode,[54] air bubbles under the sensor, insecure seal with the skin, and excessive contact gel. The sensor must be placed in a well-perfused area and properly heated before reliable values can be attained, which may take as long as 15 minutes. An electrode temperature of 44.5°C had been initially suggested with increasing underestimation of $tcPO_2$ as the temperature decreases from 45.0°-43.0°C.[41] However, subsequent studies have used lower temperatures of 44.0[22] and 43.0°C[53] to reduce the risk of burns. Sensor location must be altered intermittently to correct for transient electrode drift and avoid heat-related skin complications. Increased sensitivity has occurred with a time interval of 3-5 hours between sensor relocations in preterm infants during hospitalization[6]; however, even shorter durations of 2 hours have been associated with hyperpigmented macules and prolonged erythema in preterm infants with fragile skin.[27] Longer time intervals of 6-8 hours between site changes in older term and former preterm infants (median age 2.6 months) during home monitoring may put infants at risk for mild skin irritation resulting in slight redness that usually resolves in less than 48 hours.[53] Multiple studies have shown a linear relationship between $PtcO_2$ and PaO_2,[22] but accuracy may differ at low and high levels of PaO_2.[22] Although there are no standard thresholds for pathologically high and low levels of oxygen, Poets et al. showed sensitivities between studies ranging from 68%-100% for hypoxemia (<50 mm Hg) and 71%-92% for hyperoxemia (>80 mm Hg).[54] Given this wide variability in sensitivity, $tcPO_2$ should be used in conjunction with intermittent blood gas sampling to confirm levels of oxygenation and minimize unnecessary supplemental oxygen exposure.

Although $tcPO_2$ monitoring offers the advantage of continuous oxygenation monitoring, it is limited by a slow response time and a reduced period in which reliable data can be acquired. In contrast to pulse oximetry, which can detect immediate arterial changes at the sensor site, $tcPO_2$ monitoring must account for the time needed for oxygen to diffuse through the capillaries and across the sensor membrane.[22] This delay can range from 16-30 seconds.[53] During probe placement, oxygen saturation measurements can be immediately acquired after detection of an adequate plethysmograph waveform with no need for relocation of the probe. In contrast, a delay of approximately 15 minutes

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needed to heat the transcutaneous probe compounded with multiple site location changes to reduce the risk of burns can lead to a large percentage of the monitoring period without measurements of oxygenation. Given these limitations, pulse oximetry is considered the most widely accepted modality for continuous measures of oxygenation in the neonatal intensive care setting.

Near-Infrared Spectroscopy

"We had discovered the possible existence of an optical window into the body…"

—JOBSIS-VANDERVLIET

Principle of Operation

In contrast to pulse oximetry, which measures arterial oxygenation, near-infrared spectroscopy (NIRS) measures oxygen uptake in the tissue. This technology has been used in a variety of organ systems, with a particular interest in cerebral oxygenation in the preterm infant population. Near-infrared spectroscopy relies on the presence of chromophores, compounds whose absorption of NIR light is dependent on oxygen status, in the tissue. These chromophores include cytochrome aa_3, myoglobin, and the most often studied, hemoglobin. Using light absorption properties of oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb) in the infrared range (700-1300 nm),[36] near-infrared spectroscopy measures the difference between the oxygen delivered and the oxygen extracted by the tissue. This measurement is also known as regional oxygen saturation (rSO_2) where:

$$rSO_2 = HbO_2/(HbO_2 + HHb)$$

The basic concept of NIRS entails a probe placed on one temple of the infant's head with a laser or light-emitting diode (LED) probe as a source of NIR wavelength transmission. The lasers/LEDs are pulsed in sequential order where multiple photodetectors, attached to the opposite temple, collect the transmitted light photons that are not absorbed in the tissue. An additional reference signal is used to correct for light reflected from the skin, laser drift, and skin coloration. By measuring the difference between the amount of light transmitted through the deep tissue and the surface path, NIRS values can estimate the amount of spectral absorption that occurs in the tissue bed. Spatial resolution is currently limited to approximately 1 cm^2 with several layers of tissue, including skin, skull surface vasculature, and gray matter in one two-dimensional sample. The current primary target area is restricted to the surface of the cortex, because access to deeper brain structures would require lasers of increased intensity and risk of damage to brain tissue.[2] Near-infrared spectroscopy values have been shown to correlate with cerebral venous saturation[77] with improved precision with increased tissue homogeneity.[1] However, overall comparability and reproducibility of different NIRS devices remains poor.[52] This may be because of manufacturer-specific variations in design that include the source of monochromatic light, the number and specific wavelengths used, the frequency of light cycling, and the frequency at which the signals are updated for digital display. Modifications in sensor geometry[35] and adjustments for the variability in arterial blood pressure[29] may have promise in improving precision.

Interpretation of absolute measurements of rSO_2 is still the subject of ongoing research. Average cerebral oxygen saturation values of 77.9% ± 8.5% have been recorded in healthy term newborns,[5] but levels have been shown to be dependent on both gestational and postnatal age.[38] Although normative data are lacking in normal healthy preterm infants, a close correlation has been shown between cerebral oxygenation, as measured by NIRS, and oxygen saturation via pulse oximetry.[7] This correlation is reduced in preterm infants with respiratory disease. There has been some suggestion that alterations in neonatal cerebral oxygenation may be associated with clinical outcomes such as intraventricular hemorrhage, cognitive impairment, and mortality, while others have shown no relationship with any clinical characteristics.[38] Therefore, the role of NIRS in identifying etiologies of brain injury has yet to be determined, and more extensive research is needed before NIRS can be routinely used in the clinical neonatal setting.

Carbon Dioxide

The presence of hypocarbia or hypercarbia has been implicated with a wide range of neonatal morbidities, including chronic lung disease, intraventricular hemorrhage, and neurodevelopmental impairment.[21,44,49] For this reason, maintenance of normocarbia and avoidance of extreme levels of arterial CO_2 is imperative in preterm infants. During periods of respiratory instability in which extreme oscillations in $PaCO_2$ can occur, arterial or indwelling catheters are not adequate. Under these conditions, continuous measurements of end-tidal or transcutaneous CO_2 monitoring have become increasingly popular in the intensive care unit.

End-Tidal Carbon Dioxide Monitoring

Principle of Operation

End-tidal CO_2 monitoring originally used mass spectroscopy to estimate CO_2 from samples of exhaled gas. Because of improvements in technology allowing for portable devices, infrared spectroscopy is now the method of choice. Infrared spectroscopy is based on the principle that CO_2 molecules absorb light in the infrared wavelength of 4.26 μm. Light is transmitted through the sample using an infrared emitter with light absorption measured with photodetectors. The amount of light absorbed in the given IR spectrum is then proportional to the concentration of CO_2.

Capnography sensor designs fall into two categories: sidestream and mainstream. *Sidestream systems* require constant aspiration of expired gas, which may result in underestimation of CO_2 readings in preterm infants with low tidal volumes. This incidence may be reduced with

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the development of microstream technology, which uses a refined spectrum of discrete wavelengths, allowing for extremely small sample cells (15 μL) and a correspondingly lower sample rate of 50 mL/min.[14] The advantage of the sidestream system is it can be used on both spontaneously breathing and intubated patients. During intubation, sampling of gas at the distal end of the endotracheal tube is recommended to improve accuracy, although both proximal and distal measurements of $PetCO_2$ have been shown to provide acceptable estimates of $PaCO_2$ in healthy infants.[33] Accuracy may be affected by water vapor or secretions occluding the adapter or condensation on the photo detector. This is eliminated by vertical positioning or the use of Nafion tubing, a semipermeable polymer that allows water to pass through and evaporate. *Mainstream systems* rely on gas passing through a wide chamber, or cuvette, placed in-line with the patient circuit. As opposed to a remote device with sidestream systems, a miniature IR optical system is placed directly over the chamber. This allows for an instantaneous measurement of less than 500 msec. However, it is limited to intubated patients or patients with a closed circuit, that is, a sealed nasal/oral mask. Erroneous values caused by water condensation are reduced by slight heating of the cuvette. Additional factors that can contribute to measurement error for both sidestream and mainstream systems include temperature dependence, miscalibration, drift, noise, and pressure effects from the sampling system.[56]

In addition to instrumental design, the accuracy of end-tidal CO_2 monitoring is dependent on patient characteristics. $PetCO_2$ has been shown to accurately estimate alveolar CO_2 in healthy newborns,[28] but the agreement is poor and negatively influenced by the presence and severity of pulmonary disease[74] and inadequate gas exchange caused by atelectasis. Neonates have small tidal volumes and high respiratory rates, which often result in wide variations in end-tidal CO_2 values and underestimation of true alveolar gas, making it a prohibitive modality for estimating CO_2 during high-frequency oscillatory ventilation. Despite a poor correlation in ventilated preterm infants and its lower precision compared with transcutaneous monitoring,[61] its ability to detect extreme low and high CO_2 levels[42] may be of use for trending or screening patients for abnormal arterial CO_2 values.

Disposable colorimetric end-tidal CO_2 detectors are an efficient method of verifying correct endotracheal tube placement.[78] When placed between the ventilator and endotracheal tube, the pH-sensitive chemical indicator (metacresol purple) changes from purple to yellow when exposed to expired CO_2. The minimum and maximum CO_2 concentrations needed to establish a color change are 0.54% (0.5 kPa) and 2%-5% (2-5 kPa), respectively. Because neonatal extubation failure can have devastating consequences, calorimetric detectors can play a significant role in the intensive care unit. However, this device cannot detect hypocarbia, hypercarbia, right main-stem bronchus intubation, or oropharyngeal placement in spontaneous breathing patients.[45]

Transcutaneous Monitoring of Carbon Dioxide

"The fluids are invited by the warmth to the surface, and the functions of the skin are encouraged."

—ABERNATHY, 1793

Principle of Operation

Transcutaneous carbon dioxide tension measurements are based on the principle of CO_2 diffusion through the skin. The sensor consists of a pH-sensitive glass electrode with an adjacent silver chloride reference anode covered by a hydrophobic membrane permeable to carbon dioxide and separated by a sodium bicarbonate electrolyte solution. Changes in pH are measured as carbon dioxide from the skin diffuses through the electrode membrane. These changes are then converted to corresponding PCO_2 values. Preliminary data showed a linear correlation between $tcPCO_2$ and $PaCO_2$ with unheated electrodes. This was followed by a heated (44°C) electrode design that improved both the correlation between $PaCO_2$ and $tcPCO_2$[30] and the response time.

Data assessing the relationship between $PaCO_2$ and $tcPCO_2$ in infants have shown a wide variation in both slope and intercept values. These discrepancies were attributed to electrode calibration procedures and variations in electrode temperature that ranged from 42°C-44°C.[32] Additional data by Martin et al. demonstrated a progressive increase in the difference between $tcPCO_2$ and $PaCO_2$ as $PaCO_2$ increased ($tcPCO_2 - PaCO_2$, 5 ± 4 mm Hg and 9 ± 6 mm Hg in normocapnia and hypercapnia respectively).[43] These data suggest that as $PaCO_2$ increases, there may be an imbalance between CO_2 production and removal. It should also be noted that in contrast to $tcPO_2$, which underestimates PaO_2 in infants with chronic lung disease, $tcPCO_2$ has been shown to overestimate $PaCO_2$ under similar conditions.[59] This can be attributed to multiple factors, including metabolic events in the skin, circulatory disturbances that permit gas to accumulate in the tissues, the anaerobic heating coefficient of blood, and increased CO_2 tension with higher electrode temperature.

The determination of $tcPCO_2$ or end-tidal CO_2 monitoring should include the discussion of the risk/benefit ratio for each patient. The use of heated $tcPCO_2$ electrodes entails a risk of skin damage caused by burns that can be avoided by repeated repositioning of the sensor. This can be a serious limitation when considering low birth weight infants with fragile skin. In contrast, transcutaneous CO_2 detectors have been shown to be accurate during high-frequency oscillatory ventilation.[4] This alternative mode of noninvasive CO_2 monitoring may be a reasonable screening tool for preterm infants with small tidal volumes and during periods of rapid breathing where end-tidal CO_2 may underestimate $PaCO_2$. Regardless of the modality chosen, clinical care should include comparisons with blood gas values, especially during periods of relative hypercapnia.

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Respiratory Monitoring

"I've got to keep breathing. It'll be my worst business mistake if I don't."

—STEVE MARTIN

Respiratory instability in the preterm infant can be attributed to immaturity of the central nervous system and a highly compliant chest wall, resulting in both central and obstructive apnea. During normal respiration, the diaphragm contracts, expanding the thorax in conjunction with activation of accessory muscles that stabilize the rib cage and maintain upper airway patency. Because of the highly compliant chest wall of the preterm infant, any loss of accessory muscle tone, including intercostals stabilizing the rib cage or hypoglossus maintaining upper airway patency, may result in instability and retraction of the rib cage in response to negative pressure generated by the diaphragm during inspiration. As a result, asynchronous or paradoxic chest wall movements will occur with partial airway obstruction, which is a common respiratory pattern in the preterm infant, particularly during rapid eye movement sleep. During extreme occasions, total airway obstruction may occur, presenting as asynchronous chest wall and abdominal efforts and no corresponding airflow. Respiratory pauses may also arise because of decreased central respiratory drive, as can occur during periods of periodic breathing and spontaneous central apnea. Therefore, ideal respiratory monitoring should have the ability to detect both central and obstructive apnea.

Flow Sensors

Principle of Operation

The pneumotachometer is considered the gold standard for measuring flow and volume and is most often used during mechanical ventilation and calculations of respiratory mechanics. There are two types of pneumotachometers, *fixed orifice* and *laminar flow*. The fixed orifice design consists of a fixed orifice placed within the tubular attachment placed in the airway. The differential pressure is measured across the fixed orifice, which is proportional to the square of the flow rate. This mathematical relationship can then be used to calculate a given flow. The laminar flow design consists of a simple compartment containing a resistive element, usually consisting of a mesh screen or capillary network. The pressure drop across the resistive element is linearly related to the flow passing through the compartment and can be calibrated accordingly. The range in which there is a linear relationship between pressure and flow will be dependent on the design of the device, including the length, width, and type of resistive element used. To maintain precision, all flow must pass through the device, which may be problematic during mechanical ventilation in preterm infants with a high occurrence of endotracheal tube leaks. During spontaneous respiration, the pneumotachometer must be incorporated into a nasal/oral mask. To minimize the effect of the mask on the respiratory pattern, the mask design should include minimal dead space, the ability to flush the mask to reduce CO_2 retention, and low resistance to minimize work of breathing.

Pneumotachometer use in the clinical setting has been limited to pulmonary function measurements in spontaneously breathing patients, incorporated into a sealed nasal/oral mask, or tidal volume measurements when attached to the endotracheal tube in mechanically ventilated patients. During these periods, the device may add a significant resistive load, especially in severely ill ELBW infants. As a result, many companies have replaced the pneumotachometer with the hot-wire anemometer for volume measurements during mechanical ventilation. The hot-wire anemometer includes a heated element placed in the airway circuit. As flow passes, the sensor is cooled. The system delivers an electrical current to maintain the default sensor temperature. The amount of current needed to maintain the sensor temperature can be calibrated to a given flow. If bidirectional flow is desired, a second wire can be placed in the system. Accurate measurements of flow may be compromised if secretions accumulate on the heated element. However, because of its high-frequency response, proven accuracy, and minimal resistive load, hot-wire anemometer is a promising modality for measurements of respiration in the preterm infant, including periods of high-frequency oscillatory ventilation.[64]

Although the pneumotachometer and hot-wire anemometer give quantifiable measurements of flow and volume, additional devices such as thermistor/thermocouple sensors and end-tidal CO_2 can display qualitative estimates. The relationship between peak-to-peak amplitude of the thermistor signal and actual measures of flow has been shown to be nonlinear and frequency dependent.[25] There is also minimal correlation between $PetCO_2$ and actual measures of volume. Therefore the implementation of thermistor or $PetCO_2$ monitoring is limited to the sleep lab, where, used in conjunction with chest wall motion sensors, it can be used to identify the presence or absence of flow associated with central and obstructive apnea.

Chest Wall Motion Sensors

Principle of Operation

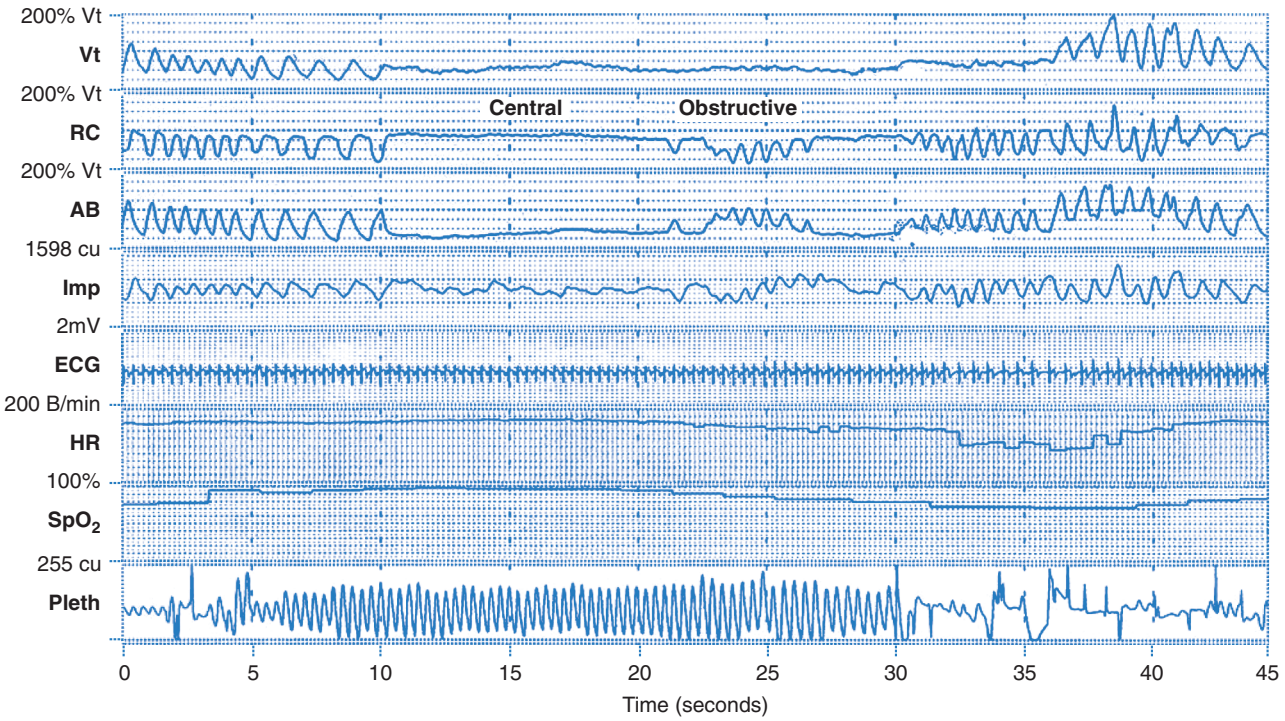
Impedance technology is the most widely used modality for measuring respiration in the hospital setting. With two electrodes placed on either side of the chest above and below the insertion of the diaphragm, impedance monitoring measures changes in electrical impedance across the thorax that occur during a breath. Specific placement of electrodes for optimal signal quality can vary between infants. This modality is based on the principle that air has a much higher level of impedance when compared with tissue. During inspiration, there is a decrease in conductivity (and corresponding increase in impedance), owing to both an increase

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in gas volume of the chest in relation to the fluid volume and increased length of the conductance path with chest wall expansion. Using a high-frequency current of greater than 25 kHz, the same electrodes used for measuring ECG can be used for detection of respiratory efforts. The ECG waveform is filtered out by manufacturer-based signal processing algorithms, thus eliminating this potential source of noise artifact. However, changes in thoracic blood volume may be falsely identified as a breath. In addition, as air moves from one compartment to the other during periods of obstruction, impedance monitoring cannot distinguish obstructive efforts from normal respiration (Fig. 37.5).

Respiratory inductance plethysmography (RIP) has been used extensively in both clinical research and pulmonary function lab settings. It is currently not used at the bedside but could be a promising alternative choice for respiratory monitoring. As with impedance, it is a noninvasive method of measuring respiration with two bands wrapped around the chest wall and abdominal areas. Each band contains a sinusoidal inductance coil with a small AC current that travels through the coil, as opposed to through the chest wall, as occurs with impedance. Respiratory inductance plethysmography relies on the principle that a current applied through a loop of wire generates a magnetic field (Faraday's law) and that a change in the area enclosed by the loop generates an opposing current directly proportional to the change in area (Lenz's law). Thus, as the chest wall expands, the coil in the band elongates, altering the magnetic properties, or inductance, of the band. The strength of this modality is the presentation of respiration as a two-dimensional model. Thus, obstructive apnea will present as asynchronous, 180-degree out-of-phase movements between the rib cage and abdomen as air flows from one compartment to the other. With the addition of a software algorithm to calibrate the rib cage and abdominal waveforms, a semiquantitative volume waveform can be acquired,[62] giving RIP the ability to identify obstructive apnea without the need for an oral/nasal flow sensor (see Fig. 37.5).

Respiratory inductance monitoring has been used extensively in infant-related research protocols, including the multicenter collaborative home infant monitoring (CHIME) study.[58] Given that RIP technology uses rib cage and abdominal excursions to measure ventilation, studies have examined the effect of body position and chest wall asynchrony on RIP accuracy. Brooks et al. found good overall agreement between RIP and tidal volume measurements via pneumotachograph in preterm infants that was not significantly affected by body position, chest wall asynchrony, or



• **Fig. 37.5** An example of an apnea with both central and obstructive components as detected by impedance and respiratory inductance plethysmography (RIP) technologies. Both modalities have the capability of identifying a central respiratory pause as noted by minimal baseline activity on the impedance channel (*Imp*) and RIP channels (*AB*, abdomen; *RC*, rib cage; *Vt*, semiquantitative volume). During periods of complete airway obstruction, Imp presents a respiratory oscillation, thereby missing the event. In contrast, RIP-based channels reveal a flat baseline on the Vt channel in conjunction with asynchronous chest wall motion on the RC and AB channels. (From Neuman MR, et al. Cardiopulmonary monitoring at home: the CHIME monitor. *Physiol Meas.* 2001;22:267-286. http://www.ncbi.nlm.nih.gov/pubmed/11411239. Accessed August 29, 2013. © IOP Publishing 2013, Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing on behalf of IPEM. All rights reserved.)

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respiratory rate.[9] However, RIP is a semiquantitative estimate of tidal volume and can vary with pneumotachograph values on a breath-by-breath basis. Even with this limitation, RIP technology has the advantage over impedance in its ability to distinguish central from obstructive apnea but has yet to make its way into clinical bedside monitoring.

Future Directions

The need for advanced diagnostic systems, including cardiorespiratory monitors, in neonatal care continues to expand. This growth should incorporate the development of safe and effective devices for use in the NICU and a collaborative research and testing effort among the biomedical engineering disciplines.[57] Areas in which improvements are needed include the development of "smart alarms" for cardiorespiratory monitoring, education of personnel pertaining to the use of equipment, automated signal quality assessment, and electronic storage of longitudinal waveforms. The implementation of more sophisticated algorithms should be countered by a less complex user interface.

As physicians continue to be bombarded with physiologic data from bedside monitors, current clinical practice uses only a fraction of the information available for patient care. Pulse oximetry waveform extrapolation is limited to simple values of baseline oxygen saturation and time in various target ranges. Future exploitation of this waveform alone may include identification of subtle pathologic SpO_2 waveform patterns[19] and the use of automated feedback controllers[13] to avoid high-risk patterns of oxygenation and improve time in any given oxygen saturation target range. Implementation of electronic servers for storage of continuous cardiorespiratory waveforms and application of sophisticated mathematical algorithms (e.g., stochastic modeling, spectral and wavelet analysis) to longitudinal datasets to identify early patterns of cardiorespiratory instability[11,50] associated with morbidity[12,18,47] is currently limited to research protocols. The major challenge for development and application of high-risk predictive models to the clinical setting requires large-scale centralized and automated storage of waveforms and development of integrated systems incorporating multiple physiologic parameters from electronic patient database records while protecting patient confidentiality. Current trials are attempting to meet this challenge by reducing this vast amount of data into a comprehensible parameter that is useful for clinical practice.

Key Points

- Continuous cardiorespiratory monitoring plays a crucial role in stabilizing oxygenation and ventilation in preterm infants.
- NICU protocols of oxygen and carbon dioxide monitoring must include a practical balance between accuracy and noninvasive acquisition.
- Alteration of monitor settings can affect patterns of oxygenation, including artifact and signal distortion of real events.
- Current clinical practice uses only a fraction of the information available from bedside monitors for patient care.

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38

Diagnostic Imaging of the Neonate

SHEILA C. BERLIN

Introduction

Diagnostic imaging is integral to the evaluation of neonates with medical and surgical conditions. Understanding the advantages and shortcomings of available imaging modalities as well as the most recent practice patterns facilitates selection of appropriate imaging. This chapter begins with a brief introduction to the benefits and potential hazards of relevant imaging modalities; the remainder of the chapter reviews the imaging approach to common neonatal disease according to organ system. This discussion highlights normal anatomy and the spectrum of imaging appearances of common neonatal pathology.

Radiography, Fluoroscopy, and Computed Tomography

Because a large number of radiographs may be performed in critically ill neonates, attention has been drawn to the potential cancer risk from cumulative doses of ionizing radiation in medical imaging. The radiation dose of a portable chest radiograph is approximately 0.02 mSv; this is a very small fraction of the 3 mSv of annual natural background radiation to which the average individual is exposed. Commonly performed fluoroscopy procedures in the newborn, such as an upper gastrointestinal series, contrast enema, or voiding cystourethrogram, can be performed at doses between 0.5 and 2.0 mSv in infants. Although performed far less frequently, computed tomography (CT) is also performed at low radiation doses; most head and body CT scans can be performed at a dose less than 2 mSv. Current literature indicates that the risk of a future cancer from low dose radiation (below 100 mSv for serial exams) is "too low to be detectable and likely nonexistent."[1] In the absence of data confirming a causal relationship between low dose radiation from medical imaging and cancer, parents and providers should be reassured that the benefits of a medically necessary exam far exceed any potential future cancer risk.[25] Even so, current recommendations endorse performing only medically necessary exams and limiting radiation exposure to doses that are "as low as reasonably achievable."[30] Such steps include using patient size–based tube current and tube voltage, attention to patient positioning, artifact removal, and beam collimation.

Infants requiring a CT scan of the brain or body are typically scanned without sedation, because scan times are usually less than 5-10 seconds. Iodine-based intravenous contrast may be administered to evaluate for cardiovascular abnormalities, neoplasm, or infectious disease. In the absence of known renal failure, neonates show no increased risk for renal toxicity after receiving iodinated intravenous contrast material.[9] A distinct disadvantage of CT imaging is the lack of portability. Because CT equipment requires room shielding, a relatively large footprint, and is highly sensitive to small fluctuations in temperature and humidity, patients must travel to the radiology department's CT suite for imaging.

Ultrasound

Following radiography, sonography is the most common imaging examination performed in the neonate. Ultrasound is particularly suitable for newborns because of its low cost, accessibility, portability, lack of ionizing radiation, and absence of known health risks. There is no need for patient sedation, and technologists can easily capture both static and cine images that include characterization of flow dynamics with color and spectral Doppler. High-quality sonographic images are dependent upon the skill of the technologist in identifying optimal sonographic windows and in the appropriate selection of ultrasound probes of varying frequencies. Because sound waves travel poorly through air and calcified bone, sonographic evaluation of anatomy can be limited if obscured by gas-filled bowel, aerated lung, and overlying bones. Another disadvantage of ultrasound is the relatively low spatial resolution relative to CT and MRI.

MRI

While ultrasound remains the screening modality of choice in the prenatal period, magnetic resonance (MR) imaging has become a valuable adjunct to identify at-risk infants who may benefit from in utero intervention as well as to prepare for optimal perinatal management. In the postnatal period, MR imaging can provide vital detailed information that ultrasound and CT cannot—particularly in the diagnosis of traumatic or anoxic brain injury and congenital anomalies. Gadolinium-based intravenous contrast may be used without risk of renal toxicity in infants without known renal

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Abstract

Diagnostic imaging is integral to the evaluation of neonates with medical and surgical conditions. Understanding the advantages and shortcomings of available imaging modalities as well as the most recent practice patterns facilitates selection of appropriate imaging. This chapter begins with a brief introduction to the benefits and potential hazards of relevant imaging modalities; the remainder of the chapter reviews the imaging approach to common neonatal disease according to organ system. This discussion highlights normal anatomy and the spectrum of imaging appearances of common neonatal pathology.

Keywords

neonatal imaging
radiography
ultrasound
computed tomography
magnetic resonance imaging
nuclear scintigraphy
radiation dose

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failure.[9] Despite scan times that may exceed 30 minutes, the majority of infants under three months of age can be scanned without sedation using the "feed and swaddle" technique.[27] The most significant barrier to MR use is the need to travel to the radiology department MR suite, frequently not in close proximity to the NICU. New dedicated infant-sized MR scanners designed to be housed in the NICU may offer a solution to the risks of transport and minimize the disruption of care for critically ill neonates.[28]

Scintigraphy

Nuclear medicine contributes to the care of newborns with congenital anomalies, infection, and neoplasm. The radiopharmaceuticals used are nonallergenic and show no toxic effects. The radiation dose for most exams is between 0.6 mSv and 5.5 mSv, in the range of CT imaging. Although most studies require that the patient remain still for a relatively long period of time, most neonates can be imaged without sedation. As with CT and US, these exams require patient transport to the nuclear medicine suite of the radiology department.

Chest

Respiratory distress is the most common indication for imaging in the newborn. The chest radiograph (CXR) plays an important role in the assessment of cardiopulmonary pathology in the neonate and young infant and is usually the initial examination of choice.

Portable chest radiographs are obtained in the anteroposterior (AP) view with the infant lying supine. The arms should be extended away from the body or above the head, and the thighs should be immobilized. With proper positioning, the radiograph should demonstrate symmetry of the clavicles and ribs and a midline appearance of the superior mediastinum. It is important to ensure proper patient positioning because a rotation-distorted image may obscure or mimic cardiac and pulmonary pathology. Further, leads and electrodes may also compromise image quality by obscuring regions of critical importance such as tube and line placement or small air leaks.

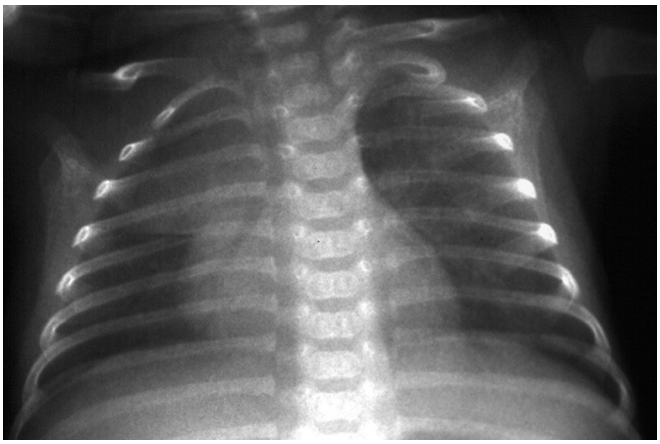
Additional imaging modalities can be used to evaluate specific neonatal chest abnormalities. Sonography is useful in the assessment of diaphragmatic motion, pleural fluid, and catheter complications. Cross-sectional imaging with CT or MRI is useful for surgical and medical treatment planning of more complex thoracic conditions. Specifically, CT is the study of choice to evaluate parenchymal and mediastinal lesions. Both CT and MR are useful in the evaluation of complex congenital heart conditions.

Evaluating a Normal Chest

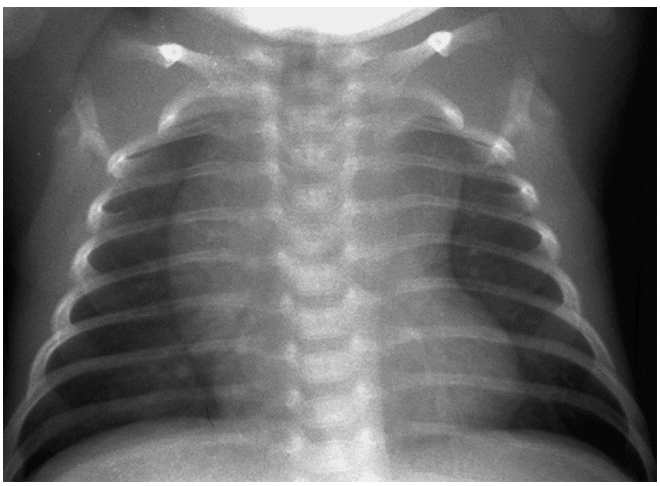
Familiarity with the normal appearance of the newborn chest radiograph improves recognition of pathologic changes. Normal lungs appear primarily radiolucent and symmetric in volume. The pulmonary vessels are seen as branching, linear shadows that taper in size as they extend from the hilum to the lung periphery. Normal vessels decrease in size and number in the lateral half of the lung and are not visualized in the lung periphery. Normally collapsed, the pleural space is visualized only when it is distended from fluid, air, or pleural thickening. The heart borders should be distinct and the diaphragm should be outlined clearly against aerated lung. The normal cardiac diameter on an AP radiograph should be less than 60% of the thoracic diameter. The normal thymus is visible in most newborns. Extremely variable in size and shape, it is composed of two asymmetric lobes and may therefore have an asymmetric appearance in chest radiography (Fig. 38.1). The "wavy" undulations of the lateral borders often silhouette a portion of the heart and can give the appearance of the cardiomegaly (Fig. 38.2).

Catheters, Tubes, and Lines

The positions of the endotracheal tube, enteric tube, and the various arterial and venous catheters should be evaluated



• **Fig. 38.1** Normal thymus. Anteroposterior chest radiograph demonstrates an asymmetrically enlarged right lobe of the thymus.



• **Fig. 38.2** Normal thymus. Anteroposterior chest radiograph demonstrates a symmetrically enlarged thymus resulting in a widened mediastinum.

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on all neonatal radiographs, as malpositioning may lead to complications. The endotracheal tube tip should overlie in the trachea between the medial ends of the clavicles and the carina. Intubation of the right mainstem bronchus is the most common site of tube malposition. The enteric tube should terminate in the stomach body, beyond the gastroesophageal junction.

Umbilical catheters can be easily identified by their characteristic paths. The umbilical venous catheter (UVC) courses superiorly and gradually posteriorly within the umbilical vein to intersect the left portal vein, continuing through the ductus venosus, left or middle hepatic vein, and then into the inferior vena cava (IVC). Its tip should be directed superiorly, ending at the right atrial/inferior vena cava (RA/IVC) junction. Malposition of the UVC within the liver is the most common complication and may result in portal vein thrombosis or portal hypertension. The umbilical arterial catheter (UAC) first extends inferiorly and posteriorly to the junction of the umbilical artery and internal iliac artery. The catheter then turns superiorly to course through the common iliac artery and aorta. The tip of the UAC should also be directed superiorly, lying below the ductus arteriosus and above or below the visceral arteries. The UAC, therefore, may be placed in a high position, ending between T6 and T10, or in a low position ending between L3 and L5. Malposition of the UAC may result in thrombosis of the aortic branches and possible ischemic injury.

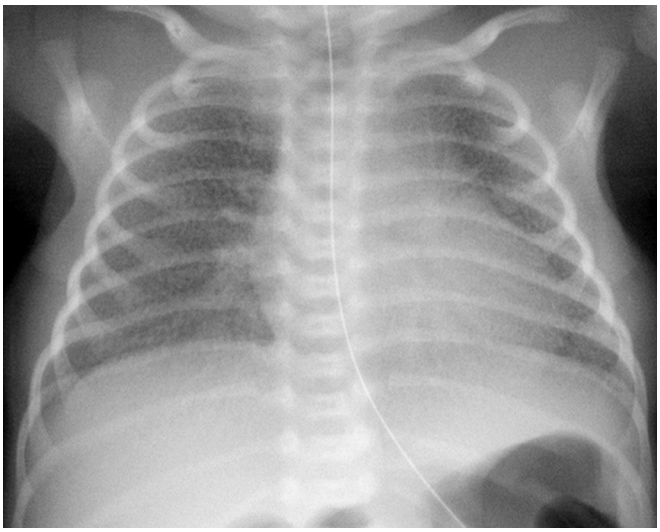
The position of percutaneously placed catheters, including peripheral inserted central venous catheters (PICC lines) and extracorporeal membrane oxygenation (ECMO) catheters, must also be documented. The tip of an upper extremity PICC line should lie within the superior vena cava (SVC) or at the RA/SVC junction. A lower extremity PICC line should end between the 9th and 12th ribs. Extracorporeal membrane oxygenation therapy is reserved for neonates with severe, reversible respiratory failure not responding to conventional treatment and may use a venous and an arterial catheter or a dual lumen venous catheter. The venous catheter is inserted through the right internal jugular vein and ends in the RA. The arterial catheter is inserted into the common carotid artery and ends near the origin of the innominate artery. Complications of all vascular catheters include malposition, thrombosis, perforation, or infection.

Respiratory Disease: Medically Treated

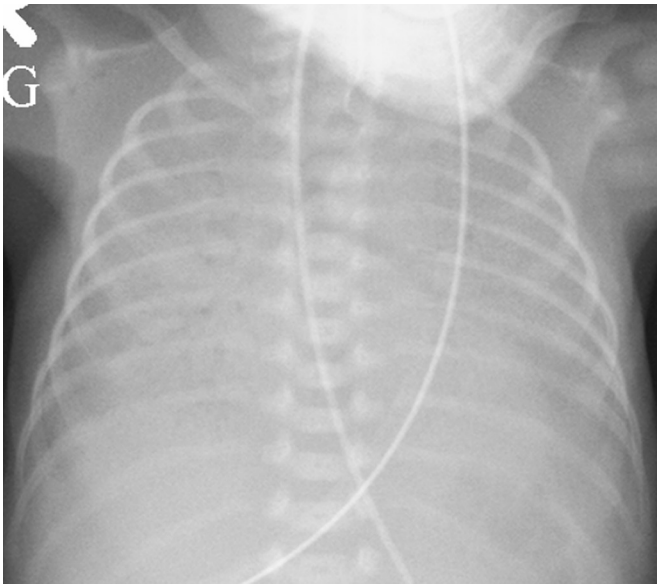
Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) from surfactant deficiency is the most common cause of respiratory distress and a leading cause of morbidity in the premature infant. The prematurity of type II pneumocytes results in an inadequate production of surfactant. This triggers a cascade of responses leading to decreased alveolar distensibility, capillary leak edema, noncompliant lungs, and respiratory distress.

The typical radiographic appearance of RDS reflects generalized alveolar collapse and shows a finely granular or ground-glass pattern with diminished lung volumes. The severity of radiographic disease is variable and usually correlates with the severity of clinical disease. Mild radiographic disease is characterized by a finely granular pattern that allows visualization of normal vessels (Fig. 38.3), whereas severe disease results in loss of defined heart borders and diaphragm (Fig. 38.4). Peripheral air bronchograms may be seen with severe disease because of air in the bronchi being visualized against a background of alveolar collapse. The distribution of disease is usually diffuse and symmetric; however, patchy or asymmetric disease may be seen. The



• **Fig. 38.3** Moderate surfactant deficiency disease. Anteroposterior chest radiograph demonstrates a fine granular pattern. The heart borders, vessels, and diaphragm are well seen.



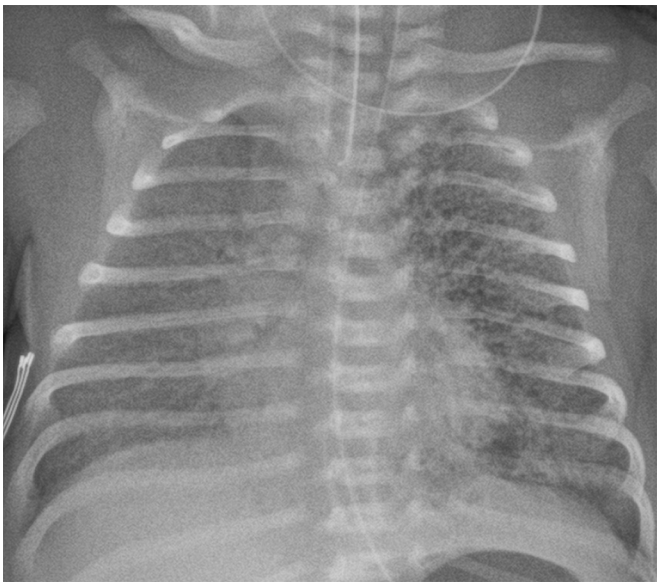
• **Fig. 38.4** Severe surfactant deficiency disease. Anteroposterior chest radiograph demonstrates diffuse ground-glass opacities. The heart borders and diaphragm are silhouetted.

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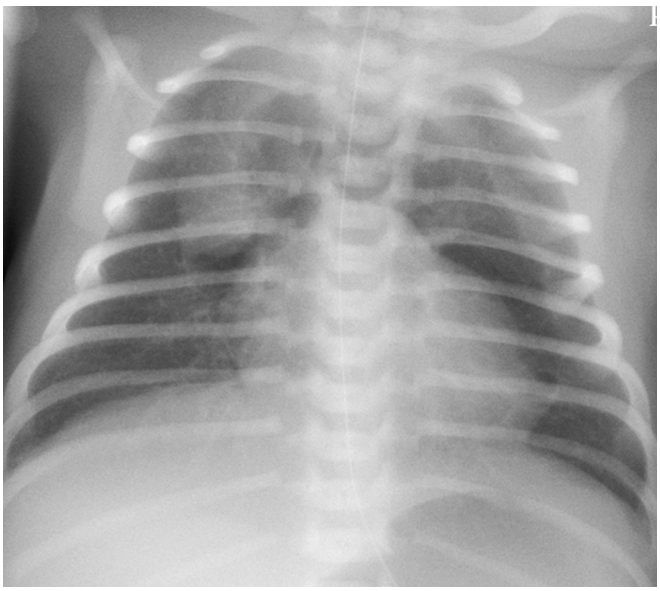
radiographic changes associated with RDS are often seen immediately after birth but can also develop over the first 6-12 hours of life. The radiographic abnormalities related to uncomplicated RDS should resolve by the time the neonate is 3-4 days old or sooner if surfactant therapy is given. Severe RDS on the initial radiograph in the first few hours of life has been proposed as predictive of continuous positive airway pressure failure in extremely low birth weight infants.[56] New diffuse worsening of bilateral opacities in the lungs may be seen with pulmonary edema or pulmonary hemorrhage. Sudden increase in focal opacity usually indicates atelectasis.

Chest radiography can be used to help assess the effectiveness of surfactant replacement therapy in infants with RDS. Lung ultrasound has also been proposed as a technique to differentiate RDS from transient tachypnea and possible need for surfactant therapy.[68] Typically, improvement in the appearance of the lungs is rapid and uniform after surfactant administration. In 80%-90% of neonates treated with surfactant, improvement occurs in one or both lungs. When there is a partial response, the improvement may be asymmetric or even restricted to one lung. Explanations for asymmetric radiographic improvement following surfactant therapy include (1) maldistribution of surfactant, (2) insufficient surfactant, and (3) regional differences in lung aeration before surfactant treatment. The absence of radiographic improvement after surfactant administration is a poor prognostic sign and suggests a diagnosis other than surfactant deficiency. Surfactant-related pulmonary hemorrhage may mimic RDS with focal or diffuse alveolar parenchymal disease.

Complications can result from the high distending pressures of mechanical ventilation that may be required in the treatment of RDS. Alveolar rupture from overdistention results in pulmonary interstitial emphysema (PIE). The radiographic appearance of PIE includes small, rounded or linear lucencies representing interstitial air coursing along the bronchovascular sheaths (Fig. 38.5). These meandering radiolucencies may be diffuse or localized. Larger focal air collections (pseudocysts) may also form in the interstitium of the lung. Pulmonary interstitial emphysema can dissect into the mediastinum or the pleural space, resulting in a pneumomediastinum or pneumothorax. Radiographic signs of pneumomediastinum include (1) lateral displacement of the mediastinal pleura; (2) continuous diaphragm sign; and (3) superior elevation of the thymus, which is referred to as the *spinnaker sail sign* or *angel wings* (Fig. 38.6). Radiographic findings of pneumothorax include (1) increased lucency, (2) identification of the visceral pleural line (Fig. 38.7), (3) increased sharpness of the adjacent mediastinal border or hemidiaphragm, and (4) visualization of a deep costophrenic sulcus. Pneumothoraces may be seen bilaterally (Fig. 38.8). Lateral decubitus or cross-table lateral radiographs can be useful in the detection of small pneumothoraces. Large pneumothoraces can produce tension, resulting in contralateral shift of mediastinal structures and depression or eversion of the ipsilateral hemidiaphragm.



• **Fig. 38.5** Pulmonary interstitial emphysema. Anteroposterior chest radiograph shows multiple rounded lucencies throughout the left lung secondary to interstitial emphysema.

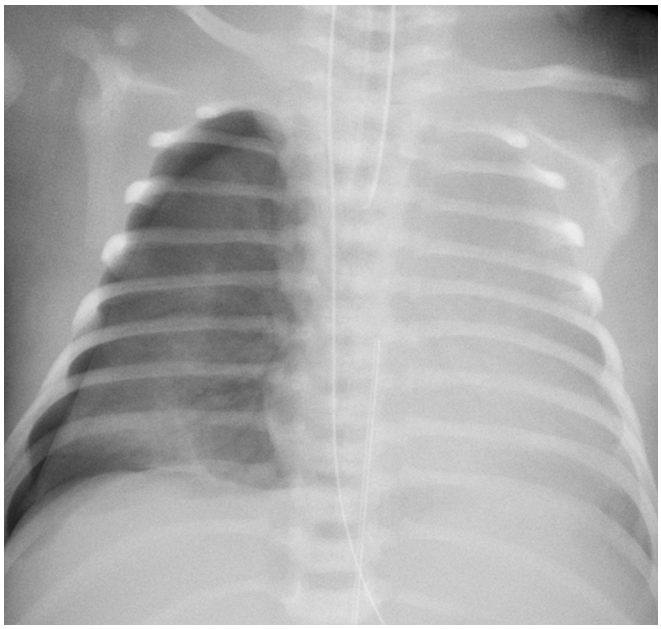


• **Fig. 38.6** Pneumomediastinum. Anteroposterior chest radiograph shows superior displacement of the thymus (thymic sail sign).

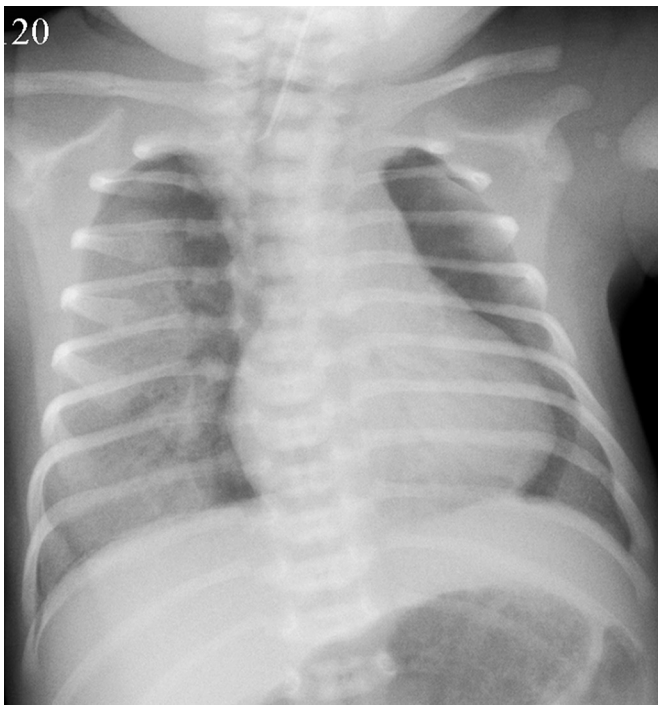
Neonatal Pneumonia

Most neonatal pneumonias are of bacterial origin, including streptococci, *Staphylococcus aureus*, and *Escherichia coli*. These infections may be acquired in utero, during delivery, or after birth. Infection typically disseminates widely throughout the lungs because of incomplete formation of the interlobar fissures at this age. First described with group B streptococcus pneumonia, diffuse granular or ground-glass opacities are often seen and are indistinguishable from RDS. Alternatively, coarse nodularity or a streaky, hazy appearance of the lungs may be seen. The presence of

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• **Fig. 38.7** Right pneumothorax. Anteroposterior chest radiograph. The visceral pleura and a deep right costophrenic sulcus are seen laterally; increased thoracic lucency is seen medially. Note there is complete opacification of the left hemithorax.

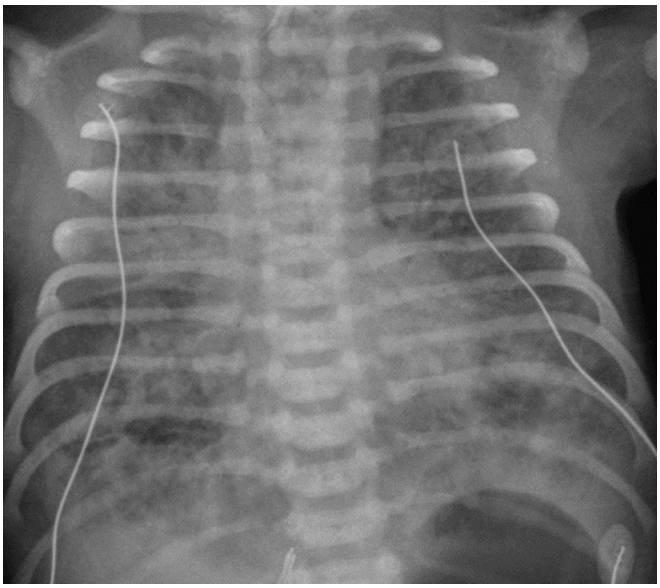


• **Fig. 38.8** Bilateral pneumothoraces. Anteroposterior chest radiograph shows increased thoracic lucency seen medially with increased sharpness of the mediastinal borders.

pleural fluid should raise the suspicion of bacterial infection, because effusions are uncommon in RDS or viral pneumonia.[24]

Transient Tachypnea of the Newborn

Transient tachypnea of the newborn (TTN) is associated with retained lung fluid that may be associated with precipitous delivery or cesarean section. Typically a clinical diagnosis, TTN has a varied and nonspecific appearance. The radiograph may appear normal or show streaky, perihilar opacities and hyperinflation. Small pleural effusions may also be seen. A normal heart size with TTN helps distinguish retained fluid from pulmonary edema or heart failure. The radiographic and clinical findings of TTN have a benign course, usually resolving within the first 24-48 hours of life.



• **Fig. 38.9** Meconium aspiration. Anteroposterior chest radiograph demonstrates coarse, patchy opacities throughout both lungs.

Meconium Aspiration Syndrome

The expulsion of meconium before birth is often related to fetal distress leading to a hypoxia-induced vagal response. It typically occurs in full-term or postmature infants. Fetal aspiration of meconium causes obstruction of small airways with associated atelectasis and air trapping. Radiographic findings of meconium aspiration syndrome are seen within the first few hours of birth and include coarse, patchy, or nodular opacities and segmental hyperinflation (Fig. 38.9). The distribution of disease is bilateral and often asymmetric. Complications include chemical pneumonitis, surfactant inactivation, pulmonary hypertension, and air-leak phenomena such as pneumothorax and pneumomediastinum. Pleural effusion may be present.

Pulmonary Hemorrhage

Pulmonary hemorrhage in infants may result from hypoxia-induced capillary damage. In premature infants whose RDS is resolving and pulmonary vasorelaxation occurring, the resultant pulmonary overcirculation from a PDA may cause pulmonary hemorrhage. In addition to PDA, periventricular leukomalacia and seizures are known associations with pulmonary hemorrhage.[61] In intubated patients, the diagnosis is usually established by detecting blood in the endotracheal tube. The radiographic appearance of pulmonary

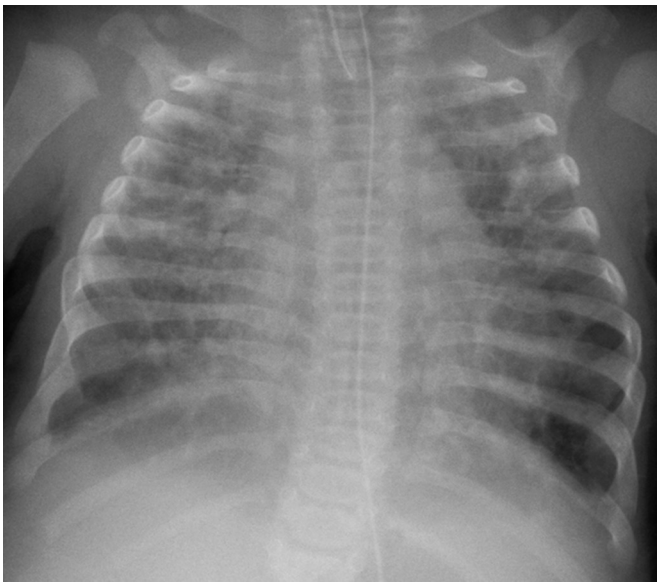
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hemorrhage is variable and nonspecific: small amounts of hemorrhage may not be visible, but more extensive hemorrhage results in focal or diffuse ground-glass opacities. Findings may mimic pneumonia or pulmonary edema. The radiographic changes from a single episode of pulmonary hemorrhage are usually transient, resolving within 24-48 hours.

Bronchopulmonary Dysplasia

Chronic lung disease in the premature infant, known as bronchopulmonary dysplasia (BPD), is most often seen in very low birth weight infants. Bronchopulmonary dysplasia is also seen in higher birth weight infants following prolonged mechanical ventilation for conditions including neonatal pneumonia, meconium aspiration, and congenital cardiac disorders. The definitions of BPD are evolving and include both clinical and physiologic criteria.[20,37,64] Pathologically, BPD is considered to be part of the group of alveolar growth abnormalities and can be recognized on imaging. Because BPD is the result of injury and repair of the immature developing lung, the pathologic and radiologic findings are affected by changes in therapy and the degree of prematurity of the infant. Bronchopulmonary dysplasia was originally described as airway injury, obstruction, inflammation, and parenchymal fibrosis. Chest radiograph findings of the later stages of BPD included hyperinflated lungs, asymmetric, coarse, patchy opacities, and cystic emphysematous changes.[2,32]

The widespread adoption of antenatal glucocorticoid administration, postnatal surfactant therapy, and refinement of assisted ventilation have decreased lung injury from oxygen toxicity and barotrauma.[22,40] Bronchopulmonary dysplasia is now rarely seen among infants of gestational age greater than 30 weeks or birth weight over 1200 grams. Modern therapies have also allowed an increased survival of very low birth weight infants. Despite the absence of prior severe RDS or barotrauma, these less mature infants often have a more insidious development of BPD, known as the "new" BPD. Arrested lung development leading to decreased alveolar and microvascular growth is thought to contribute to this condition. Radiographic and CT findings range from near normal to disordered lung architecture with hyperlucent areas, linear and subpleural opacities, and bullae typical of chronic lung disease (Fig. 38.10)[6,22,43] (see Chapter 69).



• **Fig. 38.10** Bronchopulmonary dysplasia. Anteroposterior chest radiograph shows diffuse, coarse parenchymal opacities.

Respiratory Disease: Surgically Treated

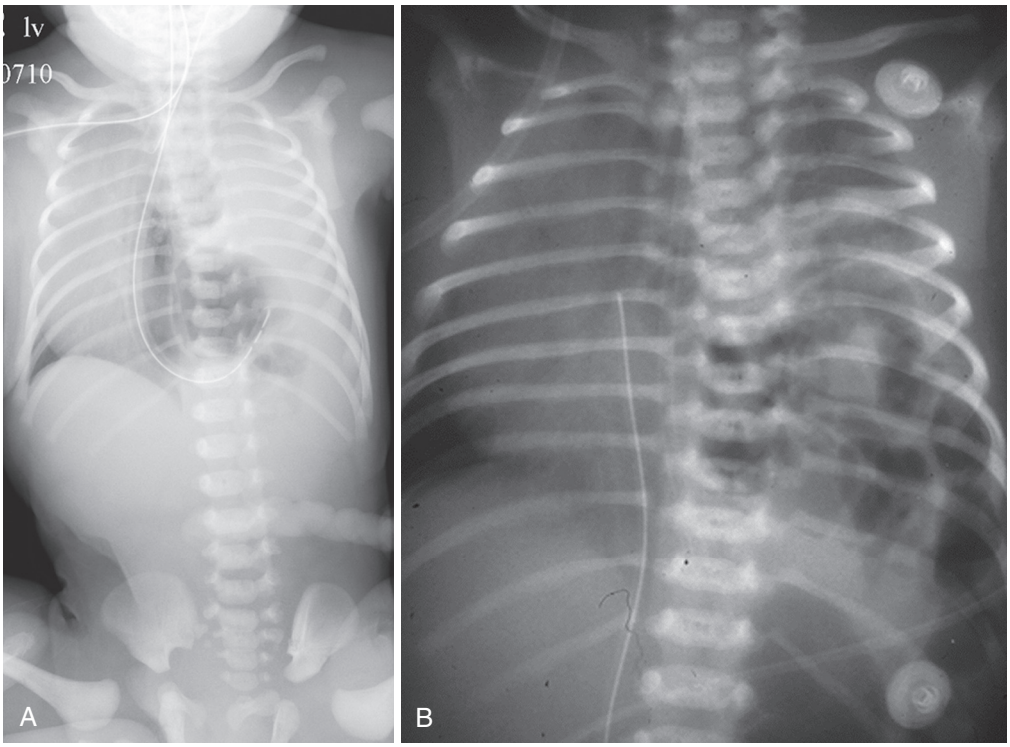
Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a complex life-threatening lesion caused by defective fusion of the pleuroperitoneal membranes during embryologic development. Patent pleuroperitoneal canals located posterolaterally are known as the foramina of Bochdalek. Bowel and solid organs may herniate through the foramen into the hemithorax, most commonly on the left side. At birth, the herniated bowel loops may be fluid-filled, making radiographic diagnosis difficult. Eventually, gas-filled bowel loops are seen in the thorax with a paucity of bowel loops in the abdomen (Fig. 38.11). The ipsilateral lung is almost universally hypoplastic, and there is usually contralateral shift of the mediastinum, resulting in contralateral lung hypoplasia. However, partial aeration of the ipsilateral lung with a smaller hernia may also occur and may be difficult to distinguish from complete eventration (Fig. 38.12). In such cases, ultrasound can be used to evaluate for continuity of the hemidiaphragm. Prenatal sonography and fetal MRI (Fig. 38.13) allow early diagnosis and may predict neonatal survival by evaluating the degree of pulmonary hypoplasia and defining associated anomalies.[58]

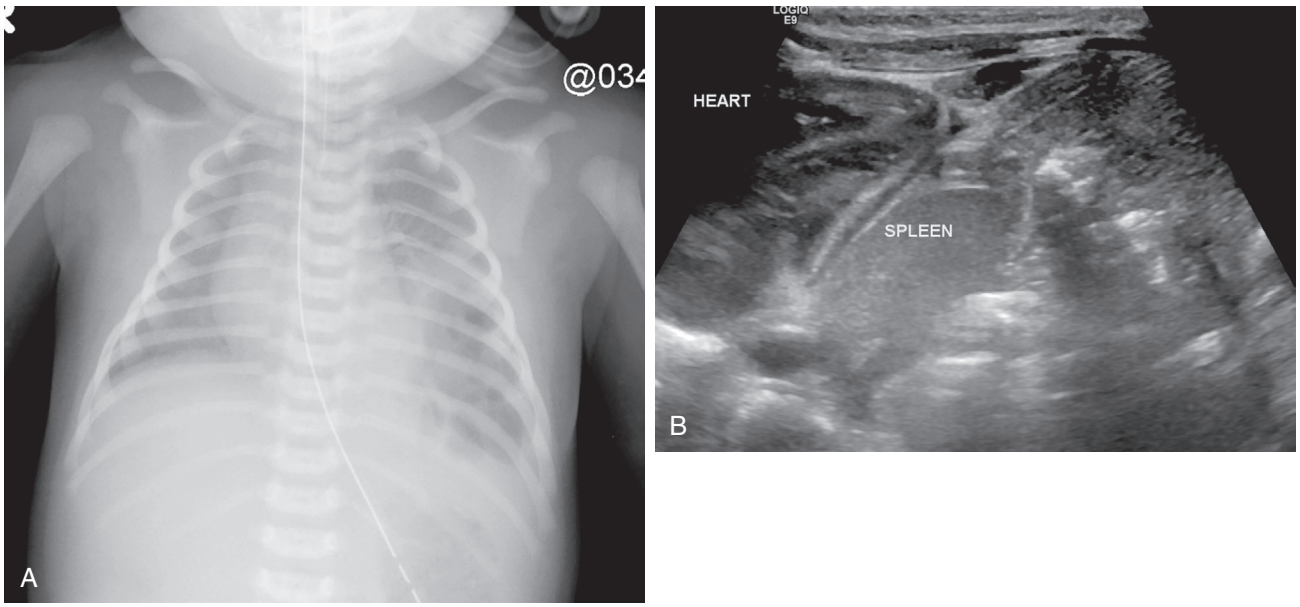
Congenital Pulmonary Airway Malformations

Congenital pulmonary airway malformations (CPAMs), previously known as congenital cystic adenomatoid malformations (CCAMs), are a group of congenital, hamartomatous cystic, and noncystic lung masses characterized by overgrowth of the primary bronchioles and a proximal communication with a defective bronchial tree.[11,38,39,66] The new terminology has been recommended because not all lesions are cystic and only one is adenomatoid. Stocker updated the classification system to include five types (0-4) based on cyst size and similarity to segments of the developing bronchial tree and air spaces: *Type 0* is acinar dysplasia of tracheal or bronchial origin and is incompatible with life. *Type 1*, the most common, has a single or multiple large cysts (>2 cm) of bronchial or bronchiolar origin; *type 2* has a single or multiple small cysts (≤2 cm) of bronchiolar origin; *type 3* is predominantly solid with microcysts (<0.5 cm) of bronchiolar-alveolar duct origin; and *type 4*, characterized by large air-filled cysts, has a distal acinar origin and is indistinguishable from pleuropulmonary blastoma on imaging. Congenital pulmonary airway malformation can also be

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• **Fig. 38.11** Congenital diaphragmatic hernia. **A,** Anteroposterior radiograph shows a gas-filled stomach and central bowel loops in an otherwise opacified left hemithorax. **B,** Left hemithorax shows gas-filled bowel loops. There is a mediastinal shift from left to right in both cases.



• **Fig. 38.12** Congenital diaphragmatic hernia. **A,** Anteroposterior radiograph shows gas-filled bowel in the lower left hemithorax with preserved aeration of a portion of the left lung. **B,** Sagittal sonographic image shows herniation of spleen into the chest.

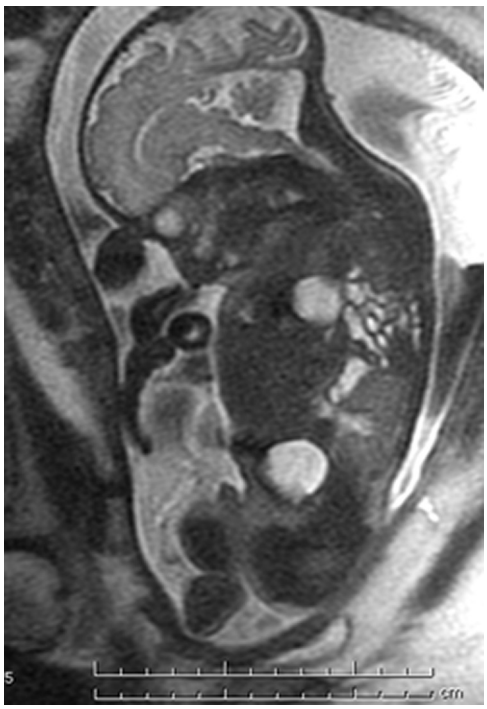
seen in association with other foregut anomalies, most commonly pulmonary sequestration.[11]

Prenatal sonography and fetal MRI classifies CPAMs mainly based on the presence of macrocysts or microcysts.[21] At birth, chest radiography and CT may show a range of findings from large single or multiple air-filled cystic structures to solid lesions that resemble consolidation (Fig. 38.14*A* and *B*). Because of the association of CPAMs with sequestration, precise vascular mapping is essential. Ultrasound may be useful in identifying an abnormal vascular systemic supply typical of sequestration (see Fig. 38.14*C*). However, CT angiography with 2D and 3D reconstructions provides the most accurate assessment of the lung parenchymal and vascular anatomy of these lesions.

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Congenital Lobar Overinflation

Congenital lobar overinflation (CLO) or emphysema is a condition characterized by progressive overinflation of one or more pulmonary lobes. This may be caused by intrinsic bronchial narrowing from weak or absent bronchial cartilage or may be caused by extrinsic bronchial narrowing from mass effect of adjacent structures. The collapsed bronchus can result in one-way valve obstruction causing air trapping and progressive distention of the distal airways in the affected lobe.[11,39] Congenital lobar overinflation most commonly affects the left upper lobe, followed by the right middle lobe and the right upper lobe. At birth, the involved lobe may be radiographically opaque because of retained lung fluid. When the fluid clears, imaging demonstrates progressively increased volume, hyperlucency, and attenuated vascular markings of the involved lobe with compression of the remaining ipsilateral lung and mediastinal shift (Fig. 38.15).[11] CT more precisely characterizes these findings and can distinguish multilobar involvement. CT is also helpful in excluding causes of extrinsic bronchial compression such as vascular anomalies or mediastinal masses (see Chapter 66).



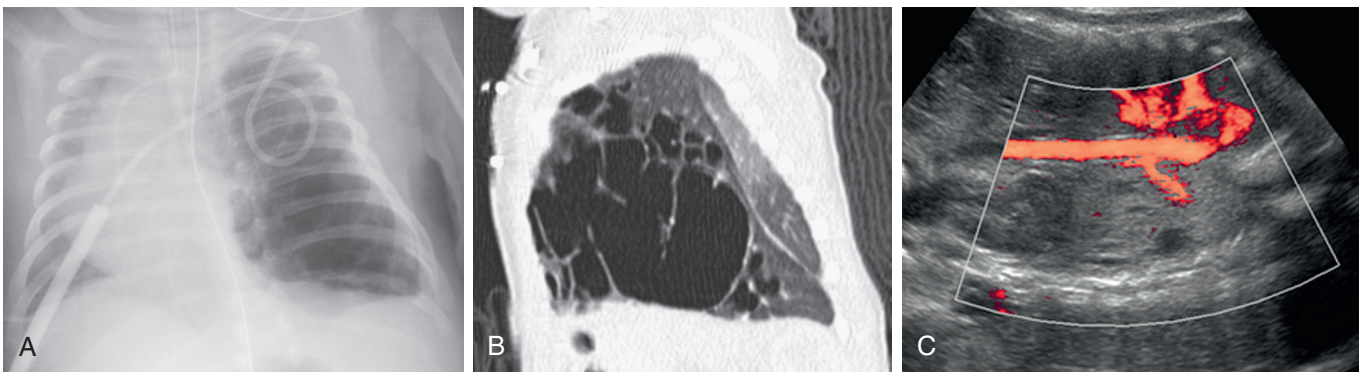
• **Fig. 38.13** Congenital diaphragmatic hernia. Sagittal fetal MRI shows multiple fluid-filled bowel loops and stomach in the left hemithorax.

Esophageal Atresia and Tracheoesophageal Fistula

The pairing of the terms esophageal atresia and tracheoesophageal fistula (TEF) describes a disorder in formation and separation of the primitive foregut and esophagus. A spectrum of malformations is noted, ranging from esophageal atresia (with or without a proximal or distal tracheoesophageal fistula) to a tracheoesophageal fistula without esophageal atresia. The most common type, involving proximal esophageal atresia with a distal tracheoesophageal fistula, accounts for more than 80% of cases. With this type, a blind-ending, air-filled proximal esophageal pouch is noted on a chest radiograph (Fig. 38.16). The presence of a distal fistula is supported by air in the gastrointestinal tract. An esophagram can be performed to evaluate for a fistulous tract. Tracheoesophageal fistula is associated with multisystem abnormalities in approximately one-third of cases, including vertebral, cardiac, renal, and limb anomalies as well as other gastrointestinal tract atresias. All infants with a tracheoesophageal abnormality should undergo additional imaging evaluation to assess for associated anomalies.

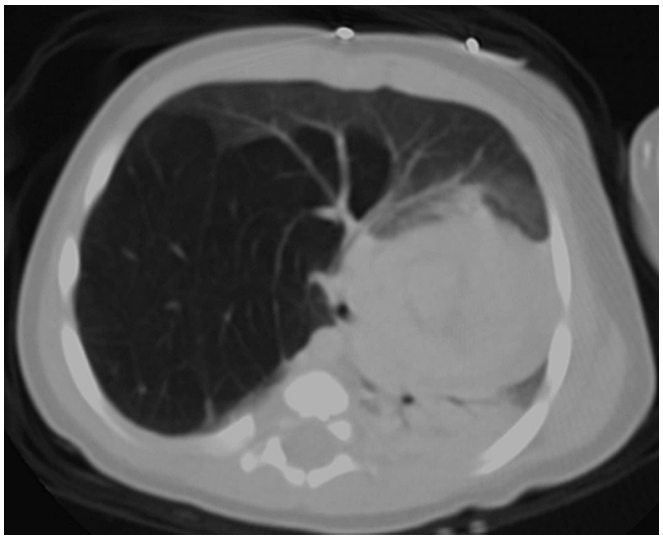
Heart

Cardiac disease in infants is usually congenital in origin. Chest radiography rarely leads to a specific diagnosis and is primarily used to exclude pulmonary conditions as a cause of respiratory distress. Echocardiography, the primary initial imaging modality, may incompletely define extracardiac



• **Fig. 38.14** Congenital pulmonary airway malformation. **A,** Anteroposterior chest radiograph demonstrates a multicystic mass in the left lung, resulting in mediastinal shift and compression of the right lung. **B,** Sagittal chest CT shows a large parenchymal multicystic mass anteriorly in the left lung. **C,** Longitudinal Doppler color fetal sonography demonstrates systemic supply from the aorta to a lung mass, representing a hybrid lesion.

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• **Fig. 38.15** Congenital lobar overinflation. Axial chest CT shows marked overinflation of the right lower lobe with attenuated vascular markings, contralateral mediastinal shift, and compression of the normal left lung.



• **Fig. 38.16** Tracheoesophageal fistula. Anteroposterior chest radiograph demonstrates an air-filled blind-ending esophageal pouch in the neck. Gas-filled stomach is seen.

vasculature and associated airway involvement. CT angiography (CTA) and cardiac MRI (CMRI) complement echocardiography by illustrating these important structures as well as providing functional information.

Great variability in cardiac size is found in congenital heart anomalies. Cardiomegaly is present in neonates with large left-to-right shunts, Ebstein anomaly, hypoplastic left heart syndrome, and cardiomyopathy. Alternatively, cardiomegaly may be seen transiently in the absence of cardiac



• **Fig. 38.17** 3D CT angiogram shows a double aortic arch with mirror image branching; the dominant right arch is larger than the left.

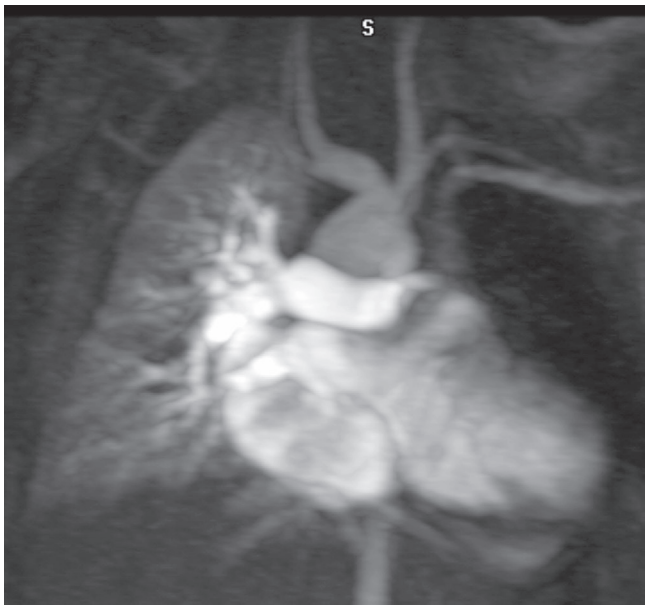
disease with hypoglycemia, hypocalcemia, severe anemia, or in infants of diabetic mothers. Enlargement of specific cardiac chambers cannot be accurately assessed by chest radiography.

In cyanotic congenital heart disease, the caliber of the pulmonary arteries is reduced, the hila appear small, and the lungs may appear more lucent. However, it is difficult to differentiate normal from small pulmonary vessels by chest radiography. Persistent pulmonary hypertension may mimic cyanotic congenital heart disease, both clinically and radiographically, because of cardiomegaly and pulmonary oligemia.

Radiography is useful in diagnosing increased pulmonary arterial vascularity associated with large left-to-right shunts seen in infants with patent ductus arteriosus, ventricular septal defect, atrial septal defect, and endocardial cushion defect. Increased pulmonary arterial vascularity becomes visible on a CXR when the ratio of left-to-right shunt is greater than 3:1. Increased branching linear shadows will be seen in the perihilar region, and vascular markings will be seen in the periphery of the lung fields. The pulmonary arterial vascularity usually appears normal with shunts of a lesser degree (see Chapter 72).

CT is particularly useful in evaluation of aortic arch anomalies (coarctation of the aorta, interrupted aortic arch, and vascular ring or sling) (Fig. 38.17), pulmonary artery anomalies (pulmonary artery stenosis and aorticopulmonary collaterals), anomalies of pulmonary venous return (anomalous pulmonary venous return and pulmonary vein stenosis), coronary artery anomalies, extracardiac anatomy (pericardial masses, airway compression and parenchymal

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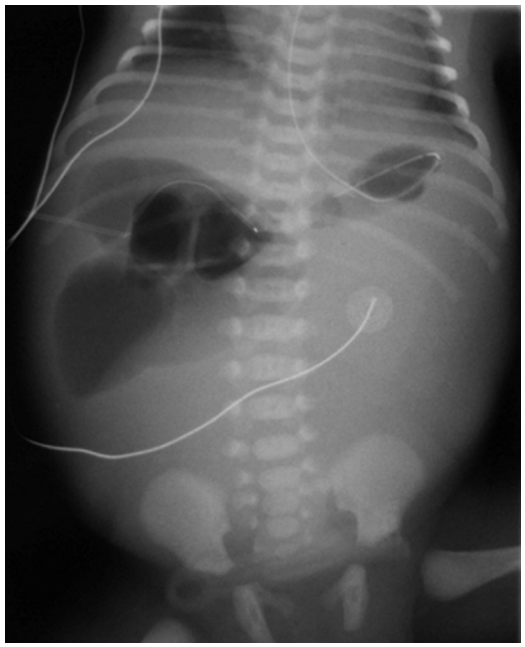
• **Fig. 38.18** Postoperative CMRI shows persistent severe left pulmonary artery (LPA) stenosis in infant with tetralogy of Fallot; no flow is seen to the left lung from the LPA.

disease), and postoperative evaluation after surgery.[23] Indications for CMRI include: cardiac chamber volume, mass, and functional analysis; cardiac morphologic analysis in complex congenital heart disease; soft tissue characterization of cardiac masses and tumors; hemodynamic analysis of pulmonary to systemic blood flow, ejection fraction, and valvular stenosis and regurgitation; and postoperative assessment (Fig. 38.18).[23]

Gastrointestinal Tract

Intestinal obstruction is the most common abdominal emergency in the newborn period. Neonatal obstruction is typically characterized as high, occurring proximal to the distal ileum, or low, involving the distal ileum or colon.[63] The clinical presentation of infants with high and low intestinal obstruction may overlap with symptoms of abdominal distention, vomiting, and poor feeding. Low obstructions are often characterized by failure to pass meconium.

Abdominal radiographs are the initial imaging examination of choice to distinguish between high and low intestinal obstructions. Radiographs in infants with high intestinal obstruction typically show few dilated bowel loops (Fig. 38.19), whereas radiographs in infants with low obstruction show many dilated bowel loops (Fig. 38.20). When bowel obstruction is present, the dilated bowel loops become elongated and are stacked in a parallel configuration. The distinction between high and low intestinal obstruction dictates the type of imaging that the infant may need. With a high obstruction, the upper gastrointestinal series (UGI) is the examination of choice. Infants with a suspected low obstruction are typically evaluated with a water-soluble contrast enema.[29]



• **Fig. 38.19** High intestinal obstruction. Supine abdominal radiograph demonstrates a few dilated proximal small bowel loops and absence of distal bowel gas.



• **Fig. 38.20** Low intestinal obstruction. Supine abdominal radiograph demonstrates multiple dilated bowel loops.

As with all radiologic examinations, proper positioning is important because even a small degree of patient rotation may distort anatomic landmarks.

High Intestinal Obstruction

Midgut Malrotation

Midgut malrotation is the most important cause of upper intestinal obstruction. Abnormal in utero rotation of the

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midgut results in abnormal mesenteric fixation and a short mesenteric base that may allow twisting of the bowel and mesentery around the axis of the superior mesenteric artery. Midgut volvulus can lead to vascular compromise, bowel ischemia, and necrosis. Most infants with malrotation present with bilious vomiting. Up to 75% of patients present in the first month of life.[55] Bilious vomiting in an infant should be considered a potential surgical emergency and, in the absence of another defined cause, evaluation for midgut malrotation should be performed.

The diagnosis of midgut malrotation by imaging is challenging and the findings variable.[5,55] The abdominal radiographic findings may be normal in infants with malrotation. A high obstruction pattern may be seen in the setting of abnormal peritoneal attachments (Ladd bands) or midgut volvulus. Dilatation of multiple bowel loops may indicate volvulus-induced ischemia. The diagnostic examination of choice is the UGI. The location of the duodenum seen on this study is predictive of the mesenteric attachment. Normally, the third portion of the duodenum (D3) courses posteriorly in the retroperitoneum, crossing the midline to reach the duodenal-jejunal junction (DJJ). This junction is normally located to the left of midline and at the level of the pyloric channel. An abnormal course of the duodenum and abnormal location of the DJJ is diagnostic of midgut malrotation (Fig. 38.21A). A spiral or corkscrew appearance of the duodenum and jejunum indicates midgut volvulus (Fig. 38.21*B*). The wrapping of the superior mesenteric artery around the superior mesenteric vein, known as the "whirlpool sign," is specific for the diagnosis of midgut volvulus.[47,57]

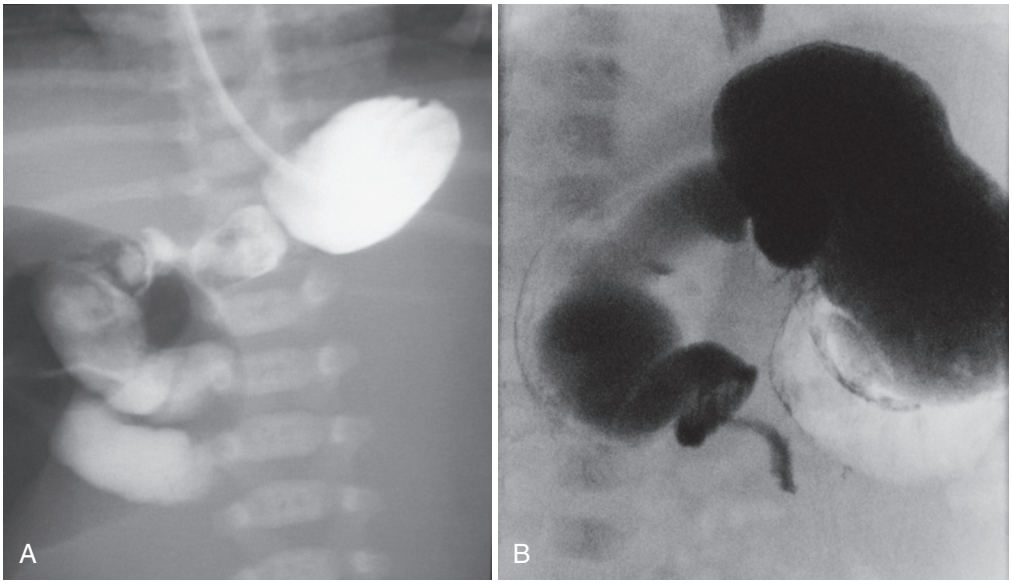
Cross-sectional imaging with sonography or CT has been proposed as an alternative method to diagnose midgut malrotation by identifying the anatomic location of D3 and its relationship to the superior mesenteric vessels. However, a normal retroperitoneal position of D3 does not exclude malrotation, and the relationship of the mesenteric vessels is highly variable and unreliable.[59] Because of the lack of sensitivity or specificity of cross-sectional imaging, UGI remains the gold standard for diagnosing.

Duodenal Atresia

Duodenal atresia is the most common cause of high intestinal obstruction in the newborn. It occurs more commonly than duodenal stenosis or web and results from congenital failure of recanalization of the duodenum during embryologic development. Because the majority of cases occur distal to the ampulla, infants often present with bilious vomiting. Associated abnormalities include Down syndrome, congenital heart disease, and other gastrointestinal anomalies. Abdominal radiography typically shows gastric distention and a dilated duodenal bulb referred to as the *double bubble* sign (Fig. 38.22). These findings are diagnostic for duodenal atresia, and when they are present, no further study is necessary.[63]

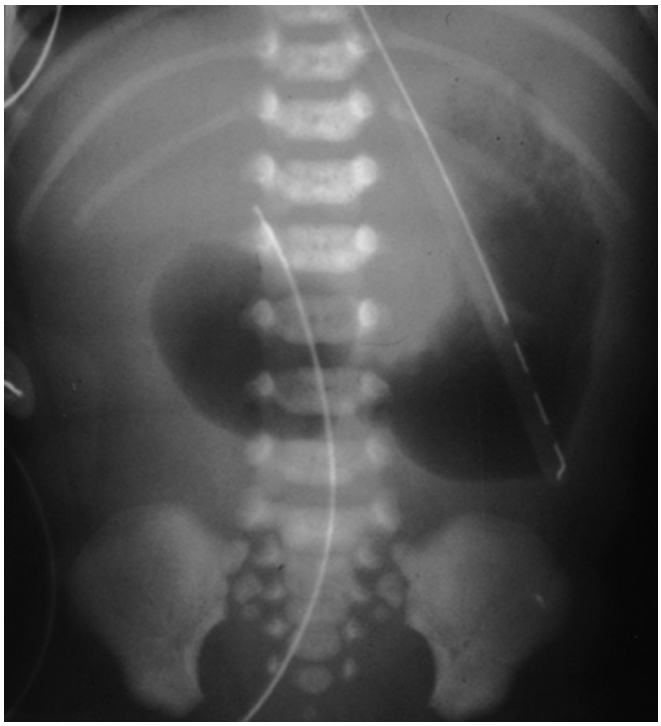
Jejunal Atresia

Jejunal atresia results from an ischemic injury to the developing small intestine. The injury may result from a primary vascular accident or a mechanical obstruction, such as an in utero volvulus. Newborns with jejunal atresia present with bilious emesis and abdominal distention. Abdominal radiographs typically demonstrate dilated small bowel loops that may contain air-fluid levels indicative of a mid–small bowel obstruction. A *triple bubble* sign may be seen, characterized by dilation of the stomach, duodenum, and

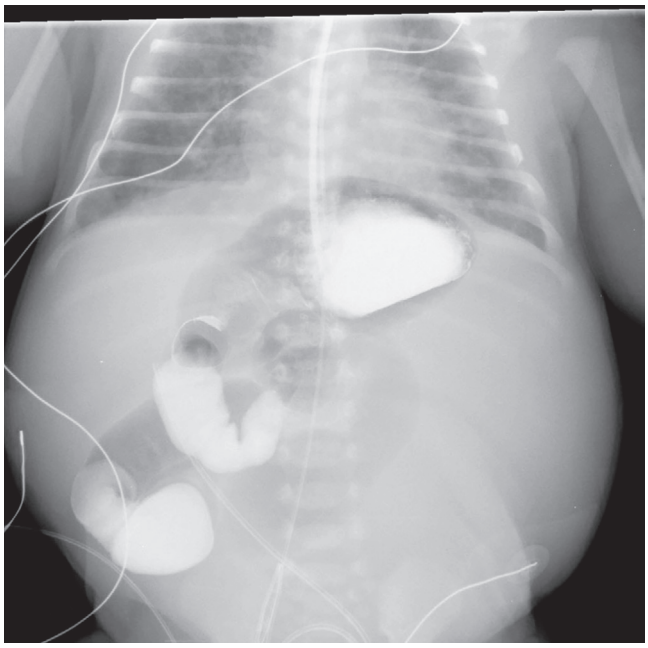


• **Fig. 38.21** Midgut malrotation. Spot film from an upper gastrointestinal series shows (A) an abnormal location of the duodenal-jejunal junction and (B) midgut volvulus with partial obstruction and corkscrew appearance of the duodenum.

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• **Fig. 38.22** Duodenal atresia. Supine abdominal radiograph demonstrates a "double bubble," representing a dilated stomach and duodenum.



• **Fig. 38.23** Jejunal atresia. Supine abdominal radiograph shows barium opacification of the stomach, duodenum, and proximal jejunum with no distal gas.

proximal jejunum. UGI will show obstruction in the proximal jejunum (Fig. 38.23). Since there may be additional sites of atresia in these patients, contrast enema is usually performed prior to surgical repair to define the anatomy of the distal bowel.[63]



• **Fig. 38.24** Hirschsprung disease. Lateral view from a contrast enema demonstrates a transition zone. The more proximal colon is dilated, whereas the caliber of the distal, aganglionic segment is mildly contracted.

Low Intestinal Obstruction

Hirschsprung Disease

Hirschsprung disease (HD) is characterized by the absence of distal enteric ganglion cells. This is caused by an arrest of the craniocaudal migration of neural crest cells during embryologic development, resulting in a failure of normal colorectal relaxation and functional obstruction. Most infants present in the first six weeks of life with abdominal distention, constipation, vomiting, and occasionally diarrhea. The condition is more common in male than female infants. Abdominal radiographic findings in HD are usually nonspecific with variable dilation of bowel and frequent absence of air in the rectum.

The diagnostic imaging examination of choice in patients with suspected HD is a water-soluble contrast enema. A contrast enema may also be therapeutic since the water-soluble contrast promotes the passage of meconium. A small, soft catheter should be used without inflation of a catheter balloon so as not to obscure a transition zone. The lateral view best demonstrates the transition zone between normal, dilated proximal colon and the contracted aganglionic distal segment (Fig. 38.24). The transition zone is most commonly located in the rectosigmoid region. Tubular filling defects may be noted in the colon, representing meconium or stool. The affected aganglionic segment always includes the rectum and extends proximally to involve a variable length of colon without skip areas. Although contrast enema is diagnostic in the majority of patients, the

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transition point identified by imaging does not always correlate with the pathologic extent of aganglionic colon.[31]

Approximately 5% of patients have total colonic aganglionosis and demonstrate a diffusely small-caliber colon (microcolon) without a transition zone. As some infants have a normal contrast enema, a rectal biopsy should be performed in patients where there is a high clinical suspicion for HD.

Functional Immaturity of the Colon

Functional immaturity of the colon, also known as *meconium plug syndrome* or *small left-colon syndrome*, is a benign transient functional obstruction of the colon seen in the newborn period. It is thought to be associated with immaturity of the myenteric plexus ganglia. There is an increased incidence with a history of maternal diabetes mellitus, preeclampsia treated with magnesium sulfate, and prematurity. Functional immaturity of the colon is the most common diagnosis in newborns who fail to pass meconium in the first 48 hours.[63] Abdominal radiography shows a low bowel obstruction with or without air-fluid levels. Water-soluble contrast enema shows tubular filling defects representing meconium plugs. The caliber of the colon is variable; it may be normal in its entirety, or there may be a dilated proximal colon with a small-caliber left colon distal to the level of the splenic flexure and a normal caliber rectum (Fig. 38.25). The diagnostic contrast enema is often also therapeutic in these patients, as it helps to evacuate residual meconium, and resolving the obstruction.

Meconium Ileus

Meconium ileus is caused by abnormal meconium inspissation in the distal ileum and is the earliest clinical manifestation of cystic fibrosis.[63] The abnormally thick meconium in these infants results in a distal small bowel obstruction. Meconium ileus may be complicated by in utero volvulus or perforation with peritonitis. Abdominal radiography demonstrates multiple dilated small bowel loops often without air fluid levels. A "soap bubble" appearance of rounded foci of gas may be noted in the right side of the abdomen. Calcified meconium resulting from meconium peritonitis can be seen in the abdomen and scrotum. Water-soluble contrast enema should be performed in infants suspected of having meconium ileus. The enema typically demonstrates a microcolon (Fig. 38.26). The contrast enema may have a therapeutic effect in some infants, particularly if contrast refluxes into the distal ileum filled with inspissated meconium.[63]

Ileal Atresia

Ileal atresia may be caused by a vascular accident similar to jejunal atresia or may result from other gastrointestinal anomalies such as meconium ileus. Abdominal radiographs in neonates with ileal atresia usually show a low intestinal obstruction pattern. Contrast enema demonstrates an unused microcolon and may be diagnostic if reflux of contrast into the distal ileum demonstrates the level of the atresia.

Anorectal Malformation

Anorectal malformations (ARM) result from improper descent of the hindgut and are associated with vertebral,



• **Fig. 38.25** Small left colon syndrome. Contrast enema demonstrates a small-caliber descending colon. Multiple filling defects throughout the colon are caused by meconium plugs.



• **Fig. 38.26** Meconium ileus with microcolon. Contrast enema demonstrates a microcolon. Filling defects in the terminal ileum are caused by inspissated meconium.

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cardiac, renal, and limb anomalies. The level of obstruction is characterized as high or low if the obstruction is above or below the puborectalis sling. In the infant with an ARM, imaging plays a significant role in treatment planning.[3] Radiographs of the chest, spine, and pelvis may show osseous anomalies. Perineal ultrasound is used to evaluate the location of the distal pouch in patients suspected of having a high type. Distal contrast study is helpful in patients with intermediate to high ARM who have undergone colostomy as this defines the location of the rectum and can demonstrate fistulae. Pelvic MR can also define the location of the rectal pouch as well as the size, morphology, and degree of development of the sphincteric muscles prior to surgical repair.[59a]

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC), seen predominantly in premature infants, is the most common acquired gastrointestinal emergency in the neonatal intensive care unit. Infants usually present with abdominal distention, abdominal tenderness, feeding disturbance, and guaiac-positive stools.

Abdominal radiography plays an important role in the diagnosis of NEC. Early radiographic findings of NEC are nonspecific and include bowel dilation and rounded or elongated loops. Focal or asymmetric distribution of fixed bowel dilation may be seen. As the disease progresses, the intramural gas—specific for pneumatosis intestinalis—is seen.

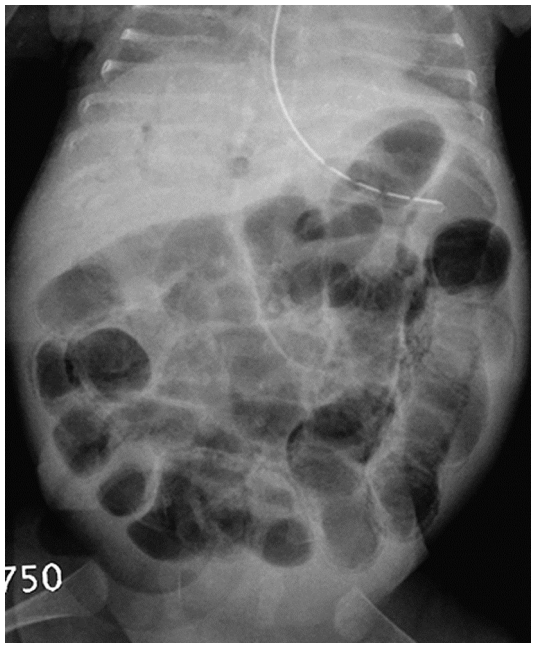
Radiographically, pneumatosis intestinalis appears as a "bubbly" pattern or as curvilinear lucencies (Fig. 38.27). This can be difficult to differentiate from stool. Pneumatosis is most commonly seen in the right lower quadrant. Intramural gas may extend into the veins of the bowel wall and then into the portal venous system. Portal venous gas is seen in the porta hepatis as branching, linear lucencies overlying the liver (Fig. 38.28) and is typically a later finding in more severe cases of NEC. Like intramural gas, this finding may be transient and may not correlate with severity of clinical disease.

Once the diagnosis of NEC is established, serial imaging is performed to evaluate for the complication of bowel perforation. A cross-table lateral radiograph or left lateral decubitus radiograph of the abdomen (left side down) is performed to assess for free intraperitoneal air (Fig. 38.29). Free air collects in the least dependent portion of the abdomen and is seen as lucencies between bowel loops just beneath the abdominal wall or as collections of gas between the liver and adjacent bowel wall. On the supine view, large amounts of peritoneal air give rise to the "football" sign, where air outlines the superior abdomen with the falciform ligament, creating the appearance of the lacing of a football (Fig. 38.30).

Sonography has been used in the evaluation of NEC.[53] Pneumatosis intestinalis is seen as fixed hyperechoic foci in a thickened, ill-defined bowel wall that has abnormal vascularity. Portal venous gas is seen as intraluminal echogenic foci within the liver (Fig. 38.31). The presence of focal peritoneal fluid collections or free peritoneal fluid containing internal echoes correlates with bowel perforation and abscess formation or peritonitis.

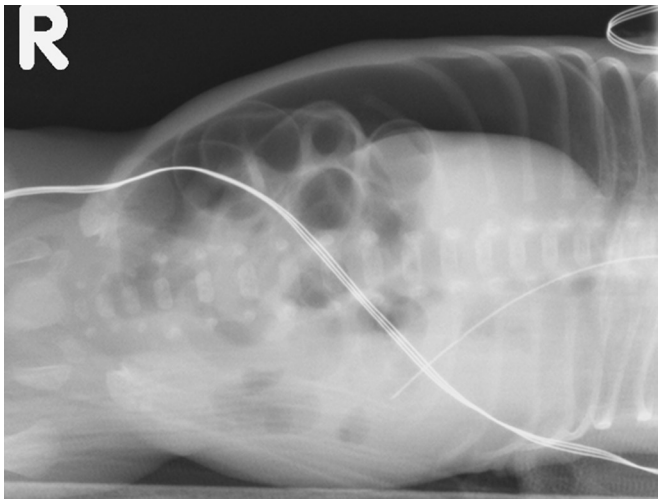


• **Fig. 38.27** Necrotizing enterocolitis (NEC) with pneumatosis intestinalis. Supine abdominal radiograph demonstrates dilated bowel and diffuse bubbly and curvilinear lucencies.

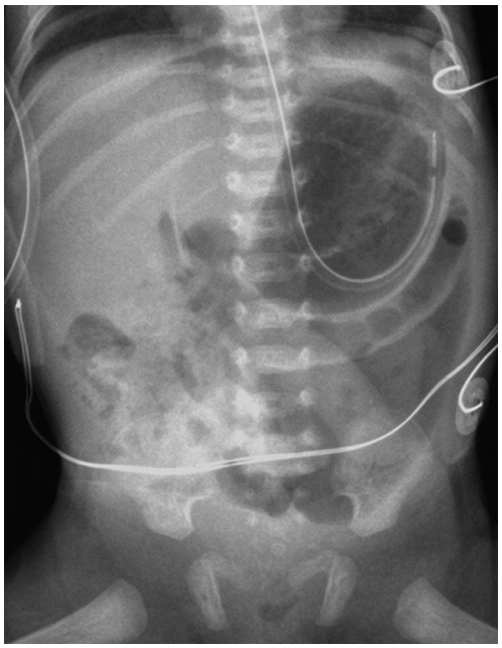


• **Fig. 38.28** Necrotizing enterocolitis (NEC) with portal venous air. Supine abdominal radiograph demonstrates linear lucencies overlying the liver representing portal air. Also note dilated bowel and diffuse pneumatosis intestinalis.

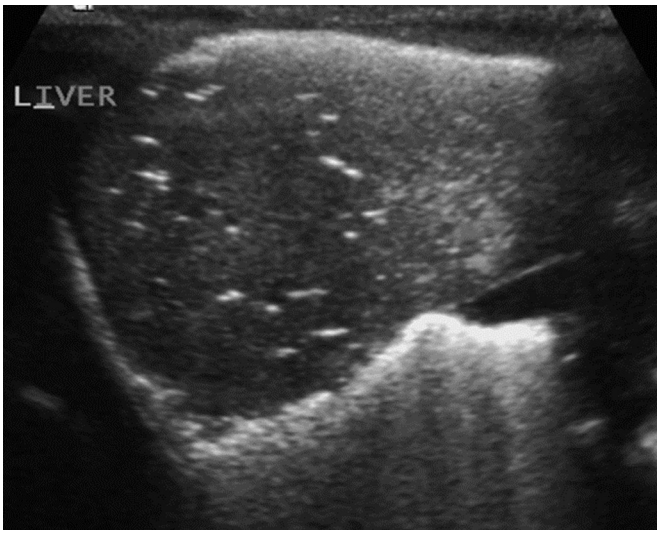
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• **Fig. 38.29** Pneumoperitoneum. Left lateral decubitus view of the abdomen demonstrates a large extraluminal air collection.



• **Fig. 38.30** Pneumoperitoneum. Anteroposterior view of the abdomen shows a large rounded collection of extraluminal air in the upper abdomen (football sign).



• **Fig. 38.31** Portal venous air. Sonogram of the liver demonstrates multiple echogenic foci within the liver, representing portal venous gas.



• **Fig. 38.32** Colonic stricture after necrotizing enterocolitis (NEC). Image from a contrast enema examination demonstrates focal narrowing at the splenic flexure, representing a focal stricture.

A delayed complication of NEC is bowel stricture, representing the sequela of necrotic areas of bowel wall. Strictures occur in 20%-30% of survivors of NEC. Strictures may be single or multiple and are usually located in the colon at the level of the splenic flexure. Water-soluble contrast enema is useful for identifying these sites of focal narrowing (Fig. 38.32) (see Chapter 85).

Hepatobiliary Tract

Biliary Atresia

The underlying abnormality in biliary atresia is obliteration of the extrahepatic biliary tree with progressive obliteration of portions of the intrahepatic biliary tree. Biliary atresia is associated with other abnormalities, including choledochal cyst, polysplenia, preduodenal portal vein, cardiac and pulmonary malformations, azygous continuation of the inferior vena cava, and malrotation.[4,33,51] Infants present with jaundice soon after birth. A frequent clinical challenge is to differentiate biliary atresia from idiopathic neonatal hepatitis as both present with conjugated hyperbilirubinemia. The principal difference between the two entities is that there is patency of the biliary tree in infants with idiopathic neonatal hepatitis.

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Sonography is the initial imaging examination for neonatal conjugated (direct) hyperbilirubinemia, as it can identify alternative etiologies such as choledochal cyst, biliary sludge, and cholelithiasis. The most specific sonographic finding for biliary atresia is the triangular cord sign.[51] This thickening of the anterior wall of the right portal vein represents the fibrous remnant of the bile duct within the hepatic hilum. The gallbladder is not identified in approximately 80% of patients and is usually small, with an abnormal shape and abnormal wall in the remainder.[7] Hepatic parenchymal echogenicity may also be abnormal. When the gallbladder is present, sonography performed before and after oral feeding can help differentiate biliary atresia from idiopathic neonatal hepatitis. In biliary atresia, the gallbladder is not affected by oral feeding, whereas contraction of the gallbladder is seen in idiopathic neonatal hepatitis.[51] However, in most cases of biliary atresia, the sonographic findings are nonspecific.

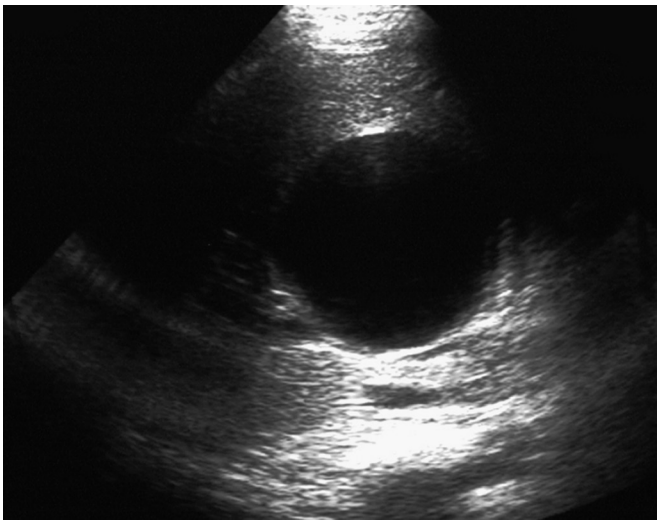
Hepatobiliary scintigraphy is a highly sensitive examination used to diagnose biliary atresia.[33,41] The infant is pretreated with phenobarbital to enhance hepatocellular function and improve specificity. Gastrointestinal excretion of the administered isotope excludes biliary atresia, whereas lack of excretion of isotope by 24 hours is highly suggestive of the condition (see Chapter 91).

Choledochal Cyst

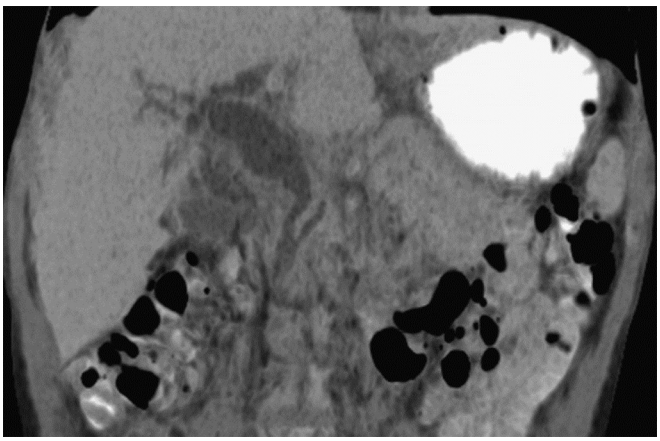
A choledochal cyst represents cystic dilation of the extrahepatic or intrahepatic biliary tree and is a rare cause of neonatal cholestatic jaundice.[34] Biliary atresia should always be ruled out in these infants given the association of these entities and similar clinical presentations.[51] Choledochal cysts are classified on the basis of their location, morphology, and the number of cysts. The most widely used classification system is by Todani and colleagues.[60] Ultrasound is the initial imaging method used to evaluate the size and location of the cyst and to evaluate for additional cystic changes of the biliary tree. The sonographic appearance includes a focal, rounded, thin-walled cyst (Fig. 38.33); fusiform dilation of the common bile duct; or cystic segments of the intrahepatic biliary tree (Fig. 38.34). Magnetic resonance cholangiography is now the gold standard for the evaluation of choledochal cysts, as these images confirm the biliary origin of the cyst and assist with preoperative planning.

Cholelithiasis

Approximately 10% of all cases of gallstones in children occur in the first 6 months of life. Neonatal cholelithiasis is associated with total parenteral nutrition, furosemide therapy, dehydration, infection, hemolytic anemia, and short-gut syndrome. Neonates who undergo parenteral nutrition are at greatest risk, and gallstones have been reported in up to 40% of such infants. The typical sonographic appearance of a gallstone is a rounded, mobile, echogenic focus within the gallbladder.



• **Fig. 38.33** Choledochal cyst. Transverse sonogram through the porta hepatis demonstrates focal cystic dilation of the biliary tree.



• **Fig. 38.34** Choledochal cyst. Coronal cross-sectional image of the liver shows fusiform dilation of the biliary tree.

Hepatic Calcifications

Isolated hepatic calcifications are relatively common in the fetal liver during prenatal sonography and may persist in the neonatal period. Neonatal calcifications may be solitary or multiple and are usually idiopathic. Intrauterine infections such as cytomegalovirus, toxoplasmosis, rubella, herpes, syphilis, and varicella can result in both hepatic calcifications and ascites. Hepatic calcifications can also be seen in congenital malformations and aneuploidy. Subcapsular calcifications may be caused by emboli from the portal or hepatic veins. These may result from umbilical venous catheter complications.[54] Perihepatic calcifications may be secondary to meconium peritonitis.

Liver Tumors

Benign liver tumors are more common than malignant liver tumors in the neonate. The most common benign tumors are hemangiomas and hemangioendotheliomas. Often first

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diagnosed by sonography, MRI is the imaging examination of choice for optimal characterization of these lesions. They appear hypointense on T1-weighted images and hyperintense on T2-weighted images with avid centripetal contrast enhancement. Infantile hemangioma cells test positive for the glucose transporter protein isoform 1 (GLUT-1). They undergo a rapid proliferative phase followed by a slow involuting phase.[16] Primary malignant hepatic neoplasms are unusual in infants. Hepatoblastoma, the most common malignant neoplasm, may appear as either a solitary mass or a multifocal or infiltrative lesion. The most common metastatic tumor of the liver is neuroblastoma. Computed tomography or MRI are used to evaluate these tumors.

Urinary Tract

Sonography is the imaging examination of choice for the initial evaluation of suspected urinary tract abnormalities in infants. The neonatal kidney typically demonstrates increased parenchymal echogenicity because of the relatively high number of glomeruli and the increased cellularity. Therefore, the renal parenchyma is often isoechoic or hyperechoic relative to the liver and spleen. The increased parenchymal echogenicity persists until age 3-4 months. The neonatal kidney also demonstrates prominent, hypoechoic pyramids because of the larger medullary volume present. This finding may persist until 1 year of age and should not be confused with a dilated collecting system.

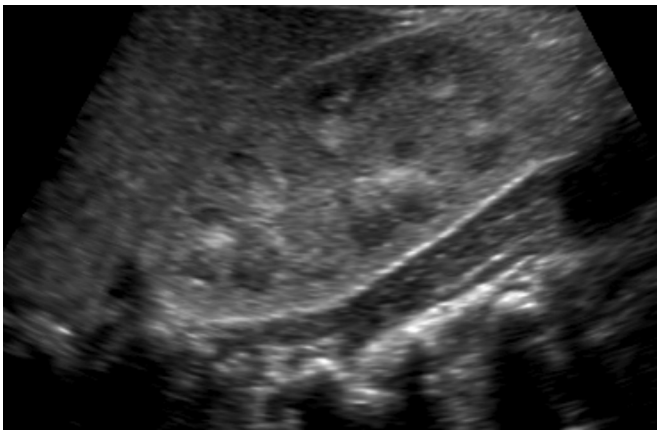
Small amounts of fluid may be seen in the renal pelvis of infants in the absence of urinary tract pathology. It is generally accepted that fluid in the renal pelvis and an AP diameter of the renal pelvis of less than 5 mm are normal findings.[19] A renal pelvic diameter of 5-9 mm is characterized as mild pyelectasis and may be associated with a small amount of fluid in the calices. These findings have been reported in 6% of normal neonates and usually resolve over the first year of life. Therefore, neonates with a renal pelvic diameter of less than 10 mm are not at increased risk for urinary tract disease and do not require further follow-up. If the renal pelvic diameter is greater than 10 mm, the infant should be evaluated for possible obstructive uropathy. The Urinary Tract Dilatation (UTD) Classification System—developed by consensus among urology, nephrology, and radiology societies—is recommended to standardize the description of the severity of both fetal and postnatal collecting system dilatation.[46]

The normal neonatal kidney may also demonstrate transient increased echogenicity of the medullary pyramids at birth (Fig. 38.35). This finding is usually diffuse and bilateral and resolves within 10 days.[17]

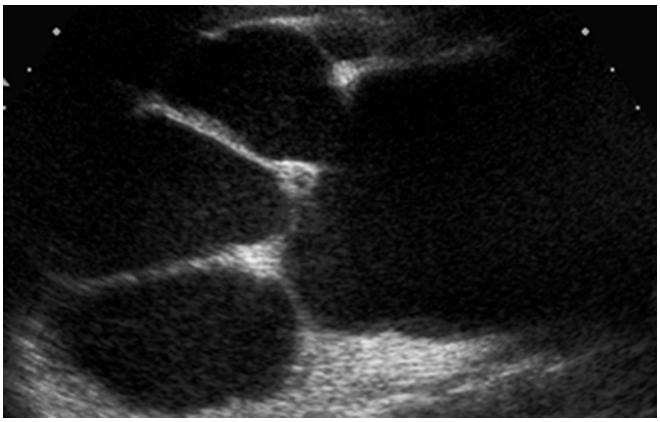
Obstructive Uropathy

The most common cause of urinary tract obstruction and flank mass in infants is ureteropelvic junction (UPJ) obstruction. Theoretical causes of UPJ obstruction include an abnormal smooth muscle arrangement or abnormal innervation of the proximal ureter, fibrous scar, or a crossing vessel at the UPJ.[49] Ureteropelvic junction obstruction is commonly identified on prenatal imaging, but infants may also present after birth with a palpable abdominal mass. Sonography is the initial diagnostic examination in children with suspected UPJ obstruction. The sonographic findings include a dilated intrarenal collecting system without ureteral dilation (Fig. 38.36). The obstruction is bilateral in one-fourth to one-third of patients. Although the diagnosis of UPJ obstruction can be made with a high degree of certainty with sonography, renal scintigraphy is needed to quantify the degree of obstruction and to determine renal function. Scintigraphic findings in UPJ obstruction include progressive increase in radionuclide activity within the renal collecting system and delayed excretion. Since ureteropelvic junction obstruction may be associated with vesicoureteral reflux, the imaging evaluation of infants with the condition should include a voiding cystourethrogram (VCUG).

Posterior urethral valves (PUV) are the most common cause of lower urinary tract obstruction and the leading cause of end-stage renal disease in boys. The valves represent obstructive folds or urethral tissue at the level of the prostatic urethra.[10,42] While the diagnosis is also often

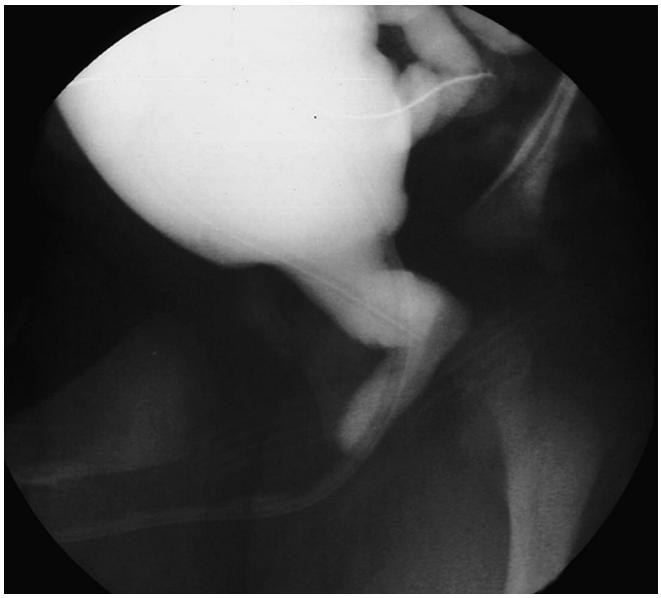


• **Fig. 38.35** Transient increased medullary echogenicity of the newborn. Longitudinal view through the kidney demonstrates increased medullary echogenicity. The distribution is bilateral and symmetric.



• **Fig. 38.36** Ureteropelvic junction obstruction. Longitudinal view through the right kidney demonstrates marked dilation of the intrarenal collecting system. The ureter was not dilated.

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• **Fig. 38.37** Posterior urethral valves. Lateral image from a voiding cystourethrogram shows a dilated posterior urethra and a small-caliber anterior urethra.

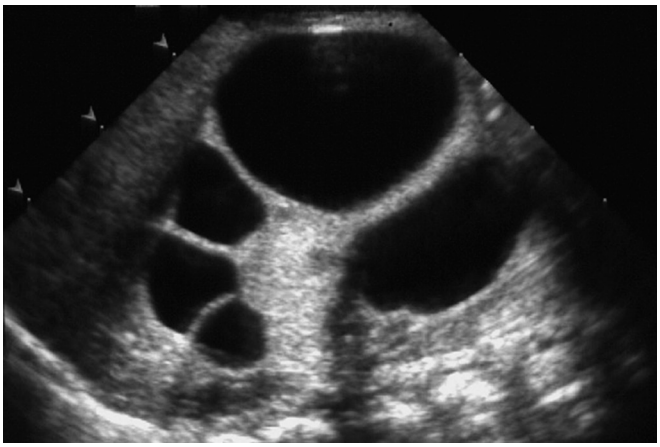
made at prenatal imaging, some infants present after birth with a palpable abdominal mass voiding abnormalities or urinary tract infection. Initial findings include bilateral hydroureteronephrosis and a dilated bladder with a thick, trabeculated wall. If abnormal, the renal parenchyma may show dysplastic changes, including increased echogenicity of the renal parenchyma, loss of corticomedullary differentiation, and small peripheral cortical cysts. The diagnosis of PUV is confirmed on a VCUG that demonstrates a dilated posterior urethra and diminution of the urethral caliber distal to the valves (Fig. 38.37).[10] There may be associated vesicoureteral reflux.

Multicystic Dysplastic Kidney

Multicystic dysplastic kidney (MCDK) results from an insult in early embryologic development that leads to pelvic infundibular atresia.[44,49] Infants with multicystic dysplastic kidney usually present with a unilateral palpable flank mass. The sonographic criteria for diagnosing an MCDK include multiple noncommunicating cysts of variable size and absence of renal parenchyma or collecting system (Fig. 38.38). Rarely, the MCDK appears as a single large cyst. Up to 50% of patients have a coexistent contralateral renal abnormality such as UPJ obstruction or vesicoureteral reflux. The natural history of an MCDK is a gradual decrease in the number and size of the cysts over several months or years as the cyst fluid resorbs.

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) is an inherited disorder characterized by nephromegaly,



• **Fig. 38.38** Multicystic dysplastic kidney. Longitudinal view of the right kidney demonstrates multiple cysts of varying sizes that do not communicate with one another.



• **Fig. 38.39** Autosomal recessive polycystic kidney disease. Longitudinal view through the kidney demonstrates renal enlargement and lack of normal renal architecture. Note numerous small cysts diffusely.

microscopic or macroscopic cystic dilation of the renal collecting system, and periportal hepatic fibrosis. Infants with ARPKD typically present with large palpable abdominal masses or renal insufficiency. The characteristic sonographic appearance is that of symmetric markedly enlarged, hyperechoic kidneys. The increased echogenicity results from the multiple acoustical interfaces associated with cystic dilation of the renal collecting ducts (Fig. 38.39).[16] High-resolution sonographic equipment may also allow visualization of tiny macroscopic cystic structures.[62] A hypoechoic rim may be noted along the periphery of the kidney, representing compressed normal renal cortex.

Renal Vein Thrombosis

Renal vein thrombosis (RVT) in neonates has traditionally been associated with hemoconcentration caused by dehydration, sepsis, or maternal diabetes mellitus. This entity has become relatively infrequent. RVT is thought to begin in the small intrarenal veins and progress to the

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hilum; thrombus within the main renal vein may not be present.[13,35] Renal vein thrombosis may also be seen in infants who develop inferior vena caval thrombi associated with an indwelling catheter. The clinical presentation of RVT includes a palpable mass, renal insufficiency, hematuria, or hypertension. In the acute period, enlargement of the involved kidney, diffuse increase in parenchymal echogenicity with echogenic striations, and loss of corticomedullary differentiation are typically seen. Over the next several weeks, the renal parenchymal echogenicity of the involved kidney becomes heterogeneous and renal size decreases. Doppler examination may show diminished perfusion and high-resistance arterial flow with reversal of diastolic flow.

Nephrocalcinosis

Nephrocalcinosis refers to the deposition of calcium in the renal parenchyma, most commonly in the medullary pyramids. Most cases of medullary nephrocalcinosis in neonates are the result of increased calcium excretion related to furosemide therapy. This entity may also be seen in association with hypervitaminosis D and distal renal tubular acidosis. Nephrocalcinosis associated with furosemide therapy gradually resolves after the medication is stopped.

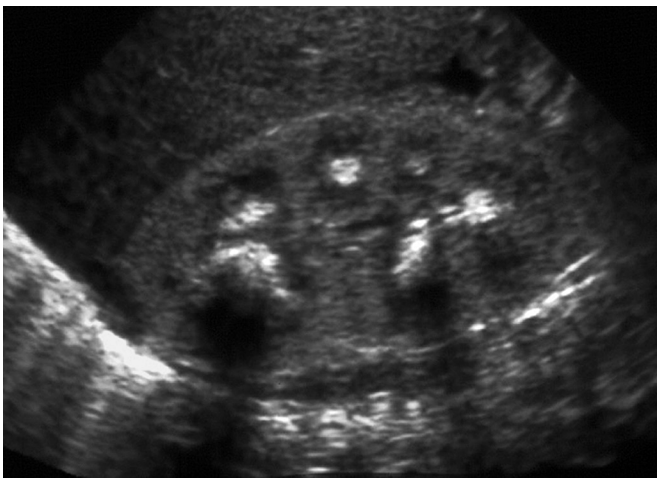
Sonography is used to diagnose and monitor the evolution of the disease. Initial findings include increased echogenicity without acoustic shadowing in the normally hypoechoic renal pyramids (Fig. 38.40). Medullary nephrocalcinosis is typically seen diffusely throughout both kidneys.

Adrenal Glands

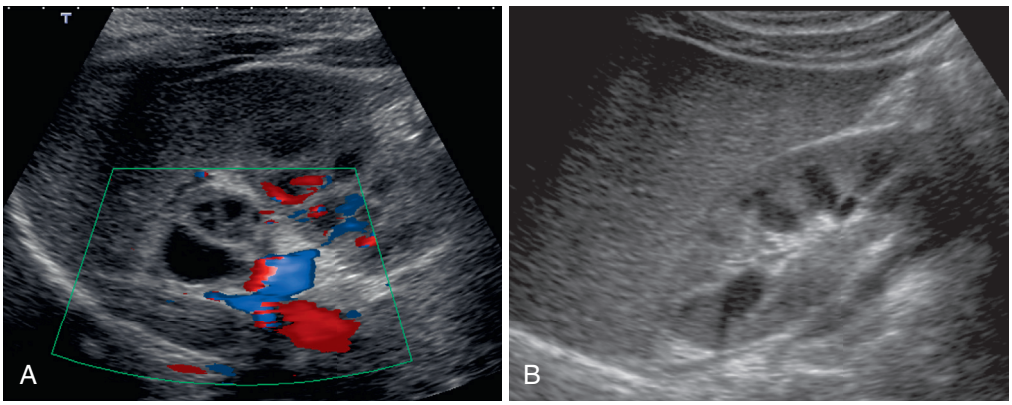
Adrenal Hemorrhage

Adrenal hemorrhage is the most common cause of a neonatal adrenal mass. Right-sided hemorrhage occurs far more commonly than left-sided hemorrhage, possibly owing to the shorter right adrenal vein. Neonates are at increased risk for adrenal hemorrhage because of the relatively large size and increased vascularity of the gland in this age group. Conditions associated with adrenal hemorrhage include perinatal asphyxia, sepsis, coagulation disorders, hypotension, and surgery. Although unilateral involvement is more common, clinical manifestations are typically seen only when there is diffuse, bilateral gland involvement, resulting in adrenal cortical insufficiency.

Sonography is the examination of choice to evaluate for suspected adrenal hemorrhage. The sonographic appearance of adrenal hemorrhage is that of an oval or triangular solid mass of variable echotexture. There may be focal or diffuse involvement of one or both adrenal limbs. Adrenal calcifications may develop weeks to months after the hemorrhage. Large adrenal hemorrhages may be difficult to differentiate from a tumor, particularly if calcification is already present. In such cases, follow-up sonographic images show a gradual decrease in size over 1-2 weeks (Fig. 38.41).[49]



• **Fig. 38.40** Medullary nephrocalcinosis. Longitudinal view sonography through the right kidney demonstrates increased medullary echogenicity with posterior acoustic shadowing.

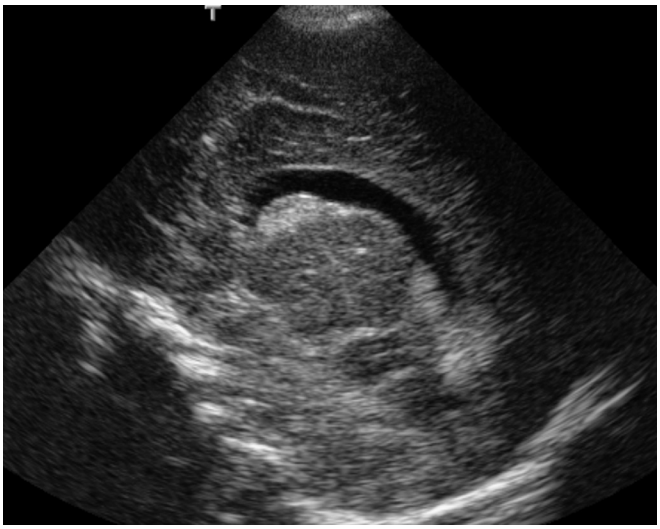


• **Fig. 38.41** Adrenal hemorrhage. **A,** Doppler color sonography demonstrates a nonvascular cystic adrenal mass. **B,** Three weeks follow-up sonography demonstrates a normal right kidney and complete involution of the mass, indicative of resolution of adrenal hemorrhage.

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• **Fig. 38.42** Neuroblastoma. Computed tomography scan through the upper abdomen demonstrates a large mass originating from the right adrenal gland.



• **Fig. 38.43** Grade 1 intraventricular hemorrhage. Sagittal view through the lateral ventricle demonstrates a subependymal hemorrhage.

Neuroblastoma

Neuroblastoma is the most common neonatal neoplasm and may present in the prenatal or neonatal period. While perinatal neuroblastoma most often arises from the adrenal gland, a primary lesion can arise from any site in the sympathetic chain. Sonography is usually the initial imaging examination of choice and demonstrates a solid or cystic suprarenal mass that may contain calcifications.[49] CT or MRI offers more precise characterization of the organ of origin and is required for staging (Fig. 38.42). Magnetic resonance imaging can be useful to assess intraspinal extension.[16] Iodine 123 (^{123}I) metaiodobenzylguanidine (MIBG) is the first-line functional imaging agent used with uptake seen in 90% of neuroblastomas. ^{123}I-MIBG identifies both the primary tumor and sites of metastatic disease. The addition of single photon emission computed tomography to ^{123}I-MIBG improves characterization of uptake.[52]

Brain

Sonography is the primary means of evaluating intracranial pathology in infants. The most frequent indication for cranial ultrasound is to evaluate for germinal matrix hemorrhage in premature infants.[67] Sonography is performed at the bedside through the anterior and posterior fontanelles with a high-frequency sector transducer. Doppler ultrasound offers effective screening of large intracranial arteries and veins for sinovenous thrombosis and vascular malformations. Evaluation of parenchymal, subarachnoid, and subdural abnormalities are limited on sonographic examination and are better characterized with MRI or CT. In addition, MRI provides detailed anatomic information about the brain and its vasculature.

Germinal Matrix Hemorrhage

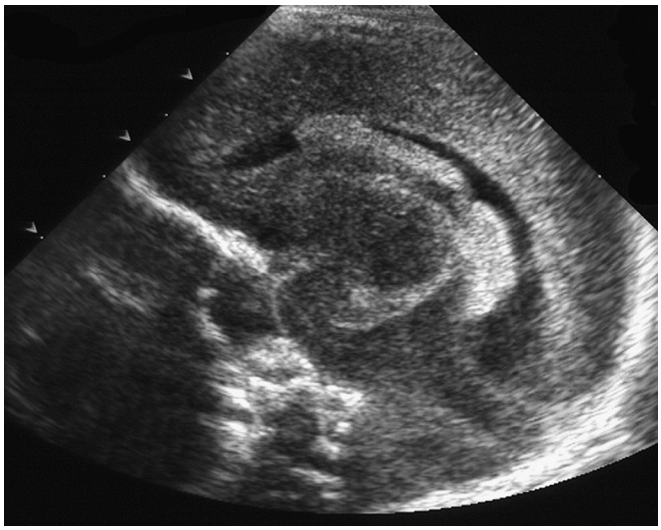
Germinal matrix hemorrhage (GMH) is seen primarily in premature infants. Infants at highest risk are those with a gestational age of less than 32 weeks or a birth weight of less than 1500 grams. Most hemorrhages occur by the first week of life. The site of origin for GMH is the caudothalamic groove, an area bordered by the ventricular surface of the caudate nucleus and the thalamus. This extremely vascular area is composed of fragile thin-walled blood vessels with little surrounding connective tissue. Conditions associated with increased intracranial blood flow in the premature infant may result in intracranial hemorrhage.

The traditional classification system for GMH is based on the presence of subependymal and intraventricular hemorrhage, ventriculomegaly, and parenchymal abnormalities (see Chapter 53). Grade 1 is subependymal hemorrhage only; grade 2 is subependymal and intraventricular hemorrhage; grade 3 is subependymal and intraventricular hemorrhage with ventriculomegaly; and grade 4 is periventricular hemorrhagic infarction. Periventricular infarcts are thought to be caused by compression of the periventricular veins by the subependymal hemorrhage.

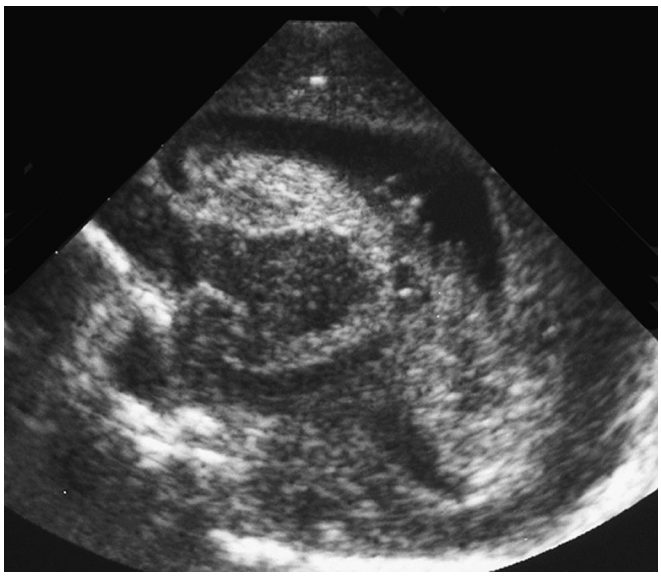
At sonography, a grade 1 hemorrhage appears as a subependymal echogenic focus inferolateral to the frontal horn of the lateral ventricle (Fig. 38.43). If the subependymal hemorrhage is large, it may efface the ipsilateral lateral ventricle. In grade 2 hemorrhage, blood is seen as echogenic material within the nondilated lateral ventricle (Fig. 38.44). In grade 3 hemorrhage, the intraventricular hemorrhage expands the ventricle, resulting in ventriculomegaly (Fig. 38.45). Grade 4 hemorrhage is characterized by additional echogenic periventricular abnormalities representing hemorrhagic venous infarct (Fig. 38.46).[63] The grade of the germinal matrix hemorrhage has been shown to affect neurodevelopmental outcome. The developmental outcome in infants with grades 3 and 4 hemorrhage is worse than those with grades 1 and 2 for whom the bleeds may not be prognostically significant.[48]

Ventriculomegaly is a frequent sequelae of intraventricular GMH that results from obliterative arachnoiditis or intraventricular obstruction from clot or debris. The

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• **Fig. 38.44** Grade 2 intraventricular hemorrhage. Sagittal view through the lateral ventricle demonstrates hemorrhage within the right lateral ventricle.



• **Fig. 38.45** Grade 3 intraventricular hemorrhage. Sagittal view through the lateral ventricle demonstrates intraventricular hemorrhage and ventriculomegaly.

ventriculomegaly may develop soon after the GMH or may be delayed by several weeks. Typically, the trigones and occipital horns of the lateral ventricles dilate before the frontal horns, and the lateral ventricles may dilate alone or to a greater degree than the third and fourth ventricles. Serial sonographic evaluation is performed in infants with GMH to evaluate for developing hydrocephalus, which may require shunting if progressive.

Periventricular Leukomalacia

Periventricular leukomalacia (PVL) represents infarction of deep white matter adjacent to the trigones and frontal horns of the lateral ventricles in premature infants. Infants with



• **Fig. 38.46** Grade 4 intraventricular hemorrhage. Coronal view through the lateral ventricles shows a large intraventricular hemorrhage on the right and adjacent echogenic parenchymal abnormality, representing a hemorrhagic infarct.

PVL may also have intraventricular hemorrhage. Cranial ultrasound performed soon after the infarction is most often normal. The earliest sonographic abnormality is increased periventricular echogenicity (Fig. 38.47). With progression of disease, cavitation may occur, resulting in parenchymal cystic areas (Fig. 38.48). These areas may communicate with the ipsilateral lateral ventricle.[14] Magnetic resonance imaging is the most sensitive imaging modality for the assessment of PVL.[12] Peritrigonal areas of hyperintensity are seen on T2-weighted images. The corpus callosum is often thinned or atrophic. In addition, irregularity of the lateral ventricular contour and asymmetric ventricular enlargement may be noted.

Neonatal Encephalopathy in Term Infants

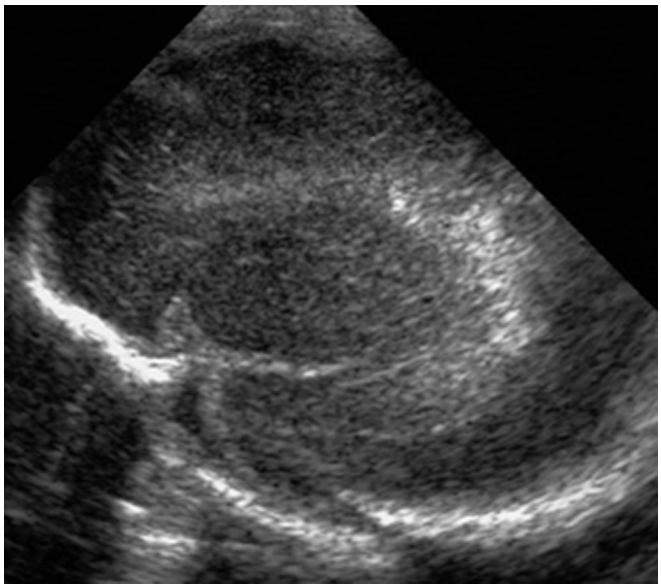
Neonatal encephalopathy is a condition that may result in severe neurologic deficit. Cranial ultrasound may appear normal or show diffuse cerebral edema (Fig. 38.49*A*). MR with special techniques like diffusion weighted imaging (DWI) play a central role in early diagnosis and prompt intervention.[8] DWI may show cytotoxic edema of hypoxic injury during the acute phase before signal intensity changes are evident on conventional T1 or T2-weighted images. Cytotoxic edema appears as high signal restricted diffusion on DWI and low signal on corresponding diffusion coefficient mapping (Fig. 38.49*B*). Diffusion restriction on DWI predicts a poor outcome.

Lenticulostriate Vasculopathy

Lenticulostriate vasculopathy (LSV) describes the sonographic appearance of echogenic vessels in region of the basal ganglia and thalamus. Since it was first described in 1988, LSV has been reported in 0.3%-32% of populations

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studied.[15] A common finding on neonatal cranial ultrasound, most infants with mild LSV show normal neurodevelopment, and no further imaging is needed. LSV may be a nonspecific marker of previous insult to the developing brain and has been associated with various congenital infections, including syphilis, rubella, toxoplasmosis, and cytomegalovirus. It also has been described in chromosomal abnormalities, fetal alcohol syndrome, bacterial meningitis, and perinatal asphyxia. Cranial ultrasound shows linear or branching areas of echogenicity in the thalami and basal ganglia that may be seen from the first week of life to several weeks of age (Fig. 38.50).[67]

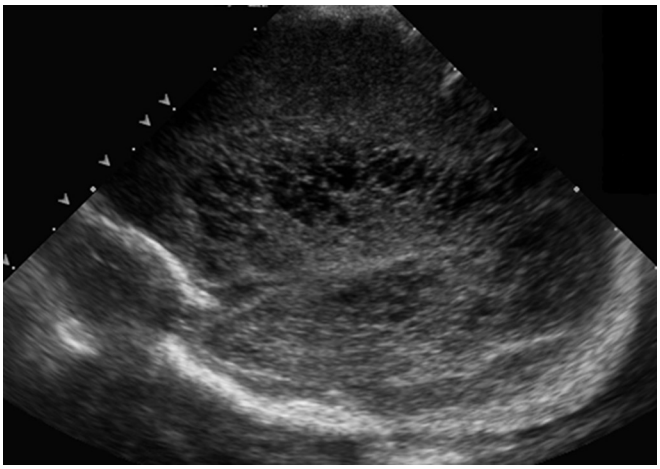


• **Fig. 38.47** Early periventricular leukomalacia. Sagittal view through the parietal region demonstrates increased echogenicity.

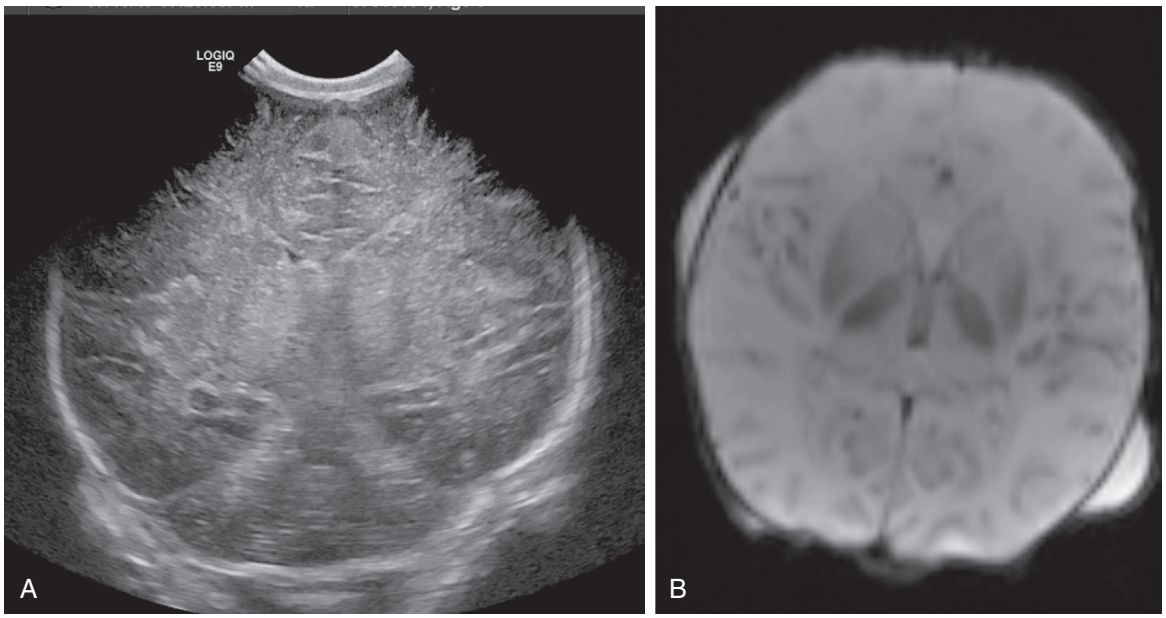
Spine

Tethered Cord

A tethered cord is defined as a low position of the conus medullaris and thickening of the filum terminale. It is seen in association with various syndromes, spina bifida, meningocele, terminal lipoma, diastematomyelia, and sacral dimple. For those infants suspected of occult spinal dysraphism, sonographic examination using a high-frequency linear transducer is the primary screening tool. Terminal positioning of the conus medullaris at or below the L2-L3 disc space vertebrae confirms a tethered cord (Fig. 38.51*A*). Magnetic resonance imaging is typically performed in all abnormal cases to better evaluate for associated abnormalities (Fig. 38.51*B*).



• **Fig. 38.48** Late periventricular leukomalacia. Sagittal view through the parietal region demonstrates extensive cystic changes.



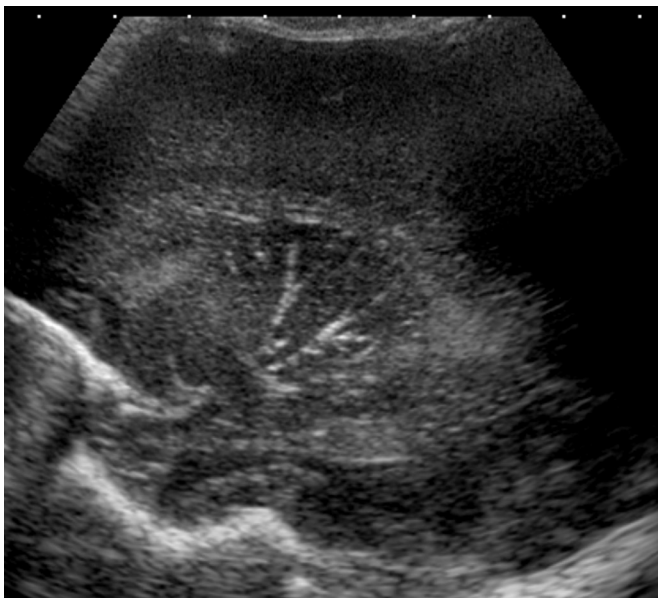
• **Fig. 38.49** Hypoxic ischemic encephalopathy. **A,** Diffuse cerebral edema with slit-like ventricles on coronal ultrasound images. **B,** Diffusion restriction in cerebral hemispheres on diffusion-weighted imaging MR.

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Skeletal

Intrauterine Infection

Intrauterine infection may involve the skeletal system. Congenital rubella and cytomegalovirus infection result in metaphyseal lesions with vertical striations that resemble a celery stalk. Congenital syphilis may cause both periostitis as well as single or multifocal metaphyseal lesions, which vary from radiolucent transverse metaphyseal bands to focal destruction and fragmentation of bone.



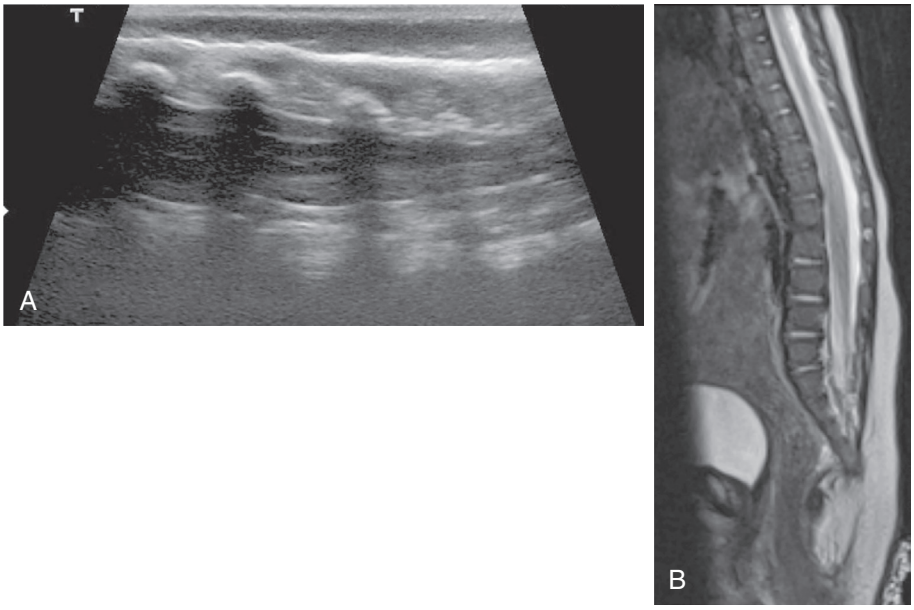
• **Fig. 38.50** Lenticulostriate vasculopathy. Longitudinal view through the right thalamus demonstrates branching linear areas of echogenicity.

Postnatal Infection

Neonatal osteomyelitis is typically caused by staphylococci, streptococci, or *Candida*. There is an increased risk of osteomyelitis in preterm infants. In infants, osteomyelitis is often seen in conjunction with septic arthritis, because the metaphysis and epiphysis have contiguous blood supplies. Skeletal radiography remains the initial mode of assessing suspected osteomyelitis. The earliest radiographic finding is soft tissue swelling that results in displacement or obliteration of fat planes. Bony changes include poorly defined metaphyseal lucency with progressively increasing bony destruction. However, these changes may not be present in the first 7-10 days. Magnetic resonance imaging is useful in the early detection of soft tissue and osseous abnormalities of osteomyelitis (see Chapter 98).

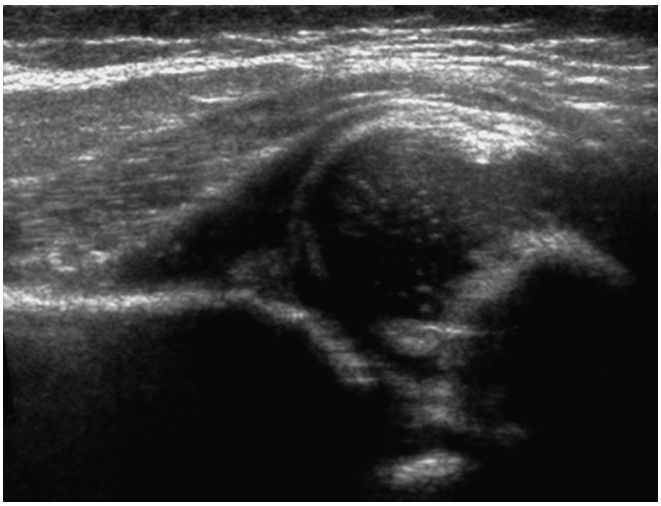
Developmental Dysplasia of the Hip

Developmental dysplasia of the hip (DDH) may be seen in infants with breech presentation in the third trimester, family history of dysplasia, or other orthopedic problems like clubfoot and metatarsus adductus. DDH is more common in girls than boys. Sonography is the examination of choice for screening evaluation after 6 weeks of age; prior to this, there is overlap in findings with transient postnatal physiologic ligamentous laxity. Ultrasound for DDH can be performed up to 4-5 months of age, after which plain films are the preferred imaging modality. Sonography directly visualizes the cartilaginous components of the hip, including acetabular morphology and coverage of the femoral head (Fig. 38.52). Hip instability is assessed through dynamic imaging using stress maneuvers.



• **Fig. 38.51** Tethered cord. **A,** Prone sagittal sonogram shows the cord terminating at the L4-5 level. **B,** T2-weighted sagittal MR confirms tethered cord at L4-5 as well as fusion anomaly at L1-2.

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• **Fig. 38.52** Developmental dysplasia of the hip. Longitudinal view through the left hip demonstrates a shallow acetabulum.

Congenital and Developmental Anomalies

Skeletal radiography plays a primary role in the evaluation of congenital and developmental abnormalities of the axial skeleton and extremities. Imaging of a specific site is performed when there is a localized concern, such as craniosynostosis, congenital spinal deformity, radial ray abnormality, or scapular nondescent. When a skeletal dysplasia is suspected, a skeletal survey should be performed. This survey includes lateral views of the skull and spine as well as AP views of the upper and lower extremities, pelvis, chest, and abdomen.

Rickets

Inadequate mineral intake, chronic lung disease, parenteral nutrition, medications, and immobilization can contribute to metabolic bone disease of prematurity and rickets. The radiologic findings of rickets precede clinical manifestations and are most pronounced at the metaphyses of long bones with the greatest rate of growth. AP radiographs of the wrist or knee demonstrate loss of the zone of provisional calcification, with metaphyseal cupping, fraying, and irregularity. There is also diffuse demineralization or osteopenia (see Chapter 97).

Future Directions

The use of diagnostic imaging in neonates continues to evolve with advances in imaging technology and options for clinical management of these patients. The increasing use of fetal MRI will lead to earlier diagnosis and treatment of infants with conditions affecting the brain, spine, heart, chest, and abdomen. MRI evaluation of the newborn continues to progress with the design of faster sequences and increased use of functional imaging. In the near future, smaller MR scanners will allow imaging of critically ill patients to be performed within the neonatology intensive care unit. New post-processing techniques like iterative reconstruction will continue to decrease doses of ionizing radiation for infants needing a CT scan. The availability of higher frequency transducers and advancements in duplex and color Doppler technology are improving anatomic imaging and the ability to visualize lower velocities of blood flow in smaller vessels. The use of hand-held ultrasound technology will grow, providing point-of-care providers diagnostic information in minutes. These collective advances not only improve image quality, but also improve delivery of safe and timely diagnostic imaging for neonates.

Acknowledgments

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Key Points

- Radiography remains the most widely used imaging modality in the newborn; cumulative radiation doses from serial neonatal radiographs are considered low dose radiation.
- The risk of a future cancer from low dose radiation used in neonatal imaging is considered too low to be detectable and may be nonexistent.
- Fluoroscopy remains the imaging modality of choice for diagnosis of intestinal malrotation, bowel obstructions, and gastrointestinal and urinary tract fistulae.
- Ultrasound, the second most widely used imaging modality in newborns, offers quick, portable and dynamic cine imaging of the neonatal brain, urinary tract, abdominal solid organs and vasculature.
- Magnetic resonance (MR) imaging is increasingly performed prenatally for congenital neurologic, thoracic, and abdominal malformations; postnatal MR is most widely used for follow-up of these malformations, early detection of hypoxic ischemic change, and cardiac disease.
- Computed tomography (CT), usually performed without sedation, is indicated for newborns with lesions not fully characterized with radiography and ultrasound. CT also offers diagnostic imaging for infants with congenital heart disease involving the aortic arch, pulmonary vascularity, or coronary arteries.

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39

Anesthesia in the Neonate

JOHN E. STORK AND SHELLEY OHLIGER

Developmental Challenges of Neonatal Anesthesia

The administration of anesthesia to the neonatal patient requires knowledge and understanding of neonatal anatomy and pathophysiology in addition to the ability to understand how the pharmacology of standard anesthetic drugs is altered in preterm and term neonates. Anesthetic care of these oftentimes critical patients is best performed by specialty trained pediatric anesthesiologists. The creation of a surgical environment that is tailored to the neonatal patient with appropriate monitors, equipment, and personnel allows for both general and regional anesthetics to be safely and successfully carried out. The safety of modern anesthetics in this vulnerable population continues to be an area of concern, as animal studies have shown neuronal apoptosis and neurocognitive deficits as a result of exposure to most modern anesthetics. While recent human data suggests that brief anesthesia exposure early in life appears to be safe, it continues to be an area of intense focus and research.

Surgery in neonates is accompanied by a humoral stress response that leads to increased complications and mortality, as shown in the landmark study by Anand and colleagues in 1987.[4] This response is diminished by adequate anesthesia (Fig. 39.1; Table 39.1), resulting in improved surgical outcomes. Consequently, over the subsequent decades, anesthesia for all surgical procedures in neonates has been accepted as both a clinical and an ethical imperative.

It is also now generally accepted that neonates are capable of sensing pain and discomfort. We have no recallable memories before 3-4 years of age (termed *infantile amnesia*), but neonates do possess consciousness and a sense of self and can form implicit memories, that is, changes in behavior based on prior experience that do not require intentional recall. Plasticity is an inherent characteristic of the developing nervous system, and early pain experiences can lead to exaggerated responses to later painful stimuli or stress, as well as impaired neurodevelopmental outcome.[56,57] Activation of brain regions in response to graded moderate pain stimuli is significantly different in school-age children and adolescents with neonatal intensive care (NICU) experience compared with controls, as measured by functional magnetic resonance imaging (MRI).[29] Based on such evidence, the goals of anesthesia in neonates are not restricted to prevention of the stress response to surgery but also effective management of pain and discomfort.[1,2]

Coincident with a new understanding of the importance of anesthesia and pain management in neonates, numerous animal studies, including some in nonhuman primates, have demonstrated abnormal neuroapoptosis and, in some, long-term cognitive deficits including delayed learning, impaired memory formation and retention, altered motor development, and altered behavioral development. These studies have shown effect after early exposure to virtually all commonly used anesthetic and analgesic agents.[7,53] Development of the nervous system is complex, involving neuronal proliferation, migration, differentiation, and "pruning" accomplished by apoptosis. This development is in part dependent on the balance of excitatory and inhibitory stimuli and neurotransmitters. Given the complexity of the process, as well as the obvious physiologic and developmental differences inherent in application of animal studies to humans, the overall impact of these studies remains uncertain. Concerns have been raised with respect to the animal data regarding dosing and the time course of exposure. A clinically appropriate dose is the minimum necessary to induce anesthesia in the species. In some species, and with some agents, this dose also results in significant mortality, increasing the difficulty of interpreting the significance. Synaptogenesis in rats occurs postnatally over the first 2 weeks of life. An analogous period in humans would range from the third trimester of pregnancy through the first 3 years of life. Whether the child might be susceptible to anesthetic toxicity during this entire period is unknown. Elucidation of the critical period is of prime importance in anesthetic management. Studies in nonhuman primates are assumed to be more translatable to humans. Infant macaques exposed to multiple sevoflurane or isoflurane anesthetics exhibited increased anxiety behaviors and motor reflex deficits.[10,48] Finally, most of the animal studies of apoptosis involve anesthesia without surgery. Because neurodevelopment is related to the balance of stimulatory and inhibitory neurotransmitters, there is some indication that the absence of surgical stress may alter the neurodevelopmental response to anesthetics.

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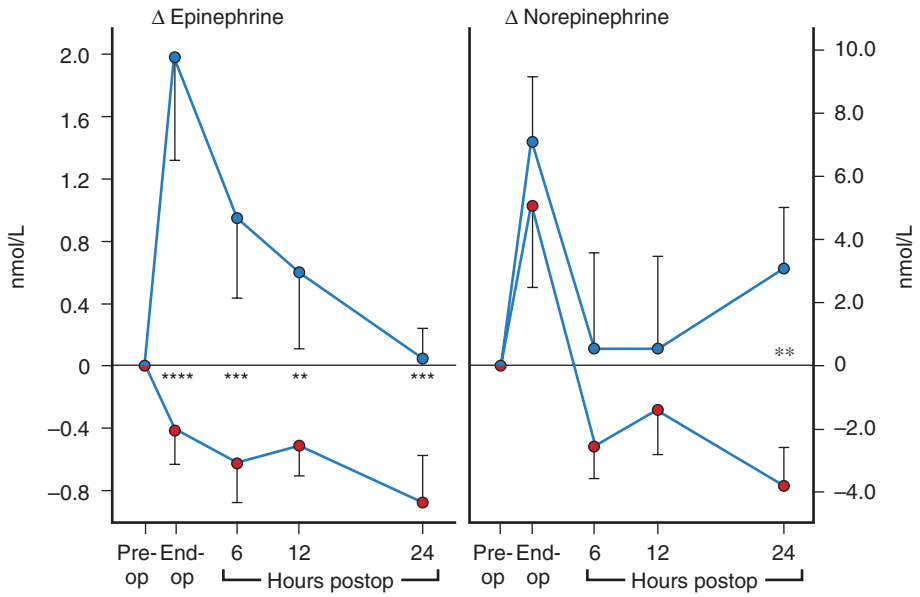
Abstract

The administration of anesthesia to the neonatal patient requires knowledge and understanding of neonatal anatomy and pathophysiology in addition to the ability to understand how the pharmacology of standard anesthetic drugs is altered in preterm and term neonates. Anesthetic care of these oftentimes critical patients is best performed by specialty-trained pediatric anesthesiologists. This chapter reviews how to create a surgical environment that is tailored to the neonatal patient with appropriate monitoring, equipment, and personnel. The preoperative evaluation and anesthetic plan take into account neonatal physiology and diseases of prematurity that may have an effect on the pharmacology of various anesthetic agents. Knowledge of these factors allows for both general and regional anesthetics to be safely and successfully carried out. Renewed interest in regional anesthesia has provided increasing data that neuraxial and regional blocks are safe to perform in the neonatal population. The safety of modern anesthetics in this vulnerable population continues to be an area of concern as numerous animal studies have shown neuronal apoptosis and neurocognitive deficits as a result of exposure to most modern anesthetics. Recent human studies are reviewed and suggest that brief anesthesia exposure early in life appears to be safe, but it continues to be an area of intense focus and research.

Keywords

neonate
prematurity
general anesthesia
neurotoxicity
neuroapoptosis
regional anesthesia

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• **Fig. 39.1** Change (Δ) from baseline of epinephrine and norepinephrine in nanomoles per liter (nmol/L) before surgery to the end of the operation and for the first 24 hours thereafter. The two groups reflect nitrous oxide-fentanyl anesthesia (*red circles*) and nitrous oxide anesthesia (*blue circles*). In the patients given fentanyl, there was no increase in epinephrine or norepinephrine, not only during surgery but also for the first 24 hours after surgery, indicating a significantly blunted stress response.

TABLE 39.1 Perioperative Complications

Complication	Control	Fentanyl
Frequent bradycardia	4	1
Hypotension, poor circulation	4	0
Glycosuria	1	0
Acidosis	2	0
Increased ventilatory requirements	4	1
Intraventricular hemorrhage	2	0
Total complications	17	2

Data from Anand KJ, et al. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet.* 1987;1:62.

Confirmation of long-term and relatively subtle effects in humans is, of course, a daunting task. Prior to 2015, human studies of the long-term effects of anesthetic exposure on the developing brain were largely retrospective and observational, employed varying study designs, and used a wide range of tools to assess neurodevelopmental outcomes.[6,15,19,20,25,26,31,32,52,62] The results were inconsistent and at times conflicting. Exposure to multiple anesthetics during infancy and early childhood was often associated with poorer neurodevelopmental outcomes, whereas a single anesthetic exposure varied between no adverse outcomes to some degree of neurodevelopmental impairment.

Two recent prospective studies with more robust methodology reveal that a single brief anesthetic in early life may have no effect on long-term neurocognitive development. The GAS study, a prospective randomized controlled trial comparing sevoflurane general anesthesia to awake regional anesthesia (spinal or caudal) for herniorrhaphy in infancy, did not reveal any difference in neurodevelopmental outcome at 2-year follow-up.[13] The PANDA study, a prospective sibling-matched cohort study, compared neurocognitive outcomes in infants receiving a short inhaled general anesthetic for herniorrhaphy to a biological sibling with no anesthetic exposure. Follow-up neuropsychological assessment of sibling pairs at ages varying from 8-15 years old showed no difference in neurocognitive outcomes.[54]

In addition, three large retrospective matched cohorts with greater than 59,000 children combined did not find sufficient data to conclude that young age at initial exposure or multiple anesthetic exposures contributed to adverse neurodevelopmental outcomes.[23,24,44]

Despite these more recent studies pointing to the safety of brief anesthetic exposure, the US Food and Drug Administration (FDA), as a result of their ongoing initiative to study the risk of anesthetic exposure on brain development, has published a warning against repeated or lengthy use of general anesthetic and sedation drugs during surgeries and procedures in children younger than 3 years of age or in pregnant women.[17] Many questions still remain regarding anesthetic safety. What is the maximum duration or dose of safe anesthetic exposure? What are the long-term risks to those requiring multiple or longer anesthetic exposures? Do additional comorbid conditions predispose patients to a higher risk of neurocognitive impairment?

No one can question the overwhelming benefit of anesthesia in the setting in which a surgical procedure, or any

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noxious procedure with significant stress, is required. The detrimental effects of surgical stress have been well shown. Similarly, the benefits of early repair of some surgical problems, such as tetralogy of Fallot or neonatal hernia with risk of incarceration, have been shown, although such repair may lead to anesthesia at a younger, and potentially more susceptible, age. Current human studies suggest that a short anesthetic during early development is safe.

When deciding to proceed with an anesthetic, the benefit versus the risk of delay in surgical procedures, particularly if performed in premature infants, should be carefully considered. Second, it seems reasonable to perform a "simple" anesthetic. There is virtually no extensive experience with many anesthetic agents in neonates. This lack of extensive experience is not unusual in neonates or pediatrics in general but may be of increased importance given the small therapeutic margin of most anesthetics. One preference is to use a predominantly narcotic technique in premature infants who may be most at risk, when appropriate. Fentanyl has little, if any, activity as either an *N*-methyl-D-aspartate (NMDA) antagonist or gamma-aminobutyric acid (GABA) agonist. It is well tolerated hemodynamically and effective at preventing the surgical stress reaction. This particular technique may prevent extubation at the conclusion of the procedure, but in this generally ill population, that is not always a consideration.

The goals of neonatal anesthesia are the same as in adults but require different skills, knowledge, and care. The differences between adults and children are most profound in neonates, particularly premature infants. Advances in neonatology and the almost routine survival of infants weighing greater than 1000 g have led to new challenges for pediatric anesthesiology. Successful anesthetic management in a neonate requires meticulous attention to detail and a thorough understanding of neonatal physiology and development, pharmacology, and pathophysiology. The neonatal period is characterized by immaturity of organ systems, homeostasis, and metabolic pathways. It is a time of major developmental changes, and the effects of anesthesia on that development are not well characterized.

Personnel, equipment, and the operating room environment need to be specifically adapted for neonates. Anesthesia-related morbidity is decreased in children anesthetized by pediatric anesthesiologists compared with children cared for by nonpediatric anesthesiologists.[30] Monitors, anesthesia delivery systems, mechanical ventilators, and environmental controls all need to be appropriate for use with neonates.

It is important to emphasize the perioperative nature of anesthetic management. Anesthesia care does not start and end at the door to the operative suite, and this is as critical in neonates as in older children and adults. Preoperative condition and management affect intraoperative care. Transport to the operating room can be one of the most critical aspects of an operation in a premature neonate. The postoperative period requires close monitoring and management of ventilation, fluid balance, and an environment tailored to the special needs of neonates. Assessment and control of postoperative pain require methods and tools specific to neonates.

Knowledge of the anatomic and physiologic differences among neonates, children, and adults is critical to careful anesthetic administration and management. Maturity of organ systems and metabolic processes varies significantly not only between adults and neonates but also between preterm and term neonates.

Anesthesia, Neonatal Physiology, and Specific Concerns

Transition Phase and Persistent Pulmonary Hypertension of the Neonate

In utero, the pulmonary circulation is a high-resistance circuit so that the lungs receive little blood flow, and oxygenation is a placental function. At birth, approximately 35 mL of amniotic fluid is expelled from the lungs, the lungs re-expand, and respiration begins. The lungs are initially very stiff (compliance very low), and the first breath may require negative forces of 70 cm H_2O or more. Pulmonary vascular resistance (PVR) decreases rapidly with lung distention, while oxygenation, pulmonary blood flow, and cardiac output increase. The increase in pulmonary blood flow coupled with decreased venous return from the inferior vena cava with clamping of the placenta causes left atrial pressure to exceed right atrial pressure, resulting in closure of the foramen ovale. The ductus arteriosus closes between 1 and 15 hours after birth.

Although PVR decreases, the pulmonary arterioles possess abundant smooth muscle, and the pulmonary vascular bed remains very reactive. In this setting, hypoxia, hypercarbia, or acidosis can cause a sudden increase in PVR and a return to a fetal circulatory pattern, a condition known as persistent fetal circulation or persistent pulmonary hypertension of the neonate (PPHN). Persistent pulmonary hypertension of the neonate is an acute, life-threatening condition, as shunt fraction increases to 70%-80%, and profound cyanosis results. Many factors during anesthesia can affect this transitional state. Anesthetic agents can markedly diminish systemic vascular resistance (SVR), resulting in a right-to-left shunt. Hypoxia or hypercarbia and acidosis from inadequate ventilation can increase PVR, as can increased sympathetic stimulation during surgical stress, with similar effects on right-to-left shunt.

Respiratory Physiology: Apnea, Central Control of Ventilation, and Respiratory Distress Syndrome

Anesthetic agents are respiratory depressants. Central regulation of breathing is obtunded under anesthesia, with a significant decrease in the ventilatory response to increased carbon dioxide (CO_2). Compared with older children and adults, in neonates, lung volume and functional residual capacity (FRC) as a percentage of body size are much less.

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Alveolar ventilation per unit lung volume is very high, because the neonate's metabolic rate is about twice that of an adult. Most of this alveolar ventilation is provided by a rapid respiratory rate of 35-40 breaths/min, because tidal volume is limited, owing to the structure of the chest wall.

One consequence of the reduced FRC and high metabolic rate in a neonate is a diminished reserve. Changes in the fraction of inspired oxygen (FIO_2) are rapidly seen as changes in PO_2, and the neonate quickly desaturates if ventilation is interrupted. This situation limits time for intubation, and airway management can be difficult. The high alveolar ventilation also accounts for a very rapid uptake of inhalational anesthetic agents, especially in premature infants, making it easy to overdose with these agents. Closing volume, which is the lung volume at which smaller airways tend to collapse, is very close to FRC in neonates. It is well known that anesthesia causes decreases in FRC. In a neonate, this low closing volume can result in airway closure at end expiration, with resultant atelectasis, ventilation/perfusion mismatch, and increased intrapulmonary shunting.

An awake infant uses laryngeal braking, resulting in an auto-positive, end-expiratory pressure (auto-PEEP) to maintain FRC, but laryngeal braking is diminished by anesthesia. In a premature neonate, alveoli are immature and thick-walled and saccular. Surfactant production begins at 23-24 weeks' gestation, but it may remain inadequate until 36 weeks' gestational age; because of this, lung volumes and compliance are decreased further in very premature infants. Although the lung is less compliant in an infant than in an older child, the chest wall in an infant is very compliant. This combination results in increased work of breathing. Because resistance to airflow is inversely proportional to the fourth power of the radius of the airway, the work of breathing is increased further in neonates, particularly small premature infants.

Changes in airway resistance are also common during anesthesia, often resulting from small endotracheal tubes and equipment factors such as inspiratory and expiratory valves in the breathing circuit. Kinking of the endotracheal tube or the presence of secretions also can adversely affect resistance. Respiratory failure from fatigue can occur easily. Most neonates require controlled positive pressure ventilation during operative procedures because of the low FRC, increased closing volume, and increased work, along with changes induced by anesthetics. Infants already being ventilated require some increase in their ventilator settings after induction of anesthesia, and some infants require increased postoperative ventilatory support.

Tracheomalacia is common in premature infants, and if low in the airway, it may not be obviated by intubation. Bronchomalacia may result in airway collapse on expiration. Continuous positive airway pressure (CPAP) or PEEP increases FRC and decreases closing volume and helps to stent open the airway during anesthesia. Slower respiratory rates should be used with positive pressure ventilation to allow time for passive exhalation and prevent air trapping. The premature lung is very susceptible to barotrauma and oxygen toxicity. Pneumothorax and interstitial emphysema may develop if high peak inspiratory pressures are used.

Periodic breathing with intermittent apneic spells is common in neonates up to 3 months of age. Small premature infants have a biphasic ventilatory response to hypoxia, with an initial increase in ventilation, followed by a progressive decrease and eventual apnea. The ventilatory response to CO_2 is decreased in premature infants and, as noted, is decreased further by anesthesia. Postoperative apneic spells are common in premature infants, although incidence decreases with advancing postconceptional age. These episodes can be secondary to the immature respiratory control system (central), a floppy airway (obstructive), or both (mixed or combined). Cote and coworkers did a meta-analysis of data from eight separate studies and found wide variability among institutions. It was clear, however, that the risk of apnea was strongly inversely related to gestational age and postconceptional age. A full-term neonate is unlikely to experience significant postoperative apnea after 45 weeks' postconceptual age, while an infant born prematurely is at risk for postoperative apnea until 55-60 weeks' postconceptual age.[10a]

Airway Anatomy

Airway anatomy in infants differs from anatomy in older children. The infant's head is much larger compared to body size, with a more prominent occiput and shorter neck than that of older children. The infant's tongue is large, but the larynx is higher and anterior, with the cords located at C4 in the infant compared with C5 or C6 in an adult. The epiglottis of the infant is soft and folded. The neonate's larynx has historically been described as conical, with the narrowest point in the subglottic area at the cricoid ring. Studies have revisited this anatomy using magnetic resonance imaging (MRI)[37] and video-bronchoscopic imaging.[12] Based on these studies, the larynx is cylindrical, although not round in cross-section but rather elliptical, with the anteroposterior dimension slightly greater. A tight-fitting, round endotracheal tube might compress the lateral laryngeal mucosa; subglottic stenosis remains a common complication, especially with longer-term intubation. Although uncuffed endotracheal tubes previously were used in neonates and children, use of newer cuffed tubes, composed of very thin, low-pressure cuffs and thin walls, is feasible in many infants, although an uncuffed tube is still required in the smallest neonates. New tubes are available with very thin cuffs, and without the Murphy eye, which decreases the length of the tube below the cuff. This ensures that the entirety of the cuff is below the cords, avoiding pressure on the cords. A cuffed tube can be sized smaller, because the cuff prevents leakage and could decrease the incidence of subglottic stenosis rather than increase it as previously believed, especially when attention is paid to cuff pressures. Intraoperatively, a cuffed tube may be essential to minimize air leakage and allow for effective positive pressure

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ventilation during surgical procedures that may significantly affect respiratory mechanics (laparoscopy, intrathoracic and intracardiac procedures with an open chest). Laryngeal and tracheal trauma is important because even modest airway edema can be serious. At the cricoid ring, 1 mm of edema results in a 60% reduction in the cross-sectional area of the airway, causing increased airway resistance and increased work of breathing. Laryngomalacia is also common in premature infants and can result in obstruction.

Cardiac Physiology

Transitional cardiac changes were discussed earlier. Immediately after birth, with an open ductus arteriosus, most of the cardiac output is from the left ventricle, and left ventricular end-diastolic volume is very high. Consequently, the neonatal heart functions at the high end of the Starling curve. As PVR decreases, output from the two ventricles becomes balanced at 150-200 mL/kg per minute. Heart rate is rapid at 130-160 beats/min. Because end-diastolic volumes are already high, the infant heart is unable to increase stroke volume to a significant degree, and increases in cardiac output depend entirely on increases in heart rate. Baseline blood pressure is lower in infants than in older children, particularly in preterm infants, because cardiac output is increased owing to a low SVR.

Almost all anesthetic agents have significant effects on the cardiovascular system. Inhalational agents tend to be cardiovascular depressants, and they can result in decreased myocardial contractility with bradycardia and subsequent decreased cardiac output. Most anesthetic agents cause decreased autonomic tone and peripheral vasodilation, decreasing afterload and preload. Because baroreceptor reflexes also are blunted by anesthesia, these decreases may make it impossible for the infant to compensate for pre-existing volume contraction or volume losses during anesthesia. Inotropic support may be necessary in a sick neonate, and almost all infants require some degree of volume loading during anesthesia. This belief may be at odds with contemporary thoughts on respiratory management, which emphasize diuresis; volume therapy needs to be carefully balanced to support tissue perfusion, urine output, and metabolic needs.

Patent ductus arteriosus is common in preterm neonates and can result in pulmonary overcirculation and congestive heart failure. The patent ductus arteriosus may close spontaneously. Medical therapy with nonsteroidal anti-inflammatory drugs is sometimes successful. A patent ductus arteriosus may require surgical ligation or, more recently, catheter-based occlusion. The potential adverse effects of anesthesia associated with ductal closure remain controversial.

Fetal Hemoglobin

The infant has approximately 80% fetal hemoglobin (hemoglobin F) at birth. Hemoglobin F has a P50 (partial pressure of oxygen at which hemoglobin is 50% saturated) of 20 mm Hg compared with a P50 of 27 mm Hg for hemoglobin A, which means that hemoglobin F has a higher affinity for oxygen and that the hemoglobin dissociation curve is shifted to the left. In utero, this hemoglobin dissociation curve favors transport of oxygen from the maternal to the fetal circulation. Put another way, for any given oxygen saturation, the infant has a lower Po_2. Unloading of oxygen at the tissue level also is diminished, although this is compensated for by an increased hemoglobin level of approximately 17.5 g/dL at birth. The decreased unloading can result in tissue hypoxia, however, if Po_2, hemoglobin, or cardiac output decreases during surgery, with secondary development of metabolic acidosis. The hemoglobin increases slightly just after birth, then decreases progressively to a level of 9.5-11 g/dL by 7-9 weeks of life, owing to decreased red blood cell life span, increasing blood volume, and immature hematopoiesis. Hemoglobin F synthesis begins to decrease after 35 weeks' gestation, and hemoglobin F is completely replaced by hemoglobin A by 8-12 weeks of life, paralleling the decrease in hemoglobin and helping to maintain tissue oxygenation.

Renal Physiology

Nephrogenesis is complete at 34 weeks' gestation, and the term neonate has as many nephrons as an adult, although they are immature, with a glomerular filtration rate (GFR) approximately 30% of the adult GFR. With increasing cardiac output and decreasing renal vascular resistance, renal blood flow and GFR increase rapidly over the first few weeks of life and reach adult levels by about 1 year of life. The diminished function over the first year is well balanced to the infant's needs, because much of the neonate's solute load is incorporated into body growth, and excretory load is smaller.

Several aspects of renal physiology are pertinent to anesthesia care. First, the neonatal kidney has only limited concentrating ability, apparently owing to a diminished osmotic gradient in the renal interstitium, whereas antidiuretic hormone secretion and activity are normal. Coupled with an increased insensible loss owing to a "thin" skin and increased ratio of surface area to volume, the limited concentrating ability of the kidney implies a tendency to become water depleted if intake or administration is inadequate. The neonatal kidney also is unable to excrete dilute urine efficiently and cannot handle a large free water load. In addition, primarily owing to a short, immature proximal tubule, infants are obligate sodium wasters. There is a tendency toward hyponatremia, especially if too much free water is administered during surgery, which can easily happen with continuous infusions from invasive pressure transducers, especially if adult transducers are used. Because of the lower GFR, the neonate also cannot handle a large sodium load and can easily develop volume overload and congestive heart failure. One final aspect concerns acid-base status: The neonatal kidney wastes small amounts of bicarbonate owing to an immature proximal tubule; infants are born with a mild proximal renal tubular acidosis, with

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serum bicarbonate of approximately 20 mmol/L. All these changes are greater in preterm infants, particularly before nephrogenesis is complete at 34 weeks.

Temperature Regulation

Given a large surface area, small body volume, and minimal insulation, neonates are extremely prone to heat loss. Any degree of cold stress is detrimental and increases metabolic demands in the neonate. Infants are unable to shiver effectively, and cold stress causes catecholamine release, which stimulates nonshivering thermogenesis by brown fat. Premature infants have less brown fat, decreasing their capacity for nonshivering thermogenesis and increasing their risk for hypothermia. The increased catechols caused by cold stress can be detrimental, causing increased peripheral vascular resistance and SVR, increased cardiac stress, and increased oxygen consumption. Anesthesia blunts thermoregulatory sensitivity[5] and interferes with nonshivering thermogenesis and brown fat metabolism.[47] Anesthesia also increases heat loss by inducing cutaneous vasodilation. Surgical factors such as major operations with open body cavities and lower ambient temperatures requested in the operating room also contribute to increased risks of hypothermia in the neonate.[59] At all times, including during transport and in the operating room, the infant must be subjected to a neutral thermal environment. An environment that is too warm can be equally detrimental. Core temperature must be carefully monitored at all times in the operating room.

Carbohydrate Metabolism

Whole-body glucose demand corrected for body mass in neonates can be twice that in adults. Carbohydrate reserves, primarily hepatic glycogen, in a normal newborn are relatively low, and even lower in an infant with low birth weight. Hypoglycemia can readily occur if the infant is deprived of a glucose source. Even transient hypoglycemia may be associated with neurologic injury in neonates.[34] In contrast with adults, in whom hyperglycemia seems to potentiate brain damage during global and focal ischemia, hyperglycemia in neonates may provide some protection from ischemic damage.[11] Generally, intravenous glucose (10% dextrose) or intravenous hyperalimentation should be continued intraoperatively, especially in infants with low birth weight without adequate glycogen or fat stores. Nonetheless, hyperglycemia can also be a problem in the perioperative period. Insulin response is deficient in preterm infants, and high catecholamines owing to illness or intraoperative stress can result in hyperglycemia. Careful monitoring of serum glucose is indicated.

Oxygen Therapy and Retinopathy of Prematurity and Chronic Lung Disease

Hypoxia is a common pathologic condition in neonates because of the incidence of lung disease; congenital heart disease and disordered transition are other frequent causes. Tissue hypoxia, or oxygen delivery to the tissues inadequate to sustain oxidative metabolism, is harmful, with well-known pathologic sequelae. There is, at present, no good method for reliably detecting tissue hypoxia, particularly in a real-time manner. Due to the fear of hypoxia, oxygen therapy was widely used, particularly during anesthesia. However, there is increasing evidence that this resulting iatrogenic hyperoxia is causally associated with multiple pathologic conditions in neonates and should be strenuously avoided.[41,51]

Oxygen is a highly reactive molecule, and free radical formation by oxygen is well known. Reperfusion injury, which refers to damage resulting from free radical formation on reoxygenation after a period of hypoxia, is well established. Retinopathy of prematurity is the most widely known complication of hyperoxia, but there is increasing evidence that oxygen may play a role in chronic lung disease, neurologic impairment, and other pathologic conditions. There is also evidence that wide fluctuations in oxygenation, as often experienced during anesthesia, may be damaging.

Monitoring of oxygenation during operative procedures is problematic. Continuous pulse oximetry is the standard of care and has contributed to the safety of anesthesia by avoidance of hypoxia. The pulse oximeter is not as helpful for detection of hyperoxia. At hemoglobin saturations greater than 95%, most infants are hyperoxic; this is altered further by varying amounts of fetal hemoglobin. Maintenance of saturations greater than 95% is almost universal in most operating rooms but is probably not the best course for neonates. It has been suggested that for ongoing management of neonates in the NICU, oxygen saturation targets of 90%-95% should be used.[18,55] Similarly, it has become common practice to use blended oxygen levels of 30%-40% during initial resuscitation. Current anesthesia practice involves minimizing excessive oxygen administration in preterm neonates as long as oxygen saturation is 90% or greater. Many neonates can be managed intraoperatively on room air. Further consideration probably should be given to the universal practice of using 100% oxygen during induction and emergence from anesthesia, although this is more problematic, because hypoxia also should be avoided, and oxygen desaturation during induction and intubation is frequent. This possibility further underscores the need for experienced personnel during induction and intubation of neonates.

Conduct of an Anesthetic

Preoperative Evaluation and Preparation

The preoperative evaluation should encompass the infant's physical condition, including significant illness, the degree of transition from fetal to newborn physiology, maturity, and the presence of any congenital anomalies. Particular attention should be paid to cardiorespiratory status, required ventilatory or hemodynamic support, blood chemistries, and nutritional support. The course of pregnancy, labor, and delivery and a full maternal history are important details. As

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is the case with older children, a family history of anesthetic difficulties may be important. Maternal diseases such as diabetes, systemic lupus erythematosus, and preeclampsia have implications for the neonate. Congenital infections, oligohydramnios, intrauterine growth restriction, and maternal drug and alcohol use are also important considerations.

Gestational age, birth weight, and postnatal age affect anesthetic care. Birth weight does not accurately reflect maturity unless the infant is appropriate for gestational age, which is defined as being within 2 standard deviations of the mean for gestational age. Infants who are small for gestational age are more mature than their birth weight would indicate. Infants who are large for gestational age are often children of diabetic mothers, and they are at increased risk of hypoglycemia in the first 48 hours after birth. Newborns are characterized by birth weight as low birth weight (≤2.5 kg), very low birth weight (≤1.5 kg), and extremely low birth weight (<1000 g). Term is gestational age of 37-42 weeks, preterm is younger than 37 weeks, and postterm is older than 42 weeks.

A history of birth asphyxia or neonatal resuscitation and Apgar scores are important. History should include complete details of the present illness and treatment. Medications and administration times, details of vascular access, and respiratory parameters including ventilator type and settings all are crucial details, especially in sicker infants. Infants on high-frequency oscillatory ventilation may need to be switched to conventional ventilation and observed for several hours to facilitate movement to an operating room. If the infant is on some other modality, such as inhaled nitric oxide or extracorporeal membrane oxygenation, arrangements may also need to be made, and transport to the operating room would require more resources and assistance.

The time of the last oral feed should be ascertained, especially in elective surgery in healthier infants. Attenuation of airway reflexes with induction of anesthesia places the infant at risk of aspiration of acidic gastric contents, which can lead to serious inflammatory pneumonitis. *Nil per os* (NPO; nothing by mouth) guidelines are summarized in Table 39.2[3]; these guidelines are more liberal for newborns than adults. This shorter length of time partially reflects more rapid gastric emptying, although in an infant, dehydration occurs much more quickly than in an adult, and this is a concern in an infant without an intravenous line. Attempts to minimize NPO time should be made to avoid interruptions in vital nutrition. As in adults, gastric emptying is delayed with stress, anxiety, and illness. Infants with diseases such as pyloric stenosis, duodenal atresia, malrotation, or other obstructive lesions are NPO before surgery, and they need an intravenous line to maintain appropriate hydration. Despite the NPO status, there usually are significant gastric contents, and rapid-sequence or awake intubation is required if there is any concern for obstruction. Emptying the stomach via nasogastric drainage is undependable and usually inadequate. Nasogastric feeds in intubated infants also should be discontinued at an appropriate time, because the infant may need to be reintubated during surgery, and a full stomach would increase the risk for aspiration.

TABLE 39.2 NPO Guidelines

Intake	Time (h)
Clear liquids	2
Breast milk	4
Formula	6

NPO, *Nil per os* (nothing by mouth).

Physical examination includes vital signs, including temperature. Volume status needs to be carefully assessed because major shifts can occur easily during surgery. Many infants requiring surgery are ill. Infants with congenital anomalies often have multiple defects, which may have an impact on anesthetic care. Often, a group of defects suggests a well-recognized and characterized syndrome. Common syndromes with their anesthetic implications are listed in Table 39.3. (This list is incomplete.)

Difficult intubation is a common problem in infants with congenital defects, and the airway needs to be carefully assessed. Because of the tendency for rapid oxygen desaturation in infants, difficulties with intubation can be extremely serious. In infants who are already intubated, tube size and position should be evaluated. The pressure at which a leak occurs around the tube should be documented. Nurses should be questioned about the quantity and consistency of secretions and need for frequent suctioning. The small tubes required in premature infants can easily be blocked by tenacious secretions and are easily dislodged. If there is any question about adequacy of intubation, the infant should be electively reintubated before surgery; emergently replacing an endotracheal tube under the drapes after beginning an operation is not a benign procedure.

A complete physical examination should be performed, with particular attention paid to cardiorespiratory status. Laboratory studies and x-ray films need to be reviewed, if applicable. Hemoglobin level usually should be greater than 10 g/dL to ensure adequate oxygen delivery to the tissues, given the decreased unloading at the tissue level by fetal hemoglobin. Metabolic acidosis should be corrected, preferably by reversal of the cause of the acidosis. Electrolyte levels help to guide fluid management; hypocalcemia should be corrected. For most operations, it is important to check that blood for transfusion is available; for major procedures, fresh frozen plasma and platelets for transfusion also may be required.

Several specific areas should be explored by the anesthesiologist. As previously discussed, the pulmonary circulation in a neonate is hyperreactive, and in a near-term infant, lung disease, asphyxia, and surgical stress can initiate episodes of pulmonary hypertension, resulting in decreased cardiac output and oxygen desaturation. Any history of such spells

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TABLE 39.3 Anesthetic Implications of Neonatal Syndromes

Syndrome	Clinical Manifestations	Anesthetic Implications
Adrenogenital syndrome	Defective cortisol synthesis Electrolyte abnormalities Virilization of girls	Supplement cortisol
Analbuminemia	Almost absent albumin	Sensitive to protein-bound drugs (thiopental, curare, bupivacaine)
Andersen syndrome	Midface hypoplasia Kyphoscoliosis	Difficult airway Impaired respiratory function
Apert syndrome	Craniosynostosis Hypertelorism Congenital heart disease possible	Difficult airway Increased ICP Cardiac evaluation, prophylactic antibiotics
Arthrogryposis multiplex congenital	Contractures Restrictive pulmonary disease	Care in positioning Difficult airway Postoperative ventilation
Beckwith-Wiedemann syndrome	High birth weight Macroglossia Neonatal hypoglycemia	Difficult airway Monitor blood glucose, continuous glucose infusion, avoid boluses
CHARGE association	Coloboma Heart defects Atresia choanae Restricted growth and development Genital hypoplasia Ear deformities	Bilateral choanal atresia may require oral airway Cardiac evaluation, prophylactic antibiotics
Cherubism	Intraoral masses Mandibular, maxillary tumors	Difficult airway Possible cor pulmonale
Chiari malformation	Hydrocephalus Cranial nerve palsies Other CNS lesions	Aspiration precautions Vocal cord paralysis Latex allergy precautions
Congenital hypothyroidism	Macroglossia Goiter Decreased metabolic rate Myxedema Adrenal insufficiency	Difficult airway Delayed gastric emptying Fluid and electrolyte imbalance Sensitivity to cardiac and respiratory depressants Stress steroids
Cornelia de Lange syndrome	Micrognathia, macroglossia Upper airway obstruction Microcephaly Congenital heart disease	Difficult airway Cardiac evaluation, prophylactic antibiotics
Cri du chat syndrome	Abnormal larynx, odd cry Microcephaly Hypertelorism, cleft palate Cardiac abnormalities	Difficult airway Cardiac evaluation, prophylactic antibiotics
Crouzon disease	Craniosynostosis Hypertelorism	Difficult airway Increased ICP
Dandy-Walker syndrome	Hydrocephalus Other CNS lesions	Increased ICP Latex allergy precautions
DiGeorge syndrome	Absent thymus, parathyroids Immunodeficiency Stridor Cardiac anomalies	Monitor calcium Exaggerated response to muscle relaxants Blood for transfusion irradiated Cardiac evaluation, prophylactic antibiotics

Continued

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TABLE 39.3 Anesthetic Implications of Neonatal Syndromes—cont'd

Syndrome	Clinical Manifestations	Anesthetic Implications
Down syndrome (Trisomy 21)	Atlantoaxial instability Macroglossia Congenital subglottic stenosis Duodenal atresia Cardiac defects (atrioventricular canal) Mental retardation	Difficult airway, use smaller tube Care with neck manipulation Cardiac evaluation, prophylactic antibiotics
Dwarfism	Odontoid hypoplasia, atlantoaxial instability Micrognathia, cleft palate	Care with neck manipulation Cardiac evaluation, prophylactic antibiotics
Eagle-Barrett syndrome (prune-belly syndrome)	Absent abdominal musculature Renal dysplasia Pulmonary hypoplasia	Respiratory insufficiency Renal failure
Ellis-van Creveld syndrome	Ectodermal defects, short extremities Congenital heart defects Chest abnormalities Abnormal maxilla	Difficult airway Impaired respiratory function Cardiac evaluation, prophylactic antibiotics
Goldenhar syndrome	Maxillary hypoplasia, micrognathia Cleft or high arched palate Eye and ear abnormalities Hemivertebra or vertebral fusion Congenital heart defects Spina bifida	Difficult airway Cervical spine evaluation Cardiac evaluation, prophylactic antibiotics
Holoprosencephaly	Midline deformities of face, brain Dextrocardia, ventricular septal defect Incomplete rotation of colon Hepatic malfunction, hypoglycemia Mental retardation, seizures	Difficult airway Postoperative apneas Cardiac evaluation, prophylactic antibiotics
Holt-Oram syndrome (heart-hand syndrome)	Radial dysplasia Congenital heart defects	Cardiac evaluation, prophylactic antibiotics
Jeune syndrome	Chest malformations Pulmonary hypoplasia and cysts Renal disease	Respiratory insufficiency, high risk of barotrauma Renal failure
Klippel-Feil syndrome	Fusion of cervical vertebrae Congenital heart defects	Difficult intubation Cardiac evaluation, prophylactic antibiotics
Möbius syndrome	Paralysis of cranial nerves VI and VII Micrognathia Recurrent aspiration Muscle weakness	Difficult airway Aspiration precautions
Mucopolysaccharidoses (Hurler and Hunter syndromes)	Macroglossia Hepatosplenomegaly Hydrocephalus Odontoid hypoplasia and atlantoaxial subluxation Valvular heart disease and cardiomyopathy	Difficult airway Abnormal coagulation Cervical spine instability Cardiac evaluation Increased ICP
Noonan syndrome	Micrognathia Webbed neck, short stature Congenital heart defects Hydronephrosis or hypoplastic kidneys	Difficult airway Cardiorespiratory evaluation Renal dysfunction
Oral-facial-digital syndrome	Cleft lip and palate Mandibular, maxillary hypoplasia Hydrocephalus Polycystic kidneys Digital abnormalities	Difficult airway Increased ICP Renal dysfunction

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TABLE 39.3 Anesthetic Implications of Neonatal Syndromes—cont'd

Syndrome	Clinical Manifestations	Anesthetic Implications
Osteogenesis imperfecta	Blue sclera, pathologic fractures, deafness Congenital heart defects Increased metabolism and hyperpyrexia	Difficult airway Careful positioning and padding Hyperpyrexia with anesthesia (not malignant hyperpyrexia)
Pierre Robin syndrome	Micrognathia Cleft palate Glossoptosis Congenital heart defects Cor pulmonale	Difficult airway, laryngeal mask airway may be useful Cardiac evaluation, prophylactic antibiotics
Potter syndrome	Renal agenesis Low-set ears Pulmonary hypoplasia	Spontaneous pneumothorax Renal failure Respiratory insufficiency
Sturge-Weber syndrome	Vascular malformations and hemangiomas (intracranial)	Possible blood loss
Treacher Collins syndrome	Facial and pharyngeal hypoplasia Micrognathia, choanal atresia Congenital heart defects	Extremely difficult airway Cardiac evaluation, prophylactic antibiotics
Trisomy 18	Congenital heart disease common Micrognathia	Difficult airway Cardiac evaluation, prophylactic antibiotics
Turner syndrome	Micrognathia Webbed neck, short stature Congenital heart defects Renal anomalies	Difficult airway Cardiac evaluation, prophylactic antibiotics Renal insufficiency
VACTERL association	Vertebral anomalies Imperforate anus Cardiac defects Tracheoesophageal fistula Radial dysplasia Renal anomalies	Cardiac evaluation, prophylactic antibiotics Tracheoesophageal fistula management
Williams syndrome	Elfin facies Infantile hypercalcemia Supravalvular aortic stenosis	Cardiac failure
Zellweger syndrome	Craniofacial dysmorphism Glaucoma Peroxisomal abnormalities in kidney and liver	Difficult airway Impaired renal drug excretion Electrolyte imbalance Abnormal coagulation

CNS, Central nervous system; ICP, intracranial pressure.

requires increased vigilance to avoid hypoxia, hypercarbia, and acidosis, which tend to increase pulmonary resistance. Bronchopulmonary dysplasia is a common chronic lung disease of premature infants. Infants with bronchopulmonary dysplasia are susceptible to excessive pulmonary vasoconstriction in response to hypoxia, hypothermia, or acidosis. Because of their chronic lung disease, these infants may have some degree of cor pulmonale, and decreases in myocardial function related to anesthetics may result in acute right heart failure. Other problems in bronchopulmonary dysplasia include airway hyperreactivity, increased airway secretions, electrolyte abnormalities because of diuretic therapy, and frequently tracheomalacia.[42]

Congenital anomalies of the heart also must be carefully evaluated. Right-to-left shunts affect the oxygenation of the infant, whereas left-to-right shunts typically result in volume overload. The infant should be carefully evaluated for signs of congestive heart failure, such as hepatic congestion, enlarged heart, and edema. The presence of single ventricle physiology is particularly important, because the anesthesiologist needs to take great care to maintain balance between the pulmonary and systemic circulations. High inspired oxygen concentration in these infants results in pulmonary vasodilation and pulmonary overcirculation at the expense of systemic circulation, with consequent acidosis. Particular attention should be paid to ventilation; in some cases,

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increased inspired CO_2 may be beneficial. Abnormal pulses on physical examination may indicate coarctation of the aorta. Antibiotic prophylaxis for endocarditis is also often important in neonates with congenital heart disease. Intrinsic arrhythmias are unusual in a neonate, although congenital heart block may occur in infants of mothers with systemic lupus erythematosus.

Neurologic function also should be carefully assessed. Hemodynamic changes during surgery may affect cerebral blood flow. A history of seizures should increase the anesthesiologist's level of suspicion for intraoperative seizure if there are unexplained tachycardias or blood pressure elevations. The presence of intraventricular hemorrhage requires increased care to maintain hemodynamic stability and is a contraindication to procedures requiring anticoagulation. A history of hydrocephalus mandates avoidance of factors that increase intracranial pressure.

Transport Within Hospital

Transport of a premature infant may be as great a risk as the surgery itself. Dedicated transport incubators, with a built-in ventilator, air and oxygen supplies, and a blender should be used if possible. If this equipment is unavailable, extra care must be taken. In addition to the inherent risks involved in the transport of a potentially unstable patient, premature neonates are particularly susceptible to cold stress. Heat loss during transport must be addressed, because the hospital corridors are rarely neutral thermal environments. If the infant is in an incubator, the incubator should be used for transport, because heat is retained even when it is unplugged. An infant on an open radiant warmer should be covered, including the head. In some institutions, plastic wrap is used to retain heat and reduce evaporative losses. Disposable chemical warmer packs are available and can be used under the infant either in an incubator or on the radiant warmer.

A need for assisted ventilation presents additional problems. During hand bagging with an anesthesia bag, CPAP or PEEP is generally lost; in most situations, a simple oxygen tank is also used, limiting ventilation to 100% FIO_2. The anesthesia bag always should include a manometer, because it is easy to reach pressures that can result in barotrauma complications such as pneumothorax. A self-inflating resuscitator can be used for room air ventilation, and a PEEP valve can be added to the device, but controlled oxygen delivery requires an additional air tank and a blender. In an intubated infant, CPAP or PEEP can be maintained using devices such as the Neopuff™. Particular care must be taken not to dislodge the endotracheal tube; small changes can result in either extubation or endobronchial intubation, particularly in a very premature infant. A laryngoscope, endotracheal tubes, and a face mask should be taken on transport in case the endotracheal tube is dislodged.

For all but the healthiest neonates, a physician experienced in neonatal resuscitation and who has the ability to manage critically ill neonates should accompany the transport. In most situations, this person should be the anesthesiologist. Monitoring during transport varies depending on the condition of the infant. As a minimum, a pulse oximeter provides pulse rate and arterial oxygen saturation. In most ill neonates, electrocardiogram (ECG) and blood pressure should also be monitored, especially if the infant has an indwelling arterial line. Any pumps providing infusions to the infant should have adequate battery power to operate throughout the transport, especially if vasoactive drips are running. Syringe pumps provide a very stable rate and have a long battery life, and the entire system is compact, minimizing the equipment needing transport. These pumps also run accurately at a low (0.5 mL/h) rate so that concentrated infusions can be used, minimizing fluid delivered to the neonate.

A complete round of resuscitative medications also should accompany any infant being transported to or from the NICU. Some transports require multiple personnel. With planning and adequate personnel, transport of infants on extracorporeal membrane oxygenation or infants receiving inhaled nitric oxide is possible.

In some situations, if the surgical procedure is appropriate, the surgeon is cooperative, and a suitable locale is available, it may be preferable to perform some procedures in the NICU. Basic requirements for a suitable locale include a clean area that can be closed off from traffic and adequate equipment, including overhead lights, surgical instruments and supplies, appropriate monitors, and anesthesia equipment. For premature neonates, an anesthesia machine is not usually needed, and a standard neonatal ventilator can be used. In many state-of-the-art NICUs, there is a dedicated operating room, with appropriate equipment, gases, and lights within the NICU, so that the most critically ill infants can be cared for with minimal transport.

Operating Room Equipment and Monitoring

The operating room should not merely replicate NICU capabilities; it should surpass them, because the neonate is subjected to the additional stress and destabilization of surgery. It is helpful if the room itself has adequate temperature control, because it may be necessary to increase room temperature to obtain a neutral thermal environment. Before draping, radiant heat lamps can be used, although care must be taken to not place the lamps too close to the infant because overheating can occur. The operating tables for neonates should use a heating pad. For longer cases, forced-air heaters with a "full access" disposable air blanket that is placed under the infant may be used. Care does have to be taken that the sheets and drapes around the infant are dry, however, as evaporative cooling can occur with the continuous air flow if the child is wet. Maintenance fluids, because they are given at a relatively slow rate, usually can be given at room temperature, but fluid warmers must be available for blood or faster fluid administration. Cooling is rarely necessary, but it is possible to overheat an infant if care is not taken. Temperature must be monitored. Core

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• BOX 39.1 Routine Monitoring Requirements

Routine

- Precordial or esophageal stethoscope
- Pulse oximeter
- Electrocardiogram
- Blood pressure (noninvasive or arterial line-umbilical artery catheter or peripheral arterial catheter)
- Core temperature—rectal, esophageal, nasopharyngeal
- End-tidal CO_2
- Peak inspiratory pressure, tidal volume, positive end-expiratory pressure
- Fraction of inspired oxygen (FIO_2)

Optional

- Central venous pressure
- Blood gases—pH, PCO_2, PO_2
- Urine output
- Electrolytes

temperature is the best temperature to monitor. It can be measured with a rectal, nasopharyngeal, or esophageal probe. Bladder and tympanic membrane probes are rarely used in neonates because of size. Skin temperature is a poor choice for monitoring temperature, as it often better approximates the environmental temperature rather than the core temperature in a small infant.

Routine monitoring requirements for neonates are listed in Box 39.1. Continuous pulse oximetry has revolutionized anesthesia, and it is a standard of care in neonates as in adults. In some situations, particularly with congenital heart disease or PPHN, two pulse oximeters may be used to monitor preductal and postductal oxygen saturations. Heart rate is monitored from the pulse oximeter and the ECG. Disposable neonatal ECG pads are needed, from a size standard and because they may adhere better to the vernix caseosa-covered skin of the neonate. Noninvasive blood pressure can be measured, and most available machines have neonatal cuffs and a neonatal mode, which uses a smaller air volume for cuff inflation and is accurate in the neonate.

Invasive arterial blood pressure measurements from an indwelling line should be routine in most sicker or more premature infants. Common sites are the umbilical artery, either radial artery, and the femoral artery (as a last resort). Dorsalis pedis is rarely useful, but an axillary or posterior tibial line may be used occasionally. The arterial line site needs to be considered in relation to the clinical condition of the neonate; if coarctation of the aorta is present, a right radial line should be used. Similarly, if a right Blalock-Taussig shunt is planned, a left radial line is appropriate. Arterial lines in the neonate must be treated with the greatest delicacy. If blood is drawn from the line, a small syringe should be used, and suction should never be applied, because the artery easily can go into spasm. The line always should be flushed gently, again with a syringe and not with a pressure bag attached to the transducer. For smaller neonates, an intravenous infusion pump (not a pressure bag) should be used to keep a continuous flow through the transducer, to prevent inadvertent flushing and to limit the rate of fluid administration through the transducer (3 mL/h with the pressure bag vs. 0.5 mL/h with the pump).

End-tidal CO_2 measurements also have become a standard of care, and they can be very helpful, but obtaining accurate measurements in a small neonate can be difficult. With a typical capnograph, the accuracy depends on the actual site of sampling, the type of anesthesia circuit used, and the volume of fresh gas flow through the circuit. Patient factors such as right-to-left shunt also may alter the values. The most accurate measurements are obtained using a low dead space circuit, with the sampling site in the endotracheal tube, not on the circuit. This location is accomplished via an endotracheal tube connector with a side port molded into it, to which the capnograph sampling tubing can be attached. Blood glucose should be monitored intermittently during anesthesia; the importance of central venous pressure, urine output, and blood gases depends on the situation.

Previously, many anesthesia machines were equipped with a rudimentary, volume-limited, time-cycled ventilator, which even with a pediatric bellows was poorly suited for neonatal ventilation. Small tidal volumes were very difficult to set, and tidal volume and pressure varied tremendously depending on the fresh gas flow. In the best of hands, these ventilators are impossible to use with premature neonates. Newer anesthesia machines incorporate significantly more sophisticated ventilators, capable of either volume-limited or pressure-limited ventilation. These ventilators can be used in pressure-limited, time-cycled mode, and they incorporate a spirometer that can measure expired tidal volumes of 10 mL. Fresh gas flow is uncoupled from tidal volume, and changes in flows do not affect ventilation. Positive end-expiratory pressure can easily be added without the external valves used in older machines. These machines can be used routinely in infants weighing as little as 500 g.

An alternative method is to bring a NICU ventilator to the operating room. Critically ill neonates with high ventilator setting may be best served by the accuracy of a NICU ventilator. Pressure-limited, time-cycled, and volume-limited ventilators are widely used to ventilate the smallest neonates. A disadvantage of pressure-limited ventilation is that tidal volume varies with changes in compliance, and care must be taken during surgery to monitor tidal volume and blood gases and end-tidal CO_2 to ensure adequacy of ventilation. Using a neonatal ventilator usually prevents the use of inhalational anesthetic agents, and it requires an intravenous anesthetic technique.

The circle breathing system, with inspiratory and expiratory valves and incorporating a CO_2 absorber, has become standard in adult anesthesia. A major advantage is that a semiclosed technique with very low gas flows can be used, conserving anesthetic agent. Similar circle systems,

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appropriately sized for infants, with lower compliance tubing and smaller bags, are commonly used in neonates.

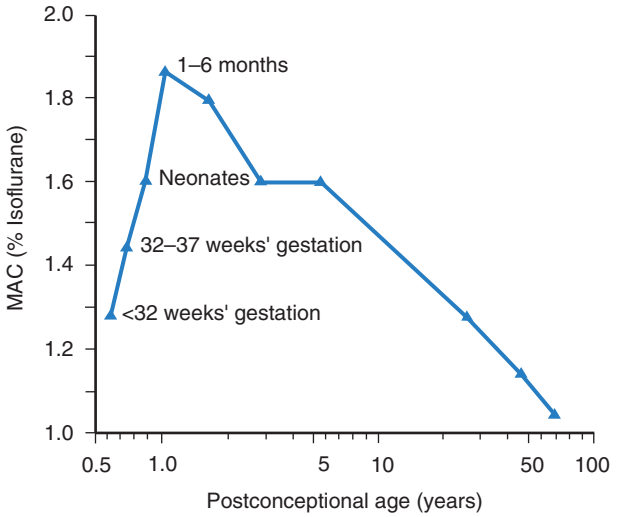
The operating room must be equipped with appropriately sized airway equipment, including Miller No. 00, 0, and 1 blades; cuffed and uncuffed endotracheal tubes; and nasopharyngeal and oropharyngeal airways. An assortment of special blades should be available for difficult airway cases. The laryngeal mask airway (LMA) is a device that fits in the pharynx, covering the glottis and the esophageal opening. A cuff seals against the walls of the pharynx. Laryngeal mask airways do not occlude the esophagus and may notably increase the risk of aspiration during positive pressure ventilation. Laryngeal mask airways are available in small sizes but are not commonly used in neonates. Laryngeal mask airways can be very helpful in assisting with ventilation and intubation in some infants with congenital anomalies such as Pierre Robin syndrome, where securing the airway may be difficult. Essentially, the LMA is positioned, and a fiberoptic bronchoscope is passed through the LMA and into the trachea. An endotracheal tube can be passed through the LMA over the bronchoscope. The neonatal fiberoptic bronchoscope is essential for difficult airway cases. This bronchoscope is limited by extreme flexibility, and it does not have a suction channel, but it passes through a 2.5 endotracheal tube.

General Anesthesia

Most infants who require surgery receive a general anesthetic. There is increasing interest in regional techniques, but most often this is still combined with a general anesthetic. Successful delivery of general anesthesia in neonates requires knowledge of developmental pharmacology to predict and understand the responses of premature infants to anesthetic drugs. Size has an effect on response to anesthetics, and developmental age has a profound impact on the dose response, distribution, and metabolism of these drugs.

Inhalational Agents

Although common in older children, inhalational anesthesia has not been used as extensively in premature infants. Higher doses of volatile anesthetics required for an inhalation induction may be poorly tolerated, causing hypotension, bradycardia, and decreased cardiac output. Careful administration of inhaled anesthetics can allow for safe use of these drugs during the maintenance phase of anesthesia. The anesthetic effect of inhalational agents depends on the partial pressure of the anesthetic in the brain and the potency of the agent. For several reasons, very high partial pressures of the inhalational agents in the brain develop much more rapidly in neonates than in older children and adults. First, as already discussed, the ratio of alveolar ventilation (per minute) to FRC in neonates is 5:1 compared with 1.5:1 in adults, and consequently alveolar anesthetic concentration equilibrates with inspired concentration very quickly. Second, a greater fraction of the cardiac output in



• **Fig. 39.2** Minimum alveolar concentration (MAC) of isoflurane and postconceptional age on a semilogarithmic scale. (From LeDez KM. The minimum alveolar concentration [MAC] of isoflurane in preterm neonates. *Anesthesiology.* 1987;67:301.)

the neonate is distributed to the vessel-rich group and consequently the brain. Finally, the solubility of the inhaled anesthetics in blood is less in neonates than in adults.[36] Brain tissue equilibrates very quickly with the alveolar concentration of anesthetic and increases the risk of overdose in a neonate.

The potency of inhalational anesthetics is expressed using the minimum alveolar concentration (MAC). The MAC is the concentration at which 50% of patients exhibit no response to surgical stimulation such as skin incision. The MAC is related to postconceptional age and is lowest in very premature neonates, increasing to a peak at a postconceptional age of approximately 1 year and then decreasing progressively from childhood through adulthood. Fig. 39.2 shows this relationship for isoflurane.[36] As shown, isoflurane is more potent (lower MAC) in premature neonates than in older infants, but this MAC is not markedly different from that of adults, and difficulties using inhalational anesthetics are related more to the rapid uptake and equilibration.

Common inhalational anesthetics are the halogenated volatile anesthetics isoflurane and sevoflurane. Desflurane is rarely used in neonates. Inhalational anesthetics are complete anesthetics, with analgesic and amnesic properties. Isoflurane is very pungent and cannot be used for mask induction. Systemic vascular resistance is decreased by isoflurane and hypotension can result, especially if preload is diminished. Moderate volume loading helps to minimize any decrease in blood pressure. Isoflurane also causes cerebral vasodilation, and in the absence of hypotension, cerebral blood flow increases. In adults, isoflurane decreases cerebral metabolism and is cerebral protective.

Sevoflurane has become very popular in pediatric anesthesia for mask induction. It is not irritating to the airway, and it is almost insoluble in blood so that equilibration between brain and alveolus occurs rapidly. Onset of anesthesia during mask induction is very fast. Cardiovascular

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effects are similar to effects with isoflurane. There is little published experience with sevoflurane in preterm infants, although it is used primarily for mask inductions in healthier neonates. Sevoflurane has been associated with prolongation of the Q-T interval of the ECG in adults and infants; this may be of concern because a long Q-T interval has been associated with sudden death. There have been no reports, however, of intraoperative or postoperative complications related to sevoflurane and cardiac repolarization abnormalities, and it is uncertain if this is of any clinical concern.[38]

Nitrous oxide is an inhalational anesthetic, but it is not in the same class as the halogenated agents. It is a weak anesthetic, with a MAC of 104% in adults, so that to reach MAC, nitrous oxide would have to be provided at hyperbaric pressures. The need for oxygen as part of inspired gases prevents achievement of these levels. Nitrous oxide also is almost insoluble, and onset of effect is fast. Insolubility and the high concentration that is necessary for any meaningful effect cause nitrous oxide to enter progressively and to expand any gas-filled space in contact with the circulation, which rapidly leads to bowel distention or expansion of pneumothorax. If ventilation is interrupted for any reason, nitrous oxide also rapidly fills the alveoli, leading to dilution of the alveolar oxygen, producing a hypoxic mixture and rapid desaturation. For these reasons, nitrous oxide is best limited to adjunct use during mask induction, with a switch to an air-oxygen mixture during maintenance anesthesia and has limited usefulness in the anesthetic management of the neonate. As previously discussed, all of the inhalational agents cause neuroapoptosis in animal studies.

Intravenous Agents

Intravenous agents for use in neonates include sodium thiopental, propofol, ketamine, various narcotics, and benzodiazepines. Sodium thiopental is an ultra–short-acting barbiturate used primarily as an induction agent. Thiopental is primarily a hypnotic, with little analgesic activity. Use is limited in smaller and sicker neonates, because it has negative inotropic activity and is a peripheral vasodilator. Hypotension is common, particularly in volume-depleted patients. At present, thiopental is not available for use in the United States.

Propofol is a phenol derivative supplied as an emulsion in lipid, which in older children and adults is used for induction and maintenance of anesthesia. Recovery from the drug is rapid in adults because of redistribution and metabolism by liver and tissues. Propofol has little analgesic effects, and for painful operations it should be used with narcotics. Propofol has been approved for children younger than 3 years, but there is little experience with the drug in premature infants. A slower recovery due to less fat and muscle for redistribution would be expected, as well as possibly slower hepatic metabolism owing to immaturity. It is a potent peripheral vasodilator, and hypotension is a common problem limiting its use in preterm neonates.[65]

Ketamine, a phencyclidine derivative, provides good hypnosis and amnesia and excellent analgesia. When used as a sole agent in adults and older children, it can cause a dissociative state with confusion, hallucinations, and other severe psychological side effects. Ketamine stimulates the sympathetic nervous system and causes minimal respiratory and cardiovascular depression, which may make it a useful adjunct in the anesthetic care of the infant. Blood pressure may increase, and increased intracranial pressure is a concern in infants with hydrocephalus or those at risk for intraventricular hemorrhage. Ketamine can be useful in breaking hypercyanotic spells in an infant with congenital heart disease and right-to-left shunt, because it anesthetizes and increases systemic vascular resistance.

Benzodiazepines are agents that produce sedation, anxiolysis, and amnesia, but little analgesia. They are incomplete anesthetic agents, although in adults they have been very useful in combination with an opioid. Midazolam is a very short-acting benzodiazepine, and it has been the most commonly used in anesthesia. Metabolism is almost entirely hepatic, and it should be expected that duration would be prolonged by immature hepatic function in a preterm neonate. Midazolam causes vasodilation, which can result in hypotension. In high doses, it can cause respiratory depression, although this is more common in conjunction with opioids. Midazolam and the longer-acting benzodiazepine lorazepam have been used for sedation in the NICU with mixed results. The Cochrane Neonatal Collaborative Review Group performed a meta-analysis of several studies on sedation in the NICU using midazolam. All three studies showed that midazolam was effective at providing sedation to the neonate. However, one study showed a higher risk of poor neurologic outcome or death in the midazolam-treated group as well as evidence of increased length of stay, which at least raises questions as to the safety of midazolam infusion in these infants.[43]

Fentanyl, a synthetic opioid, is widely used in neonatal anesthesia, and it is the most commonly used anesthetic for premature infants. It has a wide safety margin and beneficial effects on hemodynamic stability. Fentanyl can block pulmonary hypertensive crises, and it is useful in infants with pulmonary hypertension, such as infants with congenital diaphragmatic hernia, PPHN, and some cardiac defects. The pharmacokinetics of fentanyl in the early neonatal period is widely variable, depending on gestational and postnatal age and the type of surgery and medical problems of the infant.[49] Fentanyl is primarily metabolized in the liver, with only a small amount excreted unchanged by the kidneys. Clearance is lowest in the most premature infants, and it increases with gestational age and with age after birth, probably reflecting increasing hepatic maturation. Volume of distribution of fentanyl also seems to vary depending on gestational age and disease state. Neonates with increased intra-abdominal pressure seem to have slower clearance of fentanyl, likely due to the resulting decreased hepatic blood flow.

Given the highly variable pharmacodynamics, fentanyl dosing needs to be individualized and titrated to effect.

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There is a fairly wide therapeutic range, and even with high doses, hemodynamic stability is maintained. All narcotics are respiratory depressants, however, and with higher doses of fentanyl, prolonged respiratory depression occurs, necessitating postoperative assisted ventilation.

Fentanyl in combination with a muscle relaxant has become the standard for anesthesia in premature neonates. This combination may also be used during elective (nonemergent) intubation in the NICU. Although fentanyl is a potent analgesic, it is not a complete anesthetic, and occasionally in adults, awareness has occurred with high-dose fentanyl alone. In the past, it was suggested that this was of minimal importance because neonates are not "aware," especially if pain was adequately treated. This belief is less well accepted today, and benzodiazepines or inhalational agents such as isoflurane are more commonly added to fentanyl anesthesia.

Other synthetic narcotics such as alfentanil and sufentanil rarely have been used in neonates. In adults, alfentanil is less potent than fentanyl, but it has a shorter half-life, whereas sufentanil is more potent than fentanyl. Pharmacokinetics in infants is probably similar to fentanyl, and there does not seem to be any significant advantage compared with fentanyl. Remifentanil is a newer opioid whose duration of action is terminated by hydrolysis by tissue esterases. Consequently, remifentanil does not accumulate or have prolonged duration of action. A half-life of 4.4 minutes and a clearance of 80 mL/kg per minute have been reported in neonates.[50] Duration of action is very short, and it may be of use for procedural analgesia with little persistent pain. Duration can be extended by using a continuous infusion, but this can be associated with opioid-induced tolerance and hyperalgesia.[45,50]

Morphine is the principal opium alkaloid, and it is the standard against which analgesics are measured. Morphine is less potent than fentanyl, but it has a longer duration of action and is more commonly used for postoperative pain. The duration of action of morphine is increased in premature infants. As with all narcotics, respiratory depression is a major side effect. In contrast to fentanyl, morphine causes histamine release, which limits its use as an anesthetic agent; although, it is well accepted for analgesia, postoperative pain, and overall sedation. Morphine distribution in neonates has been well studied and is very predictable, although required target concentrations in neonates are still uncertain.

Dexmedetomidine is a highly specific alpha$_2$-adrenergic agonist with hypnotic, analgesic, and anxiolytic properties. It is being used with increased frequency in the pediatric setting for sedation during nonpainful procedures such as MRI as an adjunct to other anesthetics during surgical procedures and for sedation of critically ill patients in the ICU setting. Despite the sedating properties of dexmedetomidine, there is little effect on respiratory function, thereby promoting earlier extubation and decreasing the need for analgesics that have respiratory depressant properties. Numerous studies have demonstrated the effectiveness and safety of dexmedetomidine as an analgesic and sedative in infants after cardiac surgery. Adverse effects of dexmedetomidine include bradycardia and hypotension as well as paradoxical hypertension, but it has been found to be well tolerated in neonates.[16] The drug undergoes hepatic metabolism and, therefore, has decreased plasma clearance and longer elimination half-life in preterm neonates with immature hepatocyte function.[9] Preliminary data in animals studies shows evidence that dexmedetomidine may actually protect against neuroapoptosis caused by other anesthetic agents.[46]

Neuromuscular Blocking Agents

Muscle relaxants are commonly used in anesthesia for neonates. They are often grouped according to mechanism of action (i.e., depolarizing versus nondepolarizing), but it is more important to consider rapidity of onset and duration of action.

Succinylcholine chloride is the only depolarizing agent used at present, and it remains the standard for rapid onset and rapid disappearance. The ED_{95} (effective dose in 95% of the population receiving the dose) in neonates for succinylcholine is twice that of adults at 1.5-2 mg/kg. Action is terminated by metabolism by plasma pseudocholinesterase. Succinylcholine is not routinely used in children because of several rare but serious adverse reactions. In patients with myopathies or neurologic diseases, succinylcholine can cause overwhelming hyperkalemia, muscle necrosis, and cardiac arrest that is refractory to resuscitation. Bradycardia also occasionally occurs during intubation in infants with succinylcholine. For this reason, some anesthesiologists routinely administer atropine with succinylcholine. In pediatric patients, succinylcholine is reserved primarily for rapid sequence induction when a full stomach is suspected.

Nondepolarizing relaxants competitively inhibit acetylcholine at the neuromuscular junction. Vecuronium bromide is an intermediate-acting relaxant occasionally used in neonates. It has little effect on the cardiac system, although it may cause bradycardia in combination with narcotics. Cisatracurium besylate undergoes spontaneous degradation by a chemical process (Hofmann elimination), and duration is not affected by liver or kidney function. Atracurium, its parent compound, is rarely used today because it causes histamine release. Rocuronium bromide is an agent with a rapid onset of action that can be used in place of succinylcholine for rapid sequence induction. Duration of action is dose dependent and significantly longer than succinylcholine.

Most relaxants probably have a prolonged duration of action in premature neonates, and frequency of dosing should be determined using a nerve stimulator to measure response to four spaced stimuli (train-of-four response). At the completion of surgery, muscle relaxation with nondepolarizing agents should be reversed with an anticholinesterase, typically neostigmine, and an anticholinergic, such as glycopyrrolate or atropine.

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Induction of General Anesthesia

Most sick infants have intravenous access, and an intravenous induction can be performed. Premedication rarely is given to neonates, although some anesthesiologists recommend glycopyrrolate or atropine before laryngoscopy and intubation to mitigate any possible vagal response and bradycardia with intubation. Healthier infants without intravenous access can undergo mask induction, typically with 50% nitrous oxide and sevoflurane, after which intravenous access is rapidly obtained.

Infants with a full stomach, most commonly infants with intra-abdominal disease, must have an intravenous rapid-sequence induction. During rapid-sequence induction, the infant is first preoxygenated with 100% F_{IO_2} to maximize oxygenation during the apneic period of intubation. An IV induction agent such as propofol, along with a fast-acting paralytic, is administered in rapid succession. The use of cricoid pressure to prevent regurgitation of gastric contents is not routinely considered, as it can actually hinder successful intubation by obscuring the view of the glottic opening during laryngoscopy.[63] Positive pressure ventilation is avoided or provided very gently, and the infant is intubated expertly as soon as conditions are appropriate, usually after 45-90 seconds. There is little room for error with rapid sequence induction, and it should be performed only by individuals with significant expertise.

Awake intubation with continued spontaneous ventilation is an alternative, but it should be reserved for infants with concern for difficult airways, such as in Pierre Robin and Goldenhar syndromes, where maintenance of spontaneous ventilation is beneficial during situations where time to successful intubation may be prolonged. Minimal sedation can be given, but protective airway reflexes should not be obtunded. When the airway is secured, induction can continue by intravenous or inhalational route. Management of the difficult airway requires careful planning and the availability of additional "trained hands." A pediatric fiberoptic bronchoscope and a range of special-purpose laryngoscope blades may be useful. Pediatric ear, nose, and throat consultation may also be valuable. The LMA may assist with ventilation, but it does not protect the airway. The pediatric bronchoscope also can be used to intubate through the LMA. Awake intubations are known to cause higher rates of airway trauma and can have significant hemodynamic consequences in the neonate, such as arterial hypertension, pulmonary hypertensive crisis, and increased intracranial pressure due to pain and sympathetic stimulation.[35] This technique should be reserved for the most critical of circumstances.

Maintenance of Anesthesia

Maintenance of anesthesia requires monitoring as previously discussed. Temperature must be carefully controlled, and adjustments in heating or cooling must be appropriately made. Fluid and metabolic requirements also must be carefully assessed throughout the course of the surgery. Fluids should be administered with an infusion pump to prevent inadvertent overload. It is usually easiest to calculate and administer maintenance fluids separately from replacement. Maintenance fluids should include glucose unless the infant is known to be hyperglycemic. Intravenous hyperalimentation or a dextrose-electrolyte solution can be used, depending on the size, age, and clinical condition of the neonate. Third space losses should be initially replaced with a balanced crystalloid solution such as lactated Ringers. Blood loss also can be replaced with crystalloid initially.

Third space losses can be impressive, ranging from 2-15 mL/kg per hour, especially during procedures with large amounts of bowel exposed, such as for repair of gastroschisis and omphalocele. Many infants, especially if they are hypoalbuminemic, should receive some replacement as colloid, usually 5% albumin. In the sickest neonates, transfusion with packed red blood cells, fresh frozen plasma, and platelets may be required. Urine output should be followed as one sign of adequate fluid replacement.

Ventilation should be carefully controlled. Use of oxygen has been discussed; if controlled ventilation is employed, care should be taken to avoid hyperventilation and subsequent hypocapnia. Higher peak pressures can cause significant barotrauma. Accurate ventilation may be difficult to monitor because varying anesthesia circuits and adapters can result in widely varying dead space and a variable offset between end-tidal CO_2 and the actual blood P_{CO_2}. Cerebral oximetry employing near-infrared spectroscopy can provide information on changes in cerebral blood flow.

Recovery From Anesthesia

Emergence from anesthesia in the smallest and sickest premature infants is usually a prolonged event, because these neonates are not typical candidates for extubation at the conclusion of surgery; instead, they require continued intensive care in the NICU. Immaturity of drug clearance systems also prolongs recovery from the effects of most anesthetic agents in these infants. Transport from the operating room involves the same considerations of temperature maintenance and airway management that have previously been discussed. Older and healthier infants often can be extubated after surgery. Neuromuscular blockade should be reversed, as previously discussed. Hypothermia can prolong neuromuscular blockade, precluding extubation if temperature control has not been adequate, and infants with hypothermia may need to be actively warmed.

The infant should have resumed regular rhythmic respiration; to achieve this, ventilation may need to be decreased toward the end of the anesthetic to allow P_{CO_2} to increase to mildly hypercapnic levels. Volume status must be adequate, and plasma hemoglobin should be close to normal. Flexion of the hip and contraction of the rectus abdominis muscle have been used as signs of adequate motor strength, and the infant usually begins to gag on the tube. Laryngospasm can occur on extubation, and the anesthesia personnel need to be ready to treat and reintubate if necessary.

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As previously discussed, premature infants often experience periodic breathing, and there is a risk of postoperative apnea in these patients that is inversely related to gestational age. Anemia may be a risk factor for apnea, although this is controversial. A conservative approach is to avoid elective surgery and anesthesia until the former preterm infant reaches 60 weeks' postconceptional age, at which time the risk of postoperative apnea seems small. If surgery cannot be delayed, the infant should be admitted and monitored for 12-24 hours after surgery or after the last apneic episode.

Local and Regional Anesthesia

Concerns about the neurotoxicity of general anesthetic agents have awakened new interest in regional anesthesia in children and neonates.[22,40] Widespread availability of ultrasound has made it both easier and safer to perform regional blocks in children.[60,61] Regional techniques are most commonly combined with general anesthesia, with the primary indication control of postoperative pain and decreasing postoperative analgesic requirements. There are inherent technical difficulties to performing regional anesthesia in neonates, including the need for appropriate-sized catheters and the need for specialized training to perform these blocks safely and successfully.

Local infiltration or nerve block is useful in certain specific procedures such as circumcision where a dorsal penile nerve block (DPNB) or penile ring block has been shown to be safe and effective. Other simple methods such as a sucrose-dipped pacifier, or a padded and physiologic restraint chair, further decrease objective signs of distress during circumcision performed with DPNB. Eutectic mixture of local anesthetic (EMLA) cream also has been used for neonatal circumcision. When used for circumcision, EMLA is more effective than no anesthesia, but it is not as effective as DPNB.[8] Other indications for use of EMLA include venous and arterial puncture, lumbar puncture, suprapubic puncture, and minor surgical procedures. Transversus abdominis plexus (TAP) blocks and rectus sheath blocks can be used to obtain anterior abdominal wall anesthesia and periumbilical anesthesia for abdominal surgeries such as umbilical hernia.[27]

Caudal anesthesia is often used with inguinal hernias, although an ilioinguinal nerve block can be done with ultrasound guidance and may provide a longer duration of analgesia. Intercostal nerve blocks can be used for thoracotomy and flank incisions; use of ultrasound-guided paravertebral blocks may be used in these cases. An indwelling catheter also can be placed in an intrapleural location by the surgeon and continuous infusion of bupivacaine given after thoracotomy.

Caudal anesthesia is a useful option for surgeries involving the lower abdomen, groin, and lower extremities. The epidural space can be entered by the caudal route through the sacrococcygeal membrane. Caudal anesthesia given as a single injection is commonly used in combination with a general anesthetic to allow for lower concentrations of inhalational agents as well as provide postoperative pain control. After a caudal anesthetic with bupivacaine or ropivacaine, most infants are free of pain immediately after surgery, with relief continuing for at least 3-4 hours. The single shot technique utilizes a 22-gauge, short-bevel needle or 22-gauge angiocath to enter the caudal space. Caudal anesthesia requires a higher dosage of anesthetic, so the possibility of an inadvertent intravascular injection is a concern. A catheter can also be threaded into the epidural space for continuous caudal anesthesia. With the continuous technique, the catheter can be threaded up into the epidural space, often high enough to give midthoracic anesthesia if needed. This technique seems to be well tolerated without significant hemodynamic effect. The use of neuraxial catheters, including thoracic, lumbar, and caudal epidural catheters, has the ability to provide an alternative strategy for pain control in the neonate. Epidural catheters allow for the continuous infusion of local anesthetic intra- and postoperatively, thereby minimizing the need for analgesics that may result in respiratory depression or may have altered pharmacokinetic properties in the immature neonate. Despite the ability to perform these procedures, there has long been concern over the safety of these techniques in the neonatal patient. An observational study utilizing the Pediatric Regional Anesthesia Network (PRAN) was able to evaluate the incidence of complications related to the use of neuraxial catheters in patients under one month of age. With over 300 neuraxial catheters placed, the most common complications were catheter malfunction, catheter contamination, and vascular aspiration, which were all managed by removal or adjustment of the catheter. There were no reports of more serious complications, such as persistent neurologic injury, deep infection, or epidural hematoma.[39]

Regional anesthesia in the pediatric patient is almost uniformly performed under general anesthesia with an exceedingly low complication rate.[58] A regional technique without general anesthesia can be used in some neonates considered to be at high risk, such as those with severe bronchopulmonary dysplasia in whom avoidance of intubation for a general anesthetic is preferred. Inguinal hernia repair is a common procedure performed on premature infants, and caudal or spinal anesthesia is considered a reasonable anesthetic technique for the procedure. One major problem seems to be a modest rate of failure of the technique, leading to the need for additional sedation or conversion to a general anesthetic.[21,33] Despite the avoidance of a general anesthetic the most robust study comparing general anesthesia to awake regional anesthesia did not reveal an overall reduction in postoperative apnea in those patients receiving a regional anesthetic, but the infants receiving spinal anesthesia had less clinically significant apneas.[14] Spinal anesthesia can be induced using a 25-gauge Quincke needle at the L4 or L5 level (below the cauda equina). Either tetracaine or bupivacaine can be used depending on the length of procedure. Due to the duration of the block, surgical procedures must be completed in less than 90 minutes in order for spinal anesthesia to be considered.

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Caudal or spinal anesthesia can be used without additional sedation for appropriate procedures such as inguinal hernia repair. In this situation, simple nonpharmacologic comfort measures such as a pacifier are useful, and the technique seems to be well tolerated.

Given the concerns over the potential for anesthetic-related neurocognitive deficits, usage of regional and neuraxial anesthesia may well increase. However, it is important to remember there is also little experience with the increasing numbers of agents used for neuraxial and regional anesthesia, particularly in infants and neonates, and little is known concerning possible effects on the developing spinal cord. Further careful evaluation, including preclinical and animal studies, is also needed in this area.[64]

Key Points

- The goals of anesthesia care in the neonate include management of pain and discomfort associated with surgical procedures as well as prevention of the stress response.
- Animal studies have demonstrated abnormal apoptosis and long-term neurocognitive deficits in rats and primates exposed to most of the most commonly used anesthetic drugs.
- Recent prospective human studies suggest that a single brief anesthetic exposure during early development appears to be safe.
- Anesthetic management of neonates should be performed by pediatric anesthesiologists and care should occur in a setting specifically tailored to the pediatric patient.
- Preoperative evaluation and anesthetic management of the neonatal patient requires specific understanding of pathophysiology specific to these patients, including transitional circulation, PPHN, respiratory distress syndrome and bronchopulmonary dysplasia, apnea of the newborn, temperature regulation, carbohydrate metabolism, and retinopathy of prematurity.
- There are an extensive number of congenital syndromes that have anesthetic implications.
- Nearly all anesthetics, including inhalational agents, induction agents, opioids, and neuromuscular blockers, can be used in the neonatal patient, but an understanding of their pharmacokinetics and pharmacodynamics in the immature neonate is necessary for safe administration.
- The use of regional anesthesia techniques, both as part of a general anesthetic or as the sole anesthetic, can be performed safely and successfully in the neonatal patient.

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The Late Preterm Infant

KIMBERLY V. PARSONS AND LUCKY JAIN

Births between 34 and 36 6/7 weeks' gestation (referred to herein as *late preterm births*) account for a significant proportion of preterm births in North America and elsewhere. These infants are larger than usual premature infants, and they are generally passed off as mature infants, but they often manifest signs of physiologic immaturity or delayed transition in the neonatal period. Several studies have documented the high incidence of neonatal complications leading to neonatal intensive care unit (NICU) admissions in these infants. They have a higher incidence of transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS),[29] persistent pulmonary hypertension of the newborn (PPHN),[60] respiratory failure,[16] jaundice, temperature regulation problems, hypoglycemia,[3] and feeding difficulties than term infants.[21]

Concern about higher morbidity in late preterm infants has led to numerous publications with largely the same conclusions: Late preterm infants are more prone to problems related to delayed transition and overall immaturity, and they should be treated differently from their more mature term counterparts.[17,34,43,63,71] These observations have led to greater attention being paid to tracking short-term morbidity, health care costs, hospital stays, and issues such as rehospitalization. Nearly three out of four preterm births occur at late preterm gestational ages, and while there has been a steady increase over the past couple of decades, we are now seeing a decline since 2007.[43] The significant contribution of late preterm births is a worldwide phenomenon, although reported rates seem to be quite variable. The late preterm birth rate was 4.8% in Canada in 2006–2014. Danish, Finnish, Norwegian, and Swedish late preterm birth rates were 3.6%, 3.3%, 3.8%, and 3.6% respectively.[59] In Brazil, a country known to have one of the highest preterm birth rates in the world, the first national birth survey estimated the late preterm birth rate to be 8.5% in 2011.[40]

Definition

Preterm infants have been aptly and clearly classified for many decades. The World Health Assembly in 1948 described preterm infants as those weighing less than 2500 g or being less than 37 weeks' gestation. In 1950, the World Health Organization revised this definition, identifying all infants born before 37 completed weeks' gestation (259th day), counting from the first day of the last menstrual period, as preterm infants.[55] The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (ACOG) agree with this definition.[4]

Although *preterm*, *term*, and *post-term* have been clearly defined according to the week and day of gestation by the World Health Organization, American Academy of Pediatrics, and American College of Obstetrics and Gynecology, not all subgroups within the preterm gestation are well defined. There is less ambiguity about infants less than 32 weeks' gestation in the literature, being defined as *very preterm* if less than 32 weeks' gestation and *extremely preterm* if less than 28 weeks' gestation, but historically no clear definition existed for infants of 32-37 weeks' gestation. These infants were known by several different names, including *moderately preterm*, *mildly preterm*, *minimally preterm*, *marginally preterm*, and *near-term*. These near-term infants have been inconsistently defined in the literature as 34-36 weeks' gestation, 35-37 weeks' gestation, and 35-36 6/7 weeks' gestation (Fig. 40.1).

To clarify, and to place a greater emphasis on the fact that these slightly premature infants have a greater risk of morbidity and mortality than term infants, an expert panel at a workshop convened by the National Institute of Child Health and Human Development of the National Institutes of Health in July 2005 recommended that births between 34 completed weeks (34 weeks or day 239) and less than 37 completed weeks (36 6/7 weeks or day 259) of gestation be referred to as *late preterm* infants (Fig. 40.2).[56] Several factors led to this definition; 34 weeks is considered a matu-rational milestone in obstetric practice, after which surfactant is usually present in the lungs and is often used as a cutoff for giving antenatal steroids. Because there is no such thing as a normal preterm infant, and the assumptions that these infants are as healthy as term infants, use of terms such as *near-term* was discontinued. Data have shown that term infants born at 37 and 38 weeks' gestation have higher morbidity and mortality than infants born at 39 weeks' gestation.[63] Now, infants between 37 completed weeks' gestation (37 weeks or day 260) and 38 completed weeks' gestation (38 6/7 weeks or day 274) are referred to as *early term* infants Engle and Kominiarek.[17]

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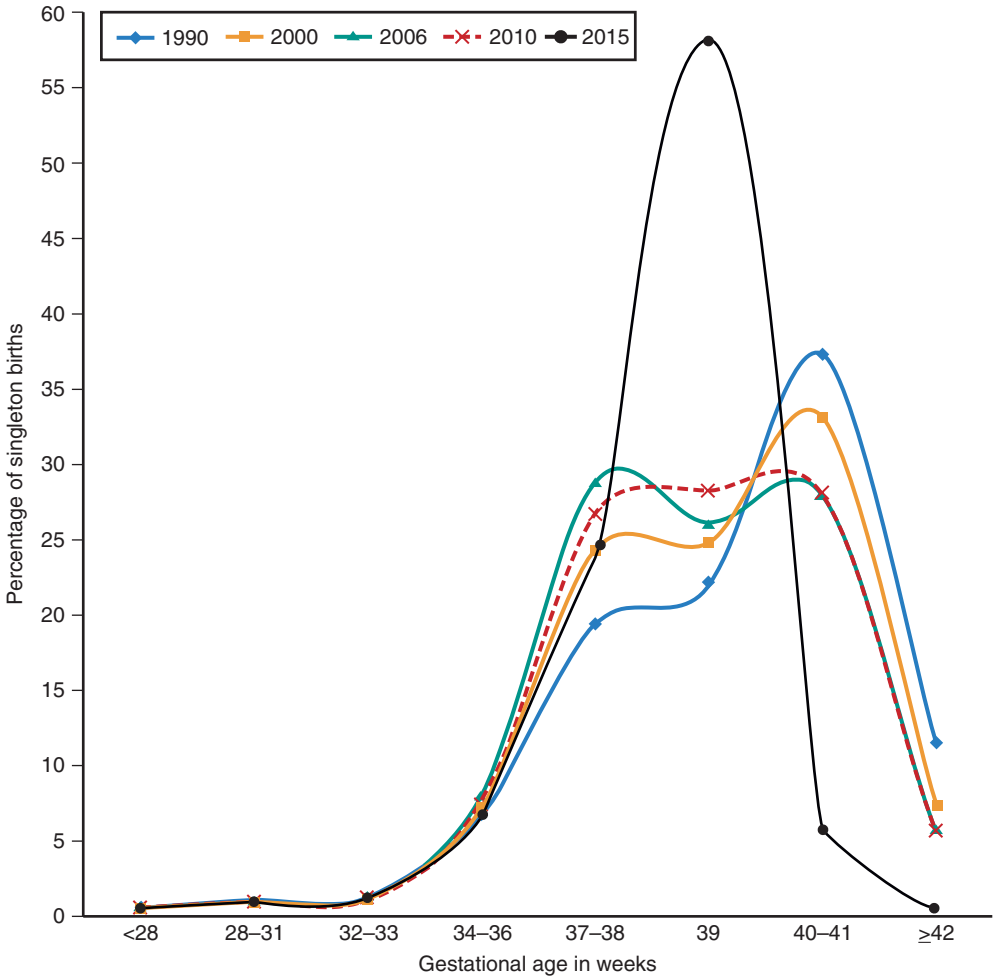
Abstract

In this chapter we hope to highlight the physiology and pathology of late preterm infants that make them unique compared to their early term, full term, and early preterm counterparts. Late preterm infants (34-36 6/7 weeks' gestation) account for a significant proportion of all preterm births. Historically, they were regarded as just smaller in size than full-term infants. However, it has now been shown that there is a high incidence of morbidity in this population, leading to neonatal intensive care unit (NICU) admission. After a steady increase in the number of late preterm births over previous decades, there has now been a decline since 2007, largely as a result of obstetrical interventions and a push to deliver more infants at 39 weeks, recognizing the increased morbidity of being born even just a few weeks early. Due to physiologic immaturity, late preterm infants are at greater risk for transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), respiratory failure, jaundice, thermoregulation problems, hypoglycemia, and feeding difficulties than term infants. LPT infants are also at greater risk for neurodevelopmental impairment. Late preterm infants should be recognized as an at-risk population and treated differently than both their more mature and less mature counterparts. Greater understanding of the associated morbidities and the development of effective interventions will help improve the short- and long-term outcomes of late preterm infants.

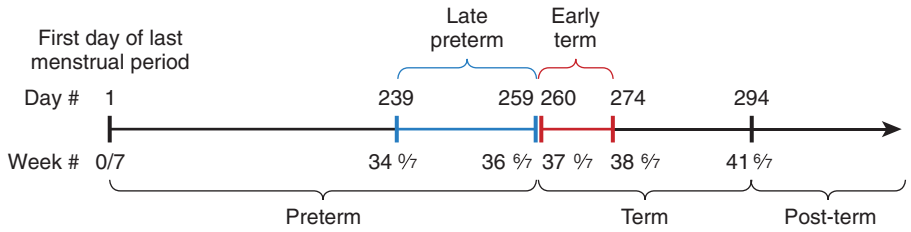
Keywords

late preterm
antenatal steroids
elective cesarean section
hypoglycemia
neurologic immaturity
respiratory distress
hyperbilirubinemia

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• **Fig. 40.1** Shifting distribution of gestational age among singleton live births, United States, 1990, 2000, 2006, 2010, and 2015. (Data from Martin JA, Hamilton BE, Ventura SJ, et al. National vital statistics reports. Vol. 61, no. 1. Hyattsville, MD: National Center for Health Statistics; 2015.)



• **Fig. 40.2** Definition of late preterm and early term. (Modified from Engle WA, Kominiarek MA. Late preterm infants, early term infants, and timing of elective deliveries. *Clin Perinatol.* 2008;35:325.)

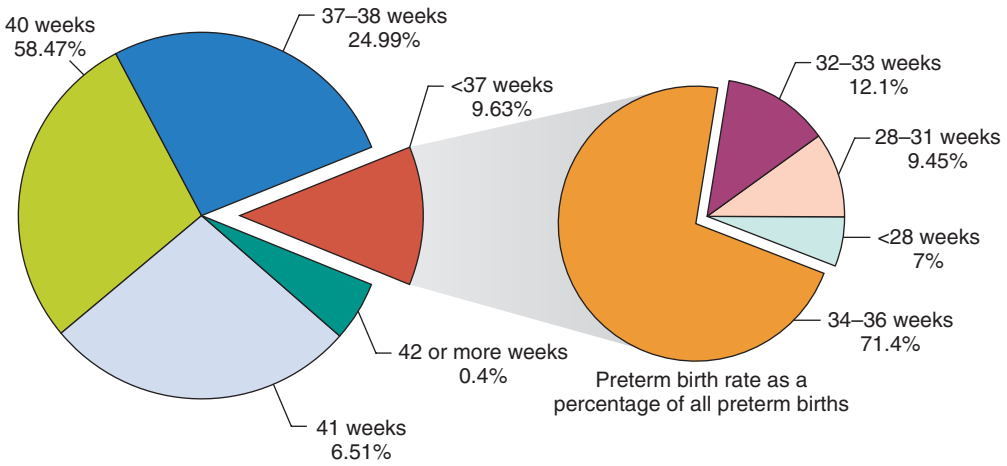
Epidemiology and Trends

In the United States, there were 3,978,497 live births in 2015, of which 9.63%, or approximately 380,000, were preterm.[43] Late preterm infants at 6.87% constituted 71% of all preterm births (Fig. 40.3). Preterm births have steadily declined since a high of 10.44% in 2007. Increased awareness of the contribution of late preterm births to the total preterm birth rate and the increased risk to the infant lead to a significant reduction in such deliveries.[43] This decrease may be attributed to national efforts to decrease elective or nonmedically indicated deliveries before 39 weeks' gestation.[49]

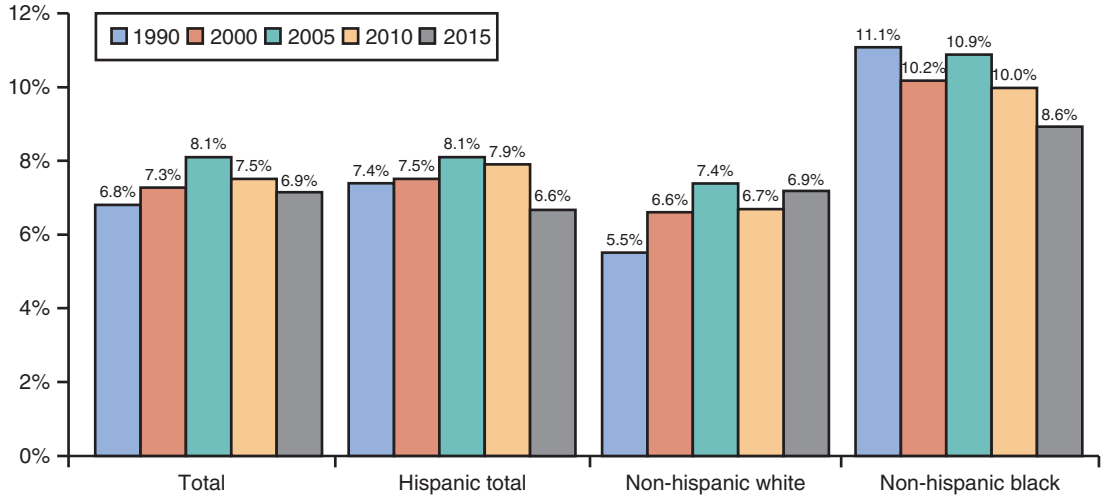
Non-Hispanic black infants have nearly 1.5 times the late preterm birth rate than non-Hispanic white infants. The late preterm birth rate was 8.6% for singleton non-Hispanic black infants, 6.6% for Hispanic infants, and 6.5% for non-Hispanic white infants, showing a significant decline across all races over the past few years (Fig. 40.4).

Earlier studies indicated that late preterm infants have survival rates within 1% of term infants,[28] but there is mounting evidence to show that late preterm infants have

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• **Fig. 40.3** Birth rate by gestational age as a percentage of all live births in the United States, 2007-2015. (Data from Martin JA, Hamilton BE, Osterman, M, et al. Births: final data for 2015. National vital statistics reports. Vol. 66, no 1. Hyattsville, MD: National Center for Health Statistics; 2017.)



• **Fig. 40.4** Percentage of late preterm singleton births by race and Hispanic origin of mother in the United States, 1990, 2000, 2005, and 2010. (Data from Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.)

significantly higher mortality compared with term infants. Mortality rates in the 2009 period linked birth and death certificate data showing that late preterm infants have three times the mortality rate (7.13/1000 live births) compared with term infants (1.98/1000 live births), and even early term infants had higher mortality (3.09/1000 live births) compared with full-term infants.

Etiology

The etiology of prematurity is complex and multifactorial, and although known clinical entities such as pre-eclampsia and premature rupture of membranes (PROM) are significant contributors to preterm births, several other causes have been implicated in the increase in the late preterm birth rate (Box 40.1).

Medical Interventions and Iatrogenic Causes

Cesarean section rates have dramatically increased in the United States and worldwide, increasing from a low of 5% in 1970 to a high of 32.9% in 2009, decreasing slightly to 32% in 2015.[43] Among the many reasons cited for this increase are increased fetal surveillance and interventions, increased age of women giving birth, increased number of multiple births resulting from fertility treatments, obesity, and heightened concerns of physicians and mothers about the risks of vaginal birth. Although spontaneous births and births from PROM declined during this period, births from medical interventions increased, with cesarean section accounting for most of the medical intervention group. In 2006, a national consensus conference coined a new term for cesarean deliveries for which no medical indication

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• BOX 40.1 Etiology of Late Preterm Births

Medically Indicated

- Preterm labor
- PROM
- Preeclampsia

Medical Interventions and Iatrogenic

- Increased medical surveillance and interventions
- Cesarean or planned induction of labor. Medical indications:
  - Abnormal presentation, abnormal placentation, maternal or fetal conditions (e.g., PROM without labor, fetal hydrocephalus)
  - Repeat cesarean section
- Cesarean or planned induction of labor. No medical indication:
  - Induction of labor or cesarean section on maternal request
  - Fear of fetal and neonatal risks with vaginal delivery
  - Increased rate of stillbirths beginning at 39 weeks' gestation
  - Hypoxic-ischemic encephalopathy, brachial plexus, and other birth traumas
  - Fear of maternal risks with vaginal delivery
  - Risk for genital tract, anus, and perineal injury and sexual dysfunction
  - Perception that cesarean delivery is "easier" and "less stressful" than vaginal delivery
  - Fear of the second stage and having to "push the baby out"
  - Maternal willingness to accept risk on behalf of the infant
  - Convenience for mother and family

Gestational Age Assessment and Obstetric Practice Guidelines

- Inaccurate gestational age assessment during elective deliveries
- Maternal obesity
- Presumption of fetal maturity at 34 weeks' gestation
- Decreasing gestational age criteria for inductions and increased rate of stillbirths beginning at 39 weeks' gestation

Advanced Maternal Age, Assisted Reproductive Technologies, and Multiple Births

- Increase in multifetal pregnancies
- Delayed childbearing and increased risk for prematurity
- Use of assisted reproductive technologies (multifetal pregnancies) and increased risk for complications associated with premature delivery (e.g., preeclampsia, diabetes)

Physician Practice Patterns and Risk/Benefit Determination

- Concern for risk of adverse outcomes
- Convenience
- Liability

PROM, Premature rupture of membranes.
Modified from Engle WA, Kominiarek MA. Late preterm infants, early term infants, and timing of elective deliveries. *Clin Perinatol.* 2008;35:325.

could be found and where maternal choice was the leading factor—*cesarean delivery on maternal request*.[1] Although the exact number of such deliveries is hard to track, it is believed that 2.5% of cesarean sections may be performed at maternal request.[1,57]

Although elective cesarean sections are discouraged before 39 weeks' gestation, a study by Tita and associates found that nearly 36% of elective repeat cesarean sections were performed before 39 weeks' gestation.[70] Among these elective cesarean births, infants born at 37 and 38 weeks had greater than 1.5 times the odds of death or complications, including respiratory compromise, hypoglycemia, sepsis, and admission to the NICU (Table 40.1).[70] Induction rates have also increased with cesarean section rates, and there was a shift toward earlier gestations in both groups.[15] Historically, however, the induction rates for late preterm births have increased 130% since 1990. In 2012, 23.3% of all singleton live births were induced, with the rate of induction increasing 4% for late preterm births since 2006.[51] Although medically indicated interventions have led to a decrease in the number of stillbirths, we do not know how much this has contributed to the increase in the preterm birth rate or whether the gains realized in preventing stillbirths are offset by increased NICU admissions and complications associated with prematurity. More recently, many states have implemented quality improvement programs to decrease elective deliveries before 39 weeks' gestation. In one multistate collaborative undertaken over 12 months, elective scheduled early-term deliveries decreased from 27.8% in the first month to 4.8% in the 12th month; in addition, rates of elective scheduled singleton early-term inductions and cesarean deliveries decreased significantly.[50]

Some studies claim that the increasing cesarean section rates stem from the changing practice standards of medical professionals and their willingness to perform cesarean sections because of the perceived safety and protection from malpractice litigation.[44] Further prospective studies are required to quantify how much of the increase in late preterm births is owing to necessary medical interventions and how much can be attributed to cesarean section by physician or maternal request.

Gestational Age Assessment and Obstetric Practice Guidelines

Gestational age measurement is an inexact science; the methods currently used, such as the Naegele rule (which assesses gestational age from the first day of the last menstrual period) and ultrasound at 20 weeks' gestation, are accurate only to ±1-2 weeks' gestational age. Combined with the fact that developmental variability exists during fetal maturation, and conditions such as maternal obesity and PROM can cause an overestimation or underestimation

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TABLE 40.1 Odds Ratios* for Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery

Outcome†	37 Weeks	38 Weeks	39 Weeks	40 Weeks
Any adverse outcome or death	2.1 (1.7-2.5)	1.5 (1.3-1.7)	Reference	0.9 (0.7-1.1)
Adverse respiratory outcome				
RDS	4.2 (2.7-6.6)	2.1 (1.5-2.9)	Reference	1.1 (0.6-2.0)
TTN	1.8 (1.2-2.5)	1.5 (1.2-1.9)	Reference	0.9 (0.6-1.3)
RDS or TTN	2.5 (1.9-3.3)	1.7 (1.4-2.1)	Reference	0.9 (0.6-1.2)
Admission to NICU	2.3 (1.9-3.0)	1.5 (1.3-1.7)	Reference	0.8 (0.6-1.0)
Newborn sepsis‡	2.9 (2.1-4.0)	1.7 (1.4-2.2)	Reference	1.0 (0.7-1.5)
Treated hypoglycemia	3.3 (1.9-5.7)	1.3 (0.8-2.0)	Reference	1.2 (0.6-2.4)
Hospitalization ≥5 days	2.7 (2.0-3.5)	1.8 (1.5-2.2)	Reference	1.0 (0.8-1.4)

NICU, Neonatal intensive care unit; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn.
*Odds ratio (95% confidence interval).
†All outcomes are adjusted for maternal age (as a continuous variable), race or ethnic group, number of previous cesarean deliveries, marital status, payor, smoking status, and presence or absence of diet-controlled gestational diabetes mellitus.
‡Newborn sepsis included suspected infections (with clinical findings suggesting infection) and proven infections.
Modified from Tita AT, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med.* 2009;360:111.

of gestational age, the task of accurate gestational age prediction is even more challenging. The ACOG more recently issued guidelines that cesarean delivery or induction on maternal request should not be performed before 39 weeks' gestation or without evidence of lung maturity.[2] This gradual shift toward lower gestational age along with the inaccuracies of gestational age measurement might have led to the increasing proportions of late preterm births.

Tocolysis and antenatal steroids are routinely recommended only for women at less than 34 weeks' gestation, because infants born at 34 weeks' gestation and beyond were believed to have mortality rates similar to that of term infants.[17] Studies have shown, however, that infants born at 34 weeks' gestation are at 50% increased risk for requiring intensive care,[18,33,47] and late preterm infants have increased morbidity such as RDS, intraventricular hemorrhage (IVH), and death,[68] and long-term morbidities such as behavioral and developmental delay.[45,79] The recent ALPS (Antenatal Late Preterm Steroids) study showed significant decreases in respiratory complications in late preterm infants born to mothers who received antenatal betamethasone at 34-37 weeks.[26] This will likely change obstetric clinical practice and outcomes for late preterm infants going forward.

Use of intrapartum fetal monitoring and prenatal ultrasound has been increasing over the years, from a rate of 68% and 48%, respectively, in 1989 to 85% and 67% in 2003.[17] Prenatal ultrasound can lead to an overestimation of gestational age in maternal conditions associated with fetal macrosomia, such as obesity and gestational diabetes, both of which have increased rapidly in the last decade. There is the possibility of earlier intervention (induction or elective cesarean section) when ultrasound estimates are used to guide the management plan.[55] Although fetal surveillance is designed to reduce adverse neonatal outcome, when coupled with antenatal tests with poor positive predictive value (biophysical profile, non-stress test), it may inadvertently increase medical interventions, with a resultant increase in late preterm and early term birth rates.[17]

Advanced Maternal Age, Assisted Reproductive Technologies, and Multiple Births

More women are now choosing to have children at a later age; it is well known that preterm birth is more prevalent among women with advanced maternal age. Women older than 35 years old also have nearly twice the rate of cesarean section compared with women 20-24 years old. Increasing numbers of women are also seeking assisted reproductive technologies (ART); 57,323 women delivered infants through ART in 2014, and more than 60% of these women were older than 35 years.[5] Of infants born by ART, 32% were of multiple gestations, with 57% of twins and 98.7% of triplets or more being born prematurely.[5] Singleton births from ART are also more likely to be preterm.[5]

Pathophysiology

It is surprising to some that late preterm infants, who are large and do not look anything like their tiny preterm counterparts, are at increased risk of medical complications related to prematurity. As their name implies, these infants are not term, however, and are prone to a host of clinical problems, including RDS, temperature instability, feeding difficulties, hypoglycemia, hyperbilirubinemia, apnea, late neonatal sepsis, prolonged hospital stay, and readmission.[18,29,56,68]

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Thermoregulation

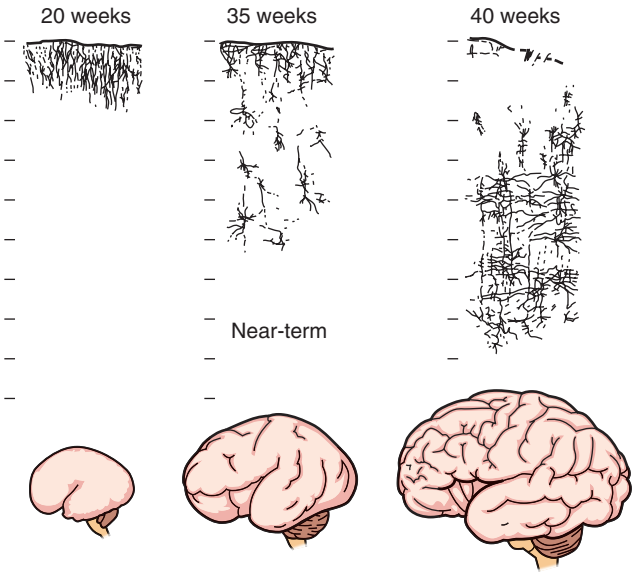
Thermoregulation in a newborn depends on the amount of brown adipose tissue, white adipose tissue, and body surface area (see Chapter 35). Nonshivering thermogenesis is controlled by the hypothalamic ventral medial nucleus through the sympathetic nervous system, which releases the neurotransmitter norepinephrine; this acts on the brown adipose tissue to liberate free fatty acids, which are eventually oxidized, producing heat. Late preterm infants have decreased stores of brown adipose tissue and the hormones responsible for brown fat metabolism such as prolactin, norepinephrine, triiodothyronine, and cortisol, which peak at term gestation. They are more likely to lose heat because of a decreased amount of white adipose tissue and less insulation. Also, their smaller size leads to an increased ratio of surface area to body weight, losing heat readily to the environment.[18,53]

Feeding

Late preterm infants have poor coordination of sucking and swallowing because of neuronal immaturity and have decreased oromotor tone, generating lower intraoral pressures during sucking.[18,37,53,56] Poor caloric intake and dehydration result in exacerbation of physiologic jaundice, leading to readmission to the hospital for dehydration and jaundice. These infants also have decreased activity of hepatic uridine diphosphate glucuronyl transferase enzyme and increased enterohepatic circulation because of immature gastrointestinal function and motility. This decreased ability for hepatic uptake and conjugation puts late preterm infants at increased risk of elevated serum bilirubin levels, and jaundice is more prolonged, prevalent, and severe in these infants.[9] One study showed that infants born at 36 weeks' gestation have an eight times greater risk of developing a total serum bilirubin concentration greater than 20 mg/dL (>343 mmol/L) compared with infants born at 41 weeks or later.[48a]

Glucose Homeostasis

The fetus gets a steady supply of glucose primarily by maternal transfer through the placenta. Immediately after birth, this constant supply of glucose is cut off, and the infant has to produce glucose primarily by hepatic glycogenolysis and gluconeogenesis.[27] The postnatal surge in catecholamines, glucagon, and corticosteroids plays an important role in maintaining euglycemic control. This increase in plasma concentrations of catecholamines causes a decline in circulating insulin concentrations and a subsequent surge in glucagon concentrations. Glucose-regulated insulin secretion by the pancreatic β cells is also immature, resulting in unregulated insulin production during hypoglycemia.[22] Late preterm infants are challenged to maintain euglycemia control secondary to developmentally immature hepatic enzyme systems for gluconeogenesis and glycogenolysis, hormonal dysregulation with inadequate adipose tissue lipolysis, and decreased hepatic glycogen stores that are depleted quickly after birth.[18,22,56]



• **Fig. 40.5** Development of the human cerebral cortex. The immaturity of the laminar position and dendritic arborization of neurons, as shown by Golgi drawings, in the cerebral cortex in a late preterm infant at 35 gestational weeks is striking compared with neurons at midgestation (20 weeks) and at term (40 weeks). (Modified from Kinney HC, et al. Perinatal neuropathology. In: Graham DI, Lantos PE, eds. *Greenfield's neuropathology.* 7th ed. London: Arnold; 2002:557-559.)

Neurologic Immaturity

At 34 weeks' gestation, brain weight is only 65% of a 40-week term infant, and cerebral volume is 53% of a 40-week infant (Fig. 40.5).[10,37] The brain of a late preterm infant is still immature and continues to grow until 2 years of age, when it reaches 80% of adult brain volume. The cerebral cortex is still smooth compared with that of a term infant, because the gyri and sulci are not fully formed on the cerebral cortex, and myelination and interneuronal connectivity are still incomplete in these infants. There is evidence that multiple insults during this critical phase of neuronal and glial maturation in these infants cause white and gray matter injury, particularly in the thalamic region and the periventricular white matter. All of this underscores the potential vulnerability of the late preterm infant to neuronal brain injury and poor developmental and long-term outcome.[37]

Respiratory

Several studies have consistently shown that late preterm and early term infants have higher respiratory morbidity and mortality, with increased risk of TTN, RDS, PPHN, and respiratory failure than term infants.[6,12,24,29,70] A review from the Extracorporeal Life Support Organization (ELSO) Neonatal Registry of nearly 14,500 infants between 1986

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and 2006 with severe hypoxic respiratory failure requiring extracorporeal membrane oxygenation found that 14.7% were late preterm and 21.5% were early term infants. Although meconium aspiration was one of the primary reasons for the respiratory failure among term infants, late preterm and early term infants had a higher incidence of PPHN and RDS as the primary cause. They also had higher mortality (late preterm, OR 2.73; early term 1.63) and complications on ECMO when compared with term infants.[58] Late preterm infants and some early term infants born by cesarean section before the onset of labor have respiratory distress despite having mature surfactant profiles. To understand this vulnerability for respiratory problems, one needs to understand the pathophysiology of fetal lung fluid secretion and clearance, because it may play an important role in the development of RDS or PPHN along with surfactant maturation.

Role of Fetal Lung Fluid Clearance in Neonatal Transition

Throughout much of gestation, fetal lungs actively secrete fluid into alveolar spaces via a chloride secretory mechanism that can be blocked by inhibitors of Na-K-2Cl co-transport. This body of fluid plays a crucial role in lung development, providing a structural template that prevents collapse of the developing lung and promotes its growth. The fetus is presented with a challenge at birth. Often at short notice, and sometimes with no notice at all, the fetus is asked to clear the airspaces rapidly of the fluid that it has been secreting through much of the pregnancy. The lung epithelium is a key participant in this process, engineering the switch from placental to pulmonary gas exchange.[11,30]

For effective gas exchange to occur, alveolar spaces must be cleared of excess fluid, and pulmonary blood flow must be increased to match *ventilation* with *perfusion*. Failure of either of these events can jeopardize neonatal transition and cause the infant to develop RDS. Clinicians are still far from completely understanding the mechanisms by which fetal lungs are able to clear excessive fluid at birth. It is clear, however, that traditional explanations that relied on "Starling forces" and "vaginal squeeze" can account for only a fraction of the fluid absorbed.[11,30] Amiloride-sensitive sodium transport by lung epithelia through epithelial sodium channels (ENaC) has emerged as a key event in the transepithelial movement of alveolar fluid.[11,31] Disruption of this process has been implicated in several disease states, including TTN and hyaline membrane disease. Using the fetal lamb model, several investigators have shown that much before the onset of spontaneous labor, the fetus begins preparation for extrauterine life by reducing the rate of lung fluid secretion and improving clearance.[30]

Developmental changes in transepithelial ion and fluid movement in the lung can be viewed as occurring in three distinct stages. In the first (fetal) stage, the lung epithelium remains in a secretory mode, relying on active chloride secretion via Cl^- channels and relatively low reabsorption activity of Na^+ channels. Why Na^+ channels remain inactive through much of fetal life is unclear. The second (transitional) stage involves a reversal in the direction of ion and water movement. A multitude of factors may be involved in this transition, including exposure of epithelial cells to an air interface and to high concentrations of steroids and cyclic nucleotides. This stage involves not only increased expression of Na^+ channels in the lung epithelia, but also possibly a switch from nonselective cation channels to highly selective Na^+ channels. The net increase in Na^+ movement into the cell can also cause a change in resting membrane potential leading to a slowing, and eventually a reversal, of the direction of Cl^- movement through Cl^- channels. The third and final (adult) stage represents lung epithelia with predominantly Na^+ reabsorption through Na^+ channels and possibly Cl^- reabsorption through Cl^- channels, with a fine balance between the activity of ion channels and tight junctions. Such an arrangement can help ensure adequate humidification of alveolar surface while preventing excessive buildup of fluid.

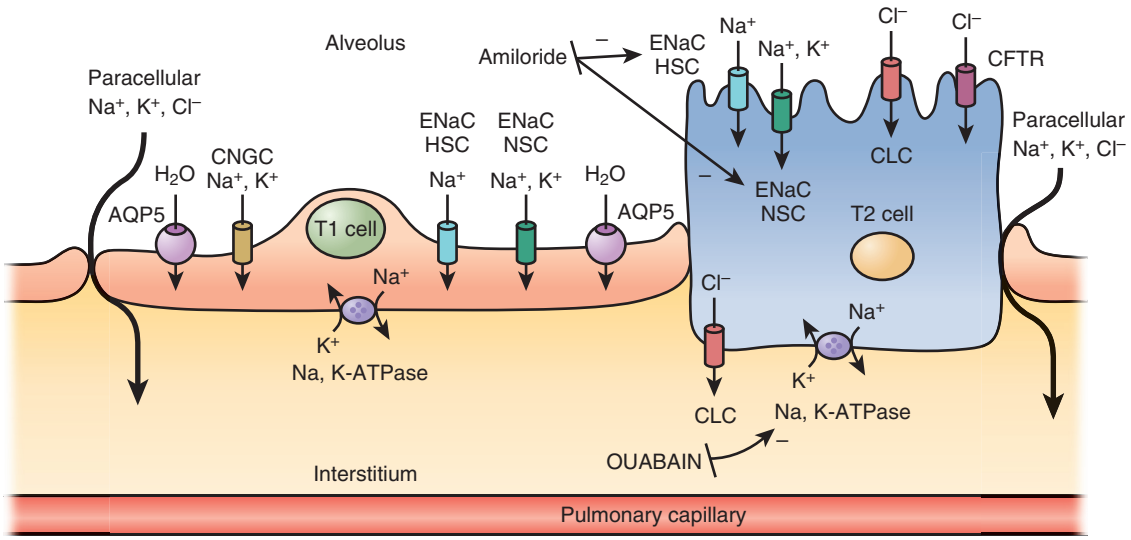
After birth, the remaining lung fluid is rapidly cleared by a two-step process (Fig. 40.6). The first step is passive movement of Na^+ from the lumen across the apical membrane into the cell through Na^+-permeable ion channels; the second step involves active extrusion of Na^+ from the cell across the basolateral membrane into the serosal space.[25] Epithelial Na^+ channels (ENaC), which regulate the first step, are rate-limiting in this process. Hummler and coworkers showed that inactivating the a-ENaC (a subunit of the epithelial Na^+ channel) leads to defective lung liquid clearance and premature death in mice.[24] Studies in human neonates have also shown that immaturity of Na^+ transport mechanisms contribute to the development of TTN and RDS.[32]

Epithelial Na^+ channel expression is developmentally regulated with peak expression in the alveolar epithelium achieved only at term gestation[65]; late preterm infants are born with lower expression of ENaC, which reduces their ability to clear fetal lung fluid after birth. High doses of glucocorticoids have been shown to stimulate transcription of ENaC in several sodium-transporting epithelia and the lung. In the alveolar epithelia, glucocorticoids were found to induce lung sodium reabsorption in the late gestation fetal lung. In addition to increasing transcription of sodium channel subunits, steroids increase the number of available channels by decreasing the rate at which membrane-associated channels are degraded, and they increase the activity of existing channels. Glucocorticoids have also been shown to enhance the responsiveness of lungs to beta-adrenergic agents and thyroid hormones.[55] The enhanced sodium reabsorption induced by glucocorticoids can be blocked by amiloride, suggesting a role for ENaC.[32]

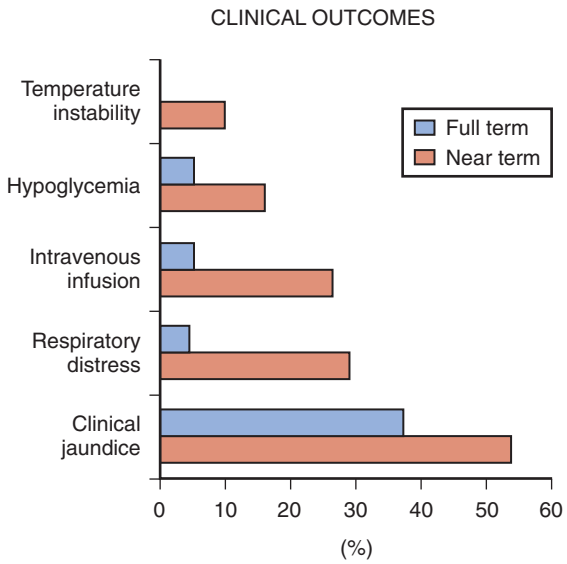
Clinical Outcomes

Morbidity in late preterm infants increases with decreasing gestational age; it is estimated to be nearly 52%, 26%, and 12% in 34-, 35-, and 36-week gestation infants,

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• **Fig. 40.6** Epithelial sodium (Na) absorption in the fetal lung near birth. Na enters the cell through the apical surface of alveolar type I and type II cells via amiloride-sensitive epithelial Na channels (ENaC), both highly selective channels (HSC) and nonselective channels (NSC), and via cyclic nucleotide gated channels (seen only in angiotensin I cells). Electroneutrality is conserved with chloride movement through cystic fibrosis transmembrane conductance regulator (CFTR) or chloride channels (CLC) in angiotensin I and II cells or paracellularly through tight junctions. The increase in cell Na stimulates Na, K-ATPase activity on the basolateral aspect of the cell membrane, which drives out three Na^+ ions in exchange for two K^+ ions, a process that can be blocked by the cardiac glycoside ouabain. If the net ion movement is from the apical surface to the interstitium, an osmotic gradient would be created, which would direct water transport in the same direction, either through aquaporins or by diffusion. CNGC, Cyclic nucleotide-gated cation channel. (Modified from Jain L. Respiratory morbidity in late-preterm infants: prevention is better than cure! *Am J Perinatol.* 2008;25:75-78.)



• **Fig. 40.7** Graph of clinical outcomes in near-term (35-36 6/7weeks) and full-term infants as percentage of patients studied. (From Wang ML, et al. Clinical outcomes of near-term infants. *Pediatrics.* 2004;114:372.)

respectively. Infants born at 34 weeks' gestation had nearly a 20 times greater risk of morbidity compared with infants who were born at 40 weeks' term gestation.[63] Because of their physiologic immaturity, nearly every organ system is affected in late preterm infants (Fig. 40.7). Data from the British Columbia Perinatal Database Registry show that late preterm infants had 4.4 times the respiratory morbidity and 5.2 times the neonatal infection rate than term infants. They also had increased length of hospital stay compared with term infants (142 hours versus 57 hours).[36] A meta-analysis of 22 studies comparing late preterm and term infants showed higher risk of respiratory distress syndrome (relative risk [RR], 17.3), IVH (RR 4.9), death less than 28 days (RR 5.9), and cerebral palsy (RR 3.1).[68] In infants with critical congenital heart disease (CCHD), being born at 34-36 weeks was associated with a higher risk of death or morbidity than being born at 37-38 weeks (adjusted absolute risk reduction [ARD] 9.1%, 95% CI 5.5%-12.7%).[66] Mortality and morbidity are described in further detail in each physiologic system in this section.

Mortality

A systematic review of severe morbidity and mortality in late preterm infants was performed by Teune et al., compiling data from 2000-2010. Late preterm infants were four times more likely to die in the first year than term infants. Tomashek and colleagues, using US period-linked birth/infant death files for 1995-2002, found that despite significant declines since 1995 in mortality rates for late preterm and term infants, infant mortality rates in 2002 were three times higher in late preterm infants than term infants (7.9 vs. 2.4 deaths per 1000 live births); early (1-6 days), late

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TABLE 40.2 Mortality Rates and Risk Ratios for Death According to Gestational Age

Gestational Age (weeks)	Early Neonatal Mortality Rate (1-7 Days)		Infant Mortality Rate (1-365 Days)	
	Mortality Rate*	Risk Ratio	Mortality Rate*	Risk Ratio
34	7.2	25.5†	12.5†	10.5
35	4.5	16.1†	8.7†	7.2
36	2.8	9.8†	6.3†	5.3
37	0.8	2.7†	3.4†	2.8
38	0.5	1.7	2.4†	2.0
39	0.2	0.8	1.2	1.2
40	0.3	Reference	1.4	Reference

*Mortality rates are per 1000 live births.
†Risk ratios are significantly different from 40 weeks.
Modified from Young PC, et al. Mortality of late-preterm (near-term) newborns in Utah. *Pediatrics*. 2007;119:e659.

(7-27 days), and postneonatal (28-365 days) mortality rates were six, three, and two times higher.[71] During infancy, late preterm infants were approximately four times more likely than term infants to die of congenital malformations (leading cause); newborn bacterial sepsis; and complications of placenta, cord, and membranes.

Young and associates, in a large cohort from Utah, showed increasing mortality and relative risk of death for every decreasing week in gestational age less than 40 weeks[80] (Table 40.2). Infants born only a few weeks before term gestation are at much greater risk of mortality; infant mortality rate in 2009 for late preterm infants was nearly three times the rate for term infants (7.13 vs. 2.36 per 1000 live births), and it was nearly 1.6 times higher for early term infants born at 37-38 weeks when compared with infants born at 39-41 weeks' gestation (3.09 vs. 1.98). The increased risk of morbidity and mortality is not limited to the immediate neonatal period. A study looking at nearly 675,000 singleton births in Sweden (between 1973 and 1979) found that infants born at late preterm gestation had increased risk of mortality at 18-36 years of age (adjusted hazard ratio 1.53 and 1.31 at early childhood and young adulthood).[14] This tells us that effects of late preterm birth are not limited to the neonatal period alone but also carry into adulthood.

Respiratory

Several studies have shown that late preterm infants have a higher incidence of RDS than term infants.[13,47,74] Wang and colleagues found that late preterm infants, despite their larger size and Apgar scores similar to term infants, had increased RDS (28.9% vs. 4.2%; odds ratio 9.14, $P < .00001$) and apnea (4.4% vs. 0%; $P = .05$) (see Fig. 40.7).[75] Estimates of incidence of RDS range from 7.4%-13.7% at 34 weeks, 4.5%-6.4% at 35 weeks, and 2.3%-3.6% at 36 weeks.[14,24,58,74,75] In a large study cohort of almost 47,000 newborns in California, the incidence of RDS was 22.1% at 33-34 weeks, 8.3% at 35-36 weeks, and 2.9% at 37-42 weeks of gestation.[19]

Data collected from 2002-2008 by the Consortium on Safe Labor reported that the odds of respiratory distress syndrome decreased with each advancing week until 38 weeks. The incidence of RDS was 10.5% at 34 weeks compared to 0.3% at 38 weeks.[29]

Along with increasing incidence of respiratory distress among late preterm infants, these infants have also been shown to require increased need for respiratory support. A study from St. Louis found the need for some kind of respiratory support at 30%, 33%, and 23% of the time at 34 weeks, 35 weeks, and 36 weeks.[73] Other studies have shown the need for mechanical ventilation at 3.3%-6.3% at 34 weeks, 1.7%-3.6% at 35 weeks, and 0.8%-2.3% at 36 weeks.[23,46] In a study of 1011 ventilated infants of 34 weeks' or greater gestation, Clark found that RDS (43%) was the most common cause of pulmonary illness, followed by meconium aspiration syndrome (9.7%), pneumonia/sepsis (8.3%), TTN (3.9%), idiopathic PPHN (3.2%), aspiration of blood or amniotic fluid (2.3%), and lung hypoplasia (1.4%).[12]

Prematurity, cesarean section, and absence of labor are independent risk factors for RDS, but together they pose a much greater risk to the infant. In a Swiss study, Roth-Kleiner and coworkers showed that term and near-term infants delivered by cesarean section before the onset of labor had much higher probability of having severe RDS.[60] Morrison and colleagues also showed that term infants have nearly seven times the odds risk for RDS when delivered by cesarean section without labor, and they showed an increasing incidence of RDS with decreasing gestational age from 41-37 weeks. Tita et al.[70] looked at nearly 24,000 elective cesarean sections and found the incidence of RDS or TTN at 8.2% for 37 weeks, 5.5% at 38 weeks and 3.4% at 39 weeks. Similarly, in a Dutch study looking at almost 34,000

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infants, Hansen and associates found that the relative risk of severe RDS increased with decreasing gestational age even among term infants, with nearly five times the odds at 37 weeks. Fetal lung maturity often is used as a criterion that late preterm and early term infants have mature lungs and are ready for postnatal life. However, several studies have demonstrated higher respiratory morbidity in neonates in spite of the mature surfactant profile. Kamath et al. showed that after adjustment for significant covariates, infants who were born at less than 39 weeks' gestation with documented fetal lung maturity had an increased risk of composite adverse outcome (odds ratio, 3.66; 95% confidence interval, 1.48-9.09; $P < .01$).[35]

Why is this slightly increased risk of RDS and TTN of concern? Most of these late preterm infants do well and are weaned off respiratory support quickly, but as shown from the mentioned studies, a few of them are at increased risk of PPHN, severe hypoxic respiratory failure, and need for extracorporeal membrane oxygenation, putting them at risk of severe morbidity and mortality. Clark showed that nearly 11% of late preterm infants developed chronic lung disease.[12] Data also show that they are prone to develop long-term respiratory complications such as asthma and decreased lung function later in life.[25,38]

Temperature Instability and Hypoglycemia

Cold stress manifests as tachypnea, poor color secondary to peripheral vasoconstriction, altered pulmonary vascular tone, and metabolic acidosis. In a late preterm infant, this condition can worsen respiratory transition and exacerbate hypoglycemia, and these signs can be misinterpreted as something more ominous, such as sepsis, prompting unnecessary interventions and work-ups. Very few studies have looked at temperature instability in late preterm infants, but from experience, preterm infants are more likely to have hypothermia and cold stress. A survey of rectal temperatures among 196 term infants in a Dallas hospital found that nearly 28% were less than 36.5°C.[39] Similarly, admission temperatures at a Rhode Island hospital NICU in infants weighing more than 2 kg and of greater than 32 weeks' gestation were reported to be between 34.5° and 36.5°C.[34] Wang and colleagues[75] found that late preterm infants were more likely to present with temperature instability (10% vs. 0%; $P < .0012$), and another study found that among late preterm infants admitted to the NICU, hypothermia was listed as the primary reason for admission in almost 5.2% of this group.[73]

Hypoglycemia is another component that can affect transition. The incidence of hypoglycemia in preterm infants is three times greater than in term newborns, and nearly two-thirds of these infants require intravenous dextrose infusions.[75] Severe hypoglycemia is a well-known risk factor for neuronal cell death and adverse neurodevelopmental outcomes, but the exact threshold for hypoglycemia is not well defined.[22,39] In 2011, the AAP Committee on Fetus and Newborn provided guidelines for screening and management of postnatal glucose homeostasis in late preterm infants, recognizing that they are an at-risk population along with term small-for-gestational-age (SGA) and infants of diabetic mothers (IDM)/large-for-gestational-age (LGA) infants (Fig. 40.8). These infants should receive their initial feed within the first hour of life and have a screening glucose 30 minutes after the first feed. The threshold for low blood glucose is <25 mg/dL in first 4 hours of life, <35 mg/dL from 4-24 hours of life, and <40 mg/dL when the infant is symptomatic (irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding). The algorithm then provides guidelines for treatment of hypoglycemia. The Pediatric Endocrine Society recommends that high-risk infants without a suspected congenital disorder (which would include late preterm infants) should maintain goal plasma glucose concentration >50 mg/dL <48 hours and >60 mg/dL >48 hours to minimize any long-term effects.[69] More studies are needed in late preterm infants to define the effects of hypoglycemia, identify at-risk infants, and determine long-term outcomes.

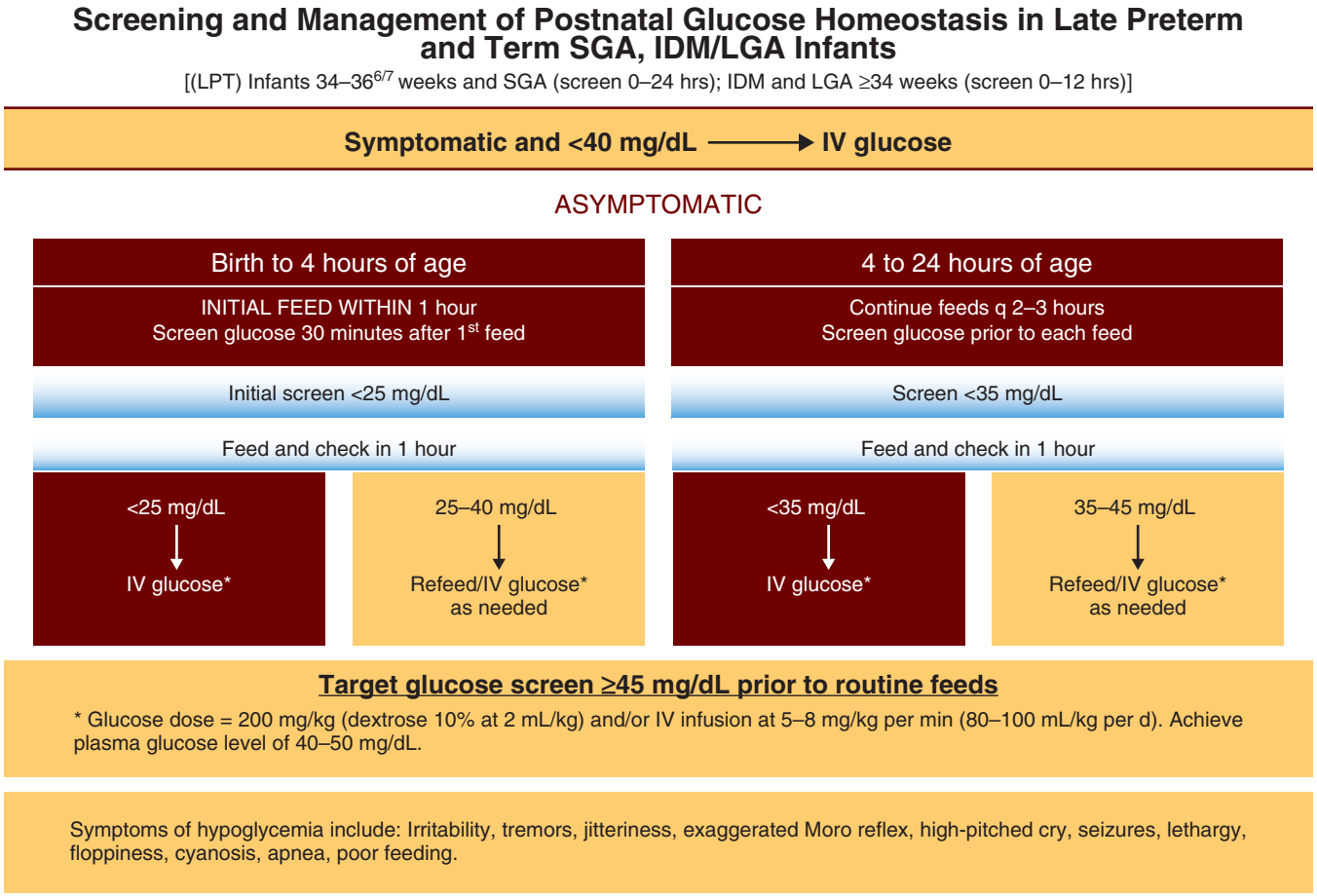
Gastrointestinal Tract

Late preterm infants adapt well to enteral feeds, but have poor oromotor tone and difficulty with sucking and swallowing coordination. Their deglutition, sphincter control, and peristaltic functions are less likely to be as mature as in term infants. One study found that approximately 27% of late preterm infants required intravenous fluids compared with only 5% of term infants (odds ratio 6.48, 95% CI 2.27-22.91, $P = .0007$), and among infants requiring prolonged hospital stay, poor feeding was cited as the primary reason in 76% of the late preterm infants.[75] Another study from St. Louis found that among late preterm infants admitted to the NICU, nearly 7.3% of infants of 35 weeks' gestation were admitted for feeding difficulties.[73] In a study of rehospitalizations after birth hospitalization, Escobar and associates found that 26% of the infants were readmitted for feeding difficulties, and late preterm infants were more likely to require rehospitalization (4.4% vs. 2% in term infants).[20] Dehydration also exacerbates physiologic jaundice in these infants, predisposing them to rehospitalization and other medical interventions. Whether the immature gut in late preterm infants predisposes them to increased risk of food allergies and diabetes in later life remains to be studied.[56]

Hyperbilirubinemia

Late preterm infants are 2.4 times more likely to develop significant hyperbilirubinemia than term infants.[61] Bhutani and associates, looking at the National Kernicterus Registry, showed that late preterm infants are at increased risk of kernicterus at bilirubin levels equal to or less than that of term infants.[9] They are also more likely to present with high total serum bilirubin levels (≥25 mg/dL) and are less likely

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• **Fig. 40.8** Screening and management of postnatal glucose homeostasis during the immediate postnatal period in late preterm and term small-for-gestational-age (SGA) infants, infants of diabetic mothers (IDM)/large-for-gestational-age (LGA) infants. (Reproduced with permission from Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants clinical report—postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2013;127(3):575–579. Copyright © 2013 by the AAP. https://doi.org/10.1542/peds.2010-3851.)

to recover without sequelae than term infants. Nearly all late preterm infants in this group were breastfeeding without adequate lactation support and with poor milk intake, and they were scheduled for follow-up appointments in 2 weeks.

Neonatal hyperbilirubinemia in late preterm newborns is more prevalent, more pronounced, and more protracted in nature than in their term counterparts. Jaundice was the most common cause of rehospitalization, and late preterm infants were more likely to be rehospitalized for jaundice than term infants (4.5% vs. 1.2% in term infants).[20] Hyperbilirubinemia is a significant problem in these infants, as shown by their overrepresentation in the kernicterus registry. The large size of late preterm infants may fool practitioners into complacency by treating them as term infants; however, close follow-up and monitoring for feeding difficulties should be mandated to prevent kernicterus in this vulnerable group.

Immunity and Infection

It has been shown that late preterm infants undergo work-ups for sepsis more often than term infants (36.7% vs. 12.6%; odds ratio 3.97, $P = .00015$) and receive antibiotics more often and for a longer duration (7-day course in 30% vs. 17% of term infants).[75] Another study found that the likelihood of having a work-up for sepsis increased with decreasing gestational age; 33% had work-ups for sepsis at 34 weeks compared with 12% at 39 weeks of gestational age ($P \leq .01$), of which only 0.4% of these infants had culture-proven sepsis.[46] Late preterm infants undergo work-ups more often for sepsis either as a part of a protocol after admission to the NICU or because of clinical manifestations of RDS, cold stress, and hypoglycemia, which may appear to be signs of sepsis to the physician.

Hospitalizations and Rehospitalizations After Discharge

Late preterm infants are more likely to require intensive care and are admitted to the NICU more often than term infants. Admission rates vary based on the policies of individual institutions and hospitals; some routinely admit all infants less than 35 weeks of gestation to the NICU, and

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others do so only if there is a need. One large population-based study found that 88% of infants born at 34 weeks' gestation, 12% born at 37 weeks' gestation, and 2.6% born at 38-40 weeks' gestation were admitted to a NICU.[17] Another study found that 97%, 53%, and 32% of infants of 34, 35, and 36 weeks of gestation required NICU admissions.[73] Duration of hospital stay is also inversely proportional to gestational age, with late preterm infants requiring much longer hospital stays (6-11 days, 4-6 days, and 3-4 days in 34-, 35-, and 36-week infants, respectively).[36,73] The most common reasons for admission include jaundice, RDS, dehydration and poor feeding, hypoglycemia, and temperature instability.[73,75]

Aside from the greater need for specialized care and the prolonged initial hospital stay, late preterm infants are also at risk for rehospitalization after discharge from the hospital.[19,63,64] Looking at a large population-based cohort in a managed care organization, Escobar and colleagues found that late preterm infants (4.4%) had a higher rate of rehospitalization than term infants (2%), and the rate was higher than for infants less than 34 weeks' gestational age (3%).[19,20] They also found that infants between 34 and 36 weeks of gestation who were never admitted to the NICU, and infants with NICU stays less than 24 hours had nearly three times and 1.3 times the risk of readmission than term infants, which indicates that clinicians may be treating these immature infants based on their weight and failing to identify all of the risk factors.

The most common reasons cited for readmission include hyperbilirubinemia (63%-71%), feeding difficulties (16%), and suspected sepsis (6%-20%).[64,72] The infants requiring rehospitalization were more likely to be firstborn, be breastfed at discharge, have labor and delivery complications, be a recipient of a public insurance at delivery, or be of Asian/Pacific Islander descent.[64] Given that late preterm infants are at a much higher risk for rehospitalization, protocols need to be designed for closer monitoring of breastfed infants of new first-time mothers and infants at risk for jaundice, especially of Asian descent, avoiding early discharge until proper feeding has been established and ensuring early follow-up after hospital discharge.

Economic Impact

The Institute of Medicine estimated that every preterm birth costs $51,600, with a total impact of $26 billion in 2005.[7] Late preterm infants are responsible for a significant share of this burden, constituting two-thirds of all preterm births. It is estimated that a relative increase in direct costs for late preterm infants is 2.9 times that of a term infant, resulting in a cost increase of $2630 per infant.[75] A large population-based study over a 1-year period (1996) in California found that hospital costs for an infant of 34 weeks' gestation were $7200; of 35 weeks, $4200; and of 36 weeks, $2600, compared with $1100 for an infant of 38 weeks' gestation. Delaying delivery by just 1 week from 34-35 weeks reduced the cost by 42% and from 35-36 weeks by 38%.[23] A similar California cohort for 2000 showed hospital costs of $7081 for infants of 33-36 weeks' gestation.[62]

Another large cohort from a Dallas hospital over an 18-year study period found that the average hospitalization cost for late preterm infants was $3098, and for 39-week term infants was $1258 ($6094 for infants of 34 weeks; $3519 for 35 weeks; and $2019 for 36 weeks).[46] Similarly, Phibbs and associates looked at all births between 24 weeks and 37 weeks of gestation from 1998-2000 in California and found that the cost reduction for delaying preterm delivery by 1 week from 34-35 weeks was $4528 and by 3-37 weeks was $8508.[52] In a study by Gilbert and associates, the average cost for each infant of 25 and 35 weeks' gestation was approximately $200,000 and $4200, but when the total cost for all infants in each gestation group was calculated, the cost for 35-week infants was $41.1 million, and the cost for 25-week infants was $38.9 million.[23] Although extremely preterm infants are very expensive to treat, the overall cost of treating the cohort of late preterm infants is similar because of the large number of infants treated. They also estimated that the excess cost of medical care for the late preterm infants for that year in this cohort compared with the cost of treating the term infants was nearly $50 million, but it is very hard to separate preventable late preterm births from unpreventable births—hence the difficulty in estimating the excess cost attributable to iatrogenic and preventable preterm birth.

The costs are not just higher in the immediate neonatal period but also higher in early childhood. A Canadian study comparing late preterm to term infants found that late preterm infants are at greater risk for morbidities such as bronchiolitis and pneumonia during the first 3 years of life and that the hospitalization costs were nearly twice that of term infants in the first 2 years and nearly 46% greater in the third year.[8]

Long-Term Outcomes and Societal Costs

Although it is well known that very preterm infants are at a higher risk of psychomotor, behavioral, cognitive, and other developmental disabilities, late preterm infants also have more subtle findings of language delay, attention deficits, lower intelligence, behavioral problems, and academic achievement. There are few studies of long-term outcomes in late preterm infants. A large Swedish population-based study, including 903,402 children (32,945 late preterm infants) who were born alive without any congenital anomalies from 1967-1983 and followed through adulthood, found a higher incidence of cerebral palsy (relative risk 2.7, 95% CI 2.2–3.3, $P < .001$), mental retardation (relative risk 1.6, 95% CI 1.4–1.8, $P < .001$), disorders of psychological development, behavior and emotional disturbances, other major disabilities (blindness, low vision, hearing loss, and epilepsy), and medical disability affecting working capacity.[48] Woythaler and colleagues, using the Early Childhood Longitudinal Study-Birth Cohort (ECLS-B), found that late preterm infants had increased odds of lower mental

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index scores (MDI <70; OR 1.51 [95% CI:1.26–1.82]) and lower psychomotor index scores (PDI <70; OR 1.56 [95% CI:1.29–1.88]) at 24 months of age.[79] Using the same cohort, they followed these late preterm infants to kindergarten and found that they are still delayed compared to their full-term counterparts based on having worse Total School Readiness Score (TSRS).[78]

Chyi and colleagues, using the Early Childhood Longitudinal Study-Kindergarten Cohort (ECLS-K), compared learning difficulties among moderately preterm (32-33 weeks of gestation), late preterm (34-36 weeks of gestation), and full-term infants using direct child assessment tests and teacher academic rating scale scores. They found that late preterm infants scored lower on direct child assessment tests than full-term infants for reading but not math in kindergarten and first grade. For teacher academic rating scale scores, late preterm infants scored lower in reading in kindergarten, first grade, and fifth grade, and scored lower in math assessments in kindergarten and first grade. Late preterm infants also showed an increased need for individualized educational programs and special education in kindergarten and first grade. In regression analysis, late preterm infants had a 24% increased adjusted odds ratio for below-average reading in the first grade and were 1.3 times more likely than full-term infants to have below-average reading across all grade levels in the teacher assessment scores. The reason for not seeing a difference in the later grades for mathematics scores was probably because of a high number of infants lost to follow-up toward the later grades (34% at fifth grade) and the higher number of disabilities seen in the lost-to-follow-up group. Talge and colleagues compared 336 pairs of late preterm and term infants and found the late preterm infants at 6 years of age had increased risk of lower IQ scores and higher incidence of teacher-reported behavioral problems.[67] These results were present after adjusting for other confounding variables such as maternal education, maternal IQ, residential setting, marital status, and child sex. A study of approximately 215,000 children from New York City in the Longitudinal Study of Early Development, data including nearly 13,200 late preterm infants, found that they had lower adjusted match and English language test scores when compared with term infants.[42] The Millennium Cohort Study, a longitudinal study of approximately 18,800 infants from the United Kingdom, found an association between late preterm birth and poor educational achievement at 5 years of age, including lower overall achievement, personal/social/emotional development, communication/language, and literacy and mathematical development.[54] Another study by Williams et al. evaluated the role of prematurity and maternal factors in first-grade academic failure; after adjusting for maternal and child characteristics, there were increased odds of failure of each component of the first-grade Criterion-Referenced Competency Test (CRCT) for children born late preterm versus term.[77]

These studies show us that late preterm birth has a significant impact on the immature preterm brain. These retrospective reports in no way confirm causality. It is unclear if the neurologic injury resulted from or predated the event that caused the late preterm birth. Societal costs are hard to estimate. A Swedish study by Lindstrom and colleagues estimated that among a cohort of approximately 500,000 adults in their twenties, moderately preterm infants of 33-36 weeks' gestation and early term infants received increased disability assistance/allowance and were less likely to attain university or postsecondary education.[41] Of neurologically disabled individuals in this cohort, 74% were born between 33 and 38 weeks of gestation.

Management

Late preterm infants are a special population that needs closer monitoring and care. A comprehensive guide for management of late preterm infants was published and is summarized in Box 40.2.[18]

Admission

It is recommended that infants of less than 35 weeks of gestation or weighing less than 2300 g should be admitted to an area where they can be monitored closely for stability. Transfer to the mother's room or regular "term" nursery environment should be considered only when they show stability of temperature, vital signs, blood glucose, and oral feeding. These infants should have a physical examination on admission and discharge, with determination of accurate gestational age on admission examination.

The obstetric estimate of gestational age is recommended if it is based on a first-trimester ultrasound. If there is a discrepancy (e.g., >2 weeks) between the gestational ages based on the obstetric estimate and the newborn examination, the use of gestational age based on the newborn examination is preferred. Vital signs and oxygen saturation should be performed on admission and monitored with appropriate frequency thereafter. Transfer to a NICU or tertiary care center should be considered if fraction of inspired oxygen (FIO_2) exceeds 0.4. A feeding plan should be developed, and formal evaluation of breastfeeding should be done at least twice daily after birth with documentation in the record by caregivers trained in breastfeeding. Serum glucose screening should be performed per existing protocols for infants at high risk of hypoglycemia—infants who are small for gestational age, large for gestational age, and infants of diabetic mothers.[76]

Discharge Criteria

Discharge should not be considered before 48 hours after birth. Vital signs should be normal for 12 hours preceding discharge: respiratory rate, less than 60 breaths/min; heart rate, 100-160 beats/min; and axillary temperature, 36.5°C-37.4°C in an open crib with appropriate clothing. There should be documentation of passage of at least one stool spontaneously, with adequate urine output, and 24

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• BOX 40.2 Admission and Discharge Criteria Management of Late Preterm Infants

Admission Criteria

- Admit infants less than 35 weeks' gestational age or less than 2300 g birth weight
- If well late preterm infants are in their mothers' rooms in the first 24 hours, close monitoring is needed

Hospital Management

- Physical examination on admission and discharge
- Determination of accurate gestational age on admission examination
- Vital signs and pulse oximeter check on admission, followed by vital signs every 3-4 hours in the first 24 hours and every shift thereafter
- Caution against use of oxyhoods with high F_{IO_2}; consider transfer to NICU if F_{IO_2} exceeds 0.4
- Feeding plan should be developed; formal evaluation of breastfeeding and documentation in the record by caregivers trained in breastfeeding at least twice daily after birth
- Serum glucose screening per existing protocols for infants at high risk of hypoglycemia

Discharge Criteria

- Vital signs normal for 12 hours before discharge
- Passage of one stool spontaneously
- Adequate urine output
- Successful feeding for 24 hours: ability to coordinate sucking, swallowing, and breathing while feeding
- If weight loss greater than 7% in 48 hours, consider further assessment before discharge
- Risk assessment plan for jaundice for infants discharged within 72 hours of birth
- No evidence of active bleeding at circumcision site for at least 2 hours
- Initial hepatitis B vaccine has been given or an appointment scheduled for its administration
- Metabolic and genetic screening tests performed in accordance with local or hospital requirements
- Passed CCHD screen
- Passed car-seat safety test
- Hearing assessment has been performed and results documented in the medical record; follow-up if necessary has been arranged
- Family, environmental, and social risk factors have been assessed; when risk factors are present, discharge should be delayed until a plan for future care has been generated
- Identification of a physician with a follow-up visit arranged for 24-48 hours
- Mother and caregivers demonstrate competency in care of the infant

CCHD, Critical congenital heart disease; NICU, neonatal intensive care unit.
Modified from Engle WA, Tomashek KM, Wallman C. Late-preterm infants: a population at risk. *Pediatrics.* 2007;120:1390-1401.

hours of successful feeding; adequate oral feeding should be present with confirmation of coordination of sucking, swallowing, and breathing while feeding. If weight loss is greater than 7% in 48 hours, further assessment should be considered before discharge.

There should be a risk assessment plan for jaundice in infants discharged within 72 hours of birth; predischarge bilirubin check (serum or transcutaneous) should be done before discharge. A transcutaneous bilirubin of greater than 12 mg should be confirmed with a serum bilirubin, and bilirubin nomograms should be used to determine the risk and need for follow-up or treatment. There should be no evidence of active bleeding at the circumcision site for at least 2 hours. The initial hepatitis B vaccine should have been given or an appointment scheduled for its administration, and the metabolic and genetic screening tests should have been performed in accordance with local or hospital requirements. A critical congenital heart disease screening should be performed. A car seat safety test and a hearing assessment should be performed, and results should be documented in the medical record.

When social risk factors are present, discharge should be delayed until a plan for future care has been generated. A follow-up visit with a physician should be arranged for 24-48 hours after discharge. The mother and caregivers should have received training and demonstrated competency in the following activities: knowledge of urine/stool frequency, umbilical cord and skin care, identification of common signs and symptoms of illness, specific instructions concerning jaundice, specific instructions regarding sleeping patterns and positions, instructions on thermometer use, and instruction regarding responses to an emergency.

Key Points

- Nearly three out of four preterm births occur at late preterm gestational ages (34-37 weeks' gestation).
- Late preterm infants are at risk for complications associated with prematurity. Due to their more mature appearance, there has historically been a lapse in early recognition and management of these issues.
- Late preterm infants have higher morbidity and mortality compared to full-term infants.
- Antenatal steroids, previously only given before 34 weeks' gestation, have now been shown to reduce respiratory complications in infants when given at 34-37 weeks' gestation.
- Late preterm infants require close monitoring for feeding issues, hypoglycemia, hyperbilirubinemia, infection, and thermoregulation in the postnatal period, both during and after their hospital stay.

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Nutrient Requirements/Nutritional Support in Premature Neonate

BRENDA B. POINDEXTER AND CAMILIA R. MARTIN

Current recommendations for the provision of parenteral and enteral nutrition to the infant born prematurely are based on the goal of approximating the rate and composition of weight gain of a normal fetus at the same postmenstrual age. For a number of reasons this goal is seldom achieved, and postnatal growth failure still remains a significant complication of extreme prematurity. Infants who experience one or more major morbidities, such as bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), or late-onset sepsis in the neonatal period, demonstrate slower growth than their counterparts who do not experience these conditions. Of particular concern is the significant association between suboptimal postnatal growth and short-term morbidities as well as adverse long-term neurodevelopmental outcomes. This relationship persists even after adjustments for severity of illness, including the perception of illness, which may alter nutritional delivery in high-risk infants.[30] These findings reinforce the principle that nutritional delivery is critical in modifying disease risk in preterm infants. To emphasize the importance of a combined approach to optimize outcomes in the premature neonate, this chapter will first describe overall nutrient requirements and then provision of intense nutritional support with both early parenteral and enteral nutrition.

Growth in the Neonatal Intensive Care Unit

In the neonatal intensive care unit, birth-weight-derived intrauterine growth curves (such as the Fenton or Olsen) are typically employed to monitor postnatal growth. It is important to recognize the inherent limitation of such curves, namely that these curves were generated by measuring infants following premature birth, which is likely not the same physiologic state for the mother and/or fetus as if the infant had remained in utero until term. The revised Fenton growth curves include an international cohort of approximately 4 million infants from six population-based studies and are available online (http://www.biomedcentral.com/1471-2431/13/59) and have been incorporated into many electronic medical record platforms.[35] The Olsen curves include more than 250,000 infants born in the United States between 22 and 41 weeks' gestation and when combined with the WHO-CDC growth charts (http://www.pediatrix.com/workfiles/NICUGrowthCurves7.30.pdf) can be used to monitor postnatal growth through 50 weeks' corrected age. The number of infants born at 22-24 weeks' gestation is very low (less than 1% of the total cohort) in both of these growth charts, limiting their generalizability as the number of infants in this gestational age range increases in neonatal intensive care units. The Vermont Oxford Network (VON) database recently published growth curves derived from birth measurements in a cohort of 156,000 infants from 852 centers in the United States. The VON curves do include more infants born in the periviable period than previously published growth curves (2000 infants born at 22 weeks' gestation and 9000 infants born at 23 weeks' gestation).[12] Growth curves based on serial intrauterine measurements such as those generated by the INTERGROWTH-21st Project[68] may change the standard for the assessment of postnatal growth and may provide a more appropriate means to examine the relationship between growth and outcomes of infants born prematurely.

Growth and Neurodevelopmental Outcomes

Postnatal growth failure has commonly been defined as weight less than the 10th percentile for gestational age. At the time of birth, approximately 20% of very low birth weight (VLBW) infants are small for gestational age (defined as weight less than the 10th percentile). After a stay in the neonatal intensive care unit, however, many of these infants will have experienced poor growth and weigh less than the 10th percentile at 36 weeks' postmenstrual age. The incidence of postnatal growth failure at 36 weeks' postmenstrual age was 79% in a large cohort of VLBW infants

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Abstract

The provision of nutrition to support optimal growth and outcomes of premature neonates includes a combined approach of both early parenteral and enteral nutrition. Growth (including weight, length, and head circumference) must be carefully monitored in the neonatal intensive care unit and strategies to avoid growth faltering employed. A thorough understanding of nutrient requirements, particularly for extremely premature infants, is necessary to avoid deficits that can compromise normal growth and development. Early initiation of parenteral nutrition, supplying 3.0-3.5 grams per kg and up to 3.0 grams per kg of lipids is recommended. Human milk is the preferred diet for premature infants, with multicomponent fortification to reduce the incidence of growth failure and to achieve appropriate bone mineralization. Future research is needed to develop better methods to monitor growth, particularly representative growth curves that are based on intrauterine growth of healthy fetuses and those that allow clinicians to not only assess anthropometric measurements but also to achieve proportional growth and body composition to support long-term outcomes. New products to specifically support the extremely premature infant and to avoid complications of nutritional support (such as cholestasis) are urgently needed. Finally, strategies that allow for a personalized approach to delivery of optimal nutrition are needed, particularly for those infants who suffer common morbidities of prematurity such as bronchopulmonary dysplasia or necrotizing enterocolitis and are at risk for growth failure during their stay in the NICU and beyond.

Keywords

nutrients
enteral nutrition
parenteral nutrition
growth
protein requirements
human milk

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born between 2003 and 2007 at centers participating in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network.[91] Improved growth outcomes in the past decade may reflect widespread use of early parenteral nutrition with protein and lipid delivery[37] at most neonatal intensive care units as well as a decline in the use of postnatal corticosteroids.[92]

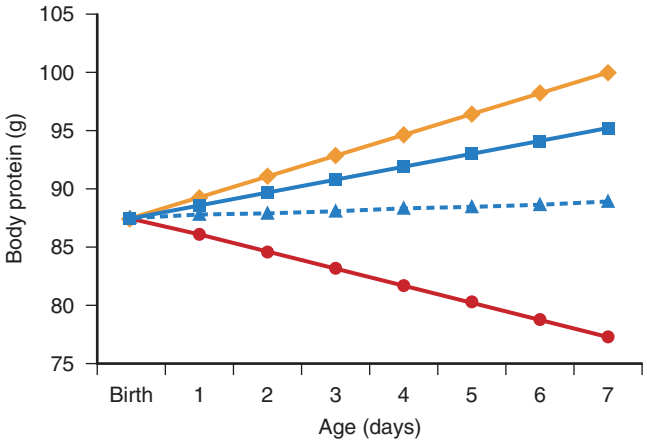
The association between weight gain in the neonatal intensive care unit and neurodevelopmental outcomes was firmly established in a cohort of 600 extremely low birth weight (ELBW) infants reported by Ehrenkranz and colleagues.[31] Infants were divided into quartiles based on in-hospital growth velocity; infants in the highest quartile gained an average of 21 g/kg per day, and those in the lowest quartile gained 12 g/kg per day. Compared with infants in the highest quartile of in-hospital weight gain, the odds of cerebral palsy, Bayley Scales of Infant Development (BSID) II mental developmental index (MDI) less than 70, and neurodevelopmental impairment were significantly higher in infants in the lowest quartile of in-hospital weight gain. Similar findings were also observed with in-hospital head growth. Since this time, multiple studies continue to demonstrate these relationships with recent evaluations using a more contemporary population, and the new edition of the Bayley (BSID III) has reported findings consistent with the earlier work by Ehrenkranz.[18,29] Other investigators have described the association between poor linear growth and neurodevelopmental outcomes.[76] As evidence continues to accumulate that early nutritional inadequacies have long-term consequences, optimizing provision of both parenteral and enteral nutrition to high-risk neonates is crucial to ensure the best possible outcomes.

Among potential causes of postnatal growth failure are significant protein and energy deficits that occur in the early neonatal period and are difficult to recoup in extremely premature infants. The cumulative nutritional deficits described in the sentinel work by Embleton and colleagues underscore the urgency in avoiding early deficits in both energy and protein intake as a means of achieving optimal growth outcomes.[33]

Nutrient Requirements

Protein and Amino Acid Requirements

Duplicating rates of in utero protein accretion remains a difficult clinical challenge. Failure to provide adequate protein, either in quantity or in quality, can significantly impact the long-term outcome of extremely premature infants. A variety of methods have been used to quantitate protein requirements in human infants: fetal accretion rates, nitrogen balance studies, plasma amino acid concentrations, and stable isotope studies investigating the kinetics of labeled essential amino acids. Clearly, the gold standard needs to be that which safely optimizes growth and neurodevelopment.



• **Fig. 41.1** Change in body protein over the first week of postnatal life for a theoretical 1000-gram birth weight, 26 weeks' gestation infant provided with 1 g/kg/day (*blue line with dashes*) and 3 g/kg/day (*solid blue line*) of intravenous amino acids.[95,104] Rate of in utero protein gain for the reference fetus (*yellow line*) and extrapolated rates of protein loss for glucose alone[24] (*red line*) are shown for comparison.

Normal human fetal development is characterized by rapid rates of growth and accretion of protein. In fact, the greatest rate of relative protein gain throughout life occurs prior to birth. At 26 weeks' gestation, the human fetus gains approximately 1.8-2.2 g of body protein per day, with the placenta supplying about 3.5 g/kg per day of amino acids to the developing fetus. The placental supply of amino acids to the fetus is in excess of that needed for accretion of protein. The extra amino acids are oxidized by the fetus and contribute significantly to fetal energy production. In contrast to the high rate of protein gain in utero, protein losses in extremely premature infants are approximately twofold higher than in term infants. In the absence of intravenous amino acids, extremely premature infants lose approximately 1.2 g/kg of protein each day, which corresponds to a daily loss of 1%-2% of total endogenous body protein stores (Fig. 41.1).

Protein requirements and recommendations for protein intake in premature infants have been made based on several different approaches. Ziegler has quantified protein and energy requirements in relation to body weight using the factorial approach.[111] In the factorial approach, nutrient requirements are determined as the sum of the needs for growth plus needs for replacement of losses. The disadvantage of this approach is that it does not account for nutrient requirements for catch-up growth. It is important to note that protein requirements are inversely related to body weight. Based on the factorial method, protein requirements for infants who weigh less than 1200 grams are estimated at 4.0 g/kg per day. Other investigators have utilized empirical approaches to estimate the amount of protein intake required to duplicate fetal growth. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommendation for protein intake in infants weighing up to 1000 g is 4.0-4.5 g/kg per day and 3.5-4.0 g/kg per day for infants weighing

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1000-1800 g.[2] This recommendation takes into account the need to make up for accumulated protein deficits observed in nearly all extremely premature infants. The ESPGHAN committee further commented that protein intake can be reduced toward discharge if the infant's growth pattern allows. An international consensus panel has also recommended 3.5-4.5 g of protein per kg per day for very low birth weight infants receiving full enteral feedings.[51]

Protein Composition of Human Milk and Formula

The protein content and composition of human milk changes throughout lactation; the concentration diminishes from about 2 g/dL at birth to about 1 g/dL for mature milk. Qualitative changes also occur during lactation, resulting in a whey-casein ratio of 80:20 at the beginning of lactation, changing to 55:45 in mature milk. Although the levels of casein, α-lactalbumin, albumin, and lysozyme remain constant, the levels of secretory immunoglobulin A and lactoferrin decrease. Because these different protein fractions have different amino acid profiles, the content of the individual amino acids is also affected.

Casein-predominant cow milk formulas have the same whey-casein ratio as cow milk—that is, 18:82. Adding bovine whey makes whey-predominant formulas, such that the whey-casein ratio becomes similar to that of human milk (60:40). Nevertheless, the protein and amino acid profile remains very different from that of human milk. Compared with human milk, whey-predominant formulas have higher levels of methionine, threonine, lysine, and branched amino acids. These differences in amino acids have not resulted in any apparent clinical consequences in either term or preterm infants. Currently, most commercially available preterm formulas are whey predominant.

Energy and Carbohydrate Requirements

Fetal Glucose Metabolism

Because the supply of glucose to the fetus depends solely on maternal glucose, cord clamping at the time of birth requires that a number of events occur to maintain glucose homeostasis in the newborn. Fetal glucose use in utero matches umbilical glucose uptake, implying that glycogenolysis and gluconeogenesis are minimal in the fetus. Several factors promote glycogen deposition in utero: blunted pancreatic β-cell regulation of insulin secretion, high insulin receptor density, and relative glucagon resistance. In late gestation, the fetus begins to prepare for the transition to postnatal life by increasing hepatic glycogen stores and brown fat deposits. Hepatic glycogen synthesis increases in response to increases in adrenal corticosteroid production, also characteristic of late gestation. At the time of delivery, glucagon levels rise and insulin levels fall. Higher levels of plasma catecholamines, both epinephrine and norepinephrine, directly stimulate increases in hepatic glucose output. The increased levels of epinephrine and glucagon stimulate lipolysis and the activity of phosphorylase, a key enzyme in glycolysis. The increased level of glucagon also results in increased activity of phosphoenolpyruvate carboxykinase, a rate-limiting enzyme in gluconeogenesis. The newborn must be able to initiate gluconeogenesis, because glycogen stores can sustain glucose production only for several hours after birth. All of these changes act together to preserve glucose homeostasis after the infant's maternal source of glucose is removed with cord clamping.

Neonatal Glucose Homeostasis

Because neural tissue makes up a greater proportion of body weight, newborns have higher rates of glucose oxidation than adults, with glucose being the primary energy substrate for the brain. The rate of glucose production in term newborns is approximately 3-5 mg/kg per minute,[23] whereas extremely premature infants have an even higher rate of glucose production of approximately 8-9 mg/kg per minute.[44] Historically, glucose intolerance in infants with extremely low birth weights was attributed to persistent endogenous hepatic glucose production in the face of increased exogenous supply, insufficient insulin production, or tissue insensitivity to insulin. However, ELBW infants are able to suppress endogenous glucose production when given parenteral glucose.

Energy Expenditure

Preterm infants have very low energy reserves, owing to limited body fat and glycogen stores in the liver. Maintaining these limited energy stores requires an energy intake that approximates energy expenditure. Energy expenditure in premature infants is thought to be in the 50-60 kcal/kg per day range, but it must be noted that data for ventilated infants and infants with extremely low birth weights are limited. Thermal stress can substantially increase energy expenditure. Conversely, activity contributes relatively little to energy expenditure in premature infants. The energy cost of growth in these infants has been estimated at about 5 kcal/g. To achieve the equivalent of the estimated third-trimester in utero weight gain of 14-18 g/kg per day, theoretically, an additional energy intake of about 70 kcal/kg per day is necessary.

Energy balance is a delicate equilibrium between energy intake and energy loss plus storage. Positive energy balance is achieved when exogenous metabolizable energy intake is greater than energy expenditure. Growth is then possible, with the excess energy stored as new tissue, usually fat. If exogenous energy intake is less than expenditure, energy balance is negative, and body energy stores must be mobilized to meet ongoing needs. During the acute phase of disease, the primary goal is avoidance of catabolism. This is difficult for infants with very low birth weights, owing to their higher maintenance energy requirements, lower energy stores, and often reduced intake.

Energy is lost either by excretion or by expenditure. Energy excreted is lost primarily as fecal fat. In preterm infants receiving full enteral feeding, approximately 90% of energy intake is absorbed. Usual measurements of total energy expenditure include the energy used to maintain

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basal metabolic rate (BMR), as well as the postprandial increase in energy expenditure (diet-induced thermogenesis), physical activity, and energy for the synthesis of new tissue. The BMR is the largest component of energy expenditure and includes energy requirements for basic cellular and tissue processes. In a critically ill patient, it also includes a "disease factor." Little is known about this component in neonates, but it may contribute significantly in neonates with fever, sepsis, and chronic hypoxia. Because the BMR can be measured only after overnight fasting, the resting metabolic rate (RMR) has been accepted as an alternative. The RMR of preterm infants on a per kilogram basis is higher than that of term infants, and the nutritional requirements on a per kilogram basis are correspondingly greater. The energy required for thermoregulation can be minimized by keeping the infant in a thermoneutral environment and limiting stimulation. For example, energy requirements for thermoregulation are negligible under thermoneutral conditions, but routine nursing procedures can increase oxygen consumption or energy expenditure by as much as 10% in stable preterm infants. Both of these components may be of considerable magnitude in a critically ill infant.

The level of energy intake and diet composition determine the magnitude of diet-induced thermogenesis, which represents the energy required for transport, metabolism, and conversion of nutrients into stored energy. Estimates of diet-induced thermogenesis in enterally fed preterm infants vary considerably, but this component of expenditure is probably small.

Total energy expenditure is affected by several factors, assuming a thermoneutral environment and minimal interference from nursing procedures. Increases in metabolic rate with postnatal age are influenced primarily by energy intake and weight gain. Energy expenditure increases with increases in metabolizable energy intake, indicating increased substrate oxidation or tissue synthesis. If the preterm infant is growing at the same rate as the fetus during the third trimester—that is, gaining approximately 15 g/kg per day—then about 15% of the total energy intake is used for synthesis of new tissue.

Energy storage is a linear function of metabolizable intake, and the accretion rate for energy is related more to the level of metabolizable energy intake than to diet composition. Energy requirements for energy storage are difficult to predict. The increase in tissue mass during growth includes the energy stored as protein, carbohydrate (usually less than 1% of body weight), and fat. Therefore, the energy stored can be assumed to equal the sum of the cost of protein plus fat gain. The energy storage component of the energy balance equation is a function of the composition of weight gain, which in turn is a function of protein and energy intake and is likely to be quite variable. Therefore, the energy intake required to produce a specific rate of weight gain cannot be predicted without specifying the composition of that weight gain. From the point of view of energy storage, protein is a poor material, because a small quantity of energy is stored per gram of weight gain. Approximately the same amount of energy is deposited in 1 g of fat tissue as in about 8 g of lean tissue.

Carbohydrates

Lactose is the predominant carbohydrate in human milk (6.2-7.2 g/dL) and supplies 40%-50% of the caloric content. Lactose is hydrolyzed to glucose and galactose in the small intestine by β-galactosidase (lactase). Despite low lactase activities in premature infants, lactose is well tolerated by premature infants, and stable isotope data suggest efficient lactose digestion. However, most premature infant formulas include glucose polymers as a significant source of carbohydrate; these glucose polymers are digested by α-glucosidases, which achieve 70% of adult activity between 26 and 34 weeks' gestation. In addition, salivary and mammary amylases may contribute to glucose polymer digestion. Glucose polymers have the advantage of increased caloric density without a rise in osmolality, and they may also enhance gastric emptying.

Recommended Energy Intake

Overall, the current recommendation for energy intake for an enterally fed VLBW infant is 110–130 kcal per kg/day.[51] It is important to recognize that this recommendation assumes that the infant is also receiving adequate protein intake. Infants who are small for gestational age or infants with diseases that increase energy requirements may need higher intakes to achieve the same growth rates. Infants with growth restriction often require an increased caloric intake for growth because of both higher maintenance energy needs and higher energy costs of new tissue synthesis.

Lipid Requirements

In humans, linoleic and linolenic acids cannot be endogenously synthesized and are, therefore, essential fatty acids. Biochemical evidence of essential fatty acid deficiency can develop in preterm infants within 72 hours. To meet energy requirements, additional intravenous lipid is required in early postnatal life.

Fat provides the major source of energy for growing preterm infants. At birth, the digestive function of premature infants is not fully developed; preterm infants have decreased gut absorption of lipids because of low levels of pancreatic lipase, bile acids, and lingual lipase. The fact that term and preterm infants absorb fat reasonably well is due to the development of alternative mechanisms for the digestion of dietary fat. One important mechanism is intragastric lipolysis, in which lingual and gastric lipases compensate for the low pancreatic lipase concentration. By 25 weeks' gestation, lingual lipase is secreted by the serous glands of the tongue, and gastric lipase is secreted from gastric glands. The fatty acids and monoglycerides resulting from intragastric lipolysis compensate for low bile acid concentration by emulsifying lipid mixtures. Lingual lipase can also penetrate the core of the human milk lipid globule and hydrolyze the triglyceride core without disrupting the globule membrane.

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Human milk provides lipoprotein lipase, bile salt stimulated esterase, and nonactivated lipase to further aid lipolysis.

Lipid digestion and absorption are also affected by dietary fat composition. Fatty acid absorption increases with decreasing chain length[58] and with the degree of unsaturation, meaning that medium chain triglycerides (MCT) with chain lengths of 6-12 carbons are hydrolyzed more readily than long chain triglycerides (LCT), and that fatty acids with more double bonds are absorbed more efficiently. In an attempt to increase the fat absorption of premature infants, the fat in commercial formulas contains relatively high levels of MCTs that can be absorbed without the need for lipase or bile salts. Standard commercial formulas for healthy term infants do not contain MCTs, and human milk typically contains 8%-12% of fat as MCTs. Unlike LCTs, MCTs are readily hydrolyzed in the gut, and the released fatty acids are transported across the gut barrier without the need for bile acids. Then MCTs are transported directly to the liver via the portal vein as nonesterified fatty acids. In addition, MCTs can enter mitochondria and be oxidized without the need for carnitine-mediated transport through mitochondrial membranes. However, inclusion of MCTs in infant formula remains controversial, because the available data do not support the assertion of improved fat absorption or improved growth in preterm infants.

In human milk, fat is transported in globules consisting of a membrane composed of a polar mixture of proteins, phospholipids, triglycerides, cholesterol, glycoproteins, and enzymes surrounding a triglyceride core containing 98% of the fat in milk. The milk fat globules are among the largest structural components of milk, having a diameter of 4 mm in mature milk. The size of the globules increases with both length of lactation and length of gestation, with colostrum having smaller globules (especially in milk of women who deliver prematurely) than mature milk. After birth, as the total fat content of human milk increases, the percentage of cholesterol and phospholipids, both of which reside primarily in the milk fat globule membrane, decreases; in addition, the total phospholipid content decreases as lactation progresses. During the first weeks of lactation, preterm milk is also richer in membranous material compared with term or mature milk, resulting in a higher content of cholesterol, phospholipids, and very-long-chain polyunsaturated fatty acids (PUFA) with chain lengths of 20-22 carbons (C20-C22). Because these membranes act as emulsifiers that allow fat dispersion in an aqueous phase and limit lipolysis and oxidation, heat treatment or addition of fortifiers and supplements might disrupt this emulsion.

The milk fat content and nutritional value of human milk vary with time, and it does not always provide a complete source of nutrients for infants with very low birth weights. Its composition and energy content may vary in a pumping session and during subsequent changes throughout lactation. The total fat content of human milk at 3 days' lactation is approximately 2 g/dL; the fat content of mature milk is approximately 4-5 g/dL, with large individual variation possible. The triglyceride content of human milk is its most variable component, changing with gestational and postnatal age, time of day, duration of individual feeds, and maternal diet. Shifts in the dietary practices of a population result in changes in the fatty acid composition of human milk, because the type and amount of fat in the maternal diet affect the composition of milk fat. Maternal diets low in fat and high in carbohydrate lead to de novo synthesis of fatty acids within the mammary gland, which results in high concentrations of fatty acids of less than 16 carbons. Therefore, although the total amount of fat present in the milk remains in the normal range, the fat is more saturated.

Fatty acids represent about 85% of the triglycerides and, therefore, are the principal component of human milk lipids. Fatty acids in human milk are derived from the maternal diet, de novo synthesis by the mammary gland, and mobilization from fat stores. The fatty acid composition of human milk fat reflects the fatty acid composition of the maternal diet. The long-chain polyunsaturated fatty acid (LCPUFA) composition of the milk of women in the United States, Europe, and Africa is quite similar, with the exception of higher amounts of n-3 LCPUFA in the milk of women whose diets contain a large quantity of fish. Medium-chain fatty acids (C8-C10) do not normally account for more than 2% of the fats, even in milk from women who have delivered preterm. Arachidonic acid (C20:4n-6) is the main LCPUFA, and eicosapentaenoic acid (C20:5n-3) is found in small quantities in human milk. Docosahexaenoic acid (C22:6n-3) is the main LCPUFA of the n-3 series.

Fatty acid composition changes with progressing lactation and with gestational age. Most striking is the higher content of C8-C14 fatty acids and of LCPUFAs in preterm milk as compared with term milk; the content of LCPUFA decreases with increasing postnatal age. This may be an advantage for preterm infants because shorter fatty acids are easier to digest, and LCPUFAs are essential for brain and retinal development.

The LCPUFAs play an important role in the development of the infant's brain during the last trimester of pregnancy and also during the first months of life. The precursor C18 fatty acids for the n-6 and n-3 LCPUFA series are linoleic acid (C18:2n-6) and α-linolenic acid (C18:3n-3). These are further elongated and desaturated to form other fatty acids, of which arachidonic acid (AA) and docosahexaenoic acid (DHA) are essential for normal growth and development. Although the capacity for endogenous synthesis of LCPUFA from precursor fatty acids exists in both preterm and term infants, it remains unclear whether DHA and AA can be biosynthesized in quantities sufficient to meet the needs of these infants.

In utero, LCPUFAs are supplied to the fetus across the placenta. After birth and within the first postnatal week, preterm infants developed a deficit of DHA and AA compared to their starting point at birth, while almost tripling their linoleic acid (LA) levels.[59] These acute changes are likely due to the lack of adipose reserves as well as the lack

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of early nutritional strategies that effectively meet the fatty acid requirements in the preterm infant. Although Smoflipid® contains DHA and AA, the use of Smoflipid® fails to correct these postnatal fatty acid deficits inducing a minimal change in DHA and a further decline in AA, and introduces a substantial increase in eicosapentaenoic acid (EPA) due to its fish oil component. Although the importance of DHA in brain and eye development has been established, accruing evidence suggests that a decline in AA is also of concern with increasing risks of late onset sepsis and retinopathy of prematurity with lower AA levels.[54,98]

Although naturally contained in human milk, DHA and AA have been added to most infant formulas for term and preterm infants. Multiple randomized controlled trials evaluating the addition of DHA and AA to preterm formulas have been conducted. Added DHA and AA have generally resulted in positive or neutral changes in growth, although there are some reports of a negative effect. Findings of improved visual acuity have been inconsistent. Formula supplemented with DHA and AA has produced positive changes in neurodevelopment measured in infancy in some, but not all, studies. A meta-analysis demonstrated no improvement in visual acuity or neurodevelopment.[85] The current recommendation is that VLBW infants receive 55-60 mg per/day of DHA and 35-45 mg per kg/day of AA.[51]

Cholesterol is a major component of cell membranes and a precursor in the synthesis of bile acids and some hormones. It is present in human milk in concentrations ranging from 10-15 mg/dL, although commercial formulas contain only trace amounts of cholesterol (approximately 1-2 mg/dL). The high cholesterol content of breast milk relative to formula is maintained at this level regardless of maternal diet. The groups that assessed the nutrient requirements for term and preterm infant formulas did not recommend addition of cholesterol to infant formulas, because there was no convincing evidence of a beneficial short- or long-term effect of such an addition. Furthermore, there is no evidence that added cholesterol would be equivalent to the cholesterol in a human milk globule.

Carnitine mediates the transport of long-chain fatty acids into mitochondria for oxidation and the removal of short-chain fatty acids that accumulate in mitochondria. Preterm infants may be at risk for carnitine deficiency, because they are heavily dependent on lipids as an energy source and because the plasma carnitine concentration of preterm infants is low, owing to limited endogenous synthetic ability. In preterm infants not receiving supplemental carnitine, plasma and tissue carnitine levels fall even in the presence of adequate precursor amino acid concentrations. Carnitine is found in human milk and is currently added to standard term and preterm formulas in amounts somewhat higher than in human milk.

Provision of Nutritional Support

The extremely premature neonate is born with glucose stores of only 200 kcal and loses 1% of body protein per day when provided with intravenous glucose alone. Consequently, extreme prematurity should be viewed as a nutritional emergency. A number of observational studies have described the influence of nutritional practices on growth and have found that differences in caloric and protein intake in the first weeks account for the largest difference in growth among premature infants.[66] In addition, there is a growing body of data that shows the association between early nutrient intake and growth and neurodevelopmental outcomes. This section reviews the basis of recommendations for nutritional support of premature infants. Practice decisions related to provision of early nutritional support provided to ELBW infants seem to be related to the perceived severity of illness of the infant by clinicians.[30] The use of standardized protocols for feeding (both parenteral and enteral) extremely premature infants can lessen variation in practice and improve outcomes.

Goals of Early Intense Nutritional Support

The goals of early nutritional support for the extremely premature infant include the following: to promote growth and nutrient accretion comparable to that of the fetus at the same gestational age, to avoid postnatal growth failure, to minimize the risk of necrotizing enterocolitis, and to optimize neurodevelopment and long-term health outcomes. Achieving full and consistent enteral nutrition in infants with extremely low birth weights is particularly challenging, given the inherent problems of immature gut motility and function, as well as the fear of necrotizing enterocolitis. Clearly, the relative risks must be carefully weighed against benefit. When sufficient data are not available to address the relative risk versus the benefit, clinical judgment must be used.

Intravenous amino acids should be given immediately after birth to provide 3.5 g/kg per day of amino acids. Many institutions utilize a neonatal "stock" or "starter" amino acid solution to ensure rapid availability. This solution, made in advance by the pharmacy, is typically comprised of a neonatal amino acid solution mixed in dextrose. To minimize deficits in energy intake, intravenous lipids should be started at 3 g/kg per day with the first day of full parenteral nutrition. In addition, trophic or minimal enteral feedings (10-20 mL/kg per day) should be initiated with expressed human milk as soon as possible after birth. Strategies related to the advancement of enteral feeds and weaning of parenteral nutrition will be discussed subsequently.

Initiation and Advancement of Enteral Feeds

The diversity of approaches to feeding preterm infants underlines the need for studies to dispel myths and find reasonable solutions to define the optimal feeding route. When neonatal amino acid solutions became available, many physicians chose to use parenteral nutrition exclusively in sick preterm infants because of concerns about necrotizing enterocolitis. Parenteral nutrition was thought

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to be a logical continuation of the transplacental nutrition the infants would have received in utero. However, this view discounts any role that swallowed amniotic fluid may play in nutrition and in the development of the gastrointestinal tract. In fact, by the end of the third trimester, amniotic fluid provides the fetus with the same enteral volume intake and approximately 25% of the enteral protein intake of a term breastfed infant.

Minimal Enteral Feeding

Trophic or minimal enteral feedings involve hypocaloric, low-volume (typically ≤24 mL/kg per day) feeds to promote intestinal maturation and do not contain sufficient calories to sustain somatic growth. Proposed benefits include maturation of the preterm intestine (both structurally and functionally), reduced liver dysfunction, and improved feeding tolerance.

Animal studies have demonstrated a decrease in gut weight, mucosal weight, mucosal protein, DNA, disaccharide activity, and mucosal height when enteral nutrition is withheld. In a neonatal piglet model, at least 40% of total nutrient intake supplied enterally is needed to sustain normal gastrointestinal growth.[15] In preterm infants, the lack of any enteral feeding leads to villous atrophy.[64]

A systematic review evaluated the effects of early (introduced before 96 hours of age) trophic feeding versus a comparable period of enteral fasting in VLBW infants and found no difference in feeding tolerance, growth, or necrotizing enterocolitis.[13] The authors concluded that the available data cannot exclude important beneficial or harmful effects and that large randomized controlled trials are needed to evaluate the effect of early trophic feeds on important clinical outcomes in VLBW infants. A multicenter randomized trial is currently underway in the United Kingdom to evaluate the speed of increasing milk feedings (SIFT; ISRCTN76463425) in VLBW infants.[1] The primary outcome of the SIFT trial will be the effect on survival without moderate or severe neurodevelopmental disability at 24 months' corrected age.

Initiation of enteral nutrition is often delayed in premature infants with intrauterine growth restriction because of the concern that these infants are at an increased risk of necrotizing enterocolitis. However, a randomized trial that evaluated early versus delayed initiation of enteral feeding for preterm growth-restricted infants found no evidence of a difference in the incidence of necrotizing enterocolitis between groups. Consequently, the authors concluded that there was no evidence of benefit in delaying the introduction of minimal enteral feeds in preterm infants with intrauterine growth restriction beyond 24-48 hours of age.[53]

In summary, the data from these studies support physiologic and clinical benefit from early minimal enteral feeding, without an increased risk of necrotizing enterocolitis. Although a large multicenter trial that more clearly evaluates early feeding may be desirable, such a trial appears unlikely.

Rate of Advancement of Enteral Feeds

The rate at which enteral feedings should be advanced in preterm infants has also been the subject of much debate. Retrospective studies have reported an association between rapid advancement of enteral feeds and NEC. However, a systematic review evaluated the effect of slow (<24 mL/kg per day) rates of enteral feed advancement on the incidence of NEC, mortality, and other morbidities in VLBW infants and found no evidence that slow advancement of enteral feeds reduces the incidence of NEC.[62] Infants who had slow rates of feeding volume advancement took longer to regain birth weight and to reach full enteral feeds.

Based on the available evidence, a reasonable approach is to advance enteral feeds by 20-30 mL/kg per day in VLBW infants and by 15-25 mL/kg per day in ELBW infants. Future studies are needed to further define the optimal rate of advancement, especially in ELBW infants.

Gastric Residuals

Measurement of gastric residuals is a common practice in many neonatal intensive care units to evaluate tolerance of enteral feeds despite a paucity of evidence to support the utility of gastric residuals in the diagnosis of feeding intolerance or NEC.[69] In the absence of other symptoms, there is no evidence to support the discontinuation of enteral feeds based only on gastric residuals.[83,97]

Standardized Feeding Guidelines

Enteral feeding practices vary considerably among different centers.[50] The use of evidence-based standardized feeding guidelines has been shown to improve nutritional outcomes (such as time to reach full enteral feeds), reduce number of days on parenteral nutrition, and encourage growth. In addition, standardized feeding guidelines, regardless of the content of the guideline, have been shown to reduce the incidence of necrotizing enterocolitis in premature infants.[38,71]

Evidence Supporting Early Parenteral Amino Acids

Numerous randomized clinical trials of amino acid dose and advancement strategy to evaluate short-term tolerance, protein balance, and safety have been conducted in premature infants. Despite differences in study populations and composition of amino acid solutions, all studies demonstrated positive nitrogen balance in response to parenteral amino acids and improved protein balance with higher amino acid intake.[46,49,78,100,103] It is also important to point out that positive nitrogen balance was found despite low total caloric intake (approximately 50 kcal/kg per day). Consequently, the initial goal of limiting catabolism and preserving endogenous protein stores in premature infants can be accomplished with provision of as little as 1.0-1.5 g/kg per day of intravenous amino acids, whereas delivery of 3 g/kg per day of amino acids will result in net protein gain that approximates that of the reference fetus (see Fig. 41.1).

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Stable isotope techniques have also been used to evaluate the effect of amino acids on protein metabolism in premature infants. In these studies, stable isotope tracers of one or more essential amino acids are used to reflect whole body protein kinetics. Rivera and colleagues found that administration of 1.5 g/kg per day of amino acids (Aminosyn-PF with cysteine added) beginning on the first day of life improved protein balance as a result of increased protein synthesis (as reflected by leucine kinetics).[78] Using similar techniques, van den Akker and colleagues demonstrated that protein anabolism produced by administration of early amino acids is accomplished through an increase in protein synthesis and not from a decrease in proteolysis (protein breakdown).[101]

Other investigators have assessed the safety and efficacy of different doses of amino acids. Thureen and colleagues conducted a randomized trial of low (1 g/kg per day) versus high (3 g/kg per day) amino acid intake in infants with extremely low birth weights immediately after birth.[95] The higher amino acid intake produced significantly greater protein accretion. In an open-label trial, te Braake and colleagues randomized VLBW infants to two different parenteral amino acid regimens.[94] Infants in the intervention group received 2.4 g/kg per day of amino acids starting immediately after birth. Infants in the control group received glucose alone on the first day of life, with a stepwise increase in amino acid intake thereafter (1.2 g/kg on day 2 and 2.4 g/kg on days 3 and 4). Infants who received amino acids on the first day of life were found to have positive nitrogen balance without any major adverse effects, whereas infants in the control group were in negative nitrogen balance on day 2. Ibrahim and colleagues evaluated an even higher initial dose of intravenous amino acids, randomizing VLBW premature infants to either 2 g/kg or 3.5 g/kg per day of intravenous amino acids on the first day of life. Similar to the studies discussed previously, the higher amino acid dose resulted in greater improvement in nitrogen balance without evidence of adverse effects.[46]

The safety of administration of early intravenous amino acids, particularly for premature infants, has been established in a variety of studies. Normal plasma amino acid concentrations have been reported using TrophAmine.[43] Rivera and colleagues studied infants with very low birth weights who were given amino acids in the first days of life and found no abnormal elevations of plasma amino acids, BUN, or ammonia.[79] Thureen and colleagues found that 3 g/kg per day of early amino acids appears to be as safe as 1 g/kg per day, based on BUN and plasma aminograms as indicators of acute amino acid toxicity.[67,95] Although most studies have not demonstrated any relationship between amino acid intake and BUN in the first days of life, two studies reported increased BUN levels in infants receiving higher amino acid intakes at 7 days of age.[11,19] As mentioned earlier, a significant proportion of the amino acids supplied to the developing fetus are oxidized and serve as a significant energy source for the fetus. Urea production is a byproduct of amino acid oxidation. In premature infants, rates of urea production are higher than in term neonates and adults, consistent with high rates of protein turnover and oxidation. Some investigators have even suggested that azotemia might be evidence of the effective utilization of amino acids as an energy supply rather than of protein intolerance, but this contention remains unproven. There are no data to support the need to advance amino acid intake slowly.

Although the initial goal of providing intravenous amino acids to premature infants to limit catabolism and preserve endogenous protein stores can be accomplished even if total caloric intake is low, ultimately both protein and energy must be supplied in quantities sufficient to support optimal growth. Protein quantity is the primary determinant of protein accretion. This is true regardless of whether parenteral nutrition is used exclusively or as a bridge to full enteral feedings. In a series of studies, Zlotkin and colleagues evaluated the effect of intravenous energy and nitrogen intake on nitrogen retention.[112] At constant nitrogen intake, increasing nonprotein energy intake from 50-80 kcal/kg per day resulted in increased nitrogen retention and weight gain. However, at low energy intake (~50 kcal/kg per day), increasing nitrogen intake from 494-655 mg/kg per day (3-4 g/kg of amino acids per day) had no effect on nitrogen retention or weight gain. However, at higher energy intakes (~80 kcal/kg per day), the same increase in nitrogen intake resulted in a significant increase in the rate of both nitrogen retention and weight gain.

Many conditions and interventions commonly encountered in extremely premature infants are known to increase protein requirements. Underlying disease states such as sepsis or surgical stress increase catabolism and can negatively impact protein accretion. In addition medications such as systemic steroids, fentanyl, and insulin can also impact protein accretion. Dexamethasone has been shown to increase protein catabolism by increasing protein oxidation and proteolysis, resulting in decreased accretion of protein.[104]

Intravenous Amino Acid Mixtures

The first parenteral amino acid solutions used in neonates were hydrolysates of fibrin or casein. Concerns about these first-generation solutions included high concentrations of glycine, glutamate, and aspartate; the presence of unwanted peptides; and high acidity. Reports of hyperammonemia and acidosis in the early 1970s were associated with the use of these first-generation solutions in neonates. Although amino acid solutions have been significantly modified, the perceived risks associated with the protein hydrolysates linger, contributing to the hesitancy by some clinicians to administer early parenteral amino acids.

The second generation of amino acid solutions consisted of crystalline amino acid mixtures (FreAmine III, Travasol, Aminosyn). The amino acid pattern of these mixtures reflects that of high-quality dietary proteins with large amounts of glycine and alanine, absence of glutamate and aspartate, and absence or poor solubility of tyrosine and cysteine.

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TABLE 41.1 Composition of Parenteral Amino Acid Solutions*

	Aminosyn-PF	TrophAmine Premasol	Primene
Histidine	312	480	380
Isoleucine	760	820	670
Leucine	1200	1400	1000
Lysine	677	820	1100
Methionine	180	340	240
Phenylalanine	427	480	420
Threonine	512	420	370
Tryptophan	180	200	200
Valine	673	780	760
Alanine	698	540	800
Arginine	1227	1200	840
Proline	812	680	300
Serine	495	380	400
Taurine	70	25	60
Tyrosine	44	240†	45
Glycine	385	360	400
Cysteine	—	<16	189
Glutamic acid	820	500	1000
Aspartic acid	527	320	600

*Amino acid concentration in mg/dL; all amino acid mixtures shown are 10% solutions.
†Mixture of L-tyrosine and N-acetyltyrosine.

The newest solutions include modifications of crystalline amino acids for use in pediatric patients. The currently available solutions include modifications of crystalline amino acids for use in pediatric and neonatal patients (Table 41.1). TrophAmine was originally formulated to match plasma amino acid concentrations of healthy term, breastfed infants; Premasol is identical in composition to TrophAmine. The composition of Primene, available outside the United States, was derived from fetal and neonatal cord blood concentrations. Both TrophAmine and Premasol supply a mixture of L-tyrosine and N-acetyltyrosine. The bioavailability of N-acetyltyrosine, however, has been questioned. Neither Aminosyn-PF nor Primene supplies a substantial amount of tyrosine. Cysteine is not supplied by most amino acid solutions, because it is not stable for long periods of time in solution. However, cysteine hydrochloride can be added during the compounding process just prior to delivery of the solution.

It is no surprise that the ideal composition of intravenous amino acid mixtures is unknown. Although these solutions are widely used in the neonatal intensive care unit, normative data on plasma amino acid concentrations, particularly in ELBW infants, has not been established. Whether the goal should be to match amino acid concentrations of term, breastfed infants or some other standard is not known. Clearly, the ultimate goal is to achieve plasma amino acid concentrations in response to provision of parenteral nutrition that optimize both growth and neurodevelopment without toxicity. To optimize nutrition and growth, particularly in a premature infant, the requirements for specific amino acids need to be more precisely defined.

Several amino acids may be "conditionally essential" in premature infants. That is, the infant's ability to synthesize these amino acids de novo may be less than needed for functional metabolic demands. Cysteine, tyrosine, and arginine are often considered conditionally essential amino acids for premature infants.

Tyrosine is not present in appreciable amounts in currently available amino acid solutions because of its low solubility. Snyderman found lower rates of weight gain, nitrogen retention, and plasma concentrations of tyrosine in premature infants given a tyrosine-deficient diet.[86] Tyrosine is synthesized endogenously from phenylalanine by phenylalanine hydroxylase. The activity of this enzyme in premature infants was thought to be inadequate for growth and nitrogen retention without tyrosine supplements. However, stable isotope studies have demonstrated active phenylalanine hydroxylation in very premature (26 weeks) and premature (32 weeks) infants.[20,24] Therefore, in the strictest sense, tyrosine is not an essential amino acid. However, it remains unclear whether enough tyrosine can be endogenously produced from phenylalanine in premature infants to support normal rates of protein accretion. *N*-acetyl tyrosine, although currently added to TrophAmine, is not highly bioavailable. Nonetheless, several studies provide indirect evidence that *N*-acetyl tyrosine improves protein accretion in preterm infants.[41,42] In addition, it is unclear whether premature infants can adequately catabolize tyrosine via oxidation by the enzymes tyrosine aminotransferase and 4-hydroxyphenylpyruvate dioxygenase. Inability to catabolize tyrosine can lead to transient neonatal tyrosinemia. Further studies are needed to better define premature infants' ability to catabolize tyrosine and to determine whether an alternative source of tyrosine is needed in parenteral amino acid solutions.

Cysteine may be a conditionally essential amino acid for premature infants but is not contained in currently available amino acid solutions. Some studies have shown that the fetal liver lacks the enzyme system to convert methionine into cysteine and that infants on a cysteine-free diet demonstrate impaired growth and low plasma cysteine levels. Other studies have demonstrated that there is enough cystathionase in extrahepatic tissues of the fetus and premature infant to synthesize cysteine when an adequate amount of methionine is provided. Studies using stable isotope techniques have demonstrated active endogenous cysteine synthesis in low birth weight infants.[82] Nevertheless, there is

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evidence to support that when cysteine hydrochloride supplements are added to parenteral nutrition, nitrogen retention is improved in premature infants.[87] Further, the addition of cysteine hydrochloride improves the solubility of calcium and phosphorus in parenteral nutrition solutions. However, it is important to note that cysteine hydrochloride supplements can produce metabolic acidosis unless appropriately buffered with acetate.

Glutamine is one of the most abundant amino acids in both plasma and human milk, yet it is not supplied by currently available amino acid solutions because glutamine is unstable in aqueous solution. Glutamine is a major energy substrate for small intestinal mucosa, as proved by a high glutamine uptake from the lumen and from arterial blood during the newborn period in rats. Adding glutamine to the parenteral nutrition (PN) solutions of animals prevents atrophy of small intestinal mucosa and smooth muscle, improves the gut immune function, and reduces the incidence of fatty infiltration of the liver. Several studies suggest that parenteral glutamine supplementation is of benefit in selected populations of critically ill adults. However, a large, multicenter, randomized clinical trial of parenteral glutamine supplementation found that parenteral glutamine supplementation did not decrease mortality or the incidence of late-onset sepsis in ELBW infants.[72]

Finally, taurine is synthesized endogenously from cysteine and is not part of structural protein. It is present in large concentrations in the retina and brain of the fetus, reaching a peak concentration at birth. When newborn nonhuman primates are fed taurine-deficient formula, growth is depressed, but this does not occur in human preterm infants, despite declining plasma and urine taurine levels. Nevertheless, there is some limited evidence that taurine supplementation might influence auditory brainstem-evoked responses. Several pediatric IV amino acid solutions (TrophAmine, Primene, Aminosyn-PF) contain one to three times the amount of taurine found in breast milk.

It is important to note that currently available amino acid solutions have not been modified for more than 20 years and that none were designed specifically to meet the needs of extremely premature infants. Future research efforts should be directed at designing a fourth generation of amino acid solutions to optimize amino acid nutrition provided to the most vulnerable infants.

Glucose

Glucose should be provided in the parenteral nutrition solution to maintain normal plasma glucose concentrations and to meet the demand for glucose use. From a practical standpoint, understanding rates of endogenous glucose production is important to avoid iatrogenic hyperglycemia. As discussed earlier in this chapter, rates of glucose production and utilization in term infants are approximately 3-5 mg/kg per minute, whereas an extremely premature infant has a much greater need, 8-9 mg/kg per minute. Infants who weigh 1000 g or more usually tolerate a 10% glucose solution initially, whereas infants weighing less than 1000 g probably need to be started on a 5% glucose solution, given their higher total fluid requirements and predisposition toward hyperglycemia. In ELBW infants, a reasonable approach is to start the glucose infusion rate at 6 mg/kg per minute, gradually advancing to 10-12 mg/kg per minute as long as hyperglycemia does not develop.

The definition of hyperglycemia also varies but is generally set at a plasma level above 150 mg/dL (8.3 mmol/L). Hyperglycemia is detected early through frequent glucose monitoring. Plasma glucose levels below 200 mg/dL usually do not require intervention. Reducing the fluid needs and insensible water loss can reduce the glucose intake. Alternatively, a lower concentration of dextrose solution can be used, although solutions less than 2.5% should be avoided.

Although some have advocated the use of insulin to "promote growth," using insulin to facilitate tolerance of added parenteral calories, other investigators found no net effect on protein anabolism in response to euglycemic hyperinsulinemia in ELBW infants.[73] In addition, increasing glucose infusion beyond the capacity for glucose oxidation can result in lactic acidosis. An international, randomized clinical trial was conducted to determine whether early insulin therapy would reduce hyperglycemia and affect outcomes in VLBW infants.[9] The study was terminated early because of futility concerns and concluded there is little clinical benefit of early insulin administration; although insulin may decrease the incidence of hyperglycemia, there was no difference in important outcomes such as mortality, and early insulin may also increase the number of episodes of hypoglycemia. Consequently, the routine use of exogenous insulin cannot be recommended. Administration of 0.05-0.1 U/kg per hour may be occasionally needed to treat hyperglycemia not responsive to decreases in the glucose infusion rate.

The appropriate balance of glucose and lipid in parenteral nutrition is critical for achieving maximal nutritional benefit. In fact, nutrient and protein retention is maximal if the nonprotein caloric balance between carbohydrate and lipid is approximately 60:40. This more closely mimics the fat content of breast milk and minimizes excess energy expenditure, which can occur if a disproportionate amount of nonprotein calories is given as glucose. Even at higher protein intakes, a parenterally fed infant with extremely low birth weight may need 80-90 kcal/kg per day for nonprotein energy supplies. The caloric requirements of a parenterally fed neonate are much lower than those fed enterally. It is important to realize that providing excessive calories via parenteral nutrition does not correlate with higher rates of growth. In addition, it should be emphasized that it is not difficult to provide adequate nonprotein energy, and it can be done without using highly concentrated glucose solutions. Therefore, glucose concentrations above 12.5% should be required only on rare occasions. In addition, glucose concentrations above 10%-12.5% should be reserved for use with central venous access.

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TABLE 41.2 Composition of Available Intravenous Fat Emulsions (% of Lipid)

	Intralipid	Lipofundin	Lipoplus	Smoflipid	Clinoleic	Omegaven
Soybean oil	100	50	40	30	20	—
Olive oil	—	—	—	25	80	—
Medium chain triglycerides	—	50	50	30	—	—
Fish oil	—	—	10	15	—	100

Intravenous Fat Emulsions

Intravenous fat emulsions are important not only to prevent essential fatty acid deficiency, but also as a significant source of nonprotein energy. They are made up of neutral triglycerides, egg yolk phospholipids to emulsify, and glycerol to adjust the tonicity. The types of currently available lipid emulsions are shown in Table 41.2.[25] Until recently, Intralipid® was the primary lipid available for use in the NICU. Intralipid®, comprised solely of soybean oil, was developed in the early 1960s and received FDA approval in 1972. In 2016, Smoflipid® received FDA approval for use in adults, although there has been some adoption in use in the NICU. Smoflipid® is composed of a blend of soybean oil, MCTs, olive oil, and fish oil (15%). Despite the difference in oil sources, recent meta-analyses have not demonstrated improved neonatal outcomes with its use, including studies aimed at reducing the incidence of parenteral nutrition–associated liver disease (PNALD).[45,48] A large clinical trial comparing Intralipid® to Smoflipid® for the prevention of PNALD in high-risk preterm infants is still ongoing (ClinicalTrials.gov Identifier: NCT02579265). Early initiation of lipid emulsions is considered safe, and it is recommended to achieve a level of 3 gm/k/day within the first few days of life. Omegaven, a solely fish oil–based emulsion, was approved by the FDA in 2018 for the treatment of parenteral nutrition–associated liver disease (PNALD).[99a]

Lipids can be started at 3 g/kg per day[96,105] without the need to slowly increase the dose in a stepwise fashion. The early administration of intravenous lipids to preterm infants has been the subject of discussion and debate primarily centered on the acute metabolic effects of early intravenous lipids and potentially adverse effects, such as chronic lung disease and bilirubin toxicity as a result of free fatty acids displacing bilirubin from albumin-binding sites. A meta-analysis found no increase in chronic lung disease resulting from early lipid administration to premature infants.[84]

The rate of intravenous lipid infusion is important, and plasma lipid clearance is improved when intravenous lipid is given as a continuous infusion over 24 hours. Lipid infusion rates in excess of 0.25 g/kg per hour can be associated with decreases in oxygenation. Lipid infusion rates well under this value can be easily achieved in clinical practice if lipids are provided over 24 hours in an amount not exceeding 3-4 g/kg/day. This level of lipid intake is usually sufficient to supply the caloric needs of preterm infants (in combination with glucose) and is usually tolerated by premature infants. Triglyceride concentrations are most often used as an indication of lipid tolerance, and maintaining triglyceride concentrations below 200 mg/dL seems prudent.

Intravenous lipid emulsions may undergo lipid peroxidation, which may form organic free radicals and potentially initiate tissue injury. Light, especially phototherapy, may play some role in increasing lipid peroxidation in intravenous lipid emulsions. However, multivitamin preparations included in the intravenous solutions are a major contributor to a generation of peroxides, and lipid emulsions may have only a minor additive effect. Based on these studies, some clinicians protect intravenous lipid solutions from light, although the importance or efficacy of this practice is unclear.

Lipid particles supplied by intravenous lipid solutions are similar in size to endogenously produced chylomicrons. Like chylomicrons, clearance of these lipid particles also depends on the activity of lipoprotein lipase. In premature infants less than 28 weeks' gestation, lipoprotein lipase activity and triglyceride clearance are reduced. Heparin theoretically releases lipoprotein lipase from the endothelium into the circulation, but there is no evidence that this increases lipid utilization in preterm infants. In addition, increased lipoprotein lipase activity may produce high levels of free fatty acids and be in excess of the clearance capacity of the premature infant. Consequently, the routine addition of heparin to lipid emulsions for this purpose (to stimulate lipolysis) is not recommended on the basis of currently available evidence.

Carnitine facilitates transport of long chain fatty acids through the mitochondrial membrane, and as such plays an important role in the oxidation of these long chain fatty acids. Premature infants receiving parenteral nutrition have low carnitine levels, but the clinical significance of this remains uncertain.

Human Milk

There is general consensus that human milk is also the optimal primary nutritional source for premature infants.[2,32] The strongest evidence of the benefit of human milk for premature infants is a reduced incidence of necrotizing enterocolitis.[60,80] Maternal milk also improves neurodevelopmental outcomes in ELBW infants. Vohr and colleagues found that infants who received maternal human milk had

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superior Bayley II scores at 24 months' corrected age compared with those who did not receive human milk. These investigators noted a dose-response effect; for each 10 mL/kg per day of maternal milk ingested, the MDI increased by 0.59 points, the psychomotor developmental index (PDI) increased by 0.56 points, and the rate of rehospitalization between discharge and 30 months decreased by 5%. It should also be noted that the beneficial effect of exposure to mother's own milk persisted at 30 months' corrected age.[106,107]

Donor Human Milk

The use of pasteurized donor human milk has been recommended for preterm infants if the mother's own milk is unavailable, in a statement by the American Academy of Pediatrics (AAP) Section on Breastfeeding and by ESPGHAN,[6,32] primarily based on evidence suggesting that avoidance of formula may reduce the risk of NEC. The impact of donor human milk on neurodevelopmental outcome has been assessed in several multicenter clinical trials. The Canadian DoMINO trial randomized 363 VLBW infants to donor human milk or preterm formula as supplemental diet to maternal milk. There was not a statistically significant difference in the primary outcome of the mean cognitive score on the Bayley Scales of Infant Development-III, although infants randomized to receive donor milk were more likely to score less than 85 on the BSID-III.[65,99] The NICHD Neonatal Research Network also has an ongoing trial to evaluate this question (NCT01534481).

Human Milk Fortifiers

Human milk does not completely meet the nutritional needs of premature infants; insufficient protein, calcium, phosphorus, sodium, zinc, vitamins, and possibly energy are provided by human milk to optimally support most premature infants. Human milk fortifiers have been developed to address many of these inadequacies. Evaluation of the available evidence has shown that multicomponent fortification of human milk improves postnatal weight gain, linear growth, and head circumference growth.[52] One randomized trial found that a higher protein intake results in less growth-faltering in human milk–fed preterm infants.[61]

Current options for human milk fortification include bovine products and human milk–based fortifier. The use of powdered products is to be avoided, given potential risk of infectious complications.[88]

Only one of the new bovine liquid human milk fortifiers has been evaluated in a randomized clinical trial. Benefits found in preterm infants with weight less than 1250 g included improvements in weight and linear growth at 28 days compared with infants randomized to a control powdered human milk fortifier.[63] There were no differences in feeding tolerance, sepsis, or NEC between the groups in this small study.

A small, multicenter, randomized clinical trial evaluated the use of an exclusive human milk diet compared with maternal milk fortified with bovine human milk fortifier and preterm formula. In this study, the incidence of NEC or death was higher in the bovine fortifier group than in the exclusive human milk group.[93] It is important to note that this study found no difference between groups for the primary outcome of the trial, which was duration of parenteral nutrition.

As discussed earlier in this chapter, although the protein content of preterm human milk is greater than term human milk, the protein content declines over the first few weeks of lactation from approximately 1.7 g/dL at 7 days to 1.2 g/dL by 42 days. The protein content of donor human milk is markedly lower, with some investigators reporting protein content of less than 1 g/dL in samples of pooled donor milk. Manufacturers of human milk fortifiers, however, assume an average protein content of human milk of 1.4-1.6 g/dL. Consequently, assumptions about the final protein content of fortified preterm human milk after the second week of lactation must be challenged, given the steady decline in the protein content as lactation progresses (Fig. 41.2).

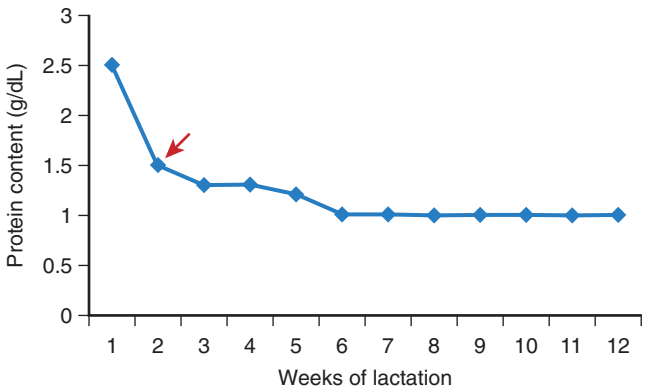
Fortification of human milk does not need to be delayed until full enteral feeds are achieved. Some have advocated for introduction of human milk fortifier as early as when enteral intake is greater than 50 mL/kg per day, in an effort to optimize growth.[81] Others have suggested a strategy of adjustable fortification with incremental increases in protein guided by measurement of blood urea nitrogen.[7] Individualized approaches to fortification have been proposed.[75]

Limited data do not provide evidence that use of multinutrient-fortified breast milk after hospital discharge has any impact on growth outcomes in infancy, and there are no data available on long-term growth outcomes.[110]

Formula

Preterm Formulas

Formulas for premature infants have been developed to meet the nutritional needs of growing preterm infants and have been in use for more than 30 years. It must be noted that the design and testing of these formulas did not



• **Fig. 41.2** Protein content of preterm human milk. Manufacturers of human milk fortifiers typically assume protein content of 1.4-1.6 g/dL (indicated by *red arrow*) and do not account for the decrease in protein over time.

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specifically include extremely premature (less than 1000 g) infants. Premature formulas contain a reduced amount of lactose (40%-50%), because intestinal lactase activity is low in premature infants. The remainder of the carbohydrate content is in the form of glucose polymers, which maintain low osmolality of the formula (300 mOsm or less with a caloric density of 80 kcal/dL). The fat blends of preterm formulas are 20%-50% MCTs, which are designed to compensate for low intestinal lipase and bile salts. It is not clear that MCTs are necessary in premature infant formulas. Recommendations for lipid intake in enterally fed VLBW infants are for 4.4-6 g per 100 kcal.[51]

Preterm formulas contain more protein than term formulas. Standard preterm formulas supply 3 g/100 kcal and "high protein" preterm formulas 3.3-3.6 g/100 kcal. A comparison of protein intake for various enteral feeds provided at 150 mL/kg per day is shown in Table 41.3. Even with use of "high protein" products, meeting the recommended protein intake of 4.0-4.5 g/kg per day of protein for infants less than 1 kg is a challenge. For infants weighing less than 1 kg, the so-called "high protein" formulas are barely adequate. Although most clinicians tend to think about daily enteral intake in terms of volume or calories per kg, quantifying protein intake on a daily basis is arguably even more important, given the crucial role of protein in overall growth and development.

Premature formulas are whey predominant, which reduces the risk of lactobezoar formation and may provide a more optimal amino acid intake. Calcium and phosphorus content are also higher in preterm formulas, which results in improved mineral retention and bone mineral content.

Specialized Formulas

Occasionally, infants do not tolerate feedings and require formulas specifically designed for conditions of malabsorption or other types of formula intolerance. These formulas are free of lactose and cow milk protein and provide alternative sources of protein (soy, casein hydrolysates, free amino acids) and carbohydrate (sucrose, corn syrup solids, tapioca starch, cornstarch). Some provide a significant percentage of the fat as MCTs. Specialized formulas are somewhat higher in protein and mineral content but similar in vitamin composition compared with formulas designed for term babies. The vitamin and mineral contents are, therefore, lower compared with formulas and human milk supplements designed for preterm infants. Multivitamin and mineral supplementation of specialized formulas is generally necessary to provide the recommended intakes for premature infants. Specialized formulas have not been tested in premature infants and, therefore, are used only temporarily, when necessary. Routine feedings for preterm infants are reinstituted as tolerated.

TABLE 41.3 Comparison of Protein Intake for Enteral Feeds at 150 mL/kg per Day

Feeding	Protein (g/kg per day)
Unfortified preterm human milk (assume 1.2-1.4 g/dL)	1.8-2.1
Unfortified donor human milk (assume 1 g/dL)	1.5
"High protein" preterm formula (24 kcal/oz)	4.0
Preterm formula	3.6
Transition/postdischarge formula	3.1
Term formula	2.1

Electrolytes

During the first week of life, sodium needs are low because of the expected free water diuresis. For ELBW infants, addition of sodium to parenteral nutrition may not be necessary for the first several days. It is, however, necessary to frequently measure sodium concentrations and assess water balance. After the initial diuresis, 2-4 mEq/kg/day is usually sufficient to maintain serum sodium in the normal range, but ELBW infants sometimes require higher sodium intakes to compensate for larger renal sodium losses. Chloride requirements follow the same time course as sodium requirements and are approximately 2-4 mEq/kg/day. When electrolytes are added to the parenteral nutrition solution, chloride intake should not be less than 1 mEq/kg/day, and all chloride should not be omitted when sodium bicarbonate or acetate is given to correct metabolic acidosis. Potassium requirements are also low in the first few days of life, and potassium should be omitted from parenteral solutions in ELBW infants until renal function is clearly established. Potassium intakes of 2-3 mEq/kg per day are usually adequate to maintain normal serum potassium concentrations.

Parenteral nutrition solutions usually require the addition of anions, either as acetate or chloride. In general, excess anions should be provided as acetate to prevent hyperchloremic metabolic acidosis. Acetate can help to avoid the metabolic acidosis associated with the addition of cysteine hydrochloride to parenteral nutrition solutions.

Sodium is essential for growth, and serum sodium concentration may not be a good measure of total body sodium stores. The sodium content of unfortified human milk is low, and premature formulas and fortified human milk provide only 2-3 mEq/kg per day at full enteral intake. Randomized controlled trials of sodium supplementation in premature infants have demonstrated improved weight gain and long-term neurodevelopmental outcome.[3,47] Provision of 3-5 mEq/kg sodium intake daily to premature infants may be necessary to match rate of intrauterine growth once full enteral feeds are established.

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Minerals

The peak of fetal accretion of minerals occurs during the third trimester, placing the infant born prematurely at risk for osteopenia of prematurity. In addition to having low stores at birth, it is difficult to provide an adequate amount of minerals in parenteral solutions or to rapidly achieve sufficient supply by the enteral route. In addition, medications such as diuretics and corticosteroids can further negatively impact bone mineralization.

Supplying adequate calcium and phosphorus in parenteral nutrition remains a significant clinical challenge because of limited solubility. It is not possible to supply enough calcium and phosphorus to support optimal bone mineralization in premature infants using currently available solutions. The solubility of calcium and phosphorus in parenteral nutrition solutions depends on temperature, amino acid concentration, glucose concentration, pH, type of calcium salt, sequence of addition of calcium and phosphorus to the solution, the calcium and phosphorus ratio, and the presence of lipid. Adding cysteine to parenteral nutrition lowers the pH, which improves calcium and phosphorus solubility.

Mineral concentrations have been increased in preterm formulas and human milk supplements designed for feeding premature infants in an attempt to meet requirements. Significant increases in calcium and phosphorus content may affect magnesium retention. Several studies have shown improvement of mineral retention or bone mineralization in preterm infants who receive higher calcium and phosphorus intakes compared with their unsupplemented peers.[77]

Consumption of unfortified human milk by infants with very low birth weights after hospital discharge resulted in bone mineral deficits that persisted through 52 weeks postnatally, indicating the need for additional minerals after discharge. Fortification of human milk with minerals has been shown to increase linear growth during hospitalization.[52]

Based on rates of fetal accretion and an estimate of 50%-70% absorption, the recommended daily requirement for calcium is 120-200 mg/kg and for phosphorus is 60-140 mg/kg.[8] The Ca:P ratio should be approximately 2:1, which is similar to the ratio in human milk. Daily requirements for magnesium are 8-12 mg/kg, assuming 40% absorption.[2]

Zinc and Other Trace Elements

The fetus accumulates stores of trace elements primarily during the last trimester of pregnancy. Therefore, the premature infant has low stores at birth and is at risk for trace mineral deficiencies if intakes are not adequate to support requirements for growth. Trace elements contribute less than 0.01% of total body weight. They function as constituents of metalloenzymes; cofactors for metal ion activated enzymes; or components of vitamins, hormones, and proteins. Immature homeostatic control of trace element metabolism also increases the risk of deficiency. Trace minerals that have established physiologic importance in humans include zinc, copper, selenium, manganese, chromium, molybdenum, fluoride, and iodine. The trace minerals that are potentially toxic in pediatric patients are lead and aluminum. Requirements for trace elements for premature infants are not well defined, owing to a lack of clinical studies that assess safety and efficacy. There is reasonable consensus that zinc should be included early in parenteral nutrition solutions (400 μg/kg per day for premature infants). Other trace elements probably are not needed until after the first 2 weeks of life. Zinc and copper are available in the sulfate form and can be added separately to parenteral solutions. Several pediatric trace metal solutions are available that contain zinc, copper, magnesium, and chromium and are usually provided at 0.2 mL/kg per day. When trace metal solutions are used, additional zinc is usually needed to provide the recommended intake for preterm infants. Supplementation with selenium is suggested after 2 weeks of age, because premature infants can become selenium deficient after 2 weeks of exclusive parenteral nutrition. In infants with cholestasis, copper and manganese should be discontinued, and chromium and selenium should be used with caution and in smaller amounts with renal dysfunction. Infants who experience abnormal gastrointestinal losses (persistent diarrhea or excessive ileostomy drainage) often require supplementation with zinc and electrolytes.

Iron

Preterm infants are at increased risk for the development of iron deficiency, which can have adverse effects on brain development. Factors such as timing of umbilical cord clamping, need for frequent blood sampling, and treatment with erythropoietin can all affect iron requirements in preterm infants. Given the inability to excrete iron from the body, careful attention is needed to avoid excess iron supplementation, which contributes to an increased risk of sepsis and poor growth.[27]

Parenteral iron is not routinely recommended. The recommended iron intake in enterally fed premature infants is 2-3 mg/kg per day.[2] In general, enteral iron supplementation may be started between 2-4 weeks of age. However, given the iron content in many preterm formulas and human milk fortifiers, an additional source of iron may not be necessary. Infants receiving an erythrocyte-stimulating agent such as erythropoietin may need a higher dose of iron. Infants who have received a recent blood transfusion may have elevated serum ferritin concentrations; if these concentrations are found to be elevated, iron supplementation should not be given until the ferritin normalizes.

Vitamins

Vitamins are organic compounds that are essential for metabolic reactions but are not synthesized by the body. They are, therefore, needed in trace amounts from enteral or

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parenteral sources. Higher amounts of select vitamins are required by preterm infants, who may have greater needs for growth or because of immature metabolic or excretory function. In addition, the vitamin content of human milk may be decreased by freezing or pasteurization.

Vitamins are classified as water soluble or fat soluble based on the biochemical structure and function of the compound. Water-soluble vitamins include the B complex vitamins and vitamin C. They serve as prosthetic groups for enzymes involved in amino acid metabolism, energy production, and nucleic acid synthesis. Needs are considered relative to dietary intake of calories and protein, as well as the rate of energy use. Water-soluble vitamins cannot be formed by precursors (with the exception of niacin from tryptophan) and do not accumulate in the body (with the exception of vitamin B_{12}). Therefore, daily intake is required to prevent deficiency. Excretion occurs in the urine and bile. Most water-soluble vitamins cross the placenta by active transport; vitamin C crosses by facilitated diffusion. Levels of water-soluble vitamins generally are higher in fetal than in maternal blood and are relatively independent of concentrations in the circulation of a nourished mother. Preterm infants and infants of undernourished mothers have lower blood levels of water-soluble vitamins at birth.

Altered urinary losses owing to renal immaturity during the first week of life predispose a preterm infant to vitamin deficiency or excess. The need for vitamin C may be greater in a preterm infant who experiences increased urinary losses and lacks *p*-hydroxyphenylpyruvic acid oxidase, an enzyme that catabolizes tyrosine and is stimulated by vitamin C. Transient neonatal tyrosinemia, however, has not been shown to be detrimental to infants.

Fat-soluble vitamins include vitamins A, D, E, and K. These vitamins function physiologically on the conformation and function of complex molecules and membranes and are important for the development and function of highly specialized tissues. They can be built from precursors, are excreted with difficulty, and accumulate in the body; therefore, they can produce toxicity. They are not required daily, and deficiency states develop slowly. Fat-soluble vitamins require carrier systems, usually lipoproteins, for solubility in blood, and intestinal absorption depends on fat absorption. They cross the placenta by simple or facilitated diffusion. Accumulation takes place throughout pregnancy and depends on maternal blood levels. Therefore, blood concentrations and body stores at birth are lower than normal in preterm infants and in infants of poorly nourished mothers.

Recommendations for vitamin D intake in premature infants are the same as for term infants. The current AAP recommendation of 400 IU/day of vitamin D is probably sufficient to prevent vitamin D deficiency rickets in preterm infants.[108]

Vitamin E in formula, required as 0.6 mg/g of PUFAs, provides adequate amounts to prevent hemolysis of red blood cell membranes when iron intake is not excessive. The recommended total intake is 3-4 IU/day for term infants. Recommendations are somewhat higher for preterm infants; however, pharmacologic supplementation of 100 mg/kg per day of vitamin E is not recommended to reduce the incidence or severity of retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage.

An adequate intake of vitamin K to prevent bleeding in the first week of life when enteral intakes are low is recommended as a 1-mg IM injection at birth in both term and preterm neonates over 1000 g birth weight. For premature infants less than 1000 g, 0.3 mg is recommended. Term infants can be given 2 mg orally as an alternative. Thereafter, 2-3 mg/kg per day or 5-10 mg daily is recommended in all babies.

Daily multivitamin or mineral preparations may be necessary for preterm infants once enteral feedings have been established. Preterm formulas and human milk fortifiers differ in the amounts of vitamins and minerals they contain; therefore, the need for supplementation varies for infants with very low birth weights.

Preterm infants who require specialized formulas or receive standard infant formulas designed to meet the vitamin and mineral needs of term infants must be able to consume 1000 mL/day and require supplementation with vitamins and minerals to provide the recommended intakes. Liquid multivitamin drops do not contain folic acid because of its lack of stability, but it can be added or given separately.

Breastfed infants who weigh less than 3.5 kg do not consume enough human milk to acquire the recommended intakes of some vitamins and minerals. Therefore, supplementation with a multivitamin, folic acid, calcium, phosphorus, zinc, and iron may be necessary, unless one of the commercially available milk fortifiers is used.

Complications of Parenteral Nutrition

Although a myriad of complications of older parenteral nutrition solutions have been reported, with the use of current parenteral formulations most of these are now rare. Some of the complications (electrolyte imbalance, hypoglycemia, hyperglycemia, hypocalcemia, hypercalcemia, hypophosphatemia) can be prevented or corrected by manipulating the constituents of the infusate. The primary complications of parenteral nutrition as currently used are cholestasis and complications related to central lines.

Hepatic dysfunction has long been recognized as an important complication of parenteral nutrition, manifested primarily as cholestatic jaundice. The initial lesion seen histologically is both intracellular and intracanalicular cholestasis, followed by portal inflammation and progressing to bile duct proliferation after several weeks of parenteral nutrition. With prolonged administration, portal fibrosis and ultimately cirrhosis may develop.

The etiology of Parenteral Nutrition Associated Liver Disease (PNALD) is unknown and most likely multifactorial. The patients at greatest risk are critically ill premature infants who are susceptible to multiple insults, such as hypoxia, hemodynamic instability, and sepsis. The most

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frequently identified risk factors in parenteral nutrition–associated cholestasis are duration of parenteral nutrition, degree of immaturity, and delayed enteral feeding.[89] There is expanding evidence that even small-volume enteral feedings can reduce the incidence of cholestasis. Early studies of parenteral nutrition suggested a possible relationship between the quantity of amino acids and hepatic dysfunction. The specific role of the quantity and composition of parenteral amino acids in the cause of cholestatic jaundice in premature infants remains unclear. Some investigators have hypothesized that fish-oil lipid emulsions prevent steatosis, potentially through improved triglyceride clearance and anti-inflammatory properties.[4]

There have been several case reports in infants of improvement in PNALD with Omegaven.[16,26] Using historical controls as a comparison group, Gura and colleagues reported the safety and efficacy of fish oil–based lipid emulsions in 18 infants with short bowel syndrome who developed cholestasis while receiving soybean emulsions.[39] At the present time, this therapy is available in the United States only through compassionate-use protocols. Data from randomized clinical trials are needed before recommending a change in clinical practice to include Omegaven for the treatment of PNALD.

Indwelling venous catheters used to deliver PN also may be the source of complications. Both peripheral and central venous routes have been used to deliver PN, but central delivery allows use of more concentrated formulations. Quality initiatives have dramatically reduced the incidence of central line–associated bloodstream infections. In addition, intense nutrition initiatives have reduced the need for prolonged central lines.

Infection is probably the most frequent serious complication associated with peripheral and central catheters. Reducing line sepsis is another benefit of a combined approach of parenteral and enteral nutrition. The most commonly implicated bacterial agents are *Staphylococcus epidermidis* and *Staphylococcus aureus*, whereas *Candida albicans* and *Malassezia furfur* are the fungal agents most often implicated. The incidence of sepsis as a complication of PN increases as gestational age decreases and the duration of PN increases. The predisposition to develop sepsis in these infants probably is multifactorial. As noted earlier, the incidence of sepsis increases in infants who have developed cholestasis. Similarly, there are numerous reports of *M. furfur* fungemia in infants receiving intravenous lipid. In both cases, the incidence increases when lipid is added to the infusate, suggesting that the lipid may provide a rich growth medium for skin flora that have colonized indwelling catheters.

Postdischarge Nutrition

Most premature infants are discharged at far below term weight and may have ongoing and catch-up requirements that may not be met by term formulas. Three large, randomized, controlled trials have compared standard infant formula with a preterm infant discharge formula.[17,55,56] Preterm infant discharge formulas have a nutrient content between preterm and standard-term formulas. Improvements in weight and length have been measured in preterm infants receiving the discharge formulas. One study also demonstrated increases in head circumference in preterm infants with birth weights less than 1250 g who received the discharge formulas.[17] Premature infants with chronic lung disease may also benefit from enriched nutrient intakes, especially additional protein, calcium, phosphorus, and zinc.[14] The ESPGHAN has recommended use of special postdischarge formula with higher protein, mineral, trace element, and LCPUFA content for preterm infants discharged on formula,[34] and the AAP has endorsed use of these formulas as well.[5] However, a Cochrane review concluded that current recommendations to prescribe postdischarge formula for preterm infants are not supported by the available evidence, because there was not a consistent effect on growth at 12-18 months' corrected age in the trials included in the meta-analysis.[110] Further research on the impact of these formulas on later growth and neurodevelopmental outcomes is needed.

Long-Term Effects of Early Nutritional Support

Few studies have evaluated the longer-term effects of early parenteral nutrition. In a single center observational study, Stephens and colleagues found an association between increased protein and energy intake in the first week of life and higher Bayley Mental Development Index scores and lower likelihood of length growth restriction at 18 months' corrected age.[90] Other observational studies have also found that a prospective strategy of initiating amino acids in the first 24 hours of life in infants weighing less than 1500 grams at birth is associated with improved weight gain at 36 weeks.[102] Wilson and colleagues demonstrated in infants with very low birth weights that early, aggressive parenteral nutrition combined with early enteral feeding reduced growth failure without an increased incidence of adverse clinical consequences or metabolic derangement.[109] The effect of early parenteral amino acids on growth at 36 weeks' postmenstrual age and growth and neurodevelopment at 18 months' corrected age was assessed from a cohort of ELBW infants enrolled in the NICHD Neonatal Research Network multicenter randomized clinical trial of parenteral glutamine supplementation.[74] Infants who received a minimum of 3 g/kg per day of intravenous amino acids in the first 5 days of life were found to have improved growth outcomes (weight, length, and head circumference) at 36 weeks' postmenstrual age. The odds of having weight less than the 10th percentile for age at 36 weeks' postmenstrual age was approximately fourfold higher for infants who did not receive early amino acids. At 18 months' corrected age, no differences in neurodevelopment were observed between the groups, but male infants who did not receive early amino acids were twice as likely to have head circumference less than the 10th percentile.[74] Other investigators

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have also reported gender-specific differences in the effects of suboptimal nutrition.[21,57]

Controversies in Neonatal Nutrition and Areas of Further Study

The Barker Hypothesis of rapid catch-up growth and later increased risk of metabolic disease has raised questions of how aggressively nutritional delivery and growth attainment should be pursued. The literature remains mixed in the balance of growth and later metabolic health, but also varies in degree of maturity and duration of long-term follow-up with some cohorts decades away from current nutritional practices.[10] Additionally, improved assessments of body composition are now being standardized, which may offer better insights in free versus fat mass and how specific types of growth correlate with long-term outcomes.[22,28,70] The risks and benefits of early rapid growth remain unclear and require further study.

Small cohort studies have suggested an increase in necrotizing enterocolitis (NEC) giving rise to the entity of transfusion-associated NEC (TANEC). TANEC has been variably defined as NEC occurring within 48 hours to any time after a blood transfusion. The mixed definitions of TANEC, the absence of effect with multiple meta-analyses, and the lack of association in large clinical trials studying restrictive versus liberal transfusion policies have raised questions about transfusion being a direct cause of NEC but rather being a proxy for other elements of acute illness such as degree of anemia.[36,40] It is not uncommon for feedings to be held for nongastrointestinal concerns; further work is needed to assess gut health and tolerance to nutritional delivery in the context of multiple exposures in the NICU to avoid unnecessary delay or interruption in critical nutrition.

Acknowledgment

The authors would like to acknowledge the significant contribution of the late Richard Ehrenkranz, MD. Dr. Ehrenkranz was not only one of the authors of this chapter in the previous edition, but also a legend in the field of neonatal nutrition, tireless advocate for research, a mentor's mentor, colleague, and friend.

Key Points

- Growth attainment in the NICU is directly linked to short-term and long-term neonatal health outcomes.
- Initiation of parenteral nutrition including 3.0-3.5 gm/k/d of protein and up to 3.0 gm/k/d of lipids is well tolerated and recommended.
- While human milk is the preferred diet, fortification and regular tracking of growth outcomes are necessary to minimize the risk of extrauterine growth restriction.
- Ongoing research is needed to further refine our nutritional strategies with the goal of moving toward better monitoring tools for growth and nutritional efficacy that allow for personalized medicine and optimal nutritional delivery for each infant.

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42

Support for the Family

SUSAN HATTERS FRIEDMAN, FRANCES THOMSON-SALO, AND A. REBECCA BALLARD

Normal Mother–Infant Attachment

The birth of an infant initiates a series of interactions with parents (particularly the mother) designed to initiate attachment and ensure survival. Attachment is a bidirectional emotional and enduring bond that is reciprocated between infant and the caregiver, a process of synchronous coregulation that influences each other's internal state.[19] Human development is sufficiently resilient to withstand some disturbance of the normal postpartum sequence of events that initiate attachment; however, significant problems of either the infant (prematurity; congenital anomalies; transitional problems such as asphyxia, trauma, or peripartum infection) or the mother (complications of pregnancy, depression) have more substantial capacity to disrupt normal processes. These complications carry a risk for disorganized attachment[59] and adverse effects on long-term neurodevelopment in addition to the risks related to prematurity or underlying anomalies.[17]

Formation of Mother–Infant Attachment

Attachment in Pregnancy

Emotional and psychological groundwork for secure attachment begins in pregnancy. Increased levels of oxytocin throughout pregnancy facilitate the formation of an emotional bond between mother and infant in humans by acting to reduce anxiety and to ameliorate responses to external stresses. Mothers who have a less anxious state of mind are more able to increase their focus on infant care and recognize and respond effectively to nonverbal infant cues.[29] Unexpected hospitalization during pregnancy, feelings of anxiety and depression, and lack of social support interfere with the development of maternal antenatal attachment.[62] Hospital care practices that reduce anxiety, such as avoiding unnecessary separation of an infant from parents, can contribute greatly to early attachment.

Fig. 42.1 is a schematic diagram of the major influences on parental behavior and the resulting disturbances that may arise from them. Experiences during labor, parent-infant separation, and hospital practices during the first hours and days of life are the most easily manipulated variables in this scheme.

Attachment During Labor

When childbirth moved from the home to the hospital, continuous support of the mother during labor became the exception rather than the routine. Although husbands/partners and female relatives routinely accompany the mother to the delivery room, they usually have little experience in providing labor support and may need support themselves. The clinical value of continuous emotional and physical care during childbirth by a trained doula is supported by the results of the 22 randomized clinical trials conducted over more than two decades.[35] Women allocated to continuous support were more likely to have a shorter labor and a spontaneous vaginal birth. In addition, they were less likely to have intrapartum analgesia or a baby with a low 5-minute Apgar score. Beneficial findings are consistent across the studies despite different cultural, medical, and social practices.

Attachment in the First Hours After Birth

Nearly 90% of newborns require no special intervention at birth. Suctioning is not typically required with clear amniotic fluid, and clearing of the upper airway can be accomplished by simply wiping the infant's mouth and nose. Even nonvigorous infants with meconium-stained amniotic fluid do not need routine intubation and endotracheal suctioning.[3] It should not be necessary to separate the newborn from the mother to administer the initial steps in stabilization. The newborn should be placed on the mother's skin immediately after birth, covered by a blanket. Early skin-to-skin care results in more rapid thermal control and decreased incidence of hypothermia in term and late preterm infants.[56]

The sensory stimuli of touch, warmth, and odor between the mother and infant are powerful vagal stimulants resulting in release of maternal oxytocin, which aids in breastfeeding and mother–infant attachment.[51] Oxytocin production in mothers is maintained postnatally by lactation and also

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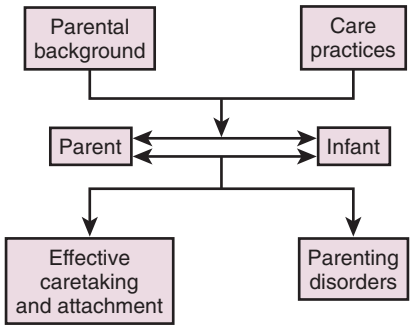
Abstract

This chapter focuses on various aspects of support for the family, including an understanding of normal mother–infant attachment, progressing to understanding the challenges of attachment with the NICU infant, understanding parental mental health issues, and finally care of the long-stay infant and their parents. This chapter reviews the complex subject of supporting infants and their families during a particularly vulnerable time of human development. Having an infant in the NICU is a significant stressor for parents and families. Avoiding unnecessary separation of the infant from the parents contributes positively to early attachment. Parental role disruption in the NICU should be minimized, and parents should be supported to bond with their infants. Interventions in the NICU to promote the parental role and increase understanding of their premature infant may help reduce stress and prepare for discharge. Parental mental health is critical for attachment, bonding, and parent participation in care in the NICU. Mental health issues with which parents may present include postpartum depression, anxiety, grief, posttraumatic stress disorder (PTSD), psychosis, and personality issues. A cohesive, multidisciplinary team is important to providing the best care for families with complex needs. Appropriate boundaries and clear communication styles are critical as well.

Keywords

anxiety
attachment
bonding
grief
parenting
postpartum depression

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• **Fig. 42.1** Major influences on parent–infant attachment and outcomes.

in response to innate infant behaviors such as suckling, clinging, facial expressions, and vocal calls.[29] Oxytocin levels in early pregnancy and the postpartum period are significantly correlated with the frequency of maternal bonding behaviors, including gaze, vocalizations, positive affect, and affectionate touch, as well as the degree of its coordination with the newborn's alert state, attachment-related thoughts, and frequent checking of the infant.[19]

In a concerted effort to promote breastfeeding, the American Academy of Pediatrics, endorsing the WHO/UNICEF publication *Ten Steps to Successful Breastfeeding*, recommends in a policy statement on breastfeeding that for healthy infants, "breastfeeding should begin within the first hour after birth (even for Cesarean deliveries) and that infants must be continuously accessible to the mother by rooming-in."[40] Routine procedures including weighing, measuring, bathing, blood tests, vaccines, and eye prophylaxis should be delayed until after the first feeding is completed. These recommendations stem from a global program launched in 1991 by WHO/UNICEF as the Baby-Friendly Hospital Initiative. A recent nationwide American quality improvement initiative of maternity care hospitals showed a rise in hospitals receiving the Baby-Friendly designation, along with an increase in breastfeeding and exclusive breastfeeding rates in those hospitals compared to hospital applicants not in the program.[20]

Attachment in the First Days of Life

Immediately after birth, parents enter a unique period in which their attachment to their infant usually begins to blossom and in which events may have many effects on the family.

The first feelings of love for the infant are often instantaneous with the initial contact. However, mothers may express distress and disappointment when they do not experience feelings of love for their infant in the first minutes or hours after birth. In a study of 100 primiparous mothers interviewed within 72 hours of delivery, 39% developed positive feelings prenatally, 42% on the first day, and 19% on the second or third day.[58] Most mothers develop affection for their infants within the first week.[64] Delay in positive feelings until after the first day was associated with labor longer than 8 hours, a feeling of disappointment with the "bonding" experience or breastfeeding, and high depressive symptoms, whereas mothers who fell in love on the first day were likely to cite privacy and the ability to hold their newborn as contributing factors.[58] Providers of health care to the maternal–infant dyad should be aware of the many factors that shape mothers' affective responses to their infants.

Sensitive Period

The period of labor, birth, and the following several days has been called a sensitive period, when the mother, and likely the father, are strongly influenced by the quality of care they themselves receive. Perceived stress, social support, and coping strategies are crucial variables in mothers' adaptation mechanisms at the time of childbirth. Social support during the antenatal or postnatal period appears to be a major factor related to mothers' psychological health.[63]

This beginning of parent–infant interactions has foundation in autonomic, neurologic, and endocrinologic systems in the mother and infant, and each become sensitized to the temporal patterns of the other, leading to the formation of a unique bond.[19] Rhythmic patterns of neonatal activity such as crying, nursing, or sucking serve as the earliest means of communication. Maternal cues of her voice, touch, and body rhythms in response create a synchronized "dance" between the mother and infant. The high level of positive arousal that infants co-construct with their parents during their face-to-face interactions accelerates the maturation of the infant's relational skills and provides essential environmental inputs for the development of self-regulation and the process of attachment.

These early interactions are not limited to infants and mothers. When fathers are given the opportunity to be alone with their newborns, they not only spend almost exactly the same amount of time with the infants as mothers do, but also respond to infant cues as effectively. Additionally, when fathers had more extended postpartum hospital contact with their infants, they were more involved in infant caretaking responsibilities.

These early affectional ties can be easily disturbed and may be permanently altered during the immediate postpartum period if a newborn requires separation from the mother for care.[41] A mother's anxieties about relatively mild conditions in the newborn (e.g., jaundice requiring phototherapy, slow feeding, mild respiratory distress) may affect her relationship with the child long afterward. Hospital routines should minimize unnecessary separation of newborns from their parents.

Feeding

Feeding, as part of the mother–infant relationship, should be an enjoyable experience in which the infant feels that his or her cues are being recognized. Supporting breastfeeding promotes attachment, pleasure, and autonomy for mother

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and infant as they learn together the intricacies of feeding. Mothers may need support to establish breastfeeding using an electric pump. A mother may feel too self-conscious to express milk in public, be anxious about whether she has enough milk, or feel valued more for her expressed milk than for herself. She may delay breastfeeding out of ambivalence, may experience anxiety, or consider herself a failure if the infant is slow to suck, or she may feel confused between the use of breasts for nutrition and sexual intimacy. Mothers who do not wish to or cannot breastfeed also need support, whether or not they express milk. Continuing to express milk for months throughout the night is exhausting even for the most committed mother.

Infants who become exhausted while feeding, who experience painful oral interventions, or who have been forcibly fed may develop an oral aversion. Feeding difficulties may contribute to insecure parent–infant attachment, and infants may become distressed during sucking because they do not feel securely attached emotionally.

Attachment Challenges With Sick or Premature Infants

Preterm children, particularly those with neurologic impairment, have been reported to be at risk for dysfunctional attachment relationships.[59] Early separation between infant and mother is associated with disorganized attachment and linked to increased parental stress.[59]

Parents who live a distance from perinatal care centers may experience additional separation because of the necessity of transporting their child to a regional NICU. If the infant must be transferred to another hospital, it is important that parents be given a chance to see and touch the infant and take a picture before transfer occurs, receive contact information for the other hospital, and accompany the infant whenever possible.[13] Transporting the mother afterward for postpartum care is beneficial; however, financial barriers and lack of insurance provider coverage are problems in some areas. Parents of transported infants often describe the separation in terms of loss and may experience a grief response even when the condition of the infant is not serious. After the initial transport, parents living far away have continued difficulty visiting their infant and may be helped with access to overnight accommodations.

The design of the NICU impacts patients and families (see also Chapter 36). Emphasis on family-centered care has promoted design of single-patient rooms rather than the traditional open-bay NICUs. The single-patient room design can decrease stressful stimuli and allow a private space for parents and infants to have their first interactions. Randomized controlled trials have shown single-patient rooms allow for increased hours of parental visitation[61] and decreased length of stay.[57] However, after controlling for social support, mothers in single-patient rooms reported more NICU stress than mothers in an open-bay NICU design.[61] NICU design benefits from parent feedback in balancing privacy concerns and providing social support to families.

The NICU environment itself is an impediment to parent bonding with their child. The incubator is a physical barrier to the parent's comforting touch; the tubes and patches obscure the infant's cues.[42] In addition, the parents may be hesitant to interact with preterm infants due to their immaturity and medical severity. Preterm infants have less "babyish" physical features and are less active, alert, and responsive than full-term infants. Their cry is perceived more aversive and distressing to parents. Parental bonding may be delayed until the infant's physical condition appears to be improved and parents are assured of the infant's survival.[36]

Neonates experience a variety of stressors while in the NICU, including painful procedures, mechanical ventilation, decreased maternal care, and auditory and light stimulation. Exposure to painful stimuli causes activation of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent release of glucocorticoids. Cumulative stress, such as a higher number of skin-breaking procedures, can result in altered programming of the HPA axis and decrease in cortisol release in response to stress. Such alterations to neurodevelopment following early-life pain exposure may account for adverse behavioral outcomes later in life, including poorer cognitive outcomes and increased internalizing behavior. Maternal care, especially kangaroo care (see below), can negate consequences related to neonatal pain and promote beneficial outcomes.[50]

Difficulty in Bonding

Staff need to be aware that if parents continue to approach their infants reluctantly, this may indicate a prolonged complicated reaction, different from a mother's reaction after birth when being close may stir mixed emotions, such as feelings of failure about the preterm birth. Parents may resist engaging with the infant because of a traumatic birth, shock at the infant's appearance, or a poor prognosis about survival and disability. When parents cannot hold their infant, they may find it hard to believe that the infant is their child, particularly with an in vitro fertilization (IVF)-conceived infant. Mothers with a very low birth weight infant may feel less effective because of the need for the nurses' care; when a parent finds it hard to attach to a very low birth weight infant, staff can talk with him or her about the infant's personality traits. It can be pointed out to parents who feel that they have to ask permission to hold their infant, that they do not have to ask permission to be loving parents. If parents become phobic about entering the unit because of its associations or their fear of bad news, this should be explored and additional support offered.

Interventions for Premature or Sick Infants and Their Parents

With advances in medical and neurodevelopmental care, preterm or seriously medically ill infants may be hospitalized

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for many months. There is increased understanding that the quality of social interactions between parents and infants in the neonatal intensive care unit (NICU) can ameliorate the adverse effects of preterm birth, increase awareness of the psychosocial effects on the family, and guide professional interventions. An integrated multidisciplinary team, composed of doctors and nurses, as well as optimally also a social worker, neurodevelopmental therapist, lactation consultant, psychiatrist, infant mental health clinician, and pastoral worker, works in partnership with families to understand the complexity of the needs of the infant and family to promote attachment and autonomy, decrease parental stress, increase sensitivity, and prepare for discharge and eventual independence. Social work support is essential for parents' needs for accommodation, transportation, and child care. All staff should be aware of parents' individual mental and physical health, and provide care that is culturally sensitive and safe. A unified needs-based care plan takes parents' changing anxieties into account and empowers them as members of the caregiving team. This approach leads to improved family satisfaction and greater staff retention. The infant mental health clinician liaison should assist the staff by contributing the infant's perspective, clarifying the parents' experiences, and engaging in therapeutic work with parents and infants to improve the parent–infant relationship.[54]

Parental Stress

Parental anxiety may remain high for months because of concerns about health and parenting challenges. The experience of in vitro fertilization (IVF) is likely to accentuate the stress, which may be increased by caring for multiples. Anxiety often lies behind forgetting information, avoidance, and aggressive behavior. If the staff make time for parents to verbalize their worries, they may be able to suggest appropriate ways to manage the peaks of anxiety.

Parents bond in different ways and need to be supported in this. Staff can encourage parents of very preterm infants to smile and sensitively share eye contact and the same emotional state to promote optimal outcomes for their infant, pointing out that the infant prefers parents to nurses, which predisposes them to bond with their parents. Care is usually not only skin-on-skin, which lowers autonomic nervous system activity,[52] but also skilled care, such as tube feeding and intensive developmental care programs. Preterm infants show faster cognitive growth when parents are consistently responsive. Parents who are prevented from holding or touching their infant for long periods face greater difficulties in feeling connected and maintaining hope.

Although families need different kinds of support and information giving, support needs to be consistent, and parents find it helpful for staff to recognize their frustration and stress responses as normal. Information on care procedures may need to be repeated regularly because parents may not retain this information during the stress of concentrating on their infant. They may feel encouraged when the staff point out how the infant's record demonstrates an improvement in his or her responses when the parents visit. Information helps parents correct the perception that their infant is in pain. Parents should be reassured that they can positively influence their infant's development through early childhood.[71]

Parents may need encouragement to connect with, support, and to nurture themselves as they become exhausted. As the staff becomes familiar with communication patterns between parents and/or support persons, they can encourage parents to reconnect with their extended families, particularly if a mother's partner cannot support her or there is no partner available. Staff should work with the parents' support network and be nonprescriptive about how parents share information with the outside world. Parents often feel lonely in the NICU when contact from friends and family declines over time and may find even a brief contact with a clinician supportive. If parents find it difficult to limit intrusive family involvement, the staff can help to manage this sensitively. Siblings may experience adjustment reactions of jealousy and anger and feel neglected; reading relevant story books may help them process these feelings.

Interventions to Support Parents and Infant

Parents of preterm infants experience high levels of stress and often lack knowledge of how to parent and interact with their infants during their hospital stay. Interventions in the NICU to aid parents' understanding about their preterm infants and to promote their role as parents may help them participate in their infant's care in a developmentally sensitive manner, thereby reducing stress and preparing them for when the infant is discharged home. Different approaches are indicated at different times to support parents, the infant, and the relationship, in what has been described as a paradigm shift from healing the infant's medical problems to a focus requiring effective partnership with families[33] and including supportive and psychoeducational interventions and perinatal psychotherapy.[8]

A successful educational–behavioral intervention program for parents of premature infants 26-34 weeks' gestation (Creating Opportunities for Parent Empowerment or COPE) found that mothers in the intervention group exhibited significantly less stress while their infant was in the NICU and less depression and anxiety at 2 months' corrected age compared with mothers in the control group.[48] In addition, infants in the intervention group had a 4-day shorter length of stay (mean 35 vs. 39 days) compared with control infants.

Weekly support groups for parents that offer information and emotional support are helpful. Linking parents with others who have had a preterm infant could help them work through some of their grief relatively quickly. Early individualized family-based interventions reduce parental stress and depression.[54] Brecht and colleagues[9] carried out a

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comprehensive review of psychoeducational programs, such as the COPE program. Such programs have been found to be effective in preventing post-traumatic stress reactions by helping parents to partner in providing care to the infant, by enhancing parental feelings of self-efficacy, and by reducing distress around the infant's birth and hospitalization. Brecht reports a trend toward early brief interventions that target parent trauma and utilize cognitive behavioral techniques with positive effects on maternal and infant outcomes.

A meta-analysis of interventions for parents to improve developmental outcomes for preterm infants found significant reduction in pooled effects for maternal anxiety and depressive symptoms and positive pooled effects on parental self-efficacy.[5] Interventions included psychosocial support, parent education, and/or therapeutic developmental interventions targeting the infant; the positive effects seen in the psychosocial aspects implicate mental health services for families in the NICU as an important adjunct to routine care.

Interventions to reduce maternal symptoms may not necessarily overlap with parental education and developmental care. A recent meta-analysis of NICU-based interventions to reduce maternal depression and anxiety symptoms found 5 out of 7 interventions for depression and 6 out of 8 interventions for anxiety reduced symptoms compared to the control group.[49] For maternal depressive symptoms, cognitive behavioral therapy was associated with significant improvement in maternal symptoms, whereas educational approaches and interventions focused on improving maternal–infant responsiveness were not.

Interventions to minimize the infant's distress center primarily on the Neonatal Individualized Developmental Care Assessment Program (NIDCAP) established by Heidelise Als,[2] which aims to reduce stress linked to the environment, increase awareness of the baby's behavior, and integrate the parents in their daily routine. The neurodevelopmental therapy team works with parents to develop individualized flexible developmental care plans based on an infant's developmental stage and behavioral cues. These continue to be important in a long hospitalization, because when reaching new developmental stages, an infant risks being overwhelmed or bored, and a care plan can offer the family greater consistency.

Infants find it both exciting and soothing to be gazed at by someone who delights in them. They respond best when parents are with them as much as possible and are willing to play with them with positive reciprocity and contingency without overwhelming them. This has positive results for cognitive and psychomotor development, and parents feel supported, knowing that their sensitivity optimizes brain development.[67] Parents, particularly fathers, report increased intimacy when they read books to their infants.[44] Infants also respond positively to a mutually supportive relationship between parents. Parents who need help to think about the infant's mind as intentional can be encouraged to carefully observe their infant and become curious about the meaning of behavior, such as playing with the pacifier, responding to imitation, fighting sleep, and being alert to their parent's feelings. This helps empower parents to respond in a holistic way.

The clinician, as well as thinking with parents about the infant's happiness, can underscore the importance of recognizing the infant as having agency and learning that negative affect expresses intention. When parents view this as being active and can share in a social exchange, infant competence increases. When parents are very anxious, encouraging neonatal behavioral observation has been found to be effective in enhancing engagement. Parents who are less sensitive and more controlling may need additional support.

Kangaroo Care (See Also Chapter 36)

Kangaroo care, now commonly referred to as *skin-to-skin contact*, originated in South America as a means of keeping at-risk infants warm with limited resources. Subsequent studies in high-income countries have indicated potential benefits in promoting breastfeeding, establishing parent–child attachment, and promoting neurodevelopment.

During kangaroo care, the diaper-clad infant is placed in flexed position directly onto the parent's chest, with maximal skin-to-skin contact, and covered with a shirt or blanket. Skin-to-skin care is useful in helping parents develop a closer tie to their infants and may be the first time that parents feel that the infant is truly theirs.[14] Specific maternal benefits to kangaroo care have been demonstrated, including reduced maternal anxiety, report of less maternal depression, and improved maternal attachment behavior in the postpartum period.[7,18]

The benefits of kangaroo care extend beyond promoting attachment. Kangaroo care promotes physiologic stability and maturation of the autonomic and circadian systems in premature infants, including more quiet sleep, longer sleep cycles, and increased respiratory regularity.[50] Kangaroo care decreases premature infant pain profiles prior to a heel stick and may be a viable analgesic for premature infants as young as 28 weeks' gestational age.[50] A meta-analysis of 21 studies involving low birth weight infants showed kangaroo care was associated with a reduced risk of mortality, nosocomial infection/sepsis, hypothermia, and length of hospital stay.[14] In addition, compared with conventional care, kangaroo care was associated with an increased weight, length, and head circumference, as well as an increase in the likelihood of exclusive breastfeeding at discharge or 40-41 weeks' postmenstrual age.

Benefits of kangaroo care are long-lasting. In follow-up at 10 years of age, premature infants who received skin-to-skin contact as neonates showed attenuated stress response, more mature autonomic functioning, organized sleep, better cognitive control, and a more reciprocal mother-child relationship.[18] A 20-year follow-up to the original Bogota study on kangaroo care found long-term social and behavioral benefits for infants who received kangaroo care, including increased brain volume, less aggression, and less antisocial behavior.[12]

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Kangaroo care should be considered for all stabilized premature infants, although there is currently no standard definition of infant stabilization or consensus of infant age for its initiation. Additional research is needed to evaluate risks and benefits to more immature infants and those requiring highly technical care, such as conventional or high-frequency mechanical ventilation.

Family Engagement

Paternal Issues

There is increased recognition of the importance of the father's presence in the NICU, both to support the infant and develop the father–infant bond. Infants move differently in response to a father's voice.[37,55] This is also relevant with same-sex parenting. Fathers want to be viewed as important to their infant while different from the mother. The stress of keeping the family financially viable and making childcare arrangements for siblings has led to paternal stress being described as invisible; fathers often cope by delegating care.

Many fathers, although initially reluctant to be close to their infant, find the contact more positive than expected; a father's early involvement may positively influence the attachment process and support the mother. When fathers are helped to care for their infants, they relax more at the bedside in opportunities for "meaningful fathering moments," which in turn contributes to increased paternal nurturing. Involving fathers in developmental care reduces neonatal stress and its neurobiological sequelae and is likely to promote better infant and family outcomes.[65]

It is important to ask each father how he can best be supported; for example, by detailed information or an overview of his infant's status. Fathers should be offered appointments that fit in with their work schedules; they often make the necessary arrangements for these appointments. They tend to prefer support to come from professionals and to be empowered through sharing information in an accessible and two-way process and with written material and Internet resources.

A dedicated fathers' group in recognition of the stress fathers feel helps them feel more secure and connected with their baby.[70] A father's behavior toward and attachment to the baby is related to many factors including genetics, personal relationships, culture, his own experiences with parenting, his ability to tolerate stress, and the baby's responses to him. Fathers commonly experience a feeling of lack of control when their infant is in the NICU. Maintaining relationships with family, friends, and staff, and consistent information given orally and written, are ways of supporting fathers. Although mothers may be allowed maternity leave, fathers may need to return to work sooner. Work may lead to some sense of control and normalcy but can also lead to feelings of guilt.

Having an infant in the NICU stresses the couple's relationship. Partnerships already in difficulty often do not survive this stress, which is a further reason for providing support to the couple.

Staff–Parent Communication

Staff–parent communication is a critical part of the NICU experience. NICU parent studies indicate a need for improved communication. It has been recommended that staff discuss the baby's diagnosis and course using "simple straightforward language void of medical jargon and presented in a warm, sympathetic manner."[32] As well, it is suggested that staff interact with parents as an "expert coach and facilitator" to enable parents to become comfortable in their baby's care.[32]

Knowledgeable and understanding team members may be more effective in communication with parents suffering from mental health issues. A study of NICU staff found that challenging interactions were more common among parents with psychotic symptoms, parents who hover (likely related to anxiety levels), or parents who have addictions, among others.[21] Psychiatric referrals are needed in some cases, and appropriate boundaries should be set with families. Recommendations have been made that all NICU parents should interact with mental health professionals for support, education, screening, and psychotherapy when needed. As well, mental health professionals should provide support for NICU staff.[39]

Family-Centered Care in the Neonatal Intensive Care Unit

Family-centered care is based on the understanding that the family is the most consistent and influential force in the growth and development of the child, that patients and family are integral partners with the health care team, and that the perspectives and information provided by families are essential components of high-quality decision making.[13,33] Parents of infants admitted to the NICU are confronted with many challenges, including physical separation from their infant, a bewildering number of care providers, inability to protect their infant from painful procedures, and, frequently, financial concerns. Family-centered neonatal intensive care endeavors to support families during this stressful time by making the NICU a welcoming environment for families, encouraging parents to participate in care, and educating parents on the NICU environment and their infant's condition.

Family-centered care has roots in advocacy by NICU parents. In 1992, a group of parents met in a conference with neonatologists to address problems identified by the NICU parents and to explore possible solutions. The components laid out in the original document published after the conference, The Principles for Family-Centered Neonatal Care, have become incorporated in national statements recommending family-centered care and remain relevant today.[30]

The NICU should be family friendly, and care should be taken to reduce stressful noises and sights. Facilities for

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parents' comfort and privacy such as rooms where they can relax should be provided, as well as a space in which fathers can work while their infant sleeps. The NICU should not be overly feminine; a father's name could be on his infant's crib. Prearranged discussion times that are scheduled to take place away from the infant's crib usually assist in communication. What the environment communicates to the family needs to be studied so that hidden barriers to communication and rigid policies can be tackled; however, parents should not feel that their actions are overly scrutinized. Nurses must be aware that witnessing distress in their infant generates feelings of anger in parents, which may compromise the parent-nurse relationship.[15] Increased support and involvement in the infant's care help allay complaints that stem from anxiety.

Some practices to be considered for implementing family-centered care include the following:

- Parents are not visitors but instead are essential components of the care team. "Visiting Policies" should address nonparent family members and friends, whereas policies related to parents should be more appropriately addressed as "participation in care."
- Parents are integral to care and are encouraged to participate in patient care rounds, communication with personnel at the change of shifts, and in the bedside care of their infant. Parents should have access to information in their infant's medical record. Many units have initiated parent documentation into the record.
- The physical environment should provide for the needs of parents, including needs for accessing information, rest, nutrition, privacy, childcare for siblings, and support for their infants by breast milk pumping. Standards for support of families are available.[74]
- Families should be incorporated at various levels as advisors. The perspective of experienced families should be integral to the unit administrative activities. These could include parents as teachers during orientation and continuing education of staff, parent advisory committees to collaborate in planning of new policies or ongoing quality improvement activities, and involvement in NICU parent support groups.

Parental Mental Health Issues

Parental mental health in the NICU is critical for attachment and bonding, participation in care, and infant development.[28] Psychiatric support in the NICU can be invaluable. Most referrals to psychiatrists during this time are for depression, anxiety, coping issues, and personality traits.[24,25,60]

Postpartum Depression

Postpartum depression (PPD) is a common complication of childbirth. It occurs in 10%-20% of postpartum women, with studies showing increased rates of 28%-70% in the NICU.[1,4,26,53] A systematic literature review showed higher depression scores of mothers of preterm LBW infants for at least 12 weeks postpartum and that higher levels of depressive symptoms can persist through the first postpartum year.[72] Risk factors include a personal or family history of depression, relationship issues, low socioeconomic status, and stressful life events. Obstetric- and NICU-specific risk factors include multiple birth, very low birth weight, recent stillbirth, less effective coping strategies, maternal role disruption, and lower perception of nursing support.[53] Symptoms may include depressed mood, decreased enjoyment (including of spending time with baby), decreased sleep (difficulty sleeping even when the baby sleeps), decreased energy, feelings of guilt/worthlessness, changes in appetite, and potentially suicidal or violent thoughts.

Differential diagnosis includes: "baby blues" (seen in the majority of women—with transient symptoms of irritability, tearfulness, and fatigue resolving within 2 weeks of delivery), postpartum psychosis, bipolar disorder, and medical illness (e.g., thyroid disease or anemia).[27] Depressed mothers are more likely to be disengaged, withdrawn, or hostile, with disrupted mother–infant bonding; thus, recognition and treatment are important. Of note, lower maternal NICU visitation rates predicted greater maternal depression at 4 months corrected age.[31]

Because of its prevalence, PPD screening and prevention measures should be integrated into NICU care. A widely used validated screening tool is the Edinburgh Postnatal Depression Scale (EPDS). A positive screen indicates that further evaluation is warranted. The EPDS is readily accessible online (e.g., through the American Academy of Pediatrics website). Mothers may be referred to psychiatry, family medicine, or obstetrics. If they are actively suicidal or homicidal, they should be evaluated emergently. Antidepressant medications and psychotherapy are treatments of choice. With mild symptoms, psychotherapy alone may be sufficient. In risk–benefit analysis regarding medications in lactation, just as in pregnancy, the well-established risks of untreated maternal depression on development should be considered.[22,23]

A recent study considered maternal stress in the NICU and child outcomes of very preterm infants. Predictors of NICU stress included maternal lower education level, stressful life events, postpartum depression, and unsettled/irregular infant behavior. They found NICU-related stress to be associated with child anxiety and poorer language skills at 4 years corrected age.[75] Another study that included nine home visits during the first year of life (to those who had been very preterm infants) by a physiotherapist and psychologist focusing on the parent–infant relationship, infant development, and parental mental health found that at 2 years of age, those in the intervention group demonstrated less dysregulation and externalizing behaviors, and parents had less anxiety and depression.[68]

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Postpartum Anxiety

Anxiety is often comorbid with PPD. Risk factors include past traumas, prior high-risk pregnancy or postpartum course, prior fetal/infant loss, low socioeconomic status, poor social support, and past history. Anxiety can become excessive, interfering with daily life and bonding with the infant.

Mothers with generalized anxiety disorder (GAD) may demonstrate excessive worry, restlessness despite appearing tired, imaginings that the situation is worse than it is, and feelings of being unable to leave the infant's bedside because of an overwhelming fear of a bad outcome.[28]

Alternatively, in obsessive-compulsive disorder (OCD), intrusive thoughts and behaviors may occur and cause maternal distress. She may, for example, avoid holding the infant for fear that she will cause harm because of distressing obsessive thoughts. Anxious mothers experience higher investment in infant health concerns and intrusive thoughts—leading to more repetitive questions and phone calls and the repetitive need for reassurance.

Rates of anxiety are elevated among mothers with infants in the NICU.[4] Maternal role disruption should be minimized. Staff should encourage mothers to look beyond the machines and alarms, to touch and talk to their babies, and to participate in feeding and diapering. The new parenting role can be stressful for anyone, but attempting to take on a much-anticipated role with severely ill infants—infants with tubes and who may not be able to be held or snuggled—can be a significant stressor. Other NICU-specific stressors include feelings of loss of control and the daily uncertainties of life and death. Mothers' perceptions of their infants' illnesses are not correlated with the actual illness severity. The mother's stress level may be related to illness perception rather than to illness severity.[10]

Anxiety can become a significant issue during any high-risk pregnancy, because the mother may have worries about the baby's health, delivery, and how well she will fill her new role. Because it can decrease the number of "unknowns" in advance, a visit to the labor and delivery unit and to the neonatal intensive care unit (NICU) can be helpful. Empowering the pregnant mother (e.g., with Lamaze) may also be useful. Because high anxiety can decrease attachment, it is important to consider. Similar to PPD, treatment for anxiety disorders includes psychotherapy and medication.

Post-Traumatic Stress Disorder

Both mothers and fathers are at risk for acute stress disorder, identified in 35% of mothers and 24% of fathers within 3-5 days of infant's admission to the NICU.[45] A smaller percentage had persisting symptoms—15% of mothers and 8% of fathers met diagnostic criteria for post-traumatic stress disorder (PTSD) 30 days later. These symptoms can persist long after the birth. Symptoms of PTSD include hyperarousal, numbing, avoidance of triggers, and re-experiencing of traumas. The mother with PTSD may actually avoid the infant or the NICU if these experiences are her anxiety triggers. She may appear irritable, be easily startled, and have difficulty with bonding. Early PTSD symptoms predict less sensitive and more controlling maternal behaviors. Mothers of VLBW infants who experienced more symptoms of PTSD were less sensitive and effective at structuring the interaction when playing with their infant.[16] Mothers with PTSD are also noted to be more controlling in their interactions with baby.

A recent study seeking to prevent PTSD among mothers of preterm infants found that a brief six-session intervention using trauma-focused cognitive behavioral therapy was effective in reducing symptoms of anxiety and depression, with benefits noted at 6-month follow-up as well.[66]

Grief

Parents should have opportunities to grieve for the healthy infant they were expecting. Shock, anger, sadness, disbelief, and denial may occur. But the parents need to make their peace and bond with their infant. Sensitive care for these families positively impacts their coping. Pediatricians Kennell and Klaus were pioneers, recognizing the strong attachment occurring between mother and baby prior to delivery.

In the event of neonatal death, the significant loss should be acknowledged and culturally appropriate rituals used, conveying compassion. Parents should be able to see and hold their deceased infant. Mementos and photographs should be offered, with the option of a funeral or memorial service also discussed.[34]

Maternal grief may begin with a period of shock, confusion, numbness, irritability, or anxiety, followed by intense sadness, longing, guilt, and somatic complaints. A follow-up visit a month later can help ensure understanding of information and give an opportunity to address concerns and questions.[28] Parents may either avoid reminders of their loss (such as contact with mothers of healthy infants) or may seek opportunities to talk about the baby. Often, a year or two passes before a mother feels back to "normal" in her ability to enjoy life and invest in other relationships. Risk factors for pathologic grief include a history of psychiatric illness, childlessness, and poor social support.[38] Those exhibiting maladaptive or destructive behaviors, dominant somatic symptoms, or lack of improvement over the course of months should be referred for evaluation.

Persisting Trauma Reactions and Complex Grief

Many parents find the ongoing NICU experience traumatic, despite the initial support they receive over the preterm birth, and this may complicate the bonding process. A parent's own trauma history may affect his or her responses. For example, the multidisciplinary team needs to be aware

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of a parent who is so anxious that he or she cannot participate in discussions about the infant's care, while still respecting the parent's dignity. Parents may face extreme distress or guilt or feel rejection toward the baby if the infant is visibly different or if they feel responsible for the fact that the infant is not as they wished. Deaths of other infants in the NICU may retraumatize parents. It is important that additional support is offered, because infants whose parents experience post-traumatic stress symptoms are more vulnerable to develop eating and sleeping difficulties in the first year of life.

Part of the experience of complex grief may include feeling guilty, for example, about reproductive loss, earlier fetal death, or having an infant with visible differences, or mourning the unavailability of the mother. Parents may feel that they face unbearable choices, whether or not their infant survives. Getting to know the infant as a person who is psychologically alive creates a memory of being the parents of their infant, supports them when they fear death, and aids decision making and grieving. Supporting parents while they face the reality that their child is dying requires a delicate balance. Staff need to be culturally sensitive, recognizing each person as a unique individual, whatever his or her ethnocultural group.[43] If parents are involved with staff in end-of-life decision making, this is usually associated with lessened grief. Mutual confidence and communication encourage freedom and creativity around the infant at this time.[11] Attention to the infant's and parents' pain is important.

Medical and parental views about prolonging life may diverge, particularly when a parent's spiritual and cultural values make it unacceptable to shorten life. The staff need to adopt an ethical embracing of difference and recognition when they cannot advise but need to maintain a dialogue to help the family work through the decision-making process.[73] Parents need to feel supported through the pain of end-of-life issues and know that their decisions were made out of parental love. They may need the staff to help access trusted supports. When a decision is made to forgo life-sustaining treatments, parents may appreciate being asked whether the staff should indicate to other parents what is happening in case they wish to avoid being there. Parents may need support in explaining to a young child why his or her infant sibling died.

Postpartum Psychosis

Postpartum psychosis (PPP) is much rarer, occurring in 1-3 per 1000 mothers. Delusions (fixed false beliefs out of line with one's cultural background), disorganized thoughts, hallucinations, rapid mood swings, insomnia, and confusion may occur, often within the first postpartum weeks. Risk is elevated in those with bipolar disorder, personal or family history, sleep deprivation, and psychosocial stressors.[27] Medical causes of mental status changes, including anoxia, electrolyte disturbances, thyroiditis, neurologic pathology, or drug-induced causes must be ruled out.

Because of its rapid onset, fluctuating course, and morbidity and mortality risks, psychiatric hospitalization for PPP is usually necessitated. Suspected cases should be referred emergently; untreated PPP carries elevated risks of infanticide and suicide. Mother-infant bonding need be less important than infant safety in cases of postpartum psychosis. Mainstays of treatment of PPP include antipsychotic and mood-stabilizing medications. Medication side effects such as sedation should be considered and, in some cases, breastfeeding may not be recommended owing to medication effects and the impact of sleep disruption on maternal symptoms. Mother–infant visits should be planned when safe and initially occur under supervision. Engagement and follow-up are critical, and child protective services usually need to be involved.

Personality Disorders

In contrast, people with personality disorders evidence chronic, inflexible patterns of behavior and perception. These patterns create dysfunction at work, in the family, and socially. Approximately 15% of adults experience personality disorders.[47] Personality disorders fit into general categories of odd/eccentric (e.g., paranoid), dramatic/erratic/emotional (e.g., borderline, narcissistic, histrionic), or anxious/fearful (e.g., dependent, avoidant). Short of a personality disorder, problematic personality traits tend to come out under periods of stress—such as during a NICU admission with an unwell infant.

Dysfunctional personality traits are an important predictor of parental problems coping with the NICU. A parent with narcissistic personality disorder may disrupt the NICU by excessive demands for special care, self-preoccupation, and lack of empathy, whereas another parent with borderline personality disorder and affective instability may cause difficulties in the team working together. Mothers with borderline personality disorder were significantly more likely to have negative birth outcomes in an Australian sample. They also had frequent comorbid substance abuse and other impairment.[6]

Addressing personality disorders in parents can help to diminish parental distress and improve physician–parent relationships and parent–infant relationships, in addition to reducing staff stress and unit chaos. To decrease NICU problems from personality disorders, the goals should be to support the parent, minimize disruption, and maintain safety. Consistent boundaries across members of staff are critical, allowing for a more predictable environment so that the focus can be on the needs of the sick infant.

Boundary Issues and Families With Multiple Risk Factors

In a long-stay admission, some families seek special treatment for their infant and themselves that tends to breach professional boundaries. Nurses on 12-hour shifts in high-technology, life-and-death situations may become

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like family and find themselves under pressure as parents unconsciously seek concessions for their infant. Parents may also seem intimidating. When staff come to feel that some parents are "special," this is a sign of difficulties to be negotiated. Caring for such families may lead to splits in the team. Multidisciplinary team meetings are important in maintaining professional boundaries and minimizing mixed messages.

A cohesive multidisciplinary team provides the best care for families with complex needs, such as parents with anger management difficulties, serious mental illness, substance use, intellectual or physical disability, disadvantaged life circumstances, extreme youth, or a history of abuse or neglect of other infants. Parents whose behavior the staff find challenging may inwardly feel despairing or ashamed; terms such as "manipulative" should be avoided in considering needed support. Significant numbers of parents with a psychotic illness have contact with infants in the perinatal period, with symptoms and medication side effects impacting on interactions as well as the parent–child relationship; however, a parent's right to be treated as a parent should be recognized whenever possible. Staff may find the care of a parent who uses drugs and alcohol challenging if the parent is substance-affected at times or does not visit. Plans enabling parents to access ongoing supports after discharge should be in place. When a parent has anger management problems, the staff needs to set boundaries and address in a nonshaming way that anger is unacceptable, because infants should not be frightened. They should also inquire whether the parent needs further support. For the infant's safety, a referral to child protective services should be considered when there is considerable ambivalence (including self-harm), although it is not always clear when a parent is unable to be a caregiver. Parents may take hospital policy personally and blame the hospital for exacerbating mental health issues. If they are dedicated parents, they may feel offended if they are offered parenting skills advice. When violence is disclosed by a parent, the staff needs to be mindful of a power imbalance between the couple, and one partner may use the hospital as an escape. A nonjudgmental approach to referral for counseling or child protective services is needed, with the inclusion in care planning, if appropriate, of the violent partner. When an infant is to transition from a parent's care to other caregivers, the infant's interests must remain primary, and ruptures of attachment should be minimized. Some parents respond to the possibility of their infant's being removed from their care by becoming aggressive and may attempt to take flight with the infant.

Perinatal Psychotherapy

Although parents of a long-stay infant receive more structured interventions and become skilled at knowing their infant, they may increasingly value a confidential space to process feelings about the NICU experience. When they have difficulty relating to their infant, a flexible psychotherapeutic intervention to consolidate internal and external supports is indicated, usually consisting of less structured therapeutic sessions and coping strategies. The clinician needs to respond promptly to the request for help with a crisis or for supportive psychotherapy. Parents may be initially offered weekly appointments together, then flexibly as needed. Ideally, professional help is provided in the NICU environment because families may be reluctant to keep off-site appointments. Parents use this time to process the grief and anger about having a preterm infant, or anxiety about the effects on the couple's sexual relationship, while also focusing on finding joy in their infant.

Insight-oriented psychotherapy aims to help parents become aware of how the reactivation of past painful experiences contributes to difficulties in relationships with their infant or staff. Some parents decline the offer of medication and try to process their difficulties by talking. For example, a mother's sadness about her own mother's unavailability may be evident without being too distressing for her infant.

Parents' inconsistent messages negatively affect the attachment process, and the clinician should aim to reframe this. A parent's negative attributions from the first month onward, or suggestions of malevolence, need to be challenged so that they do not continue, and the pathologic link with the past must be lessened so as not to contribute to insecure attachment.[46] Guided observation of the infant can also modify the traumatic representation of the infant. When a parent rejects a tiny or ill infant, that infant urgently needs support to reduce the extreme ambivalence and negativity and to lessen the likelihood of infant withdrawal.

As parents explore feelings about loss or abuse and process recurrent traumatic memories, they usually feel relieved that traumatic feelings around their infant's birth can be lessened and value this time for themselves. It may be that the integrated care given to long-term NICU families prevents the neglect and abuse that might otherwise stem from unrelieved parental stress at this time.

Parents who feel sensitively cared for by staff are likely to be more sensitively caring of their infant, who in turn is less likely to become a vulnerable child. Above all, parent-inclusive assistance that will support these infants and their parents needs to be determined.[69]

A follow-up telephone call after discharge consolidates the support. Parents who may not be able to accept support during the hospital stay often renew contact with the staff much later and engage for a considerable time.

Discharge Planning

Even though parents wish for a long-stay infant to be discharged or transferred to a hospital nearer home, they may also be reluctant for this and feel abandoned by the staff. They may be anxious about managing the care of an infant on oxygen with a nasogastric tube even with outreach care, as well as resuming care of siblings, who may have adjustment reactions. Sustained discharge planning is supportive, including any necessary skills training. If single-room care

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is not available, the opportunity for parents to room-in with their infant for at least a night in the hospital before discharge should relieve many of their fears about managing at home.

In summary, because the newborn completely depends on the parents for survival and optimal development, it is essential to understand the process of bonding as it develops from the first moments after birth. Although we have only begun to understand this complex phenomenon, individuals responsible for the care of mothers and infants should evaluate hospital procedures and ensure early, sustained mother–infant contact. Care practices should be developed that promote contact of the mother and father with their infant and help them learn and explore the wide range of sensory and motor responses of their newborn infant, whether healthy or requiring intensive care. Parental mental health should be optimized in the NICU to aid in bonding and caregiving.

Acknowledgments

Marshall Klaus and John Kennell, the original authors of this chapter, were pioneers in identifying the importance of this subject, and much of their work remains relevant, constituting a core of this knowledge.

Key Points

- Having an infant in the NICU is a significant stressor for parents and families.
- Avoiding unnecessary separation of the infant from the parents contributes positively to early attachment.
- Maternal oxytocin levels in pregnancy and postpartum are correlated with maternal bonding behaviors.
- NICU parents should be supported to bond with their infants.
- Parental role disruption in the NICU should be minimized.
- Parental mental health is critical for attachment, bonding, and parent participation in care in the NICU.
- A cohesive, multidisciplinary team with appropriate boundaries is important to provide the best care for families with complex needs.
- Interventions in the NICU to promote the parental role and increase understanding of their premature infant may help reduce stress and prepare for discharge.

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43

Principles of Drug Use in the Fetus and Neonate

JACQUELYN D. MCCLARY

Fetal Drug Disposition

The use of medications during pregnancy, prescription and over-the-counter, is a common and increasing occurrence. Multiple studies have demonstrated that approximately 90% of pregnant women take at least one medication during the pregnancy.[10] The average number of medications used during pregnancy has increased by 68%, from 2.5-4.2, over the past 30 years, and the use of four or more medications has increased from 23%-50% of pregnant women.[10] When interviewed, patients, physicians, and pharmacists all cite safety of the mother and fetus as a top priority when making decisions about medication use.[13] Unfortunately, safety data for the vast majority of medications is limited.

Most of the drugs administered to the mother reach the fetus; the extent of fetal exposure depends on maternal drug disposition and placental drug transfer. The result of maternal drug disposition is the steady-state concentration of the drug in the maternal circulation, which ultimately determines the amount of the drug available for distribution to the fetal compartment. The steady-state concentration is impacted in varying degrees by maternal absorption, distribution, metabolism, and excretion of drug, all of which are altered during pregnancy.

Maternal Pharmacokinetics

Drug absorption is affected by a number of factors, including gastric emptying time and intestinal motility, which significantly change during pregnancy. Gastric emptying time is increased and intestinal motility is decreased during pregnancy. The result is a reduced rate of absorption of many medications with a potential increase in the extent of absorption due to the prolonged transit time through the intestinal tract. Intestinal metabolizing enzymes are also altered during pregnancy, which can result in either an increase or decrease in drug absorption. Together, these factors impact the oral bioavailability of a drug and ultimately the maternal steady-state concentration.

Steady-state concentration may also be altered by physiologic changes that occur during pregnancy and that influence drug distribution (Tables 43.1 and 43.2). Maternal total body water, extracellular fluid, and plasma volume all increase gradually during pregnancy by about 32%, 36%, and 52%, respectively (see Table 43.2). Maternal cardiac output also increases by about 40%-50% as a result of increases in both heart rate and stroke volume. The increase in body water is the primary reason for the observed decreases in peak drug concentrations with standard dosing of water-soluble drugs. When the drug dose is kept constant in the presence of increasing body water, the drug's apparent volume of distribution (Vd) increases, and steady-state drug concentrations decrease. Such a decrease in steady-state concentrations may alter the therapeutic effect of the drug in the mother and influence the amount of drug available for diffusion across the placenta. Similarly, the increase in cardiac output affects drug transfer by limiting the time a drug resides in the villous space of the placenta and is available for transfer to the fetus.

Coincident with the changes in body water distribution and cardiac output, the amount of maternal fat increases at a relatively constant proportion to the increase in body weight (see Table 43.2). The result is an increase in Vd for lipophilic drugs and the potential for accumulation within the adipose tissue. Minimal changes in drug efficacy are expected under these circumstances; however, the adipose tissue can act as a reservoir and slowly release the drug into systemic circulation. An increased half-life and prolonged drug effects may be observed.

Complicating the picture even further is the fluctuation in serum proteins during gestation. Both albumin and α_1-acid glycoprotein are decreased during pregnancy, resulting in an increase in the free (active) fraction of various highly protein-bound drugs. For example, the free fraction of tacrolimus may increase as much as 91% during mid and late pregnancy.[8] This unbound drug is not only the active moiety but is also the form that is available for metabolism and elimination by the mother and transfer to the fetus.

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Abstract

The exposure of a fetus or neonate to medications is a common occurrence. Fetal drug disposition depends on maternal pharmacokinetics, which are altered throughout pregnancy and influenced by the placental handling of a drug together with fetal pharmacokinetics. Most pharmacologic agents detectable in the maternal circulation cross the placenta and enter fetal circulation. The impact these medications have on the fetus is often unknown, so that currently fewer than 30 drugs have been positively identified as human teratogens. After birth, sick or premature neonates may be exposed to a number of medications that could have long-lasting consequences.

Keywords

maternal medication
placental drug disposition
placental and fetal pharmacokinetics
teratogen
absorption
metabolism
distribution
elimination

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TABLE 43.1 Influence of Pregnancy on the Physiologic Aspects of Drug Disposition

Pharmacokinetic Parameter	Physiologic Change	Pharmacokinetic Impact
Absorption	↑ Gastric emptying time ↓ Intestinal motility ↑ or ↓ Intestinal enzyme activity	↓ Rate of absorption ↑ or ↓ or Unchanged extent of absorption
Distribution	↑ Plasma volume ↑ Total body water ↑ Cardiac output ↑ Body fat ↓ Plasma proteins	↑ Volume of distribution ↑ Free (active) drug fraction
Metabolism	↑ or ↓ Hepatic enzyme activity (see Table 43.3)	↑ or ↓ Hepatic clearance
Excretion	↑ Renal blood flow ↑ Glomerular filtration rate ↑ Active renal transport	↑ Renal clearance

TABLE 43.2 Changes in Maternal Body Composition That Can Influence the Characteristics of Maternal Drug Distribution

Time of Gestation (wk)	Body Weight (kg)	Body Fat (%)	Plasma Volume (L)	Extracellular Fluid Volume (L)
0	50.0	16.5	2.50	11
10	50.6	16.8	2.75	12
20	54.0	18.6	3.00	13
30	58.5	20.0	3.60	14
40	62.5	19.8	3.75	15

Data from Mattison DR, et al. Physiologic adaptations to pregnancy: impact on pharmacokinetics. In: Yaffe SJ, et al, eds. *Pediatric pharmacology: therapeutic principles in practice*. Philadelphia: Saunders; 1992:81.

Changes in hepatic metabolism during pregnancy affect the normal rate and extent of drug transformation and ultimately renal elimination. During pregnancy, hepatic blood flow may increase, leading to increased drug metabolism in the liver; however, this is controversial. Less debated is the alteration in the activity of hepatic enzymes during pregnancy. Enzymes from the cytochrome P450 (CYP) family and those responsible for glucuronidation reactions (UGT) exhibit changes in activity as a result of pregnancy, which can potentially affect maternal and fetal drug exposure (Table 43.3). For example, labetalol is a commonly used antihypertensive agent in pregnant women, and it is extensively metabolized by UGT enzymes that have increased activity during pregnancy. Therefore, as expected, the clearance of labetalol after oral administration is increased during the second and third trimester by as much as 30%, and the half-life is significantly shorter in the pregnant compared with nonpregnant patient.[2] The consequence for the mother is an increase in total daily dose to maintain the same steady-state concentration and well-controlled blood pressure, which is critical for both mother and fetus.

Alterations in renal elimination during pregnancy also impact mother and fetus. These changes result from the increase in renal blood flow by 10%-40% and the increase in glomerular filtration rate by about 40%.[19] As a result, there is enhanced elimination of drugs typically excreted unchanged in the urine (e.g., penicillin, digoxin). Active renal transporters (OCT2, P-gp, OAT1) also exhibit increased activity during pregnancy, further enhancing elimination of some medications (metformin, digoxin).[26] The net result is a lower steady-state concentration that may or may not be clinically significant for the mother but will likely result in less drug exposure to the fetus.

Placental Handling of Drug

In addition to maternal pharmacokinetics, the placenta also plays a major role in determining fetal drug exposure. From the fourth week of gestation until term, the surface area of the placenta increases dramatically to accommodate the increasing needs of the maturing fetus. The surface area of the villi, which represents the real area for exchange, is about 3.4 m^2 at 28 weeks' gestation, compared with about 12.6 m^2 at term. In contrast, the thickness of the placental membrane decreases with advancing gestation. During late gestation (about 32 weeks), the tissue barrier separating the maternal and fetal circulations may be less than 2 mm, and the areas become specialized in the transport functions

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TABLE 43.3 Pregnancy-Induced Effects on Metabolizing Enzymes

Enzyme	First Trimester	Second Trimester	Third Trimester	Drugs Impacted
CYP1A2	Decreased 33%	Decreased 50%	Decreased 65%	Caffeine
CYP2A6	No data	Increased 54%	Increased 54%	Nicotine
CYP2C9	No change	No change	Increased 20%	Phenytoin
CYP2D6	No data	No data	Increased 50%	Dextromethorphan, fluoxetine
CYP3A4	No data	No data	Increased 50%-100%	Nifedipine, protease inhibitors
UGT1A4	Increased 200%	Increased 200%	Increased 300%	Lamotrigine
UGT2B7	No data	No data	Increased 50%-200%	Digoxin, enoxaparin

Modified from Anderson GD, Carr DB. Effect of pregnancy on the pharmacokinetics of antihypertensive drugs. *Clin Pharmacokinet.* 2009;48:161.

• BOX 43.1 Mechanisms of Drug Transfer across the Human Placenta

Simple Diffusion

- Facilitated transport
- Active transport
- Pinocytosis (phagocytosis)

of the placenta (i.e., rapid diffusion of substances) rather than the metabolic ones. By term, the placenta has only a single cell layer of fetal chorionic tissue separating the fetal capillary endothelium from the maternal blood. This separation, with its loose intercellular connections, presents little hindrance to small molecule transfer. Both the decreasing membrane thickness and increasing surface area with advancing gestation favor the greater transfer of drugs as gestation progresses.

Very little specific information defines the mechanisms of the processes and extent of drug transfer across the placenta. A number of interdependent variables influence the rate and extent of drug transfer across the placenta from the maternal to the fetal compartment. Most investigators and clinicians believe that the vast majority of compounds found in the maternal circulation will cross the placenta and enter the fetal compartment. Therefore, the fundamental questions are about the rate and extent of this activity. Unfortunately, even today this information is only partially available for just a few chemical entities. Similarly, the mechanisms by which drugs are transferred across the placenta are not always clear, and more than one type of transfer may be involved.

The possible modes of drug transfer across the placenta are listed in order of importance in Box 43.1. For most drugs and other compounds, it is presumed that the primary mode of transfer is by simple, passive, nonionic diffusion, which requires no energy. Pinocytosis and phagocytosis require energy and likely occur much too slowly to have any significant impact on drug transfer, whereas facilitated and active transport play a role for some drugs.

Corticosteroids are an example of a drug class that undergoes facilitated diffusion. No energy is required to transfer steroids across the placenta, but the steroid must form a complex with a specific carrier on the placenta to be transferred from maternal to fetal circulation. Active transport occurs in a similar way, but energy is required for active transport to take place. Metformin is thought to undergo active transport via the placental OCT3 transporter, resulting in fetal concentrations that are 70% to greater than 100% of maternal concentrations.[26] Another important aspect of active transport involves the efflux of drugs back to maternal circulation subsequent to binding with a carrier on the placenta. Digoxin is one such drug that binds to the carrier protein P-gp.[26] P-gp is expressed on the maternal side of the placental-trophoblastic layer, where it mediates active efflux from the fetal compartment. This efflux is unidirectional from the fetal to maternal circulation and is probably responsible for the removal of a number of highly lipid-soluble compounds and drugs from the fetal compartment.[29] As stated, most drugs are transported across the placenta by simple diffusion, and the factors that influence this process have been more extensively evaluated than those affecting the other transport mechanisms discussed. Simple diffusion is described by the Fick equation as follows:

$$\text{Rate of diffusion} = K\,A\,(C_m - C_f)/d$$

where *K* is the diffusion constant of the drug, which is dependent on the drug's physicochemical characteristics; *A* is the surface area of the membrane to be traversed; *Cm* and *Cf* are the concentrations of the drug in maternal and fetal blood, respectively; and *d* is the thickness of the membrane to be traversed. Thus, $C_m - C_f$ represents the concentration gradient across the placenta, which is primarily regulated by the surface area (A) and thickness (d) of the placenta. As previously mentioned, changes in these characteristics as pregnancy progresses allow for easier transfer of drugs from maternal to fetal circulation.

The important physicochemical characteristics that influence passive drug transfer across membranes (i.e., placenta), as represented by K in the Fick equation, are

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• BOX 43.2 Physicochemical Factors That Influence the Transfer of Compounds across the Human Placenta

Degree of Lipid Solubility

- Lipid soluble favored over water soluble.

Molecular Weight (MW)

- MW <100 daltons readily crosses the placenta.
- MW 100-500 daltons slower diffusion.
- MW 600-1000 daltons variable placental transfer.
- MW >1000 daltons impermeable.

pH

- Un-ionized form under physiologic or pathologic conditions favors transfer.

Protein Binding

- Low protein binding favors transfer across the placenta.

outlined in Box 43.2. The characteristics that facilitate placental transfer include high lipid solubility, the un-ionized form under physiologic and pathophysiologic conditions, low molecular weight (<500 daltons), and low protein binding. Very few clinically important drugs meet all these "ideal" characteristics, which explains the high degree of variability reported in various studies of placental transfer.

Other factors important to drug transfer across the placenta include differences between the maternal and fetal osmotic pressures and pH, as well as changes in uterine or placental blood flow. Under normal circumstances, the maternal osmotic pressure is higher than that in the fetal compartment, and a pH difference of 0.1-0.15 unit exists between the fetal and maternal blood (i.e., fetal umbilical blood is −0.1 unit of pH lower than maternal blood). If alterations in either the osmotic pressures or pH occur, drug transfer will be affected. With regard to changes in blood flow, the placental flow increases from 50 mL per minute at 10 weeks to 600 mL per minute at term, whereas uterine blood flow approaches 150 mL/kg per minute of newborn body weight at term.[25] Depending on the physicochemical characteristics of the drug, blood flow may have an important influence on the rate and amount of drug transfer.

The degree to which the placenta metabolizes a drug, if at all, also influences the amount that is estimated to cross the placenta and the amount of active drug that reaches the fetus. Many cytochrome P450 (CYP) mixed-function oxidase enzymes have been isolated from the human placenta.[29] The placenta also possesses some capacity to catalyze phase II conjugation reactions, which enhance water solubility of the affected drugs and ultimately drug transfer.

The number of different substrates biotransformed by enzymes located in the placenta is large, but the actual content of CYP enzymes in placental tissue is low, and the activity appears to be much lower than that determined in the fetal or adult liver. Thus the actual contribution of placental enzyme activity to the biotransformation of administered drugs is believed to be inconsequential and of limited clinical significance for most drugs administered maternally. Nevertheless, the differential placental metabolism of certain corticosteroids (e.g., prednisolone, in contrast to betamethasone)[5] and the resulting poor clinical outcomes with prednisolone compared with betamethasone in enhancing fetal lung maturation suggest a significant effect of placental metabolism in certain clinical scenarios.

Fetal Pharmacokinetics

Contrary to the popular belief that the fetus resides in a privileged and protected environment, it is clear that it is exposed to virtually every chemical entity to which the mother is exposed. Thus, the absorption of most drugs into the fetal circulation is both rapid and complete. Most of this absorption is believed to occur through passive nonionic diffusion down the concentration gradients between maternal and fetal blood (which oppose each other in the placental villi), where they are separated by only a single layer of cells. However, as described earlier, a number of energy-dependent placental transporters have been characterized and are responsible for drug influx and efflux.[29] In addition, the fetus may undergo continued drug exposure after its elimination because of the recirculation of amniotic fluid through the fetal gastrointestinal tract.

Once a drug is within the fetal circulation, we have little knowledge of its fate or potential activity. It will likely be distributed to the fetal organs in a manner similar to that observed after birth. However, it is not known whether there are any unusual fetal barriers to drug distribution analogous to those of the blood–brain barrier or the anterior chamber of the eye. In fact, it is not even known whether these barriers actually exist during fetal life. Additionally, a drug may have an increased affinity for a specific fetal tissue that is not the typical target tissue. For example, tetracycline has a high affinity for fetal teeth and warfarin for fetal bones.[4] Protein binding will also affect drug distribution. The fetus has lower levels of serum proteins, and the proteins that are present have a lower affinity for binding drugs. The serum protein levels increase with gestational age, but free drug levels remain high secondary to the binding affinity of fetal proteins.

Once a drug has reached various organs, it is often not known whether it has any effect at all. It is clear that both receptor number and receptor affinity change during development. Likewise, receptor–effector coupling undergoes a programmed maturation. Thus, even though a drug may interact with specific receptors, there may be no discernible pharmacologic effect, because the effector mechanisms have not yet developed.

There is no question that the mean residence time for drugs in the fetus is longer than that observed in older children and adults because of the immaturity of drug clearance mechanisms. For drugs undergoing significant hepatic metabolism, there are many unknown factors. Although

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TABLE 43.4 Expression of Cytochrome P450 Forms in the Fetal Liver and the Adrenal Gland

Organ/Gland*	CYP Form
Liver†	1A, 2D6, 3A, 3A5, 3A7†
Adrenal†	1A1, 2A5, 3A,† 3A7, B1, 17
Questionable expression	2C, E1

*Primary form/isoform expressed at specific site.
†Primary site for CYP expression in the human fetus (fetal adrenal > liver containing CYP protein).

most hepatic metabolic pathways are less active in the fetus than in the adult, this is not universally true. Moreover, in the fetus, the adrenal gland has a significant complement of drug-metabolizing enzymes that, although active during fetal and neonatal life, disappear by 6 months of postnatal age. Thus the true ability of the fetus to metabolize drugs is largely unknown, but it at least partially depends on the particular drug under consideration, the gestational age of the fetus, and its drug metabolism phenotype.

As noted, multiple enzyme systems are involved in xenobiotic metabolism within the body. Of the phase I or oxidative enzymes, cytochrome P450 predominates. The human fetal liver contains many different CYP forms (Table 43.4), although they are present in fewer numbers and with less density than in the adult liver. The liver of the human fetus does exhibit some CYP450 activity, but the overall functional capacity of fetal CYP activity is very low, and its metabolic capacity is qualitatively and quantitatively very different from the activity observed in the adult liver. For example, nevirapine is metabolized by the adult liver via CYP 3A4, 2B6, and 2D6, but in the fetus only negligible metabolism of the drug occurs and it does not impact overall fetal drug exposure.[6]

The enzyme activity observed in the fetus is primarily caused by CYP3A7 expression, which is minimally expressed in the adult liver. CYP3A7 may serve as a detoxifying enzyme and protect the fetus from steroids and retinoic acid derivatives. Other enzymes expressed also serve protective roles for the fetus, such as CYP2E1, which is involved in fetal alcohol metabolism.[4] Although our understanding of the expression of CYP forms by the fetus is growing exponentially, unfortunately the extent of our understanding of their function remains limited. Nevertheless, the available data clearly indicate that the overall functional capacity of the fetus to effectively metabolize xenobiotics is limited.

Even more limited is the ability of the fetus to clear drugs that are entirely eliminated by renal excretion. The ontogeny of glomerular filtration and tubular secretion has been well studied, and renal elimination is not a significant mechanism of drug excretion for the fetus. Furthermore, any drug that is renally excreted by the fetus is eliminated into the amniotic fluid, which the fetus may swallow, leading to redistribution of the drug and the need for elimination again.

Exposure of the Fetus to Drugs

As discussed, most of the pharmacologic agents present in the maternal circulation cross the placenta and enter the fetal circulation and are, therefore, potentially harmful to the fetus. The adverse effects of in utero exposure to drugs can vary from reversible effects such as altered thyroid or renal function to irreversible effects such as fetal death, intrauterine growth restriction, structural malformations, and mental retardation.[16,18] Unfortunately, the details of drug interaction with the maternal-placental-fetal unit for most drugs are extremely complex and not well studied. In a review of 172 medications approved by the Food and Drug Administration (FDA) from 2000–2010, the teratogenic risk was undetermined for 97.7% of the medications.[1] This lack of knowledge not only places the fetus at risk but may also cause prescribers to inadequately treat pregnant women for fear of a drug's teratogenic potential.[10]

A number of drugs are possible teratogens in humans; however, at present only a few (<30) have been positively identified as such.[4] Preclinical testing during drug development is typically performed using a rodent model; however, not all human teratogens are teratogens in different animal species, and further postmarketing phase IV epidemiologic evaluations for teratogenic effects are vitally important. It has been estimated that to establish that a given drug changes the naturally occurring frequency of a congenital deformity by 1%, a sequential trial involving about 35,000 patients would be required. In the case of abnormalities that occur quite often in the population, physicians may not be alerted to the direct causal relationship between exposure of the fetus to the drug and the resulting adverse effect. Therefore, for most medications, it remains virtually impossible to prove teratogenicity, and prescribers must often rely on international pregnancy drug registries, the experience and reports of others, or animal studies to guide drug therapy during pregnancy.

The teratogenic effects of thalidomide, discovered in the 1960s, illustrate the totally unpredictable nature of drug toxicity in the fetus during the first trimester. Thalidomide doses that induced analgesia with no demonstrable undesirable side effects in the mother produced major structural defects in the fetus.[11] The discovery that thalidomide caused congenital malformations was made possible because this drug was widely used, induced dramatic and rare congenital defects, and had a high probability (estimated at 20%-35%) of producing a teratogenic effect after exposure from the third to the eighth week after conception. Unfortunately, these three criteria are rarely met when one is attempting to assess the teratogenicity of other drugs.

In the absence of any clear data for a particular drug's teratogenic potential, other factors can be taken into consideration to help predict the risk of drug exposure to the fetus. The timing of drug exposure is frequently a critical determinant of the effect of a drug on the fetus. During the first week of gestation, the most common adverse effect of drugs is the termination of pregnancy, which may occur

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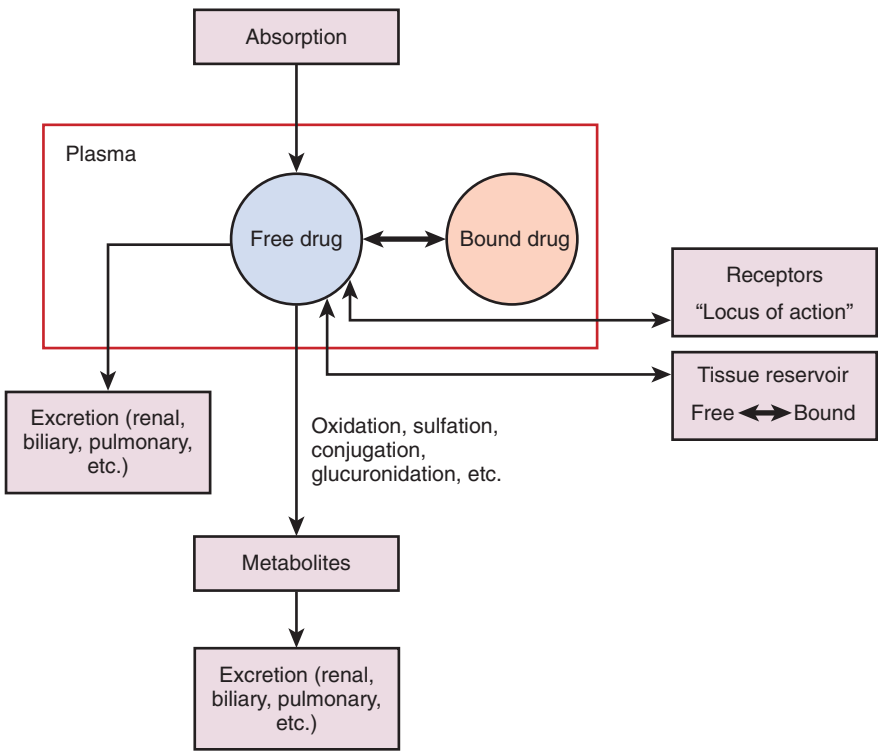
before the woman even knows that she is pregnant. Exposure of the preimplantation embryo to embryotoxic drugs may retard development, perhaps by decreasing cell numbers in the blastocyst, or it may even produce malformations. In the second to the eighth week of gestation, drugs may produce dramatic and catastrophic structural malformations, such as the neural tube defects associated with valproic acid and carbamazepine. Other adverse effects during this period of organogenesis may include fetal waste, transplacental carcinogenesis (diethylstilbestrol), and intrauterine growth restriction. From the third to the ninth month of gestation, the effects of drugs on a fetus are widely varied and relatively specific to the drug administered. For example, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) may cause oligohydramnios, tetracycline is associated with staining of the teeth and bones, and paroxetine may slightly increase the risk for cardiac malformations.[16]

In addition to the drug itself and timing of administration, the drug dose, maternal disease state, and number of medications administered are also important factors impacting teratogenicity. Epilepsy is one disease state in which these factors must be considered. Many antiepileptic drugs (AEDs) are associated with an increased risk of congenital malformations as well as adverse cognitive outcomes of the child. However, uncontrolled epilepsy also can be harmful to the fetus. Prolonged seizures have been associated with fetal loss, and frequent tonic-clonic seizures are associated with poorer cognitive development of the child.[28] It has been suggested that the teratogenic effects of AEDs are more common in women on multiple anticonvulsant medications and those on higher doses.[28] For these reasons, it is ideal to optimize an epileptic woman's drug regimen before conception with the fewest drugs possible at the lowest effective doses. Frequent monitoring throughout pregnancy is also required, as the state of pregnancy can significantly impact the pharmacokinetics of AEDs, possibly impacting both seizure control and fetal well-being.

The decision of whether to give a drug during pregnancy is difficult. If a mother is not healthy, the baby may not be healthy. If drug therapy can improve the mother's health, it seems it should also benefit the fetus. However, limited or incomplete knowledge of fetal outcomes for most drugs complicates the picture. Available information on the potential adverse effects for some of the commonly prescribed known or suspected teratogens is listed in Table 43.5.[15,16]

Neonatal Drug Disposition

At birth, a term infant in North America typically receives three medications: an ophthalmic antimicrobial agent, vitamin K, and the hepatitis B vaccine. Sick and premature infants receive an increasing number of drugs, with the constant introduction of new drugs or old drugs with new indications into the neonatal therapeutic armamentarium. The appropriate and safe use of these drugs requires a thorough understanding of the various pharmacologic profiles. Fig. 43.1 illustrates many of the interrelationships of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at the locus of action.[9] To produce its characteristic effect, a drug must be



• **Fig. 43.1** Interrelationships of absorption, distribution, biotransformation, and excretion of a drug and its concentration at the receptor site.

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TABLE 43.5 Selected Therapeutic Agents With Known or Suspected Teratogenic Potential

Drug	Potential Defect(s) and Adverse Effects	Additional Information
Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs)	Skull ossification defects, oligohydramnios, fetal lung hypoplasia, renal failure	Critical time period is ≥14 weeks' gestation
Carbamazepine	Neural tube defects, craniofacial defects, developmental delay	Critical time period is first trimester
Fluconazole	Abnormal facies, limb defects, cleft palate, congenital heart defects	Greatest impact at doses >400 mg/day for multiple weeks
Isotretinoin	Hydrocephalus, central nervous system defects, small/absent ears, hearing or eyesight problems, small or missing thymus, micrognathia, spontaneous abortion, stillbirth, developmental delay, congenital heart defects	Risk of defects is high with any dose or duration
Lithium	Ebstein anomaly, altered thyroid function, cardiac arrhythmias, hypoglycemia, polyhydramnios	Critical time period is ≤8 weeks' gestation for Ebstein anomaly; other adverse events are rare and associated with use later in pregnancy and higher doses
Methimazole	Esophageal atresia, choanal atresia, hypothyroidism, goiter, aplasia cutis	
Methotrexate	Craniofacial/skull abnormalities, limb defects, developmental delay	Critical time period is 8-10 weeks' gestation; greatest impact at doses >10 mg/week
Misoprostol	Skull defects, cranial nerve palsies, facial malformations, limb defects, spontaneous abortion	
Mycophenolate mofetil	Ear abnormalities; cleft lip and palate; anomalies of the distal limbs, heart, esophagus, and kidney; spontaneous abortion	Critical time period is first trimester
Paroxetine	Cardiac malformations, respiratory distress, persistent pulmonary hypertension of the newborn	Other selective serotonin reuptake inhibitors associated with respiratory distress and pulmonary hypertension, but less risk of cardiac defects
Phenytoin	Fetal hydantoin syndrome with mild to moderate growth and mental deficiencies, limb anomalies, and dysmorphic facies (low nasal bridge, short nose, eyelid ptosis), vitamin K deficiency with resultant hemorrhage	Critical time period is 3-12 weeks' gestation for hydantoin syndrome; critical time period for hemorrhagic disease is ≥13 weeks' gestation
Propylthiouracil	Face/neck defects, goiter, hypothyroidism, hydronephrosis	
Streptomycin	Hearing loss	
Tetracyclines (doxycycline, minocycline, tetracycline)	Discoloration of fetal teeth, inhibition of bone elongation/growth	Critical time period is ≥12 weeks' gestation
Thalidomide	Limb reduction defects, limb hypoplasia, ear and eye abnormalities, cardiac defects, developmental delay	Critical time period is 3-8 weeks' gestation
Valproic acid	Neural tube defects, cardiac defects, developmental delay, autism	
Warfarin	Nasal hypoplasia, stippled epiphyses, developmental delay, spontaneous abortion, fetal hemorrhage, fetal death	Critical time period is first trimester for nasal hypoplasia and stippled epiphyses; other adverse effects may occur from exposure at any time during pregnancy

Data from Mother to Baby. Fact sheets. Available at: https://mothertobaby.org/fact-sheets-parent. Accessed October 25, 2017.
Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed October 28, 2017.

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present in sufficient concentrations at its sites of action or receptor sites. The concentration of the drug at the receptor site depends not only on the amount of drug administered but also on the interrelationships listed in the preceding and shown in Fig. 43.1. Those factors that have been evaluated in the newborn infant differ substantially from those in the adult and even in the young infant beyond the neonatal period.[9]

Absorption of Drugs in the Neonate

Drug absorption is the passage of a drug from its site of administration into the circulation. In neonates who can tolerate gastric feedings, the oral route of drug administration is the most common because of its convenience and safety. The absorption of a drug or substance through the gastrointestinal system may be defined as the net movement of a drug from the gastrointestinal lumen into the systemic circulation draining this organ. This process entails the movement of drugs across the gastrointestinal epithelium, which behaves like a semipermeable lipid membrane and constitutes the main barrier to absorption. The various processes operating to induce the transepithelial membrane movement of drug molecules include simple diffusion through lipid membranes or aqueous pores of the membrane; filtration through aqueous channels or membrane pores; carrier-mediated transport, such as active transport or facilitated diffusion; and vesicular transport, such as pinocytosis. Of these, the most important is the process of simple diffusion, because most drugs administered orally are absorbed through this process.

The rate and extent of gastrointestinal drug absorption are partly determined by the physical and chemical characteristics of the drug. Polarity, nonlipid solubility, and a large molecular size tend to decrease absorption. In contrast, nonpolarity, lipid solubility, and a small molecular size increase absorption. The degree of ionization, determined by the pK_a of the drug and the pH of the solution in which it exists, is an important determinant in drug absorption. The gastrointestinal epithelium is more permeable to the nonionized form, because this portion is usually lipid soluble and favors absorption. The degree of drug ionization changes as the pH increases from the stomach through the distal portion of the gut.

Ionization also changes with the substantial changes in gastric pH observed during the neonatal period. Gastric acid production is generally low at birth, and the gastric pH is usually 6-8. In the first few hours of life, a burst of acid secretion occurs, decreasing the pH to values of 1-3. Acid secretion then returns to a low level, and the gastric pH remains near neutral for the first 10 days of life.[27] The gastric pH then tends to fall and approaches adult values by 2 years of age. These initial fluctuations in gastric acid secretion do not appear to occur in premature neonates, because their gastric pH remains near 6-8 for the first 14 days of life.[3] Clinically, the result of any decrease in pH is the increased absorption of weak acids (e.g., furosemide, phenobarbital), because they are more likely to be in the un-ionized, lipid-soluble state. Conversely, an increase in pH enhances the absorption of weak bases (e.g., morphine, erythromycin) and limits the absorption of weak acids.

The slow gastric emptying time and intestinal motility in the newborn may also affect drug absorption. The primary site for drug absorption is the proximal bowel, which has the greatest absorptive surface area. With slower motility and emptying, it takes longer for a drug to reach this site of absorption, and the rate at which absorption can occur may be limited. Conversely, a slow transit time or slow intestinal motility may facilitate the absorption of some drugs, such as iron, which is primarily absorbed in the duodenum.

The colonization of the gastrointestinal tract by bacteria is another process that influences intestinal drug absorption. Intestinal flora are involved in the metabolism of bile salts and selected drugs, as well as intestinal motility. The gut flora vary with age, type of drug delivery, and type of feeding. Concurrent drug therapy also plays a role, particularly because antibiotics, which decrease intestinal flora, are some of the most commonly administered medications to neonates. Although the actual characterization of the colonization of intestinal flora relative to age is limited, data suggest that all full-term, formula-fed, vaginally delivered infants are colonized with anaerobic bacteria by 4-6 days of postnatal life. By 5-12 months of age, an adult pattern of microbial reduction products appears to be established.

Additional factors such as pancreatic and biliary function and the activity of intestinal drug-metabolizing enzymes and efflux transports can also alter absorption. As expected, this function and activity is not fully developed in the neonate, further contributing to the differences in absorption observed between neonates and older children or adults.[27]

Overall, the differences in the neonatal gastrointestinal tract likely impact the rate of drug absorption but not the extent. The gastrointestinal absorption of drugs is relatively slow in the neonate, which can prolong the time to reach the steady-state concentration but not the actual concentration achieved. Thus the clinical significance of altered absorption in the neonate is likely minor for the majority of medications.

Drug Distribution in the Neonate

Distribution of a drug into the extravascular tissues is largely influenced by body composition, which is much different in a neonate compared with an older infant or adult. Total body water is about 70%-75% of body weight in a term infant and is an even greater percentage of body weight in preterm neonates. In comparison, an adult has a total body water percentage of 55%-60%.[14] The extracellular water compartment of a neonate is also larger, whereas the fat content is lower. At 28 weeks' gestation, body fat is only 1%-3% of body weight, and at term, it is 15%-28%.[4] In addition, the fat that is found in neonates is about 50%

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water, compared with 25% water in an adult. The end result of these differences is a larger Vd for hydrophilic drugs, whereas lipophilic drugs may not distribute as extensively as expected. In the case of water-soluble medications, a lower peak serum concentration, higher milligram-per-kilogram doses, and delayed excretion are often observed. For example, the Vd for micafungin in neonates has been reported as 0.44–0.62 L/kg, compared to 0.26 L/kg in adults. To achieve therapeutic plasma concentrations of micafungin in neonates, a dose of 15 mg/kg is required, compared to 5 mg/kg in adults.[24]

Protein binding also plays an important role in neonatal drug distribution. The unbound or free concentration of a drug in plasma is considered to be the pharmacologically active fraction of the drug. For some drugs, the binding to plasma proteins is decreased in the newborn compared with that in the adult (Table 43.6).[27] Reasons for this deficiency include decreased albumin concentrations in the neonate as well as qualitative differences in neonatal albumin. Albumin is the primary drug-binding protein in both neonates and adults, but the albumin found in neonates has less affinity for drugs compared with adult albumin. Competitive binding to albumin by many endogenous substrates such as hormones may also decrease protein binding. Hyperbilirubinemia may accentuate this competition, because bilirubin is able to displace some drugs, such as phenytoin, from the albumin-binding site. This activity contrasts with the well-known drug–protein binding interaction with bilirubin, in which drugs such as sulfonamides or their excipients may displace bilirubin from its binding site. Regardless of cause, the decrease in protein binding observed in neonates leads to an increase in free or active drug. This outcome suggests that a more intense pharmacologic response may be obtained in the newborn infant than the adult for the same total drug concentration. Clinically, decreased protein binding in the neonate does not typically affect initial dosing, but it is important to consider this factor in the application of adult therapeutic plasma concentrations to the neonatal patient.

TABLE 43.6 Comparative Protein Binding of Medications Used in Neonates

Drug	Percent Protein Bound	
	Neonate	Adult
Ampicillin	10%	18%
Digoxin	20%	32%
Morphine	20%	42%
Nafcillin	69%	89%
Phenobarbital	32%	47%

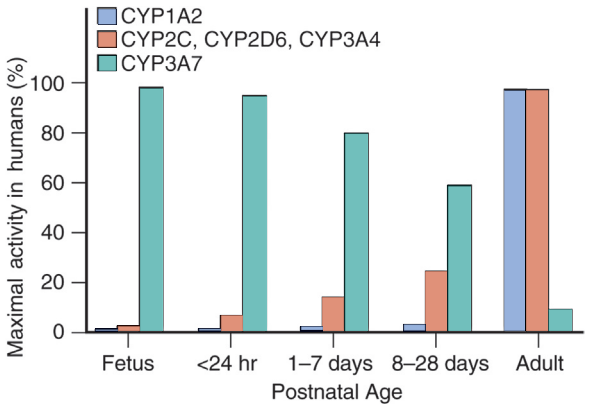
Data from Tayman C, et al. Neonatal pharmacology: extensive interindividual variability despite limited size. *J Pediatr Pharmacol Ther.* 2011;16:170.

Drug Metabolism in the Neonate

Many drugs are lipophilic and require conversion to more water-soluble metabolites for efficient elimination from the body. These metabolic processes most often occur via drug uptake into the liver and are traditionally categorized as either phase I or II reactions. In a phase I reaction, a more polar compound is formed through oxidation, reduction, or hydrolysis of the parent molecule. Phase II metabolism involves conjugation with endogenous substrates such as sulfate, acetate, and glucuronic acid. Drugs may be conjugated directly or made more amenable to conjugation after the introduction of a functional group by phase I metabolism (e.g., hydroxylation). Typically, the metabolites formed by either type of reaction are inactive; however, some drugs can be transformed into active metabolites (e.g., theophylline to caffeine). It is well recognized that the neonate may have limited uptake of drug into the liver and is deficient in many of the enzymes responsible for phases I and II drug metabolism.[9,27]

Phase I metabolism is mediated primarily by the cytochrome P450 enzymes. These enzymes are present in several tissues throughout the body, including the intestine, lung, kidney, and adrenal glands, but are the most highly concentrated in the liver. Numerous isoforms have been identified; the primary enzymes involved in drug metabolism are listed in Table 43.7. Considerable individuality is evident with respect to substrate specificity, polymorphic expression, and susceptibility to induction and inhibition.

The general pattern of development of cytochrome P450 enzymes is illustrated in Fig. 43.2. In the fetal liver, studies have shown that CYP3A7 is by far the most significant cytochrome P450 enzyme in terms of protein expression and activity. CYP3A7 concentrations decline during the neonatal period as CYP3A4 concentrations increase.[27] CYP3A4 is the most abundant cytochrome P450 enzyme in adults, accounting for 30%-40% of hepatic cytochrome P450 and as much as 70% of the content of cytochrome P450 in the intestine. Most other cytochrome P450 enzymes develop rapidly in the neonatal period. Whether they are triggered



• **Fig. 43.2** Maturational change in the activity of the cytochrome P450 isoenzymes implicated in human drug metabolism (see text for details).

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TABLE 43.7 Characteristics of the Primary Cytochrome P450 Enzymes Involved in Human Drug Metabolism

Enzyme	Total Cytochrome P450 in Adult Liver (%)	Selected Substrates	Inhibitors	Inducers
CYP1A2	15-20	Caffeine, theophylline, R-warfarin	Ciprofloxacin, cimetidine, erythromycin, amiodarone,	Omeprazole, tobacco smoke
CYP2C8/9	20-30 (includes CYP2C19)	Ibuprofen, phenytoin, S-warfarin	Fluconazole, amiodarone, trimethoprim	Rifampin
CYP2C19		Omeprazole, diazepam, phenobarbital, indomethacin, lansoprazole		Carbamazepine, prednisone, rifampin
CYP2D6	1-5	Dextromethorphan, codeine, propranolol	Amiodarone, cimetidine	Dexamethasone, rifampin
CYP3A4/5	30-40	Carbamazepine, erythromycin, ritonavir, midazolam	Erythromycin, cimetidine, grapefruit juice, fluconazole, amiodarone, ritonavir	Barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin, rifabutin

by the loss of a maternal repressing factor or stimulated by transcription factors intrinsic to newborns, concentrations of CYP2D6 and CYP2E1 increase within hours of birth, followed closely by the CYP2C and CYP3A4 enzymes.[9] By 1 month of age, hepatic concentrations are about 25%-30% of those in adults. The notable exception is CYP1A2, which develops more slowly, reaching less than 5% of adult concentrations in the first month.[9] It is generally assumed that premature babies exhibit greater impairment in drug metabolism than full-term infants; this response has been documented in several studies involving drugs metabolized by a wide range of cytochrome P450 enzymes.[12,22] It may result from the greater degree of immaturity of these enzymes at birth, a delay of the postnatal surge in cytochrome P450 concentration observed in full-term babies, or a combination of these two factors.

The pharmacokinetics of many drugs in neonates is consistent with the pattern of development of the cytochrome P450 enzymes shown in Fig. 43.2. Caffeine, which is administered for the treatment of neonatal apnea, exhibits an extremely prolonged half-life of several days in neonates compared with 4-6 hours in adults.[12] This result is caused by the delayed development of the CYP1A2 enzyme, which is responsible for the demethylation of caffeine, the primary metabolic pathway. The structurally related bronchodilator theophylline also exhibits reduced clearance and a prolonged half-life in neonates. However, the effect is not as dramatic as that observed with caffeine, because theophylline is partially oxidized by other cytochrome P450 enzymes, such as CYP2E1 in addition to CYP1A2. For drugs metabolized primarily by CYP2D6 or CYP2C, it seems reasonable to expect drug clearance to be low at birth but to increase rapidly during the first month of life. Data on tolbutamide and phenytoin, which are substrates for CYP2C9, support this view. The half-life of tolbutamide was found to decrease from 46 hours to 6 hours within the first 2 days after birth in a neonate exposed to the drug by placental transfer from the mother.

The clearance of drugs metabolized by CYP3A4 may be reduced less in neonates than substrates for other cytochrome P450 enzymes if CYP3A7 is capable of contributing to the metabolic process. CYP3A4 and CYP3A7 show more than 85% amino acid sequence homology and have partially overlapping affinities for both endogenous and exogenous substrates.[20] The catalytic activity of CYP3A4 toward drugs such as midazolam, carbamazepine, and nifedipine is greater than that of CYP3A7, whereas the latter appears relatively active in metabolizing erythromycin.[20] However, even if catalytic activity is low, CYP3A7 may contribute to the overall clearance of a drug at birth, owing to the high concentrations present. This activity may account for the observation that the elimination of CYP3A substrates such as carbamazepine[23] and the reverse transcriptase inhibitor nevirapine[17] during the first week of life is relatively similar to that observed in adults.

The metabolism of phase II drugs is mediated by a number of different enzymes, the most important of which are *N*-acetyltransferase (acetylation), sulfotransferase (sulfation), and uridine 5′-diphosphate glucuronosyltransferase (UGT) (glucuronidation). Acetylation and glucuronidation are not completely developed at birth, whereas sulfation appears to be reasonably well developed relative to other pathways of drug metabolism. Glucuronidation is an important route of metabolism for many drugs (acetaminophen, morphine, zidovudine) as well as endogenous compounds such as bilirubin.[27] Although UGT activity is generally presumed to be immature at birth, establishing a clear pattern for its development is complicated by the existence of numerous isoforms of the enzyme with broad and overlapping substrate specificity. UGT1A1, which is

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involved in the glucuronidation of bilirubin, is virtually absent in the fetus, and develops slowly over several months after birth. A somewhat similar pattern of development exists for UGT1A6, which is responsible for the glucuronidation of acetaminophen. UGT2B7 catalyzes the formation of morphine-3-glucuronide and morphine-6-glucuronide. Its activity is decreased in newborns and increases to adult levels by 2-6 months of age, thus morphine clearance in neonates remains well below that of older children.[27] For some medications such as acetaminophen, increased sulfation partially compensates for the reduced glucuronidation in neonates. The proportion of a dose of acetaminophen excreted as a sulfate conjugate is higher in neonates than older children or adults. Similar to observations with drugs metabolized by cytochrome P450, glucuronidation in premature infants is impaired to a greater extent than it is in full-term infants.[21]

Conclusions based on studies of drug metabolism in the term and preterm neonate must be interpreted with caution because of the small numbers of subjects in many investigations and the potentially confounding effects of genetics and disease states on metabolism. Nevertheless, the available data suggest the following tentative conclusions:

1. The rate of drug metabolism is generally low at birth in full-term babies and even lower in premature infants regardless of the specific route of metabolism. Decreased clearance and a prolonged drug half-life require drug administration with longer dosing intervals.
2. Many of the enzymes responsible for metabolism exhibit significant development during the first month of life. Dosing regimens appropriate during the first few days of postnatal life may not be appropriate 3-4 weeks after birth, because dose requirements may increase and dosing intervals decrease.
3. The development of individual drug-metabolizing enzymes varies widely among neonates and may be delayed in premature infants. Predicting clearance is difficult, and dosing regimens must be individualized for patients based on the careful observation of the patient's response and tolerance; monitoring of plasma drug concentrations may be useful for selected drugs.

Renal Excretion of Drugs

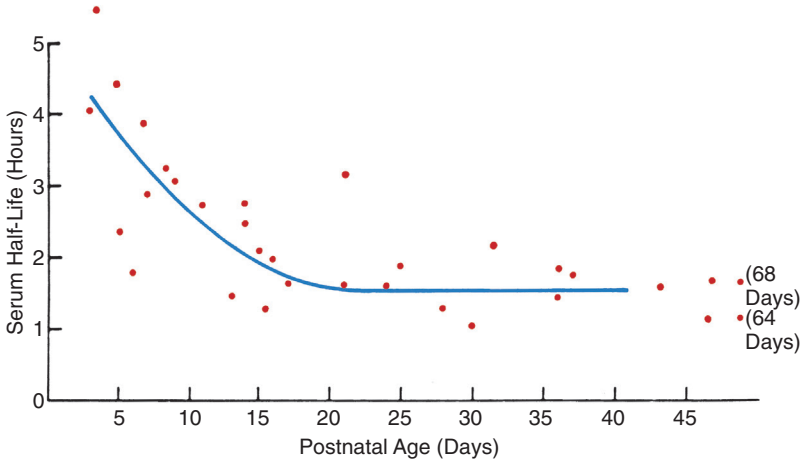
The kidneys are the most important organs for drug elimination for most agents. In the newborn, the most frequently used drugs, such as antimicrobial agents and caffeine in the premature neonate, are excreted by way of the kidney. Renal elimination of these drugs reflects and depends on neonatal renal function, which is characterized by a low glomerular filtration rate (GFR), low effective renal blood flow, and low tubular function (secretion and reabsorption) compared with that in the adult. The neonatal glomerular filtration rate is about 50% of the adult value and is greatly influenced by gestational age at birth. A term neonate has a glomerular filtration rate of 2-4 mL per minute per 1.73 m^2, whereas the glomerular filtration rate at less than 34 weeks of gestation is about 0.7-0.8 mL per minute per 1.73 m^2. The most rapid changes in renal function occur during the first week of life, but adult values are not reached until 6-12 months after birth in term neonates.[14,27] As expected, it takes even longer for the GFR to reach adult values in preterm infants secondary to the smaller number of glomeruli present.[14] Medications administered to the neonate can also cause a decrease in GFR and ultimately reduced elimination of concurrent drugs. For example, indomethacin inhibits prostaglandin synthesis, which leads to an increase in renal vascular resistance and thus a reduction in renal blood flow. The consequence of this is a decreased clearance of other medications such as gentamicin that are dependent on glomerular filtration for elimination.

Effective renal blood flow may influence the rate at which drugs are presented to and eliminated by the kidneys. Available data suggest that there is low effective renal blood flow during the first 2 days of life (34-99 mL per minute per 1.73 m^2), which increases to 54-166 mL per minute per 1.73 m^2 by 14-21 days and further increases to adult values of about 600 mL per minute per 1.73 m^2 by age 1-2 years. These data are probably not applicable to premature infants with very low birth weight, particularly those who weigh less than 750 g at birth. It is assumed, pending definitive data, that the glomerular filtration rate and renal blood flow in these micronates are substantially lower than those in bigger premature infants, such as those who weigh more than 1000 g at birth. Nevertheless, renal function in these patients is highly variable and reflected in the highly variable body clearance of a number of commonly administered drugs.

Tubular secretion and reabsorption are also variable and immature in neonates. Tubular secretion approaches adult values by 7-12 months of age in term neonates, while reabsorption maturation is more gradual and continues through adolescence.[27] In premature neonates, tubular function is even more limited. Drugs that require tubular secretion for elimination (e.g., furosemide, morphine) typically exhibit decreased clearance during the neonatal period.

The pharmacokinetic behavior of drugs eliminated through the neonatal kidneys exhibits characteristics similar to those underlying hepatic biotransformation. For instance, the half-lives of many antimicrobials, such as ampicillin (Fig. 43.3), show marked interindividual variability at birth, which narrows somewhat with advancing age. The plasma half-life also shortens progressively after birth, achieving adult rates of elimination within 1 month. Studies of the pharmacokinetics of ceftazidime and famotidine have shown direct correlations between plasma drug clearance and the maturational changes in renal function.[15] The drug-dependent variability in the elimination process partially reflects the major renal mechanisms of drug excretion. Those drugs that undergo substantial elimination by glomerular filtration (e.g., aminoglycosides) may be excreted more rapidly than those requiring substantial tubular excretion (e.g., penicillins).

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• **Fig. 43.3** Postnatal changes in the serum half-life of ampicillin. (From Axline SG, et al. Clinical pharmacology of antimicrobials in premature infants. II. Ampicillin, methicillin, oxacillin, neomycin, and colistin. *Pediatrics*. 1967;39:97. Copyright American Academy of Pediatrics, 1967.)

As with hepatic metabolism, the renal excretion of certain drugs may be as efficient as that in adults. However, usually drug excretion by way of the neonatal kidneys is deficient relative to that in an adult. Pathophysiologic insults further compromise the inherent deficiency in drug elimination, complicating individual drug dosage regimens. Hypoxemia decreases the already slow glomerular and tubular functions in neonates, leading to the slower renal excretion of drugs, as shown with amikacin. Intrauterine growth restriction leads to a decrease in the number of nephrons and renal mass, leading to a prolonged half-life of drugs such as vancomycin.[7] Moreover, very small infants, who receive the most drugs in the neonatal population, exhibit the worst functional deficiency in drug elimination.

Age-related (gestational and postnatal) changes have been considered in the dosage regimen recommendations for antibiotics and other drugs used in the treatment of infants. Drug doses, particularly for those agents excreted by the kidneys, are dynamically changing as functions of gestational and postnatal ages. In general, the total daily dose of a drug is directly related to the postconceptional age, and the fetal maturity is inversely related to dose interval. Thus, as an infant matures, the total daily dose increases and the dose interval decreases. However, the neonate is often unpredictable, and rigorous monitoring of drug efficacy and patient tolerability are required regardless of gestational and postnatal age.[15]

Key Points

- Most drugs administered to the mother reach the fetus; the extent of fetal exposure depends on maternal drug disposition and placental drug transfer.
- Drug absorption, distribution, metabolism, and elimination all fluctuate throughout pregnancy, impacting maternal serum concentrations of medications and ultimately fetal exposure.
- The primary mode of drug transfer across the placenta is by simple, passive diffusion which occurs most readily for a drug with high lipid solubility, low protein binding, low molecular weight and in its un-ionized form.
- Fewer than 30 drugs are positively identified as human teratogens, while the vast majority of medications approved by the FDA are categorized as undetermined teratogenic risk.
- The pharmacokinetic processes of absorption, distribution, metabolism, and elimination are immature in a neonate and develop at varying rates after birth. The immaturity is more pronounced and the development slower in preterm neonates.
- Neonates often have a larger volume of distribution but delayed excretion compared to older children or adults, resulting in the need for higher mg/kg doses of medications with potentially longer dosing intervals.
- Dosing regimens for neonates over the first 3–4 weeks of life are dynamic and require adjustment based on maturational changes in hepatic metabolism and renal elimination.

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44

Principles of Drug Use During Lactation

JACQUELYN D. MCCLARY

It is not disputed that breastfeeding has many benefits for both mother and baby and is the optimal nutrition for infants. With an increase in education and support of breastfeeding mothers throughout the United States, the rate of breastfeeding is on the rise. The Centers for Disease Control and Prevention report an increase of breastfeeding initiation from 79% in 2011 to 81.1% in 2013, with a steady annual increase since 2008.[5] As the incidence rises, there are more situations in which lactating women are exposed to various medications and more questions regarding the safety of these medications to the infant. Almost all medications enter the breast milk, but the amount in breast milk, and more importantly the amount absorbed by the infant, is rarely well defined. Despite this lack of information, most drugs are considered safe while breastfeeding. In the absence of specific details for a particular drug's passage into breast milk, the clinician can evaluate the physicochemical characteristics of the drug as well as the patient characteristics to determine the appropriateness of breastfeeding while the mother is taking the medication.

Passage of Exogenous Compounds From Maternal Blood to Milk

In general, drugs enter breast milk by passive diffusion. The presence and concentration of compounds in breast milk depend on a number of important factors, including the drug's molecular weight, degree of ionization, protein binding in blood, lipid solubility, and specific uptake by mammary tissue, as well as the amount and composition of the milk. The constituents of breast milk vary relative to the postpartum period and could influence drug distribution and accumulation within breast milk, depending on the drug's physiochemical characteristics. Drug characteristics that minimize the risk of transfer into breast milk are shown in Box 44.1.

Small compounds with molecular weights of less than about 200 daltons appear freely in breast milk and are presumed to have passed through pores in the mammary alveolar cell. Large compounds such as insulin or heparin, or those that are protein bound, do not enter the milk. Intermediate-sized compounds must penetrate the lipoprotein cell membrane by diffusion or active transport. Drugs or other chemicals that are very lipid soluble readily cross the alveolar cell, and because breast milk contains a considerable amount of lipid, these compounds are trapped in the milk. In general, drugs that are not ionized at blood pH traverse the alveolar cell membrane with greater ease than highly ionized compounds. Therefore, weak acids, which are more likely to be ionized at the plasma pH of 7.4, are less likely to enter breast milk, whereas weak bases pass into breast milk more readily. Because breast milk pH is 7 or slightly less, once a weak base crosses into breast milk, it may become more ionized and trapped.

A number of important variables specific for the type of drug, age, and time after delivery or disease influence a drug's ability to penetrate into breast milk. The interrelationships between these and other variables yet to be identified are complex, making it very difficult to predict the actual amount of drug distribution into the milk. Although many investigators and clinicians have attempted to collapse the many important characteristics into one simple surrogate marker of drug penetration into breast milk—the ratio of milk to plasma protein (M/P ratio)—this parameter is overly simplistic and often misrepresents the true nature of drug distribution into breast milk. The M/P ratio is defined as the ratio of the drug concentration in breast milk to the drug concentration in maternal plasma at a simultaneous point in time after maternal drug administration. A low M/P ratio (<1) is supposed to indicate no accumulation of drug in the mother's milk.[3] However, the M/P ratio is based on the assumption that the drug concentrations in maternal blood and milk are constant and in equilibrium at the time of sampling, which is most often not true. Based on its limitations, the M/P ratio should be used with caution, if at all, as a means of quantitating drug distribution in breast milk and infant exposure.

Alternatively, the relative infant dose (RID) can be used as a more accurate tool to estimate infant exposure to a drug if there are data available on the concentration of drug in the breast milk and volume of milk ingested by the infant

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Abstract

Almost all medications enter breast milk, but the amount that an infant is exposed to through breastfeeding is rarely well defined. Physicochemical characteristics of the drug can be used to determine the appropriateness of breastfeeding while a mother is taking a medication. With few exceptions, each therapeutic class of medications includes at least one option that can be safely taken while breastfeeding. Commonly prescribed medications such as antibiotics and antidepressants are almost all considered compatible with breastfeeding. For antihypertensive and pain medications, there are some drugs that should be avoided; however, there are multiple alternative options that are considered safe within each category. Regardless of the medication being taken, the lowest effective dose should always be prescribed, monotherapy should be used when possible, and the nursing infant should be monitored for any side effects associated with the medication.

Keywords

medication
lactation
breastfeeding
drug
breast milk

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• BOX 44.1 Drug Characteristics That Minimize Transfer into Breast Milk

- Molecular weight >200 daltons
- Weakly acidic
- High degree of protein binding
- Water soluble

(often estimated at 150 mL/kg/day). The RID can then be calculated by dividing the infant dose measured in the breast milk (mg/kg per day) by the maternal dose (mg/kg per day) and expressing it as a percentage. It has been suggested that a RID greater than 10% may be of concern; however, every drug is different and depending on the specific patient and drug characteristics, a RID greater than 10% may be acceptable.[15]

Delivery of Compounds to and Disposition by the Infant

After ingestion of a drug via breast milk, the drug must either act locally in the infant's gut or be absorbed by the infant into systemic circulation to produce an effect. Generally, if a drug is not orally bioavailable (e.g., vancomycin), the infant will not absorb the medication, even if it is present in breast milk. However, it is possible that the bowel of a very young infant may permit the absorption of large molecules that are normally excluded. Another potential barrier to absorption is found in milk proteins that bind certain drugs and impede absorption. Unfortunately, for most drugs, the extent of oral absorption by the breastfed infant is unknown. If absorption does occur, the infant's handling of the medication is often unclear and changes with postnatal age. Ultimately, close monitoring of the infant for adverse effects associated with the maternal drug therapy is required.

Compounds in Breast Milk

Antibiotics

Fortunately, most antimicrobial agents in breast milk appear to be safe for nursing infants. Some antibiotics, particularly those with broad antimicrobial spectra, may change the infant's intestinal flora and cause diarrhea or thrush, but this quickly resolves upon discontinuation of the antibiotic and is not considered a contraindication to breastfeeding. Two antibiotic classes that are sometimes considered contraindicated in breastfeeding include sulfonamides and tetracyclines.

Sulfonamide derivatives are sometimes avoided during lactation, because they have the potential to displace bilirubin from albumin. The amounts present in breast milk, combined with the actual bioavailable dose to the infant, suggest that maternal sulfonamide administration is acceptable during breastfeeding except in neonates at high risk for hyperbilirubinemia, including extremely premature neonates or those with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Tetracyclines in breast milk purportedly have the potential to cause dental staining, and many sources have suggested that women taking tetracyclines avoid breastfeeding. Closer examination of these suggestions against breastfeeding during tetracycline therapy appear to be based on theoretical grounds rather than any supporting evidence. Moreover, the bioavailability of tetracyclines under the conditions of breastfeeding suggests that the maternal administration of tetracycline and its analogues is safe and without complications in infants.[6]

Overall, maternally administered antibiotics are considered safe for the breastfed infant, and only in rare instances should mothers requiring antibiotic therapy be recommended to discontinue breastfeeding their infant.

Anticoagulants

The use of anticoagulants may be critical to health of a mother with a history of pulmonary embolism, venous thrombosis, or other clotting disorder. Both parenteral and oral anticoagulant options are available that are compatible with breastfeeding. Heparin has a molecular weight of about 20,000 daltons and does not enter breast milk. Newer synthetic heparin has a much lower molecular weight (3000 daltons) but is still too large for passage into breast milk. Additionally, heparins are unstable in gastric contents, so any small amount that might pass into breast milk would be quickly degraded. Oral anticoagulants of the indanedione group, as well as bishydroxycoumarin and ethyl biscoumacetate, are found in milk and have been associated with infant coagulopathies. It is unknown if newer agents, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban, transfer into breast milk, but each of these agents has at least one physicochemical property that favors transfer.[1,7,14] Therefore, warfarin is considered the oral drug of choice, as it is a weak acid with a high degree of protein binding and it is undetectable in breast milk.

Anticonvulsants

Anticonvulsants are a common concern for breastfeeding mothers, whether being used for treatment of a seizure disorder or as a mood stabilizer. Valproic acid, lamotrigine, and topiramate are a few of the commonly used anticonvulsants. Valproic acid is known to have teratogenic potential when taken during pregnancy but is thought to be compatible with breastfeeding because of the low levels of drug transferred to milk (RID = 1.4%-1.7%).[15] Lamotrigine and topiramate, on the other hand, are more readily transferred into breast milk, with a RID of 9.2%-18.3% and 3%-23%, respectively.[15] Despite the fact that these drugs can be detected at significant levels in the plasma of breastfeeding infants, there are minimal reports of adverse effects in the infants. Breastfeeding while taking any of the above anticonvulsants should be encouraged, with appropriate

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monitoring of the infant for any signs of toxicity (e.g., apnea, sedation).

Other anticonvulsants that are less commonly used include phenytoin, phenobarbital, and lithium. Phenytoin is found in small amounts in breast milk and is considered compatible with breastfeeding. Barbiturates, including phenobarbital, appear to be safe. However, phenobarbital is metabolized much more slowly in neonates than adults; it is possible that the drug may accumulate in the breastfed infants of phenobarbital-treated mothers. These infants should be monitored for lethargy and poor weight gain.

Lithium has been contraindicated during lactation because of a few case reports that described significant cardiovascular and central nervous system signs in two infants. It would appear from a closer evaluation of these cases that transplacental exposure cannot be ruled out, and maternal drug interaction may have predisposed these infants to a level of lithium toxicity beyond what would have occurred from breastfeeding alone. As a result, breastfeeding mothers who require lithium therapy should be permitted to continue to breastfeed, with close infant monitoring that could include the measurement of blood lithium concentrations in the infant 1-2 weeks after initiating breastfeeding, renal function tests, and thyroid function tests. Consideration should be given to an alternative anticonvulsant if an adjustment in the mother's therapy is not likely to compromise her health.

Antidepressants and Antipsychotics

Postpartum depression affects up to 20% of women and left untreated can be detrimental to both mother and baby.[13] Unfortunately, breastfeeding mothers often discontinue therapy to avoid perceived harm to the infant, despite the fact that there are many antidepressants that are considered safe while breastfeeding. Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are the most common antidepressants used in breastfeeding mothers. Sertraline is the most well-studied SSRI; it produces very low or undetectable milk and infant plasma levels.[15] Fluoxetine, which has a long half-life and active metabolite, is also well studied. There are reports of significant fluoxetine plasma levels in infants but no adverse effects have been identified.[15] In general, SSRIs and SNRIs are considered compatible with breastfeeding, and few if any adverse effects in the infant have been reported. Sertraline is often the drug of choice for nursing mothers; however, if another SSRI/SNRI is more effective or better tolerated by both mother and baby, it is an acceptable alternative.

The exacerbation of psychotic disorders is also very common in the postpartum period and is often treated with a newer class of drugs, the atypical antipsychotics. Quetiapine, risperidone, and olanzapine are three drugs within this class that have some data available from breastfeeding mothers/infants. For each of these medications, there are few reported adverse effects in the breastfeeding infant, and the RID is low for olanzapine (1.2%) and quetiapine (0.07%-0.1%).[10] For risperidone, the RID is widely variable (2.8%-9.1%) and dependent on maternal dose, so it is recommended that the lowest effective dose be used and that the infant be monitored closely for signs of toxicity such as somnolence or lethargy.[10]

Antihypertensives

There are multiple drug classes available to treat hypertension in breastfeeding women. Within each class, some drugs have more information about compatibility with breastfeeding than others, but there are multiple safe options for the treatment of hypertension in a breastfeeding mother. β-blockers are often one of the first drug classes used in treating hypertension, and most are compatible with breastfeeding. Metoprolol, propranolol, and labetalol have been used in breastfeeding mothers with no adverse effects experienced in the exposed infants. Other β-blockers (atenolol, acebutolol) have been associated with cyanosis, hypotension, and bradycardia and should not be used in breastfeeding mothers.[15]

Angiotensin-converting enzyme inhibitors (ACEIs) are also a mainstay in the treatment of hypertension. Two drugs in this class have data to support their use while breastfeeding. Captopril and enalapril have a RID of 0.002% and 0.175%, respectively, and neither has been associated with adverse effects in exposed infants.[15] A related class of drugs, angiotensin receptor blockers (ARBs), is often substituted for ACEIs if a patient experiences side effects from the ACEI. In the case of the breastfeeding mother, there are far more data and experience with ACEIs, so ARBs should be avoided if possible.

Calcium channel blockers may also be used to treat hypertension, typically as adjunct therapy, and have been used successfully in breastfeeding mothers without causing harm to the infant. There are studies evaluating the use of nifedipine, verapamil, and diltiazem, and all are considered compatible with breastfeeding.

Finally, diuretics are often part of a multidrug regimen to treat hypertension, and these are also likely to be compatible with breastfeeding. Theoretically, if a nursing woman became dehydrated because of diuretic use, milk production could be impacted, but this is controversial, and there is no contraindication to diuretic use and breastfeeding.

Oral Contraceptives

A common problem confronting health care providers is the maternal concern over the use of oral contraceptives during lactation. Contraceptives with a high concentration of estrogen and progestin may depress lactation, especially if they are begun soon after parturition. It is best to start treatment about 4 weeks after delivery, ensuring that lactation is already well established, and to use the lowest dosage possible. Previously, it was believed that progesterone-only contraception would decrease the risk of lactation suppression, but more recent data suggest no difference between progesterone-only or combined oral contraceptives with regard to successful breastfeeding and milk production.[9] Thus, any of the contemporary oral contraceptives, which

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contain low maternal hormone doses, are considered compatible with breastfeeding.

Pain Medications

Pain medications are frequently needed while breastfeeding, especially after cesarean section. Depending on the severity of pain, the medications used range from acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) to opioids. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, are acidic drugs with low lipid solubility and high protein binding; thus, transfer into breast milk is not favored.[4] In a case report of ibuprofen use while breastfeeding, the RID was 0.0008%, reflective of the physicochemical properties of the drug.[17] For acetaminophen, the RID is higher (8.81%) but still likely to be safe, considering it is commonly used in infants for the treatment of pain and fever.

Opioids are reserved for more severe pain but are often necessary after surgery (e.g., cesarean section) or injury. The concern for the breastfed infant with any maternal opioid use is most often sedation or lethargy. The choice of opioid, use of the lowest effective dose, and a limited duration of therapy can decrease this risk. Morphine and hydrocodone are preferred agents over codeine, oxycodone, and tramadol. Morphine has poor oral bioavailability in infants, along with a RID of 9.1%. Hydrocodone efficacy is largely a result of its active metabolite, hydromorphone, which also has a relatively low RID (0.2%-9%).[15] Codeine and oxycodone are not as predictable as morphine or hydrocodone and are associated with higher rates of infant sedation (16.7% and 20.1%, respectively).[15] Codeine, oxycodone, and tramadol are metabolized by CYP2D6 in an unpredictable manner to active metabolites. This is thought to be the underlying cause of the death of a breastfed infant associated with maternal codeine use. An increased rate of maternal metabolism of codeine to morphine likely played an important role in this scenario.[11] To avoid recurrence of this event, the Food and Drug Administration (FDA) has issued a warning against breastfeeding while taking tramadol or codeine and has required changes to the labeling of these medications.[16]

Reflux Medications

Medications for gastroesophageal reflux are readily available as over-the-counter products and, therefore, are likely to be commonly used during lactation. There are two drug classes, histamine-2 (H2) blockers and proton pump inhibitors (PPIs), that should be evaluated for safety while breastfeeding. The H2 blockers include famotidine, ranitidine, and cimetidine. Famotidine and ranitidine have relatively low RIDs (1.9% and 1.3%-4.6%, respectively) and are considered compatible with breastfeeding.[15] Cimetidine may be actively transported into breast milk, resulting in a much higher RID (up to 32.6%).[15] Therefore, cimetidine should be avoided during lactation given the safer alternatives. Proton pump inhibitors (e.g., omeprazole, lansoprazole) are also a safer alternative to cimetidine, as there is minimal drug transfer into breast milk and any drug that is present is not well absorbed by the infant.

Nontherapeutic Agents in Breast Milk

Caffeine

One hour after the ingestion of an average cup of coffee, a peak breast milk caffeine level of about 1.5 mg/mL is reached. Caffeine levels in breast milk are about half the corresponding maternal blood level. Although the daily amount of caffeine consumed by a nursing infant might be small, the long half-life of caffeine could cause symptoms such as wakefulness or jitteriness and might be considered in the evaluation of infants whose mothers consistently consume large quantities of caffeine-containing products (e.g., cola, diet aids, coffee, tea).

Nicotine

Nicotine from smoking or replacement therapy (e.g., patch) is transferred into breast milk along with its active metabolites. If the mother is smoking, the toxic additives that are part of the cigarette and the secondhand smoke are also transferred to the infant. In a study of smoking cessation using nicotine patches in breastfeeding women, the dose of nicotine transferred to the infant steadily decreased as the nicotine patch dose was reduced.[15] Breastfeeding women should be encouraged to use nicotine replacement therapy to limit infant exposure to nicotine as well as other toxins in cigarettes.

Marijuana

Tetrahydrocannabinol (THC), the active ingredient in marijuana, is transferred into breast milk, but the amount varies depending on the frequency of the mother's use. Similar to nicotine, the toxic additives and secondhand smoke are significant concerns, as marijuana smoke contains an additional 150 compounds.[8] If absorbed by the infant, THC would be expected to rapidly distribute into the brain and theoretically impact the infant's brain development, but this has not been well studied. For these reasons, nursing mothers should be counseled to avoid THC.

Ethanol

Ethanol, a small molecule, is freely diffused into breast milk and achieves levels equivalent to those in blood. Infrequent and moderate amounts of alcohol ingestion are not a contraindication to breastfeeding, but care should be taken to avoid breastfeeding at times when the concentration of alcohol in the breast milk will likely be high. For every drink consumed, the mother should avoid breastfeeding for at least 2 hours.

Narcotics

Breastfeeding while abusing narcotics, such as heroin, oxycodone, or codeine, should not be promoted. Heroin readily transfers into breast milk; however, the extent of exposure to the infant can vary widely depending on the frequency and amount the mother uses. Drug purity can also impact infant exposure, not only to heroin but to other compounds that may be mixed with the heroin. Similar rationale is applied to the abuse of prescription narcotics

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(e.g., oxycodone, codeine); the varying dose and frequency of maternal use put the infant at risk for side effects from these drugs (see Pain Medications). In the setting of illicit drug use, the risks of unpredictable drug exposure outweigh the benefits of breastfeeding.

Conversely, methadone and buprenorphine, an opioid and partial opioid agonist respectively, are frequently used in breastfeeding mothers as part of an addiction program, and the infant has most likely been exposed to the drug in utero as well. These medications do transfer into breast milk, with a RID of about 2%-3% for methadone and <1% for buprenorphine.[2,12] The use of these medications while breastfeeding may actually alleviate some of the withdrawal symptoms that these infants often exhibit, and breastfeeding while on methadone or buprenorphine as part of a treatment program should be encouraged.

Conclusions Concerning Breastfeeding and Maternal Drug Therapy

As with the fetus in utero, the nursing infant is exposed to nearly everything entering the body of its mother. Clinicians are often faced with difficult decisions when counseling a mother regarding the safety of a medication while breastfeeding. There are rarely clear data that define a drug as safe or harmful to a breastfed infant. In those gray situations, the following simple guidelines may be helpful:

1. Therapy should be with single agents if possible. In the case of long-term therapy, consideration should be given to monitoring the infant's activity and growth.
2. The physiochemical characteristics of multiple drugs within a given therapeutic class should be evaluated. Based on these properties, the drug least likely to pass into breast milk or be absorbed by the infant should be prescribed.
3. Attempt to minimize the dosage to the infant. Use the lowest effective dose, and counsel mothers to avoid nursing at maternal peak plasma levels.
4. Signs and symptoms in a nursing child should be correlated with maternal drug ingestion.

Key Points

- Most drugs are considered safe while breastfeeding.
- The relative infant dose (RID) derived from drug concentration in breast milk and volume of milk ingested can be used to estimate infant exposure to a drug.
- The physicochemical characteristics of different medications within a drug class should be used to guide drug selection.
- Illicit drug use is a contraindication to breastfeeding; however, mothers who demonstrate compliance with a treatment program should be encouraged to breastfeed.

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45

Pharmacokinetics in Neonatal Medicine

KELLY C. WADE

The safe and effective use of medications in the newborn intensive care unit (NICU) requires an understanding of the principles of pharmacokinetics (PK) and pharmacodynamics (PD) that guide individual dosing and aim to provide drug exposures designed for the best clinical outcomes and lowest risk of toxicity. The PK of drugs in neonates is unique and cannot be extrapolated from older children or adults (for excellent comprehensive reviews see references 1, 6, 14, 20). Biological variation among infants in the NICU is extensive: infant's weight varies at least 10-fold (0.5-5 kg), gestational age at birth varies between 22-42 weeks, and postnatal age ranges from 1-150 days. Infants are undergoing dramatic changes in body size, body composition, cardiac output and perfusion, renal and hepatic function, and ontogeny (age-related maturation) of drug metabolizing enzymes. This means that infants in the NICU will exhibit wide variations in drug exposures, and care providers often need to consider dose adjustments for these differences. Basic knowledge of PK and PD drives rational dosing across a broad spectrum of prematurity, clinical conditions, and drug classes. The interplay of PK and PD relationships allows clinicians to target specific drug concentrations that have been associated with therapeutic efficacy (Fig. 45.1).

Anti-infective drugs are the most common class of drugs used in the NICU and provide a useful context to understand basic principles of PK and PD (see Fig. 45.1). The goals of antimicrobial therapy are simple: eradicate the pathogen, minimize toxicity, and prevent emergence of resistant organisms.[3,8] The PK of a drug explains the dose-concentration relationship, whereas the PD of a drug explains the relationship between the concentration of the drug in the body and the therapeutic or toxic response. With basic PK knowledge, clinicians can predict the concentration of drug in the plasma at a given time after a given dose. If a specific drug plasma concentration is known, then dose modification can be determined to provide the desired drug concentration in that infant.

This chapter reviews basic PK and PD principles and the mathematical formulas that enable clinicians to predict an infant's dose-exposure relationship.[1,14,19,20] Both drug- and infant-specific factors can be used to explain the large variation in drug exposures that are expected among infants in the NICU. Optimal dosing in neonates requires that care providers understand the basic principles of the PK and the developmental and physiologic basis for the variation in drug exposures among term and preterm infants. Examples illustrate the use of simple PK calculations to predict differences in drug exposures among very preterm and term neonates.

Drug Disposition Explains Drug Exposure Over Time: Absorption, Distribution, Metabolism, and Excretion

Drug disposition describes how drugs enter and exit the body and explains how concentrations in the body change over time (Figs. 45.2 and 45.3). Four basic processes explain the disposition of drugs through the body: absorption, distribution, metabolism, and excretion. These processes are affected by chemical properties of the drug, patient-specific physiology, body composition, developmental maturation, and pathophysiology relating to disease state. Applying PK principles in neonates requires an understanding of drug disposition and the impact of both developmental pharmacology and patient-specific physiology.[1,6,14,20]

Drug Absorption and Route of Drug Administration

Absorption specifically refers to the process of drug transfer from its site of administration to the bloodstream (see Fig. 45.2). Drugs typically enter the body via intravenous (IV), enteral (per oral, PO), intramuscular, intrapulmonary, subcutaneous, or percutaneous routes and are then absorbed into the circulation as free drug. The route of administration affects the concentration of the drug over time (see Fig. 45.3). Bioavailability of a drug refers to the fraction of the administered dose that reaches the circulation but does not

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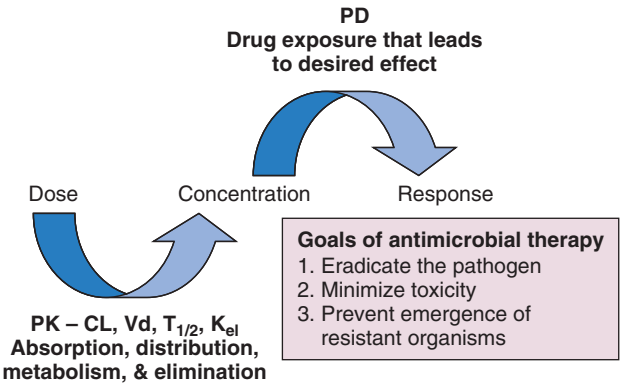
Abstract

The safe and effective use of medications in the newborn intensive care unit (NICU) requires an understanding of the principles of pharmacokinetics (PK) and pharmacodynamics (PD) that guide individual dosing and aim to provide drug exposures designed for the best clinical outcomes and lowest risk of toxicity. The PK of drugs in neonates is unique and cannot be extrapolated from older children or adults. In the NICU, infants are undergoing dramatic changes in body size, body composition, cardiac output and perfusion, renal and hepatic function, and ontogeny (age-related maturation) of drug metabolizing enzymes. This means that infants in the NICU will exhibit wide variations in drug exposures, and care providers often need to consider dose adjustments for these differences. Basic knowledge of PK and PD drives rational dosing across a broad spectrum of prematurity, clinical conditions, and drug classes. This chapter reviews basic PK and PD principles that explain rational dosing across a broad spectrum of prematurity, clinical conditions, and drug classes. Clinicians will understand the drug- and infant-specific factors that explain the variation in PK and drug exposures that are expected among infants in the NICU. Clinicians will be able to apply basic mathematical formulas to derive infant-specific PK parameters, predict an infant's drug exposure after a given dose, and modify the dose as needed to achieve the desired therapeutic exposure.

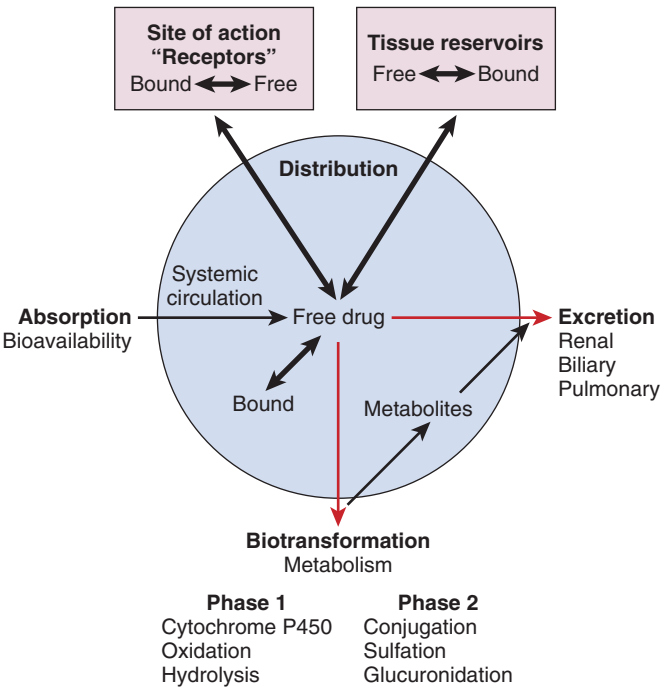
Keywords

pharmacokinetics
pharmacodynamics
neonatal pharmacology
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therapeutic drug exposure

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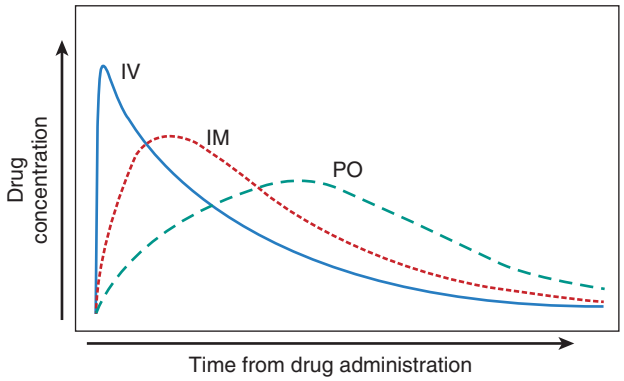
• **Fig. 45.1** PK/PD principles guide rational drug dosing by connecting the relationships between dose and therapeutic response. Use pharmacokinetic (PK) knowledge to determine what dose will achieve the desired concentration that has a pharmacodynamic (PD) association with the best therapeutic response and limited toxicity. CL, Clearance; K_{el}, elimination rate constant; $T_{½}$, half-life.



• **Fig. 45.2** Picture depicting drug disposition. Many interrelationships exist between the phases of absorption, distribution, metabolism, and excretion as a drug moves through the body, to and from the site of action and exits the body.

consider the rate of drug absorption. Bioavailability is determined by comparing the respective area under the plasma concentration curves (AUC) after a non-IV form of administration with the AUC after an IV administration. IV administration of a drug provides the most consistent, reliable absorption into the circulation and, therefore, defines a bioavailability of 100%.

For enteral medications, the bioavailability depends on biochemical properties of the drug, the formulation, and patient-specific factors such as gastric acidity, gastric emptying time, and intestinal absorption and transit time. Bioavailability is reduced by incomplete absorption and



• **Fig. 45.3** Plot of drug concentration over time after a single dose comparing different routes of administration. Drug concentrations represent the disposition of drug through the body. Route of administration changes the shape of the drug concentration. IV, Intravenous; IM, intramuscular; PO, per oral.

by first-pass metabolism as the drug enters the portal circulation where it can be metabolized in the liver before reaching the systemic circulation. Drugs administered enterally enter the circulation more slowly than IV bolus-administered drugs and therefore achieve a lower maximum drug concentration (C_{max}) later after administration (see Fig. 45.3). Drug-specific dose adjustment is needed when converting IV to enteral formulations to achieve consistent exposure.

Neonates have unique absorption properties that impact drug concentrations after enteral administration.[1,6,14,20] Reduced gastric acidity can increase absorption of acid-labile molecules (penicillin) and decrease absorption of weak organic acids (phenytoin, phenobarbital). Slower gastric emptying time and intestinal motility can change the time to absorb the drug and amount of drug absorbed. Enteral absorption often improves as infants become older. Absorption of enteral medications is often decreased in infants with GI pathology or changes in perfusion to the GI system. Anticipating differences in bioavailability helps guide dose adjustment when converting between IV and PO route of administration.

Bioavailability after intramuscular (IM) and percutaneous (topical) administration can be affected by tissue mass, perfusion, drug permeability, and surface area. In neonates, reduced muscle perfusion and contractility can limit absorption after IM administration.[1,14] When drugs are applied topically, the percutaneous absorption of the drug is directly related to the degree of skin hydration and relative surface area and inversely related to the thickness of the stratum corneum. Percutaneous application of medications in premature infants can lead to large systemic drug exposures given their larger surface area and thin stratum corneum.

Drug Distribution and Volume of Distribution

Distribution refers to the process by which drugs move from the central circulations through various compartments and

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peripheral tissues in the body according to physiochemical properties such as the molecular size, ionization constant, and relative hydrophilic/lipophilic properties (see Fig. 45.2). The central compartment typically refers to the vascular space with rapid distribution to the heart, kidney, and liver. From the central compartment, drugs distribute at a slower rate to the peripheral compartment(s) that can include brain, fat, and muscle. From the peripheral tissues, drugs traverse back into the central compartment to be eliminated. Drug distribution depends on drug-specific factors (molecular size, ionization constant, relative hydrophilic/lipophilic properties, protein binding) and infant-specific factors (body composition, membrane/tissue permeability, cardiac output). Distribution is an important concept to understanding PK, because it relates to the maximum drug concentration after a given dose and the volume of distribution (Vd). The kinetics of drug transfer to and from the peripheral and central compartments also affects the kinetics of drug excretion and the shape of the drug concentration curve over time.

The apparent volume of distribution (Vd) for a drug is defined as the hypothetical fluid volume through which the drug is dispersed. It is calculated by dividing the total amount of drug given by the concentration of drug in plasma (Table 45.1, Eq. [3]). Vd does not refer to any physiologic compartment nor the blood volume. Instead, Vd relates to the hypothetical volume of the total compartment that explains the concentration of the drug achieved after administering a given amount.

Understanding the factors that contribute to variation in Vd is helpful in determining the optimal dose of a medication to achieve a desired peak concentration (C_{max}) in a specific patient. An infant with a higher Vd will have a lower peak concentration of drug in circulation. High Vd can

TABLE 45.1 Simplified Mathematical Equations for Basic Pharmacokinetics (PK) Analysis: Intravenous Drugs That Follow First-Order Kinetics

PK Parameter	Abbreviation	Units	[#] Equation
Drug concentration	$[C_{max}]$ at end infusion $[C_t]$ at time t	mg/L	[1] $[C_{max}] = \frac{\text{Dose mg}}{\text{kg}} \div \text{Vd}\left(\frac{\text{L}}{\text{kg}}\right)$ max concentration after injection [2] $[C_t] = [C_{max}] \times (e^{-Kt})$ concentration at time t
Volume of distribution	Vd	L/kg	[3a] Vd = amount drug given (mg/kg) ÷ (plasma [drug] mg/L) [3b] $Vd = CL \div K_{el}$
Elimination rate constant	K_{el}	hr^{-1}	[4a] $K_{el} = (\text{Ln}[C_{t1}] - \text{Ln}[C_{t2}]) \div \Delta\text{tor} = \text{Ln}[C_{t1}/C_{t2}]/\Delta t$ *where $[C_{t1}]$ = conc at Time 1 or Time 2 and Δt is difference in hours between t^2-t^1* [4b] $K_{el} = CL \div Vd$ [4c] $K_{el} = 0.693 \div T_{1/2}$
Half-life	$T_{1/2}$	hr	[5a] $T_{1/2} = 0.693 \div K_{el}$ (note that 0.693 = Ln2, time for exponential two fold decline) [5b] $T_{1/2} = (0.693 \times Vd) \div CL$
Clearance	CL	L/hr * kg	[6a] $CL = K_{el} \times Vd$ [6b] $CL = (0.693 \times Vd) \div T_{1/2}$ [6c] $CL = (\text{Dose}/\tau) \div \text{average steady-state [drug]}_{ss}$ where τ is dose interval in hours
Calculations After Single-Dose Infusions Accounting for Drug Elimination During Infusion			
Drug concentration at time t	C_t t_{inf} = infusion time (hr) t is any time after infusion end	mg/L	[7] $C_{max} = (R_0/CL) \times (1 - e^{-Ktinf})$ where R_0 = (dose/infusion time) in units (mg/kg * hr) [8] $C_t = (R_0/CL) \times (1 - e^{-Ktinf}) \times e^{-Kt}$ *Because CL = Vd × k then rearrange [8] to solve for Vd or dose to achieve $[C_t]$ if $[C_t]$ and t_{inf} are known* [9] $Vd = (R_0/[C_t \times K]) \times (1 - e^{-Ktinf}) \times e^{-Kt}$ [10] $\text{Dose} = (Vd \times T_{inf} \times C_t \times K) \div ([1 - e^{-Ktinf}] \times e^{-Kt})$
Calculations After (*n*) Multiple Doses After Bolus Injection or Short Infusion Time Models			
Drug concentration after multiple doses (*n*)	C_{max} (*n*) *Max C after n doses* C_t (n) *C at time t after infusion after n doses* C_t (ss) *C at time t after infusion at steady-state*	mg/L	*For a bolus injection* [11] $C_{max}(n) = (\text{Dose}/Vd) \times [(1 - e^{-nK\tau}) \div (1 - e^{-K\tau})]$ (n = doses, τ = dose interval) [12] $C_t(n) = (\text{Dose}/Vd) \times [(1 - e^{-nK\tau}) \div (1 - e^{-K\tau})] \times e^{-Kt}$ [13] $C_t(ss) = (\text{Dose}/Vd) \times [1/(1 - e^{-K\tau})] \times e^{-Kt}$ (as $n = \infty$ then $[1 - e^{-nK\tau}] = 1$) *For a short infusion time (t_{inf})* [14] $C_t(n) = (R_0/CL) \times (1 - e^{-Ktinf}) \times [(1 - e^{-nK\tau})/(1 - e^{-K\tau})] \times e^{-Kt}$ [15] $C_t(ss) = (R_0/CL) \times (1 - e^{-Ktinf}) \times [1/(1 - e^{-K\tau})] \times e^{-Kt}$

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indicate that the infant has an increase in total body water and extracellular fluid or that the drug has a wide distribution to peripheral tissues where it also might be sequestered. Gentamicin is a highly polar, hydrophilic molecule that distributes readily in extracellular fluid. Preterm infants have a high body water content and, therefore, require a higher dose of gentamicin to achieve the same peak concentration as a term infant.

Plasma protein binding can have significant effects on distribution. Drugs that exhibit high protein-binding capacity often have smaller Vd, because they bind to plasma proteins and are maintained in the circulation. Protein binding is also affected by availability of binding proteins, differences of binding capacity among different proteins, and increases in bilirubin or free fatty acids that can reduce drug protein binding. Protein binding also influences drug activity and elimination. Drugs that remain unbound to proteins ("free" drugs) are not only pharmacologically active but also more available for metabolism and/or elimination. Neonates typically have a higher proportion of "free drug" compared to total drug due to difference in binding proteins. Increased concentrations of bilirubin and free fatty acids can also compete with drugs for protein binding.

Drug Metabolism

Biotransformation is the process that typically converts lipophilic drug molecules into more polar, hydrophilic derivatives (see Fig. 45.2).[1,2,5,14] Polar metabolites are less likely to diffuse across cell membranes, less likely to distribute into peripheral tissues, and more likely to be eliminated from the body. These polar metabolites are typically inactive, although some metabolites exhibit partial activity. Drugs undergo metabolism or biotransformation to polar metabolites by endogenous enzymatic pathways in the liver or less often in the kidneys, intestinal mucosa, or lungs. Biotransformation can also produce active metabolites from prodrugs, as with theophylline or valganciclovir, or toxic metabolites, as in the case of acetaminophen metabolite *N*-acetyl-p-benzoquinone imine.

The metabolism of drugs is typically classified into two phases, nonsynthetic phase 1 and synthetic or conjugation phase 2.[1,2,5] Enzymes responsible for phase 1 metabolism convert a parent drug to a polar metabolite by introducing or unmasking a more polar site typically from oxidation, reduction, hydrolysis, or demethylation. The cytochrome P450 enzymes found in the liver and other tissues are primarily responsible for phase 1 oxidative metabolism. The most common cytochrome P450 drug-metabolizing enzymes are the CYP3A4 and CYP3A5 isoforms that together are responsible for metabolism of about 50% of medications. CYP isoforms are differentially expressed across human development; notably, CYP3A4 and 3A5 are only expressed after birth, whereas CYP3A7 is expressed in the fetus but expression declines after birth.[1,2,5]

Enzymes responsible for phase 2 metabolisms typically add an endogenous substance to the drug to form a highly polar metabolite using UDP-glucuronosyltransferase, glutathione S-transferase, N-acetyltransferase, or sulfotransferase.[2,5] Expression of phase 2 enzymes varies with both postnatal and postmenstrual age. At birth, sulfation is relatively developed; however, acetylation and glucuronidation are not well developed.[1,2,4,5,7] Glucuronidation is an important pathway for metabolism of morphine and acetaminophen. Morphine clearance is low in neonates, and different morphine-glucuronide metabolites predominate as glucuronidation pathways are underdeveloped at birth.[7] In neonates receiving acetaminophen, sulfation compensates for some of the glucuronidation deficiencies at birth such that sulfate-conjugated metabolites become the predominant excreted form.[4] Phase 2 drug metabolism varies greatly among preterm and term infants in the NICU. While glucuronidation capacity is low after birth, it subsequently increases with weight and postnatal age, resulting in changes in the metabolism of drugs among infants in the NICU.[1,4,5,7]

In general, neonates exhibit reduced hepatic metabolism that leads to increased drug concentrations, delay clearance, and longer half-life of medications that require biotransformation prior to excretion.[1,6,14] This delay in hepatic metabolism is due to decreases in production in many drug-metabolizing enzymes and limited uptake of drugs into hepatocytes. Metabolism may also be enhanced or impaired by environmental, genetic, and physiologic factors. Environmental influences include concomitant medications that may induce or inhibit drug-metabolizing enzymes; fluconazole inhibits CYP2C9 and CYP3A4, whereas phenobarbital induces CYP2B and CYP3A. The cytochrome P450 genes also exhibit wide genetic variation explained by single nucleotide polymorphisms that can diminish or enhance enzyme activity and significantly affect drug metabolism. For example, codeine is metabolized to morphine by CYP2D6; children whose CYP2D6 genotype leads to ultra-rapid metabolism of codeine can experience morphine toxicity.[15] Other factors affecting hepatic metabolism include uptake of drugs into hepatocytes, hepatic blood flow, body temperature, and disease states affecting perfusion.

Hepatic processes change rapidly over the first month so dose adjustment is often necessary with advancing postnatal age and maturation. Fentanyl is metabolized by hepatic CYP3A4 mediated N-de-alkalation to norfentanyl. Fentanyl elimination depends on liver blood flow, hepatic uptake, and CYP3A4 activity. Not surprisingly, fentanyl PK is highly variable in neonates, half-life ranges from 317-1266 minutes, and clearance increases threefold in the first 2 weeks of life.[12] In the first 48 hours after birth, fentanyl clearance increases 40% between infants born at 29 weeks' gestation compared to 41 weeks' gestation.[13] Understanding the differences in drug metabolism is important to understanding drug exposures in neonates; if neonates cannot effectively metabolize a drug, then higher concentration of active drug can potentiate effects of the drug or lead to toxicity. In the absence of specific drug-metabolizing enzymes,

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neonates may use alternative pathways and produce different metabolites with different activity or toxicity profiles. As drug-metabolizing capacity improves with age, higher doses are necessary to achieve desired concentration and response.

Drug Excretion

The excretion of active drugs or their metabolites is the process by which drugs are removed from the body. Drug excretion primarily occurs through the kidney and liver (see Fig. 45.2).[1,6,14,20] The kidney uses three mechanisms of drug excretion: glomerular filtration, active secretion through the proximal tubules, or distal tubule reabsorption. Glomerular filtration is very low in the first few days after birth and increases with hemodynamic changes and improved renal perfusion. Glomerular filtration also increases with gestational age; preterm infants typically have delayed renal clearance and longer half-life compared to term infants.[1,6,14,20] Disease states common in critically ill newborns such as neonatal encephalopathy, sepsis, acute kidney injury, and congenital heart disease all have been associated with reduced glomerular filtration and reduced drug excretion.

Tubular processes related to drug secretion and reabsorption are also important to renal elimination yet incompletely understood particularly in neonates. Drug secretion in the proximal tubules uses transport systems that typically eliminate organic anions. Secretion transporter proteins secrete drugs that are conjugated with glucuronic acid, glycine, and sulfate, such as penicillin or furosemide. Tubular secretion is less developed in newborns, thereby partially explaining the prolonged half-life of penicillin and furosemide.[1,14,20] Membrane transporters in the distal tubule can actively reabsorb drugs from the tubular lumen back into the systemic circulation. Tubular reabsorption is also delayed in neonates. Glomerular filtration rate typically improves with maturation faster than tubular mechanisms.

The liver uses four mechanisms of drug excretion: drug metabolism, excretion into bile, fecal elimination, and enterohepatic recirculation. Hepatic drug elimination can be dependent on hepatic blood flow and the metabolic capacity of liver. Patients with hepatic insufficiency have decreased elimination of drugs because of alterations in protein levels and protein binding, decreased liver blood flow, decreased uptake into hepatocytes, and altered hepatic enzymatic reaction. Patients with hepatic insufficiency, however, exhibit marked variability in drug metabolism and elimination. Infants with hepatic insufficiency typically benefit from lower doses of drugs that are eliminated by hepatic biotransformation and therapeutic drug monitoring when possible.

Regardless of excretion mechanism, the rate at which drugs are eliminated from the circulation is essential to the PK properties of drug clearance (CL), elimination rate constant (K_{el}), and half-life ($T_{½}$) (see formulas in Table 45.1, Eq. [4.6]). Drug CL is defined as the volume of blood from which all drug is removed per unit time; K_{el} represents the elimination rate constant, in other words, the slope of the drug concentration time curve on a semi-logarithmic plot; and $T_{½}$ is defined as the time it takes to clear half of the drug from plasma. Clearance can be affected by body weight, body surface area, cardiac output, hepatic function, renal function, plasma protein binding, concomitant medications, and variation in expression of drug metabolizing enzymes. At steady state, drug input is equal to drug elimination and, therefore, the dose given (dose/interval) is equal to the amount of drug removed (CL x drug concentration at steady state).

Drug Disposition Impacts PK Characteristics of Drugs in Neonates

Drug disposition (absorption, distribution, metabolism, and excretion) exhibits marked complexity and interpatient variability in neonates given the infant specific differences in body size and composition, maturation, postnatal age, organ function, and clinical disease (pathophysiology).[1,14,20] In neonates, the Vd is often higher for hydrophilic drugs leading to lower maximum drug concentration. Elimination (K_{el}) and CL are often slower due to reduced rates of biotransformation and renal elimination. The expected changes in drug metabolism with maturation can be highly variable and depend on both the drug, the metabolic pathways, and clinical disease. The PK characteristics of drugs, specifically Vd and CL, need to be studied across a broad range of prematurity, body compositions, postnatal ages, and disease states.

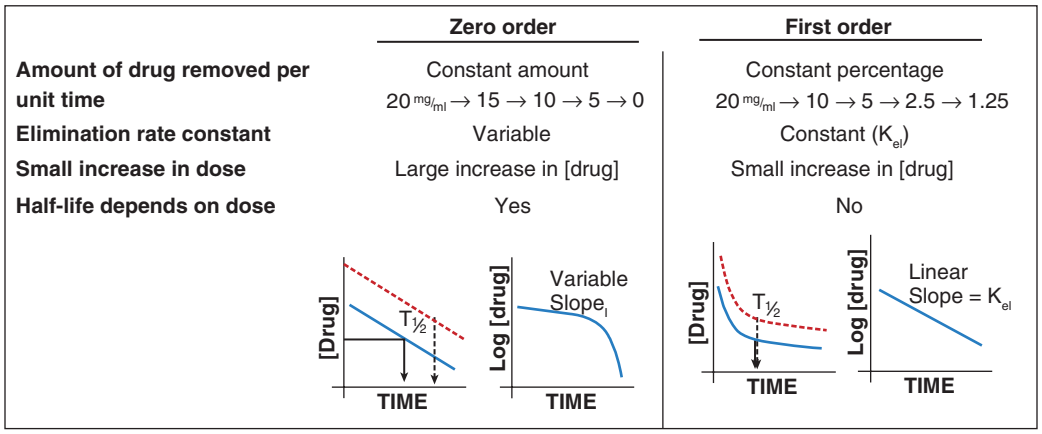
Pharmacokinetic Models Describe Concentration of Drug Over Time

Pharmacokinetic models describe the mathematical relationship between the dose of a medication administered to a patient and the drug concentration over time after a given dose (Figs. 45.4 and 45.5). These drug concentration-versus-time curves describe the disposition of drug through the body and are the basis for the mathematical models (kinetics of decay) that predict individual drug concentrations over time in specific patients. Drug concentrations are typically only available from the blood and serve as a surrogate for drug concentration at sites of action to correlate with pharmacologic response.

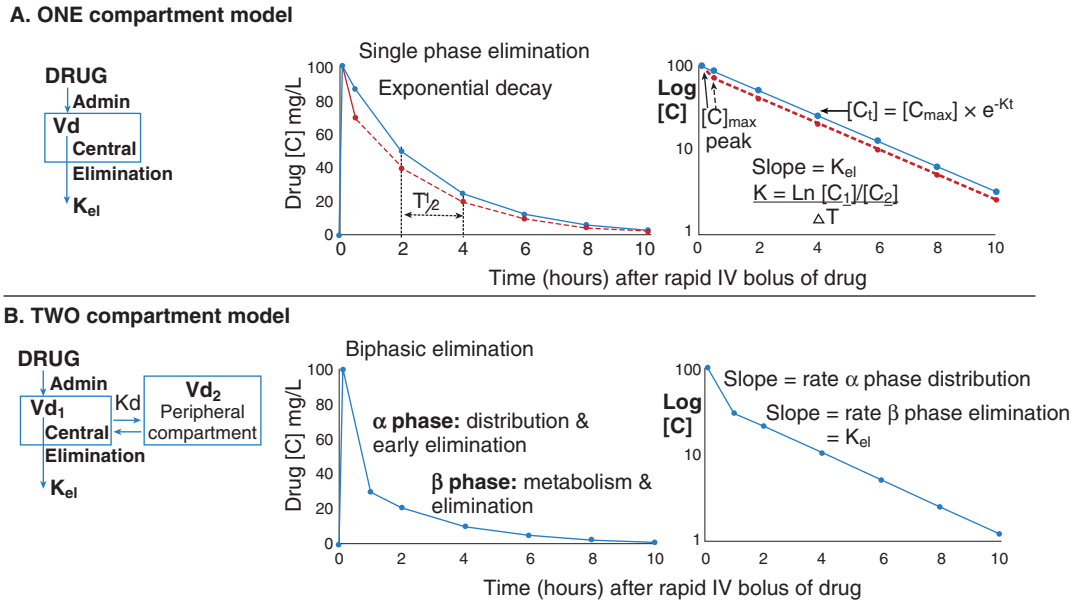
First-Order or Zero-Order Kinetics

The drug-concentration-over-time graphs in Fig. 45.4 depict the rate of elimination of a drug from the body on a linear and semi-logarithmic plot. Most drugs follow first-order kinetics, and mathematical equations in Table 45.1 are appropriate for drugs that are eliminated using properties of first-order kinetics.[19,20] For drugs that follow first-order kinetics, a constant percentage of drug is metabolized

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• **Fig. 45.4** Kinetic properties of drug elimination. Drugs that follow zero order kinetics have a constant decrease in concentration over time. Drugs that follow first-order kinetics have a constant percentage of decrease in concentration over time. This affects the shape of the concentration curve over time on both a linear and semi-logarithmic plot. K_{el}, Elimination rate constant; $T_{½}$, half-life.



• **Fig. 45.5** Drug concentration over time profile after single IV bolus of a drug that follows first-order kinetics. One (A) and two (B) compartment models are shown with associated graphs of drug concentrations plotted over time on a linear (*left*) and semi-logarithmic (*right*) scale. A one-compartment model is a simplified, hypothetical example of a drug with instantaneous distribution. In reality (dashed line in A with peak measured 30 minutes after end of infusion), drugs that have a rapid distribution phase and longer elimination phase can approximate one compartment model, allowing the use of simplified formulas to calculate PK parameters. [C_{max}] allows calculation of the Vd. The drug concentration at any time t ([C_t]) can be calculated using C_{max} and exponential decay factor (e^{-Kt}). C, Drug concentration; IV, intravenous; K_{el}, elimination rate constant; $T_{½}$, half-life; Vd, volume of distribution.

over time. Since the rate of elimination (K_{el}) is proportional to the amount of drug in the body, then a large amount of drug is removed per unit time initially with a small amount drug when concentrations are low. When drugs follow first-order kinetics, the concentration time curve shows an exponential decrease in the plasma drug concentration over time, and a linear decrease in drug concentration on logarithmic scale (see Fig. 45.5). The half-life of drug elimination is independent of drug dosage. Most drugs used in neonates follow first-order kinetic properties, including ampicillin, gentamicin, and phenobarbital.

Rarely, drugs may follow what is called zero-order kinetics or nonlinear, saturable kinetics. In drugs that follow zero-order kinetics, a constant amount of drug is metabolized or eliminated per unit of time regardless of concentration. The drug concentration follows a linear decrease of serum concentration over time (see Fig. 45.4). The elimination rate constant (K_{el}) is highly variable, with a

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smaller percentage of the drug eliminated at the beginning and a higher percentage of the residual drug eliminated toward the end, as demonstrated on log-transformed scale. The half-life of drugs whose elimination follows zero-order kinetics is dependent on drug dosage; larger doses yield a longer half-life. One example is ethanol. After ingesting alcohol, the liver's alcohol dehydrogenase quickly becomes saturated such that only a fixed amount can be metabolized over a given amount of time. There is a maximum yet constant amount that the body can eliminate at any given time. Small increases in dose can yield large increases in levels, because the amount of drug removed is constant and not proportional to the dose. Phenytoin is another zero-order kinetic drug, owing to saturable kinetics of the metabolizing enzymes.[9] Some drugs that typically follow first-order kinetics can follow zero-order kinetics when given at a very high dosage if enzymatic metabolism becomes saturated until the drug concentrations decrease to the point that enzymatic reactions are no longer saturated and then first-order kinetics can resume.

One- Versus Two-Compartment PK Models

The mathematical principles that describe the first-order kinetics of the dose-to-concentration relationship over time often use a compartmental approach to represent how a drug distributes through the body and the different rates of concentration changes in the body over time (see Fig. 45.5). In one-compartment models, a drug hypothetically distributes instantaneously in a homogeneous fashion into one compartment representing the entire body, and then the concentration declines linearly on logarithmic scale with one rate constant (K_{el}) as the drug is eliminated. This simplified, one-compartment hypothetical model is most appropriate for drugs that are administered by fast infusion, rapidly distribute throughout the central compartment (short alpha phase), and have a relatively long beta phase of elimination that is the primary determinant of drug concentration over time (shown in dashed curve in one compartment example in Fig. 45.5).

The two-compartment model is used to describe a drug with first-order kinetics that moves through the body in two distinct phases (see two-compartment model of Fig. 45.5). The alpha phase typically describes the drug's initial distribution throughout the circulation with a relatively rapid rate of concentration decline, followed by the slower beta phase that describes the drug elimination from the body, in which drug concentrations decline more slowly. Two different exponential rates of decay are demonstrated by the change of slope in the semi-logarithmic plot of a concentration-versus-time. The distribution and elimination properties of widely distributed drugs that enter and exit numerous compartments often require multicompartment models. The mathematical principles underlying multicompartment models are beyond the scope of this chapter.

Body Composition and Organ Function Affect Pharmacokinetics

In neonates, developmental changes in body composition, renal, and hepatic function, as well as pathophysiology with clinical disease, can affect PK characteristics of drugs, specifically Vd and CL.[1,14,20] Much of the variation in Vd across varying gestational ages and postnatal ages can be explained by differences in body composition. Neonates have higher proportions of extracellular and total body water compared to older infants and children. Premature infants have the highest amount of total body water. Therefore, hydrophilic drugs that distribute in water have larger Vd in newborns and even larger Vd in premature newborns. Infants with larger Vd will have lower peak drug concentrations unless they receive a higher dose. Infants with excess extracellular fluid, such as those with ascites or hydrops, can also have large Vd for hydrophilic drugs.

For lipophilic drugs, the body composition of fat can affect drug distribution into adipose tissue. If more drug is sequestered in fat, then plasma drug concentrations will be lower, Vd higher, and even the drug elimination characteristics (CL) can be affected since drug sequestered in fat is less available for elimination. Very preterm infants with minimal body fat will have smaller Vd and less storage of lipophilic drugs (e.g., benzodiazepines, fentanyl) in peripheral fat; whereas large-for-gestational-age infants born to diabetic mothers can sequester lipophilic drug in their peripheral tissue and, therefore, exhibit larger Vd and lower plasma drug concentration.

Infants with low protein stores will have greater proportion of free drug for a given total plasma drug concentration. The free drug component is the pharmacologically active moiety and may be more likely to distribute into peripheral tissues (larger Vd). The increased proportion of free or unbound drug can also contribute to faster elimination and shorter half-life since free unbound drug is more available for drug excretion mechanisms. However, the higher proportion of active, unbound drug relative to total drug concentration may explain toxicity at a similar total drug concentration. Neonates can also have a higher proportion of free drug compared to older infants due to endogenous competitors of protein binding, such as bilirubin or free fatty acids.

Age-dependent differences in drug binding in tissues can also affect distribution. Drugs can have extraordinarily large Vd if they are bound to proteins in the peripheral tissues. The disposition of these drugs through the body typically requires a two- or three-compartment model to account for the transfer of drug in and out of peripheral tissues (see Fig. 45.5). For example, digoxin has low plasma concentration and very large Vd; the drug is bound to proteins in skeletal and cardiac muscle and thus sequestered in the peripheral tissue.[11] Infants and children have increased myocardial uptake of digoxin partially explaining the higher Vd in infants.

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At birth, elimination of drugs through the kidney is inefficient leading to delayed drug clearance and prolonged half-life of many drugs. Renal elimination is limited by renal blood flow and functional immaturity of the kidney, specifically glomerular filtration and tubular capacity for secretion and reabsorption. Glomerular filtration of drugs is dependent on renal blood flow and protein binding of the drug in plasma. Drugs bound to proteins are typically too large to pass through glomeruli. Tubular secretion and reabsorption of drugs involve transport processes that are impacted by prematurity yet remain incompletely understood.[1,14]

Hemodynamic changes after birth lead to increased renal blood flow and rapid changes in glomerular filtration rate (GFR) over the first week after birth. Glomerular filtration is decreased in premature infants, and although the GFR increases after birth, its increase does not match the increased GFR seen in term infants. In 3-day-old neonates, mean GFR increased significantly with advancing gestational age from 24 through 37 weeks.[17] After birth, GFR increases significantly over the first 10 days after birth although less dramatically in very preterm infants.[16] Delayed renal clearance in the youngest, most immature infants can lead to high plasma drug concentration. Dose adjustment for prematurity at birth and again for advancing postnatal and postmenstrual age is often warranted for drugs with renal elimination.

Infants with significant renal disease have changes in drug disposition as reflected in differences in Vd and CL. In addition to the expected reduction in GFR, infants with significant renal disease often have electrolyte abnormalities that can affect the serum pH, which in turn affects the ionization state of drug molecules. Infants with significant renal disease also can accumulate organic acids in the plasma that compete with protein-bound drugs for albumin binding, thereby altering the Vd and availability of free drug for renal clearance. Alteration in pH of tubular fluid also affects the ionization state of a drug molecule, which in turn can affect tubular reabsorption.

Patients with liver disease or hepatic congestion often accumulate active drugs owing to their diminished metabolic capabilities and decreased first-pass metabolism. Patients with liver disease typically have low albumin or altered glycoprotein levels that may affect fractional protein binding of drugs, thereby altering availability of free drug and volume of distribution. Slow gut motility or bowel wall edema can impair enteral absorption.

Patients with cardiac dysfunction can exhibit altered perfusion, edema, hepatic congestion, and/or decreased renal perfusion. All phases of drug disposition (absorption, distribution, metabolism, and excretion) can be affected, and change in PK properties of Vd and CL would be expected. Altered tissue perfusion and increased total body water, as is seen in cardiac, renal, or hepatic dysfunction, can unpredictably alter Vd and CL based on patient physiology and drug-specific properties.

Basic Pharmacokinetic Calculations for Clinicians

Basic PK principles can guide clinicians in how to use drug concentrations derived from therapeutic drug monitoring to determine appropriate dosing for an individual infant. This bedside PK approach, albeit simplified, is appropriate for many drugs used in newborns. Drug concentrations at different time points are used to derive infant-specific Vd, CL, K_{el}, and $T_{1/2}$. These infant-specific PK parameters can then be used to determine what dose modifications are needed to achieve the desired drug concentrations over time for that specific infant (see Table 45.1). (For a more thorough explanation, see references 19, 20).

This approach is most appropriate when the PK properties of the drug can be approximated by a one-compartment model. In reality, these simplified formulas can provide good estimates if the drug has a rapid distribution phase followed by a long beta phase of elimination, when therapeutic drug monitoring occurs during the elimination phase, and when the drug is administered by short infusion time and long dosing intervals (see Fig. 45.5). In these scenarios, the drug concentrations at a given time after infusion are primarily impacted by the prolonged elimination beta phase.

This simplified approach of a one-compartment model is appropriate for gentamicin. Gentamicin PK properties (Vd, K_{el}, $T_{1/2}$, and CL) can be estimated using a peak level obtained 30 minutes after the end of drug infusion when equilibrium is expected to be established in circulation and a trough level obtained before the next dose. The peak level will be somewhat lower than if measured at the end of the infusion. However, by obtaining the peak concentration 30 minutes after the end of infusion, there can be two drug concentrations within the beta phase of elimination to allow calculation of K_{el}.

Peak concentration achieved from the dose of gentamicin is used to estimate Vd. In simplest terms, the volume of distribution is the amount of drug infused divided by the amount of drug measured in the plasma. If 4 mg/kg is given and 10 mg/L is measured in the blood, then the Vd is 0.4 L/kg (see Table 45.1, Eq. [3a]). This Vd is slightly larger than would be predicted if peak was obtained at the end of infusion. This small difference is likely insignificant in the effort to target a therapeutic peak concentration. For precise calculation of Vd, one would use calculations that incorporate time of infusion and time after end of infusion (see Table 45.1, Eqs. [7.10]).

In the gentamicin example, two drug concentrations obtained during the beta phase of elimination are needed to calculate K_{el}. Since the peak level was obtained after short alpha phase, then the peak and trough concentrations represent two concentrations during the beta elimination phase. The elimination rate constant (K_{el}) represents the slope of the line (change in concentration per change in time) on log plot as shown in Table 45.1, Eq. [4a].

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The half-life ($T_{1/2}$) is the time it takes to reduce the drug concentration (C) in half as shown in Eq. [5a], Table 45.1, and relates to the slope (elimination rate constant K_{el}) of concentration time curve on a semi-logarithmic plot. Half-life can be estimated from the drug concentration time curve (see Fig. 45.5) or from the elimination rate constant ($0.693/K_{el}$) or Vd and CL (see Table 45.1, Eq. [5]).

Clearance (CL) is a measure of the rate of drug elimination from the body. Clearance is formally defined as the volume of blood from which all drug is removed per unit of time. Clearance can be calculated using Vd and K_{el} (see Table 45.1, Eq. [6]). At steady state, drug input is equal to drug elimination; therefore, the dose given (dose/interval) is equal to amount of drug removed (CL x drug concentration at steady state) (see Table 45.1, Eq. [6c]).

Pharmacokinetic Calculations Accounting for Infusion Time

In special circumstances when drugs are infused over long time periods, then the maximal concentration of drug measured at the end of infusion may be lower than expected and may overestimate the Vd. The lower C_{max} is because drug is being eliminated during the same time drug is being infused. In this case, more complicated exponential equations would be necessary to estimate the Vd while taking drug elimination into account (see Table 45.1, Eqs. [7, 8, 9, 10]). The concentration of drug at end of infusion (C_{max}) is derived using the rate of the infusion (R_0 defined as dose mg/kg divided by the time of infusion t_{inf}), the CL, and the fraction of drug removed during the infusion time (see Table 45.1, Eq. [7]). If the peak concentration is obtained 30 minutes after the end of the infusion to allow for equilibrium after rapid distribution phase, then multiply C_{max} by the decay factor (e^{-kt} where t = 0.5 hour) to predict this peak level at the time used in therapeutic drug monitoring (see Table 45.1, Eq. [8]). Clinicians can predict the concentration at any time relative to C_{max} at the end of infusion by adjusting the time parameter "t" in the decay factor (e^{-kt}) (see Table 45.1, Eq. [8]). Because CL is derived from the ratio of Vd and K_{el}, this equation can be rearranged to calculate Vd while considering drug loss owing to elimination during infusion time (see Table 45.1, Eq. [9]). For calculations during continuous infusions it is wise to consult a pharmacist.

Fortunately, most drugs in the NICU are administered IV over short (≤60 minutes) infusion times. These infusion times are short compared with the slow drug elimination rate and longer dosing intervals. Therefore, only a very small quantity of drug is eliminated during the actual infusion, allowing the use of simplified calculations.

Pharmacokinetic Calculations After Multiple Doses

Therapeutic drug monitoring often takes place after multiple doses have been administered. Different formulas can be used that incorporate both the dosing interval referred to as tau (τ) and the number of doses (*n*). If multiple doses have been administered, but it is not known if steady-state has been reached, then formulas allow for calculation of C_{max} after *n* doses. Once C_{max} is determined, then the decay factor ($e^{-kt'}$) allows for calculation of drug concentration at time t after the *n*th dose (see Table 45.1, Eqs. [11, 12, 13]). Once at steady-state, CL can be determined from the dose, interval, and average steady-state drug concentration (see Table 45.1, Eq. [6c]).

Pharmacodynamics

The pharmacodynamics (PD) of a drug explain the relationship between the concentration of a drug in the blood and the biochemical and physiologic effect of that drug on the body.[1,3,8] The effect of a drug can relate to either its efficacy or toxicity. The PD properties are drug specific, because they reflect their mechanism of action, potency, desired effect, and/or toxicity profile. Many drugs, such as dopamine, bind to physiologic receptors; agonists mimic the effects of endogenous ligands, whereas antagonists block the effects of endogenous ligands. The pharmacodynamics of receptor-binding drugs is altered during development because of changes in receptor binding, receptor density, and downstream signal transduction. Disease states, maturity, and concomitant medications can also alter drug pharmacodynamics.

When clinical trials do not show desired efficacy, then one needs to reconsider the dose-exposure-response paradigm presented in Fig. 45.1. Lack of efficacy may be caused by the dose being too small and thus yielding subtherapeutic concentrations. Alternatively, the dose may have achieved the desired concentration, but in the young infant that plasma concentration did not correlate with the desired response.

PD principles are well established for the treatment of infections.[3,8] Antimicrobial drugs target the pathogen; therefore, the exposure targets for bacterial or fungal eradication are likely to be appropriate across diverse age groups. Most infants in a NICU receive an antimicrobial drug; therefore, it is worth reviewing the PK/PD paradigms that guide drug dosing for the effective treatment of infections.

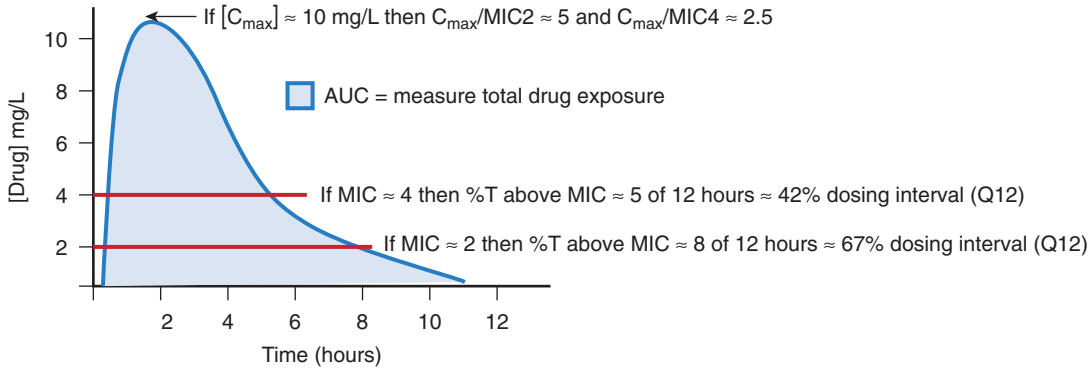
The goals of antimicrobial therapy are simple: Eradicate the pathogen, minimize toxicity, and prevent emergence of resistant organisms (see Fig. 45.1). Once a drug has been chosen, the hard part is choosing the right dosing strategy to accomplish these goals. The PK properties of a drug, specifically the CL, K_{el}, $T_{1/2}$, and Vd, explain the relationship between dose and concentration. PD tell us what concentration is necessary to kill the organism and reduce the risk of emerging resistance based upon human, animal, and in vitro studies. Optimal treatment of infections requires clinicians to incorporate both PK/PD principles (see Fig. 45.1) and use doses of antimicrobial drugs designed to meet PK/PD exposure targets.[3,8] The concentration of the drug in the plasma is just one important aspect of treatment. Infant factors such as immunocompetence, bacterial load, and drug concentration at the site of infection are also important, but they are difficult to modify.

Two important determinants of effective antimicrobial therapy are the drug exposure profile and the minimal

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inhibitory concentration (MIC) of a given bacteria or organism (Fig. 45.6).[3,8] The drug concentration curve demonstrates three important measures of exposure: (1) the maximal concentration referred to as C_{max} or Peak, (2) the area under the concentration curve (AUC) that refers to a measure of total drug exposure, and (3) the time or percent of dosing interval that the drug concentration is maintained above the MIC of the organism (% time). Effective therapy means optimizing this concentration curve relative to the MIC as illustrated by the three PK/PD exposure targets: C_{max}/MIC, AUC/MIC, and % T > MIC.[3,8]

These three PK/PD exposure targets guide effective treatment.[3,8] Antimicrobial drugs can be classified into three major categories: concentration-dependent killing, time-dependent killing, and time-dependent killing with some moderate persistent effects (Table 45.2). Gentamicin is concentration dependent; therefore, the higher the dose, the higher the C_{max}, the more killing is achieved. Gentamicin also has a significant postantibacterial effect, meaning that the higher the C_{max}, the more bacterial growth is subsequently suppressed after levels decrease. Beta-lactam antibiotics, such as ampicillin, are not concentration dependent; efficacy is associated with the percent of time that the concentration is maintained above the MIC. For ampicillin, effective bacterial killing starts to occur when levels are twofold greater than MIC. Increasing ampicillin concentration to more than fourfold MIC does not decrease the bacterial burden. Ampicillin has no postexposure antibacterial activity, so bacterial growth can occur when concentrations are below the MIC. Beta-lactam antibiotics require more frequent dosing or prolonged infusion time to sustain drug levels above the MIC for at least 50% of the dosing interval. Finally, bacterial killing with vancomycin is independent of concentration; however, there is a modest postantibacterial effect such that higher levels are associated with prolonged killing even as levels decrease. Vancomycin efficacy is associated with the AUC/MIC exposure target. Antimicrobial



• **Fig. 45.6** PK–PD exposure targets guide optimal treatment of infections. This graph shows how a drug concentration changes over time after dose. The drug exposure is shown relative to potential minimal inhibitory concentrations (MIC) of an offending organism. Effective therapy meets one of three potential PK/PD exposure targets: C_{max}/MIC, AUC/MIC, and the %T > MIC (%T > MIC refers to the percent of time the concentration of drug is above the MIC during dosing interval). As the MIC increases, the PK/PD exposure target becomes more difficult to obtain. AUC, area under concentration curve.

TABLE 45.2 Pharmacokinetics (PK)—Pharmacodynamics (PD) Relationships and Exposure Targets for Optimal Antimicrobial Treatment

Antimicrobial Activity	PK–PD Exposure Target	Definition	Drug Class	Dosing Goal
Concentration-dependent killing with postantibiotic effect	C_{max} / MIC	Bacterial killing is proportional to maximal concentration achieved relative to MIC of offending organism	Aminoglycosides Fluoroquinolones Daptomycin	Enhance peak concentration
Time-dependent killing	Time [drug] > MIC	Bacterial killing is proportional to the amount of time the drug concentration is maintained above the MIC of offending organism	Beta-lactams Penicillins Cephalosporins Carbapenems	Enhance duration of exposure by short dosing intervals
Time-dependent killing with postantibiotic effect	AUC / MIC	Bacterial killing is proportional to the amount of total drug exposure relative to MIC of offending organism	Vancomycin Clindamycin Linezolid Azoles	Enhance amount of drug using both dose and interval

Adapted from Table 37.3, Remington JS, Klein JO. *Infectious diseases of the fetus and newborn infant.* 8th ed. Philadelphia: Elsevier Saunders; 2016.

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drug dosing guidelines are designed to optimize these PK/PD exposure targets. However, because the exposure targets are all relative to the MIC, the higher the MIC, the harder it is to achieve the exposure target, even if the MIC is within the sensitive range for that drug.

When approaching drug choice and dosage, it is necessary to consider factors that affect PK/PD target attainment and potential outcomes. Patient-specific factors such as maturity, organ function, and fluid status affect attainment of PK/PD targets. Pathogen-specific factors determine susceptibility to drugs. Drug-specific factors such as tissue penetration, formulation, and the availability of PK information in neonates are also important. Finally, the site of the infection and ability to achieve adequate drug concentration at the site of infection can affect outcomes. Neonates are notorious for their susceptibility to meningitis and severe abdominal infections associated with ascites and large fluid shifts. Clinical disease states affect the disposition and PK of drugs in patients.

Example of Simple Pharmacokinetic Calculations to Derive Dose Adjustments

Clinicians can use the formulas in Table 45.1 to perform simple calculations to estimate an individual infant's Vd, CL, K_{el} and $T_{½}$ and then to determine dose modification for that individual infant.[19,20] To demonstrate the use of these formulas, the extended-interval dosing of gentamicin in three newborns of varied gestational age is reviewed (Box 45.1). Gentamicin serves as one of the best examples of PK/PD-derived dosing

• BOX 45.1 Examples of Pharmacokinetic Calculations

A. Mary is a 40-week-gestation term infant who received a 4 mg/kg IV dose of gentamicin every 24 hours. The dose is infused over 30 minutes (t_{inf} = 0.5 h), and she has a peak concentration of 10 mg/L measured 30 minutes after end of infusion (t′ = 0.5 hr from end of infusion), and a trough concentration of 0.3 mg/L drawn 1 hour before the next dose. The time between the peak and the trough is 22 hours. Standard pharmacokinetic (PK) formulas yield the following individual PK characteristics, including K_{el}, $T_{½}$, Vd, and CL.

STEP 1: CALCULATE ELIMINATION RATE CONSTANT AND HALF-LIFE

Eq. [4a] $K_{el} = \ln([C_1]/[C_2])\ \text{mg/L}/\Delta t\ \text{hr}$ or
$= \ln(10/0.3)/22$
$= \ln 33.33/22$
$= 0.159\ \text{hr}^{-1}$

Eq. [5a] $T_{½}\ \text{hr} = 0.693/K_{el}$
$= 0.693/0.159$
$= 4.3$ hr (q 24 hr = 5–6 half-lives)

STEP 2: CALCULATE VD AND CL

Eq. [3a] $\text{Vd L/kg} = [\text{Dose}]\ \text{mg/kg}/[\text{Gent}]\ \text{mg/L}$
$= 4\ \text{mg/kg}/10\ \text{mg/L}$
$= 0.4\ \text{L/kg}$

Eq. [6a] $\text{CL} = K_{el}\ \text{hr}^{-1} \times \text{Vd L/kg}$
$= 0.159 \times 0.4$
$= 0.0636\ \text{L/(kg} * \text{hr)}$

EXTRA CREDIT:

The delay in measuring the gentamicin trough 30 minutes after infusion ends ensures that both the gentamicin peak and trough are in the drug elimination phase.

What are the Vd and CL if corrected for 30-minute delay in drawing gentamicin peak and 30-minute infusion time?

t_{inf} = 0.5 hr, t = 0.5 hr, and R_0 = dose/t_{inf} mg/kg * hr, K = K_{el} = hr^{-1}

Eq. [9] $\text{Vd} = (R_0/[C_t \times K]) \times (1 - e^{-K\text{tinf}}) \times e^{-Kt}$
$\text{Vd} = ([4/0.5]/[10 \times 0.159]) \times (1 - e^{-((0.159)(0.5))}) \times e^{-((0.159)(0.5))}$
$\text{Vd} = 5.03 \times 0.076 \times 0.8953 = 0.326\ \text{L/kg}$

Eq. [6a] $\text{CL} = K_{el}\ \text{hr}^{-1} \times \text{Vd L/kg}$
$= 0.159 \times 0.326$
$= 0.052\ \text{L/(kg} * \text{hr)}$

Note: These are estimates that assume a constant K_{el} during infusion and time before gentamicin peak as would be seen in a one-compartment model. It does not account for a faster K_{el} in the alpha distribution phase.

B. Jack was born at 30 weeks' gestation and weighed 1500 g. He should not receive the same dose as Mary. Using knowledge of prematurity, organ maturation, and fluid status, one could predict that he would have a larger Vd, delayed CL, and longer $T_{½}$. It could be predicted that Jack would need a larger dose and longer interval.

If infants born at 30 weeks' gestation have a Vd of 0.52 L/kg and $T_{½}$ of 11 hours, then can you estimate Jack's peak (30 minutes post end of infusion) and trough levels (1 hour before the next dose) if he received a 4 mg/kg dose every 24 hours or a 4.5 mg/kg dose every 36 hours? In this example, the 4.5 mg/kg dose every 36 hours leads to more optimal gentamicin exposure.

Dose 4 mg/kg q 24 hr
STEP 1: ESTIMATE PEAK GIVEN VD

From Eq. [3a] Vd L/kg = [Dose] mg/kg/[Gent] mg/L
Rearrange to

$\text{Peak [Gent] mg/L} = [\text{Dose}]\ \text{mg/kg}/\text{Vd L/kg}$
$= 4\ \text{mg/kg}/0.52\ \text{L/kg}$

Peak [Gent] mg/L = 7.7 mg/L

Dose 4.5 mg/kg q 36 hr
STEP 1: ESTIMATE PEAK GIVEN VD

From Eq. [3a] Vd L/kg = [Dose] mg/kg/[Gent] mg/L
Rearrange to

$\text{Peak [Gent] mg/L} = [\text{Dose}]\ \text{mg/kg}/\text{Vd L/kg}$
$= 4.5\ \text{mg/kg}/0.52\ \text{L/kg}$

Peak [Gent] mg/L = 8.7 mg/L

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• BOX 45.1 Examples of Pharmacokinetic Calculations—cont'd

STEP 2: CALCULATE K_{EL} USING EQ. [5A]

$K_{el} = 0.693 / T_{1/2}$ hr $= 0.693/11 = 0.063\ hr^{-1}$

STEP 3: ESTIMATE C_2[TROUGH] 22 hr AFTER PEAK

Eq. [4a] $K_{el}\ hr^{-1} = Ln\,[C_1]\ mg/L - Ln\,[C_2]\ mg/L/\Delta t\ hr$

$0.063\ hr^{-1} = Ln\,[7.7] - Ln\,[trough]\ mg/L/22\ hr$

Rearrange to solve for [trough]

$Ln\,[trough] = Ln\,[7.7] - (22\,(0.063)) = 0.655\ mg/L$

gent [trough] $= e^{0.655} = 1.92\ mg/L$

STEP 2: CALCULATE K_{EL} USING EQ. [5A]

$K_{el} = 0.693 / T_{1/2}$ hr $= 0.693/11 = 0.063\ hr^{-1}$

STEP 3: ESTIMATE C_2[TROUGH] 34 hr AFTER PEAK

Eq. [4a] $K_{el}\ hr^{-1} = (Ln\,[C_1] - Ln\,[C_2])\ mg/L/\Delta t\ hr$

$0.063 = (Ln\,[8.7] - Ln[trough])\ mg/L/34\ hr$

Rearrange to solve for [trough] mg/L

$Ln\,[trough] = Ln\,[8.7] - (34\,(0.063)) = 0.021\ mg/L$

Gent [trough] $= e^{0.021} = 1.02\ mg/L$

C. Ava was born at 25 weeks' gestation and weighed only 500 g. With more prematurity comes larger volume of distribution and slower clearance. By measuring a few gentamicin levels, we could derive her individual Vd, CL, K_{el}, and $T_{1/2}$. Ava had a gentamicin peak of 6.8 mg/L after a 4 mg/kg dose and a trough of 3 mg/L at 22 hours after the peak dose. Use equations in Table 45.1 to estimate what dose and interval she would need to have a desired peak of 8-10 mg/L and the desired trough concentration of less than 2 mg/L. Predict her gentamicin peak and trough levels after three doses.

To Estimate Optimal Dose

STEP 1: ESTIMATE VD GIVEN PEAK [GENT] mg/L

Eq. [3a] $VdL/kg = [Dose]\ mg/kg/[Gent]\ mg/L$

$= 4/6.8$

$= 0.59\ L/kg$

STEP 2: WHAT DOSE WOULD ACHIEVE PEAK 8.5 mg/L

Eq. [1] $[Dose]\ mg/kg = Vd\,L/kg \times [Gent]\ mg/L$

$= 0.59 \times 8.5$

$= 5\ mg/kg$

To Estimate Optimal Dosing Interval

STEP 3: CALCULATE K_{EL}, $T_{1/2}$, CL

EQ. [4A, 5A, 6A]

$K_{el} = (Ln\,[C_{t1}] - Ln\,[C_{t2}])\ mg/L/\Delta t\ hr$

$= (Ln\,[6.8] - Ln\,[2.8])\ mg/L/22\ hr = 0.04\ hr^{-1}$

$T_{1/2} = 0.693/K_{el}\ hr^{-1} = 17.3\ hr$

$CL = K_{el} hr^{-1} \times Vd\,L/kg = 0.04 \times 0.59 = 0.024\ L/(hr * kg)$

STEP 5: ESTIMATE TROUGH 1 HOUR BEFORE 48 HOURS DOSING (46 HOURS AFTER PEAK)

Eq. [4a] $K_{el}\ hr^{-1} = (Ln\,[C_1] - Ln\,[C_2])\ mg/L/\Delta t\ hr$

$0.04 = (Ln\,[8.5] - Ln\,[trough])\ mg/L/46\ hr$

Rearrange to solve for [trough]

$Ln\,[trough] = Ln\,[8.5] - (46\,(0.04)) = 0.3\ mg/L$

Gent [trough] $= e^{0.3} = 1.3\ mg/L$

STEP 4: AFTER A 5 mg/kg DOSE, PEAK 8.5 mg/L, HOW MANY HOURS NEED TO ELAPSE BEFORE TROUGH WOULD APPROXIMATE 1 mg/L?

Eq. [4a] $K_{el} hr^{-1} = ln\,[C_1] - Ln\,[C_2]\ mg/L/\Delta t\ hr$

$\Delta t\ hr = Ln\,[peak] - Ln\,[trough]\ mg/L/K_{el}$

$\Delta t\ hr = Ln\,[8.5] - Ln\,[1]/0.04 = 53\ hr$

In 53 hr (three half-lives), levels will be ≈ 1 mg/L, thus q48 hr is reasonable. Gentamicin levels are expected to decline from 8.5 to 4.25 to 2.12, and finally, to 1.06 mg/L

STEP 6: WHAT IS BEST DOSE FOR AVA AT 25 WEEKS?

Gentamicin 5 mg/kg q 48 hr yields

Gentamicin peak 8.5 mg/L and trough 1.3 mg/L

Estimate Peak and Trough after *n* = three doses, dose interval τ = q 48 hr

Eq [14]

$C_{max}\,(n) = (Dose/Vd) \times [(1 - e^{-nK\tau})/(1 - e^{-K\tau})]$

$C_{max} = 5\ mg/kg/0.59\ L/kg) \times [(1 - e^{-(3)(0.04)(48)})/(1 - e^{-(0.04)(48)})]$

$= 8.47 \times [(1 - 0.00315)/(1 - 0.1466)]$

$= 8.47 \times (0.00685/0.8533)$

$= 9.9\ mg/L$

Eq [15]

$C_t\,(n) = (Dose/Vd) \times [(1 - e^{-nK\tau})/(1 - e^{-K\tau})]$

$\times e^{-Kt}$ (conc at time t = 46 hr after peak, after three doses)

$C_{t'} = 5\ mg/kg/0.59\ L/kg) \times [(1 - e^{-(3)(0.04)(48)})/(1 - e^{-(0.04)(48)})]$

$\times e^{-(0.04)(46)}$

Or $C_t = C_{max} \times e^{-Kt}$

$= 9.9\ mg/L \times e^{-(0.04)(46.)} = 9.9 \times 0.158$

$= 1.56\ mg/L$

Gent, Gentamicin.

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guidelines for neonates across the gestational age spectrum. Gentamicin has concentration-dependent killing.[3,8] In adults, first dose peak levels of 8 to 10 mg/L are associated with survival in gram-negative bacteremia.[10] In adults, once-daily high-dose regimens have shown enhanced efficacy with less toxicity. Decreased renal toxicity is attributed to the reduction in renal drug accumulation because the uptake of drug into the kidney becomes saturated, limiting the amount of update at high concentrations (saturable drug uptake).[18] The extended interval allows for appropriate washout. In the examples found in Box 45.1, *A-C*, Mary, Jack, and Ava are three newborns who all receive gentamicin as empiric coverage for early onset sepsis.

This example demonstrates how PK properties of drugs in newborns are affected by gestational age. As predicted, prematurity was associated with larger Vd, delayed CL, and longer $T_{1/2}$. In this example, Ava, a 25-week gestation infant, had a threefold reduction in gentamicin CL and a 1.5-fold increase in Vd when compared with Mary, a term infant. Ava has the lowest renal clearance such that after three doses, gentamicin accumulates to higher peak and trough concentrations. Repeat peak and trough levels may be warranted if treatment is continued beyond two doses. With a few gentamicin levels, individual PK properties could be predicted and optimal dosing determined for Jack and Ava that target the PD properties of gentamicin.

Key Points

- The success of drug therapy is determined by complex interactions between the administered drug and its drug exposure profile, the host, and the disease process or the pathogen.
- Wide variation of drug exposures among infants in the NICU can be partially explained by specific drug properties and differences in body composition, organ function, and disease states.
- Optimizing antimicrobial therapy needs to consider both the pharmacokinetic (PK) drug exposure profile and the pharmacodynamics (PD) of drug–organism interactions.
- When therapeutic drug monitoring is available, clinicians can use plasma drug concentrations to estimate individual PK parameters. Once patient-specific PK parameters are known, dosing can be individualized to achieve desired exposure.
- PK studies are needed in premature and term neonates over wide ranges of postnatal ages to determine the effective dosing regimens that target PD exposures.

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46

Infants of Substance-Using Mothers

MARK L. HUDAK

Misuse or abuse of certain illicit and prescription drugs in the United States adversely affects public health in diverse ways and substantially increases overall health care expenditures. Some antenatal drug exposures can produce significant short-term consequences or serious permanent long-term injuries in the child (Table 46.1). The US Department of Health and Human Services, through its annual National Survey on Drug Use and Health (NSDUH), extrapolates the annual use of illegal drugs (including marijuana, cocaine, hallucinogens, methamphetamine, inhalants, and heroin) and the nonmedical use of prescription drugs (pain relievers, tranquillizers, sedatives, and stimulants). The 2016 NSDUH found that 20.1 million Americans age 12 or older, or 7.5% of this population, admitted to misusing or abusing one of more of these types of drugs within the past month of being surveyed. Heavy or binge drinking and smoking in the past month, which also negatively impact public health but are not necessarily illegal activities, occurred at significantly greater rates of 24.2% and 23.5%, respectively.[106]

For many years, marijuana has been the most commonly used recreational drug among the US population age 12 or greater. Recently, a number of states have legalized its use. In 2016, the NSDUH estimated that 4.0 million people (1.5% of the population age 12 or greater) had a marijuana use disorder. The survey estimated the prevalence of substance use disorders for cocaine (867,000), methamphetamine (684,000), heroin (626,000), and inhalants (600,000). In comparison, 1.8 million people had a prescription opioid use disorder. In past surveys, the NSDUH has reported lower, but still unacceptably high, rates of substance use in pregnant women compared to the general population. However, the rate of misuse of prescription opioids during pregnancy has increased by an alarming degree.

Antenatal drug exposure can have a host of effects on the developing fetus. Drugs act as teratogens (from the Greek, meaning "monster producing") when time-dependent fetal exposures cause major morphologic abnormalities of the developing organ systems during the embryonic period (roughly the first 8 weeks of development) or when continued exposure during later fetal life results in minor morphologic abnormalities or physiologic defects. Thalidomide, a medication that became available in Europe in 1959 as an aid for sleeping and "morning sickness" in pregnant women, was distributed for use by physicians in the United States without formal federal approval and serves as the archetypal example of a teratogen. Use of this drug was linked to an epidemic of phocomelia in newborn infants, half of whom died in the first year of life. This tragedy shattered the illusion that the uterine environment sequestered the fetus from adverse effects due to drugs. As a result, in 1962, Congress passed the Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act of 1938 that gave the Food and Drug Administration (FDA) additional authority to regulate drug use in pregnant women.

Drugs can also have other direct and indirect effects on the fetus. Drugs can directly affect fetal growth and maturation; can alter levels of brain neurotransmitters or expression of neural receptors; and can disrupt normal brain morphogenesis throughout the continuum of neurogenesis, proliferation, migration, organization, and synaptogenesis. Examples of indirect effects include uteroplacental insufficiency caused by vasoconstriction of uterine or placental vessels and drug-induced alterations of maternal behavior that secondarily compromise maternal, and hence fetal, well-being. Poor nutrition, diseases transmitted through sexual contact or by needle stick, exposure to violence, and inadequate access to health care can all result in maternal and fetal harm.

Near the time of birth, maternal drugs can produce signs of acute toxicity in the newborn infant, cause persistent abnormal neurobehavior, or result in signs of withdrawal. For some fetal drug exposures, long-term outcome studies suggest a quantifiable impact on internalizing and externalizing behaviors as well as on cognition, especially with respect to higher-level executive functioning.

The distinction between an acute or chronic drug effect and the signs of drug withdrawal is important but on occasion difficult to determine for certain. Signs of acute neonatal drug toxicity abate as the drug is eliminated from the infant. Signs of chronic drug effect on neurobehavior may remain static for a prolonged time independent of fluctuations in total body storage and blood or cerebral spinal fluid concentrations of drug. Alcohol can cause both acute toxic effects (depressed sensorium) and chronic effects (fetal

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Abstract

Antenatal drug exposure can affect fetuses in many ways. Teratogens can cause a spectrum of abnormalities from major congenital anomalies to minor malformations. Drugs may also adversely impact somatic growth and maturation of organ systems; alter brain development and long-term cognitive and behavioral functions; cause short-term toxicity due to drug effect; or result in transient neurobehavioral abnormalities consistent with drug withdrawal. Fertile women should minimize smoking; exposure to alcohol, marijuana, and illicit drugs; and misuse of prescription drugs such as opioids, and benzodiazepines to optimize fetal health. Cigarette smoking and marijuana use in pregnancy should be discouraged. Obstetricians should identify pregnant women with alcohol and substance use disorders through screening and refer these women for appropriate treatment. Women with opioid use disorders and their fetuses have improved outcomes with medication-assisted treatment. New opioid prescription during pregnancy should be avoided if possible, and if necessary, short-acting preparations should be prescribed at the minimum effective dose for the minimum duration needed. Most infants exposed close to birth to long-acting opioids will exhibit signs of withdrawal before 5 days of age. Infants at risk for withdrawal should be monitored carefully and treated with intensive nonpharmacologic methods as first-line therapy. Physiologic stabilization using oral opioids may be necessary, and rigorous adherence to a standardized treatment protocol will minimize duration of hospital stay and postnatal drug exposure. Infants exposed antenatally to opioids may be at increased risk for attention deficit disorder and for internalizing and externalizing behavior abnormalities.

Keywords

fetal drug exposure
drug withdrawal
opioids
neonatal abstinence syndrome
marijuana
cocaine
drug effect

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TABLE 46.1 Summary of Effects of Prenatal Drug Exposure

	Marijuana	Opioids	Cocaine	Methamphetamines
Short-Term Effects				
Fetal growth	None	Moderate	Moderate	Moderate
Birth defects	None	Possible	None certain	None
Neonatal withdrawal	None	Severe	None	None
Neurobehavior	Mild, transient	Dominated by withdrawal	Mild, transient	Mild, transient
Long-Term Effects				
Growth	None	None	None	Too few data
Behavior	Mild	Mild	Mild–moderate	Too few data
Intelligence	Mild	No consensus	Mild	Too few data
Language	None	Too few data	Mild	Too few data
Achievement	Mild	Too few data	No consensus	Too few data

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alcohol syndrome) depending on whether the exposure occurred just prior to birth or for a sustained period of time including early gestation. Signs of neonatal withdrawal worsen as levels of the active drug moiety decrease due to its metabolism and excretion. Many intrauterine drug exposures have been associated with signs of neonatal withdrawal.[59] The overwhelming majority of cases of neonatal withdrawal result from intrauterine opioid exposure. Antenatal fetal exposure to benzodiazepines and barbiturates is a less common cause of neonatal withdrawal.

Prenatal and Perinatal Considerations

Prevention of drug effects on the fetus and newborn must begin with preconceptional education of women of childbearing age, their families, and their physicians. Because teenage females who become pregnant are more likely to have engaged in risky behaviors such as illicit drug use, alcohol, and smoking than their nonpregnant peers, early education about drug effects on a fetus and newborn that begins at home and is reinforced in elementary and middle school curricula is important. The pediatrician also has an important role in screening adolescent females for high-risk behaviors and providing factual information in a nonjudgmental manner about the consequences of unhealthy lifestyle choices.

Women of childbearing age and their sexual partners should be counseled to discontinue use of illegal nonopioid drugs before conception. Women with an illicit or prescription opioid use disorder should be encouraged to enroll in a supervised opioid maintenance treatment program. Women who are pregnant should be counseled to seek prenatal care as soon as possible and to abstain completely from use of any illegal drugs and from use of other prescription drugs that are not medically indicated. If a pregnant woman requires new or continued treatment for a medical or mental health condition, her physician should choose the drug class or the specific medication within the drug class that might be expected to confer the highest fetomaternal benefit-to-risk ratio. Often, however, limited data are available to guide decisions. Nonetheless, the pregnant woman should be given the most current evidence-based information about possible short- and long-term consequences to the fetus of any drugs that she uses or that might be recommended for use. Consistent with guidelines from the Centers of Disease Control and Prevention, new opioid prescriptions for pain should be considered only when other medications such as ibuprofen are inadequate. If opioids are required, only immediate-release, short-acting opioids should be prescribed, at the lowest dose and with shortest duration necessary. Concomitant use of opioids and benzodiazepines is contraindicated. These recommendations are particularly critical in women of childbearing age where both a woman and her fetus could be affected by injudicious prescription of opioids.[39] The obstetric provider should conduct periodic SBIRT (screening by interview; brief intervention; referral to treatment) procedures for each pregnant woman under care.[6] A short screening interview can help to determine whether a pregnant woman is likely to be engaged in surreptitious drug use. Several short questionnaires, including CAGE questions adapted to include drugs (CAGE-AID),[21] 4P,[26] and CRAFFT,[71] have been validated. The four CAGE-AID questions are listed in Box 46.1. If two or more yes responses are obtained, this screen has a 70% sensitivity to identify use of illegal drugs or misuse of prescription drugs. A brief intervention consisting of short, focused education and referral to appropriate treatment can be performed for those women who admit to a problem.

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• BOX 46.1 CAGE Questions Adapted to Include Drugs (CAGE-AID)

1. Have you ever felt you ought to cut down on your drinking or drug use?
2. Have people annoyed you by criticizing your drinking or drug use?
3. Have you felt bad or guilty about your drinking or drug use?
4. Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?

If a pregnant woman admits to or is suspected to be engaged in such drug use, she should be asked to provide informed consent for biologic testing. Urine testing is preferred, and positive tests should be confirmed with mass spectrometry/gas chromatography. The clinician should be aware of limitations of testing. Tests vary widely with respect to which specific drugs are assayed. Threshold detection levels are set to avoid false positives, but levels that fall below the threshold owing to low dose exposure or a long interval between the most recent exposure and testing will provide a false negative result. Positive results may result from legitimate use of prescription drugs or in some cases from intense secondhand exposure.

A flexible and nonjudgmental approach to the care of women who abuse illicit drugs or misuse prescription drugs should be adopted, and appropriate community resources for education (e.g., community support groups) and treatment (e.g., rehabilitation centers) should be incorporated into the care plan. The goals of the provider are to establish a trusting relationship with each woman so that she continues regular prenatal care to reduce harm to the woman and her fetus without necessarily counseling cessation of the drug (e.g., in the case of a pregnant mother in an opioid maintenance program), to recognize and treat potential comorbidities, and to counsel about the possible maternal and fetal effects of the use of other drugs. In particular, because catastrophic obstetric complications can accompany the use of certain drugs, the pregnant woman should be educated about the signs of antepartum hemorrhage, premature rupture of membranes, premature onset of labor, and meconium-stained amniotic fluid so that prompt diagnosis and treatment can ensue.

Owing to guilt or to fear of legal action (incarceration, initiation of child welfare proceedings), a pregnant woman with illicit drug use may not have sought prenatal care before presenting with an obstetric complication, the onset of labor, or a medical comorbidity. The legal consequences to a woman abusing illicit drugs or misusing prescription opioids varies among states. Some states have passed punitive legislation whereas others have worked to encourage prenatal access to comprehensive care and treatment without legal repercussions. Emergency room visits and hospital admissions may afford the only windows of opportunity to evaluate such a patient and then to refer her for appropriate multidisciplinary treatment. During obstetric-related hospitalizations, providers can counsel a woman about the prevention of future drug-exposed pregnancies, sexually transmitted diseases, and HIV infection.

Neonatal Considerations

Providers who care for infants during the initial birth hospitalization should understand that maternal self-reporting, restricted implementation of screening procedures, and maternal drug tests do not identify all infants with significant antenatal exposure to drugs. Newborn caregivers should be knowledgeable about patterns of illicit drug abuse or the misuse of prescription drugs in their community. Guidelines for neonatal biologic testing at birth for exposure to illicit drugs are commonly based on associated conditions, such as maternal self-reporting of alcohol or drug use, inadequate or no prenatal care, presence of certain sexually transmitted maternal diseases, premature onset of labor, abruptio placentae, intrauterine growth restriction, congenital malformations, and overt signs of neonatal withdrawal. However, restricting testing of mothers and infants based on these or similar criteria will fail to detect all exposed infants. For these reasons, some have advocated for universal drug testing of all pregnant women or newborns. In 2013, most hospitals in the Cincinnati, Ohio, area implemented a policy of universal maternal testing but allowed the mother to opt out.[95] A study at one Cincinnati hospital showed that this approach did identify substance-exposed infants that conventional screening procedures would have missed.[116]

Marijuana (Cannabinoids)

Whereas the principal active cannabinoid in marijuana (δ-9-tetrahydrocannabinol) readily crosses the placenta, a major metabolite (11-nor-9-carboxytetrahydrocannabinol) remains sequestered in the maternal circulation.[9] However, marijuana remains in the body tissues of chronic users for as long as 30 days and so can result in prolonged fetal exposure.

Marijuana does not independently affect somatic fetal growth and results in no known congenital anomalies. If marijuana affects newborn neurobehavior, the effects are subtle. Newborns have not demonstrated signs of withdrawal secondary to marijuana exposure. No study has discerned an independent effect of prenatal marijuana exposure on childhood growth through adolescence. Multiple studies have suggested that prenatal marijuana exposure exerts long-term effects on behavior (inattention and impulsivity), problem-solving skills, and underachievement in reading and spelling, but not on IQ or language.[13] However, some preparations of marijuana (and synthetic cannabinoids) available today are much more potent than in the past, so that the results of existing studies that evaluated long-term outcomes of fetal exposure to lower potency marijuana may not accurately reflect current risk.[41]

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The American Academy of Pediatrics considers maternal marijuana use to be a relative contraindication to breastfeeding. The American College of Obstetrics and Gynecology also discourages marijuana use by lactating mothers.[33]

Opioids

Opioids are a class of chemical compounds that activate μ-opioid (but also κ- and δ-opioid) receptors primarily in the central nervous system (CNS) to produce supraspinal analgesia. The term opiate refers to a subclass of alkaloid opioids. Naturally occurring opioids are present in the opium poppy (e.g., morphine) and occur endogenously (e.g., enkephalins, endorphins, endomorphins). Opioids can be synthetic (e.g., methadone and fentanyl are synthesized from nonopioid precursors) or semisynthetic (e.g., heroin and buprenorphine, which represent modifications of natural opioid compounds) in origin. Other acute effects of opioids include sedation, euphoria, miosis, respiratory depression, and decreased gastrointestinal motility. Prolonged use results in physical and psychologic dependence. As a class of drugs, opioids demonstrate a narrow therapeutic index within a given patient. However, the observed range in dose that achieves a similar therapeutic effect in a large population is fairly wide because of genetic differences in pharmacokinetics and pharmacodynamics.[103] Opioids acutely inhibit the release of noradrenaline at synaptic terminals. The synthetic opioid methadone exerts secondary effects by acting as an N-methyl-d-aspartate receptor antagonist to block the actions of glutamate, the primary excitatory neurotransmitter in the CNS. In patients who are chronically exposed to some opioids, tolerance can develop, because over time the rate of noradrenaline release increases toward normal. The molecular mechanisms that result in substance abuse disorder and produce signs and symptoms of withdrawal are complex and incompletely understood.

Opioids are variably lipophilic compounds of low molecular weight that cross both blood–brain and placental barriers. Because heroin is more lipophilic than morphine, it crosses the blood–brain barrier more rapidly and causes a greater euphoric "high." Methadone is well-absorbed orally; it has a mean half-life of approximately 1 day so that it produces a sustained effect compared to heroin that has a much shorter half-life of 15-30 minutes.

Opioid use in pregnant women carries risks for the mother, fetus, and newborn. Intravenous injection of heroin exposes the mother and her fetus to potential drug overdose, to a greater risk of acute bacterial endocarditis, and, owing to contaminated needles, to serious viral infections (e.g., hepatitis B and C, HIV/AIDS). Other direct and indirect prenatal complications of heroin use include extrauterine pregnancies owing to salpingo-oophoritis, premature labor, premature rupture of membranes, antepartum hemorrhage, fetal demise, and low birth weight. Mothers who use heroin experience rapid fluctuations in opioid concentration because of its short half-life so that the fetus may also suffer intermittent withdrawal effects. Therapeutic opioid maintenance therapy employs an opioid with a long half-life to minimize fluctuations between peak and trough fetal drug levels. A more stable maternal opioid level reduces overall fetal stress.

Maternal opioid detoxification is generally not recommended because of concerns about a possible increased risk of fetal distress and fetal loss during withdrawal[93] as well as a high rate of maternal recidivism. In situations where a mother does not have access to a supervised opioid maintenance program, the American College of Obstetricians and Gynecologists has stated that medically supervised detoxification may be considered.[32] Opioid maintenance therapy with daily methadone (a full μ-opioid agonist and a Food and Drug Administration [FDA] Schedule II controlled drug) for pregnant women can sustain opioid concentrations in the mother and fetus in ranges that minimize opioid craving, suppress abstinence symptomatology, block heroin-induced euphoria, and minimize fetal stress. Other benefits from this once-controversial treatment are optimization of prenatal care and general maternal physical and mental health as well as preparation for potential signs of withdrawal in the newborn infant. Disadvantages of methadone include greater difficulty in achieving successful detoxification after delivery and a more severe and prolonged course of neonatal abstinence syndrome (NAS) compared, for instance, with heroin exposure. These issues have encouraged the development of other opioids as alternative treatments to methadone.

Buprenorphine is a semisynthetic opioid with partial μ-opioid agonist and kappa-opioid antagonist properties that was first introduced in France in 1996 as an alternative to methadone. This drug demonstrates high receptor affinity and low intrinsic activity compared with other opioids. In adults, buprenorphine evokes fewer autonomic signs and symptoms of opioid withdrawal following abrupt discontinuation. In contrast to methadone, which is typically dispensed on a daily basis by methadone clinics, obstetricians who receive special training can dispense buprenorphine for a week or more. In late 2017, the Food and Drug Administration approved an intramuscular preparation of buprenorphine (RBP-6000) that can be dosed once a month. Benefits of this preparation include convenient monthly dosing and the elimination of any possibility of drug diversion.

Subsequent to the Drug Addiction Treatment Act of 2000 that allowed office-based treatment of addiction using FDA Schedule III-V drugs, buprenorphine was approved by the FDA in 2002 as a Schedule III controlled drug for the treatment of opioid dependence. Neither methadone nor buprenorphine is approved for use in pregnant women, and both were categorized by the FDA as class C pregnancy drugs (i.e., animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Nonetheless, buprenorphine, either alone

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(Subutex) or in combination with naloxone (Suboxone), has been used both as a first-line treatment for heroin addiction and as a replacement drug for methadone. Results from the MOTHER (Maternal Opioid Treatment: Human Experimental Research) study suggest that newborns experience some benefits when mothers are maintained on buprenorphine rather than on methadone. Buprenorphine-exposed infants demonstrated shorter hospital stays (10 vs. 17.5 days) and treatment durations for NAS (4.1 vs. 9.9 days) and required a lower cumulative dose of morphine (1.1 vs. 10.4 mg) compared with infants born to mothers on methadone maintenance.[64] Nonetheless, it is not currently recommended that mothers already on a successful methadone maintenance regimen switch to buprenorphine until it can be shown that this transition does not result in a higher than expected rate of nonadherence to treatment.

Birth Defects

Surprisingly, it is still uncertain whether opioids are teratogenic. A number of studies have suggested an increased risk of fetal anomalies. As an example, one study reported that fetal exposure to opioids resulted in a slight increase in the risk of certain types of congenital heart disease (conotruncal defects, atrioventricular canal, hypoplastic left heart syndrome), neural tube defects (anencephaly, spina bifida), and gastroschisis. The effect was important as evidenced by odds ratios for these anomalies that ranged from 1.8-2.7.[18,79] However, a recent systematic review found that 10 of 12 methodologically adequate case–control studies and 7 of 18 cohort studies found statistically significant associations between maternal opioid use and congenital malformations. In the case–control studies, the most frequent associations occurred with oral clefts and ventricular septal/atrial septal defects, whereas the cohort studies found clubfoot to be the most frequent association.[79]

Growth

The preponderance of evidence suggests that opioids have a mild independent effect on fetal growth, but many confounders exist. Birth weight percentiles of babies born to mothers who adhere to methadone maintenance therapy are greater than those of babies born to heroin addicts.[66] Some studies suggest that buprenorphine-exposed fetuses demonstrate better growth than fetuses exposed to methadone. Analysis of data in the NIH-sponsored Maternal Lifestyles Study revealed that opioid-exposed infants born at or after 33 weeks' gestation had lower birth weight after controlling for other potential confounders.[8] However, prenatal exposure to opioids does not affect long-term growth.[101]

Neonatal Neurobehavior/Withdrawal

Prevalence

Neonatal abstinence syndrome (NAS) is the term that encompasses the constellation of clinical signs associated with opioid withdrawal. Signs of withdrawal develop in 55%-94% of neonates exposed to opioids in utero. The incidence of NAS has increased dramatically in the past decade. Reviews of national hospital discharge records from 2000-2012 found that the incidence of NAS among newborns discharged after birth increased from 1.20-5.8 per 1000 hospital births per year. Rates of NAS varied with geography from a high of 16.2 per 1000 births in the East South Central United States (Kentucky, Tennessee, Mississippi, and Alabama) to a low of 2.6 per 1000 births in West South Central United States (Oklahoma, Texas, Arkansas, Louisiana).[90] Rates of NAS are high in northern New England and in some areas of the Pacific Northwest.

Epidemiology

The distribution of specific opioids that cause NAS likely varies substantially from region to region. In Appalachia and northern New England, the use or misuse (nonmedical use) of prescription opioids (especially of extended-release and long-acting opioid preparations such as OxyContin®) has been a key driver of the growth of the epidemic. Beginning in January 2013, the state of Tennessee implemented mandatory reporting of infants with NAS. Data from January to November 2017, as detailed in Table 46.2, support this supposition and demonstrate that pregnant women commonly access multiple sources of opioids.[109]

How do pregnant women access these potent drugs? The 2016 NSDUH reported that 53% of the population that is dependent or addicted to pain relievers acquired drugs at no cost or purchased drugs from relatives or friends, 38% used drugs remaining from prior physician prescriptions or

TABLE 46.2 Sources of Antenatal Opioid Exposure in Tennessee Infants with Neonatal Abstinence Syndrome (January-November 2017)

Source of Maternal Drug	Cases (%)*
Medication-assisted treatment	69.2
Legal prescription of an opioid pain reliever	5.2
Legal prescription of a nonopioid	8.6
Prescription opioid obtained without a prescription	28.5
Nonopioid prescription substance obtained without a prescription	15.2
Heroin	5.1
Other nonprescription substance	20.3
No known exposure	0.3
Other	3.1

*The sum of cases exceeds 100%, because an infant may have had antenatal exposure from more than one source.

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stole drugs from a physician office, and the remaining 9% obtained them by purchase from a dealer or some other way.[106]

Risk Factors

The clinical presentation of NAS varies with the opioid, maternal drug history (including timing of the most recent use of drug prior to delivery), maternal metabolism, net transfer of drug across the placenta, placental metabolism, infant metabolism and excretion, genetics, environmental care, and other factors. Maternal use of other drugs such as cocaine, selective serotonin reuptake inhibitors, barbiturates, hypnotics-sedatives, and cigarettes[29,89] may influence the severity and duration of NAS.

Studies have found either a correlation[34,36,37,54,83,86,96,105] or no correlation[15,19,31,73,82,100] between maternal methadone dose and the incidence and severity of NAS. However, there were substantial variations in the mean and range of daily methadone dose among the populations. Studies that found no correlation tended to include infants born to mothers who had been prescribed higher doses of methadone (50-200 mg/day), whereas those who did note a relationship between maternal dose and NAS sequelae reported lower maternal doses (e.g., less than 50 mg/day) or included women undergoing partial detoxification.[34] So there may be a threshold dose above which nearly all infants will exhibit signs of withdrawal. There is also significant interindividual variability in maternal methadone metabolism[40] that can result in different cumulative fetal exposure in mothers on equivalent methadone regimens.

Some evidence suggests that the presence of certain single-nucleotide polymorphisms of the opioid receptor (OPRM1) and the catechol-O-methyltransferase (*COMT*) genes in babies with NAS correlates with shorter lengths of hospital stay and less severe signs of withdrawal as measured by the need for pharmacologic treatment.[114] These findings are consistent with other studies that have linked these same single-nucleotide polymorphisms to the risk of opioid addiction in adults.

Clinical Presentation

Because opioid receptors are concentrated in the CNS and the gastrointestinal tract, the predominant signs and symptoms of pure opioid withdrawal reflect CNS irritability, excessive autonomic activity, and gastrointestinal tract dysfunction (Table 46.3). Excess environmental stimuli and hunger will exacerbate the perceived severity of NAS. Methadone and buprenorphine may produce slightly different patterns of signs of withdrawal. Abnormal motor findings (tremors, hyperactive Moro reflex) are more common in methadone-exposed infants, whereas buprenorphine-exposed infants are more likely to demonstrate autonomic and gastrointestinal signs (nasal stuffiness, sneezing, loose stools).[48]

Because of differences in drug half-lives, the onset of signs attributable to neonatal withdrawal from heroin may be present at birth or begin within 24 hours of birth, whereas withdrawal of an infant of a mother on a daily methadone maintenance program typically commences around 24-72 hours of age.[119] For both opioids, evidence of withdrawal is occasionally delayed beyond 7 days of age.[65] A consensus has developed that buprenorphine-exposed infants experience a slightly later onset and less severe signs of NAS compared to infants withdrawing from heroin or methadone,[77] but outliers do exist, and some buprenorphine-exposed infants undergo severe withdrawal.[67,74,99] If more than 1 week has elapsed between the last maternal opioid use and delivery of the infant, the incidence of neonatal withdrawal is relatively low.[104] In the acute phase, seizures of unknown etiology and long-term significance have been reported in 2%-11% of infants withdrawing from opioids[55,65,119]; however, abnormal electroencephalograms (EEGs) without overt seizure activity have been reported in greater than 30% of neonates.[91,112] Hence, it is not completely certain that opioid withdrawal in fact causes seizures rather than precipitates marked hypertonicity, hyperactivity, hyperreflexivity, and increased clonus. Subacute signs of opioid withdrawal may last up to 6 months.[35]

Preterm infants have been described as being at lower risk of drug withdrawal with less severe and/or prolonged courses. Infants born at less than 35 weeks' gestation whose mothers received methadone maintenance had significantly lower total and CNS abstinence scores than did term infants of mothers receiving similar methadone dosages.[37] Lower gestational age has correlated with a lower risk of neonatal withdrawal.[81] The apparent decreased severity of signs in preterm infants may relate to developmental immaturity of the CNS that minimizes expression of motor signs, differences in total drug exposure, or lower fat depots of drug. Alternatively, the clinical evaluation of the severity of abstinence may be more difficult in preterm infants, because scoring tools to describe withdrawal were largely developed in term or late preterm infants.[46,80]

TABLE 46.3 Clinical Features of Neonatal Narcotic Abstinence Syndrome

Neurologic Excitability	Gastrointestinal Dysfunction
Tremors	Poor feeding
Irritability	Uncoordinated and constant sucking
Increased wakefulness	Vomiting
High-pitched crying	Diarrhea
Increased muscle tone	Dehydration
Hyperactive deep tendon reflexes	Poor weight gain
Exaggerated Moro reflex	Autonomic signs
Seizures	Increased sweating
Frequent yawning and sneezing	Nasal stuffiness
	Fever
	Mottling
	Temperature instability

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Diagnosis

A diagnosis of NAS is established by admitted or suspected maternal use of opioids, supportive findings on maternal or infant biological testing, and some subset of the constellation of clinical signs in Table 46.3. The legal implications of testing and the state or hospital requirement for maternal consent for infant testing vary from state to state and from hospital to hospital.[58] Each hospital should adopt a policy for maternal and newborn testing to avoid discriminatory practices and to comply with local laws.

Biologic testing is most commonly accomplished using neonatal urine specimens. A urine sample must be collected as soon as possible after birth, because many drugs are rapidly metabolized and eliminated.[12,23,24] A negative urine test may not identify remote use of opioids because opioids as well as amphetamines, benzodiazepines, and cocaine metabolites are usually cleared within 1-3 days after birth. Marijuana and cocaine metabolites may be detectable for weeks, depending on maternal usage.[92]

Drugs that are excreted in the hepatobiliary system as well as drugs excreted by the fetal kidneys into the amniotic fluid are concentrated in meconium, which forms in the second and third trimesters. Hence, meconium analysis is most useful when the history and clinical presentation strongly suggest neonatal withdrawal but maternal and neonatal urine screening results are negative. Drawbacks of testing for drugs in meconium are that it is not typically performed by hospitals and that reporting of results may be delayed beyond initial hospital discharge. Meconium must be collected before transitional, human milk or formula stools are passed—otherwise, the assay may not be valid or the reference laboratory may reject the sample. Assay of meconium, although not conclusive if results are negative, is more likely to identify infants of drug-abusing mothers than is testing of infant or maternal urine.[87,97] Other specimens that have been tested in research laboratories are maternal and neonatal hair.[88,113] Testing of umbilical cord tissue using drug class–specific immunoassays has been shown to be in concordance with testing of paired meconium specimens at rates of 97%, 95%, 99%, and 91% for the detection of amphetamines, opiates, cocaine, and cannabinoids, respectively.[84] The availability of this tissue from the moment of birth (in contrast to the inherent delay in collecting urine or meconium) has made this an attractive method of testing in situations in which urine testing is negative.

Withdrawal signs in the newborn may mimic other conditions, such as infection, hypoglycemia, hypocalcemia, hyperthyroidism, intracranial hemorrhage, hypoxic-ischemic encephalopathy, and polycythemia/hyperviscosity.[24,27] If none of these diagnoses are present, a diagnosis of NAS should be entertained. Corroboration may require interviewing the mother about illegal drug use by her partner, friends, and parents as well as her prescription and nonprescription drug use.[24,27]

Neonatal testing should be performed, but by the time signs develop results may not be confirmatory. It is important that the clinical signs are not attributed solely to drug withdrawal on the basis of a positive maternal history without considering and excluding other causes.

Assessment

Infants at risk for NAS should be carefully monitored in the hospital for the development of signs consistent with withdrawal. The appropriate duration of hospital observation is variable and will depend on a careful assessment of the maternal drug history. An infant born to a mother on a low-dose prescription opioid with a short half-life (e.g., hydrocodone; average half-life 4 hours) may be safely discharged if there are no signs of withdrawal by 2-3 days of age, whereas an infant born to a mother on an opioid with a prolonged half-life (e.g., methadone or buprenorphine) should be observed for a minimum of 5-7 days. Maternal or infant screening for comorbidities, such as polydrug abuse and infection with HIV or hepatitis C virus, should be performed. In some populations, more than 25% of mothers of infants with NAS have concomitant hepatitis C.

Discrete and serial clinical scoring of signs of NAS can assist with therapeutic decisions. The Lipsitz tool, also known as the Neonatal Drug Withdrawal Scoring System,[80] is a relatively simple metric with good sensitivity for identifying clinically important withdrawal. However, the Finnegan Neonatal Abstinence Scoring System (Fig. 46.1)[45] is now the predominant tool used in the United States.[98] This more comprehensive instrument assigns a cumulative score based on the interval observation of 21 items relating to signs of neonatal withdrawal.[50] It is important that scoring is done after a baby has received optimal comfort care (i.e., after feeding, diaper changing, and quieting) and that scoring is performed per standardized recommendations. The Finnegan tool has been normalized in opioid-naïve infants. Median scores remained at 2 during each of the first 3 days of life, with 95th percentile scores of 5.5 and 7 on days 1 and 2, respectively.[120]

Recently, a number of centers have adopted use of frequent evaluation of an infant's functional performance as an alternative to quantitative instrument-based assessments. One center has reported a novel comprehensive paradigm for care and assessment that markedly improved neonatal outcomes. Infants were provided hospital care outside of the NICU in rooms that facilitated family rooming-in and environmental control and optimized provision of nonpharmacologic care. Each infant was assessed with respect to feeding (e.g., does the baby take at least one ounce per feeding?), sleeping (e.g., does the baby have uninterrupted sleep for at least one hour?), and consolability (e.g., can a caregiver quiet a baby in 5-10 minutes?)—an evaluation abbreviated as ESC (eat, sleep, console). Vital signs and weight were also monitored. This center witnessed a dramatic fall, compared to historical controls, in hospital length of stay and the use of pharmacologic treatment in babies exposed prenatally to methadone.[51]

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NEONATAL ABSTINENCE SCORE

Date: _____ Weight: _____

System	Signs & Symptoms	Score	Time AM / PM	Comments
Central Nervous System Disturbances	Excessive High Pitched Cry	2		
	Continuous High Pitched Cry	3		
	Sleeps < 1 Hour After Feeding	3		
	Sleeps < 2 Hours After Feeding	2		
	Sleeps < 3 Hours After Feeding	1		
	Hyperactive Moro Reflex	2		
	Markedly Hyperactive Moro Reflex	3		
	Mild Tremors Disturbed	1		
	Moderate - Severe Tremors Disturbed	2		
	Mild Tremors Undisturbed	3		
	Moderate - Severe Tremors Undisturbed	4		
	Increased Muscle Tone	2		
	Excoriation (Specific Area)	1		
	Myoclonic Jerks	3		
	Generalized Convulsions	5		
Metabolic / Vasomotor / Respiratory Disturbances	Sweating	1		
	Fever < 101° F (37.2° - 38.2° C)	1		
	Fever ≥ 101.1° F (≥38.4° C)	2		
	Frequent Yawning (> 3 - 4 Times/Interval)	1		
	Mottling	1		
	Nasal Stuffiness	1		
	Sneezing (> 3 - 4 Times/Interval)	1		
	Nasal Flaring	2		
	Respiratory Rate - 60/min	1		
	Respiratory Rate - 60/min with Retractions	2		
Gastrointestinal Disturbances	Excessive Sucking	1		
	Poor Feeding	2		
	Regurgitation	2		
	Projectile Vomiting	3		
	Loose Stools	2		
	Watery Stools	3		
	TOTAL SCORE			
	Initials of Scorer			

• **Fig. 46.1** Neonatal abstinence score used for the assessment of infants undergoing neonatal abstinence. Evaluator should check sign or symptom observed at various time intervals. Add scores for total at each evaluation. (Adapted from Finnegan LP, Kaltenbach K. The assessment and management of neonatal abstinence syndrome. In: Hoekelman RA, et al, eds. *Primary pediatric care*. 3rd ed. St Louis: Mosby; 1992:1367.)

Nonpharmacologic Treatment

A plan to institute early supportive care is critical in infants who are at risk for withdrawal. Effective measures include minimizing environmental stimuli (both light and sound) by placing the infant in a dark, quiet environment; avoiding autostimulation by careful swaddling; responding early to an infant's distress signals; adopting appropriate infant positioning and comforting techniques (vertical rocking while the baby is held in the C-position); and providing frequent small volumes of hypercaloric formula or human milk to minimize hunger. In an infant with severe signs of withdrawal, necessary caloric intake to achieve growth has been reported to be as high as 150-250 cal/kg per day because of increased energy expenditure and loss of calories from regurgitation, vomiting, and/or loose stools.[56,117] The infant should be observed carefully to recognize fever, dehydration, or weight loss promptly. The major goals of therapy are to ensure that the infant achieves adequate nutrition and sleep, establishes a consistent pattern of weight gain, and begins social integration. Additional supportive care in the form of intravenous fluids, replacement electrolytes, and gavage feedings are rarely necessary to stabilize the infant's condition in the acute phase.

When possible and if not contraindicated for other reasons, mothers who adhere to a supervised drug treatment program (and who have tested negative for other drugs) should be encouraged to breastfeed so long as the infant continues to gain weight. Breastfeeding or the feeding of human milk has been associated with less severe NAS that has a later onset and less frequently requires pharmacologic intervention.[1,60] Methadone is present in very low concentrations in the human milk of mothers on methadone

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maintenance therapy. Cumulative daily intake of methadone in fully breastfed infants has been estimated to range from 0.01-0.15 mg/day during the first 30 days of life[62] and 0.15-0.30 mg/day between 30 and 180 days of life.[63] Similarly, the amount of buprenorphine excreted in human milk is small. Although more information is needed to evaluate long-term neurodevelopmental outcome of infants exposed to small quantities of buprenorphine, there is no clear reason to discourage breastfeeding in mothers who adhere to methadone or buprenorphine maintenance treatment.[2] Given the relatively small amounts of opioid ingested via breast milk, it is likely that the process of breastfeeding has potent therapeutic benefit for both mother and baby. Each nursery should adopt a protocol for the evaluation and management of neonatal withdrawal, and staff tasked to care for and assess NAS infants should be trained to use an abstinence-scoring instrument in a consistent manner to minimize interobserver variability.

Pharmacologic Treatment

For the infant who does not respond to optimized nonpharmacologic management, drug therapy may be appropriate to reduce the severity of signs of NAS to mild to moderate but tolerable levels and to prevent complications such as fever, feeding intolerance or weight loss, sleeplessness, and seizures. Since the introduction of the abstinence scales in the 1970s, single or serial withdrawal scores have typically guided the decision to initiate pharmacologic treatment. Infants should be scored at the initial appearance of NAS symptoms and then every 3-4 hours based on feeding times. A typical protocol has been to initiate pharmacotherapy when scores average 8 or higher over three scoring intervals or 12 or higher over two scoring intervals. However, no studies to date have compared the use of different withdrawal score thresholds for initiating drug therapy on short-term outcomes (e.g., severity and duration of withdrawal signs, weight gain, duration of hospitalization, need for pharmacologic treatment, or cumulative drug exposure). Although severe withdrawal may be life-threatening, withdrawal of mild to moderate severity is a self-limiting process. Initiation of drug therapy with the intent to achieve drug levels that result in near resolution of signs of withdrawal guarantees prolongation of drug exposure and of hospitalization, which can disrupt maternal–infant bonding. The only certain benefit of drug treatment is a short-term reduction in clinical signs. No study has addressed whether long-term morbidity related to NAS is decreased by drug treatment, nor whether continued postnatal drug exposure increases the likelihood or extent of long-term neurobehavioral and cognitive problems.

Over the past four decades, a variety of drug preparations have been used to treat NAS, including opioids (tincture of opium, neonatal morphine solution, methadone, and paregoric), barbiturates (phenobarbital), benzodiazepines (diazepam, lorazepam), clonidine, and phenothiazines (chlorpromazine). Most US clinicians now use an opioid (oral morphine or methadone) as their drug of first choice. The AAP recommended against using paregoric, because paregoric contains variable concentrations of other opioids as well as toxic ingredients such as camphor, anise oil, alcohol, and benzoic acid.[5]

If the goal of treatment is to achieve substantial diminution of signs of withdrawal, initiation of drug therapy should begin with an intermediate dose that can be increased as necessary to achieve adequate relief but not completely eliminate the signs of NAS. Recommended initial and maximum doses of opioids and secondary drug treatments are detailed in Table 46.4. When the infant is on a stable and effective dose, a process of steady committed weaning should commence. In practice, weaning regimens vary and have not been systematically studied. Some providers tie weaning strictly to Finnegan scores; one or two abnormal or incorrect scores will then prolong the weaning process or lead to an increase in opioid dose. Other providers will wean by 10%-20% of the initial total dose every 12-48 hours if most of the time the infant exhibits only mild signs of withdrawal, feeds acceptably, demonstrates reasonable weight gain, and sleeps adequately. Failure to achieve acceptable control of signs of NAS despite doses of opioids in the higher ranges of usual practice (see Table 46.3) may indicate prenatal exposures to other nonopioid drugs and suggests the need to consider adding a second medication (phenobarbital; clonidine) in another drug class.[85,98] Phenobarbital, a sedative–hypnotic, is sometimes used as the primary treatment of NAS, but it is also the most commonly used medication to supplement opioid therapy. Adjuvant phenobarbital therapy may be helpful in relieving signs of NAS in severely affected infants and allows tapering of opioid therapy, but prolonged outpatient phenobarbital therapy has been reported.[107] Clonidine is an α_2-adrenergic receptor agonist that has been used successfully in combination with an opioid or other drug in older children and adults to treat the signs of withdrawal.[49,118] There are only limited case series in newborns. Via a negative feedback mechanism, clonidine reduces central nervous system sympathetic outflow and palliates symptoms of excess autonomic activity such as tachycardia, hypertension, diaphoresis, restlessness, and diarrhea. In a small case series, six of seven infants with NAS showed significant resolution of signs when treated with oral clonidine.[57] In a randomized, double-masked, controlled trial, Agthe and co-investigators compared the efficacy and safety of treating NAS with diluted tincture of opium (DTO) plus oral clonidine (1 mcg/kg every 3 hours) versus DTO plus placebo in 80 infants with prenatal exposure to methadone and/or heroin.[3] The combination therapy significantly reduced the median length of treatment for all infants and for infants exposed to methadone, but more infants in the DTO/clonidine group required resumption of DTO after initial discontinuation. Additional pharmacokinetic and safety information is needed before clonidine can be recommended for routine use. Recently investigators have reported success using a sublingual preparation of buprenorphine, achieving shorter duration of treatment and hospital stay compared to a regimen of oral morphine.[72]

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TABLE 46.4 Drugs Used in the Treatment of Neonatal Narcotic Withdrawal

Drug	Initial Dose	Increment	Maximum Dose	Comments
Primary Therapy				
Oral morphine[3,61,69,76]	Maintenance dose 0.2-0.3 mg/kg/d Divided every 3-4 hours	0.08-0.16 mg/kg/d	1.2 mg/kg/d	With moderate signs of NAS, start at 0.24 mg/kg/d (0.03 mg/kg every 3 hours or 0.04 mg/kg every 4 hours) If signs of NAS are not sufficiently relieved after initial dose, may give additional dose of 0.03-0.04 mg/kg to achieve adequate level
Oral methadone[75,114a]	Maintenance dose 0.2-0.3 mg/kg/d Divided every 6-12 hours	0.1-0.2 mg/kg/day	0.5-0.6 mg/kg/d	Because of prolonged time for methadone to reach steady-state level, consider loading with 0.2 mg/kg followed by institution of maintenance dose in 6-12 hours
Adjunctive Therapy				
Oral clonidine[3,57]	0.5-1 micrograms every 6 hours		1 microgram every 4 hours	If signs of NAS are controlled with opioid plus clonidine, wean opioid first and then wean clonidine
Oral phenobarbital[5]	Loading dose 10-20 mg/kg Maintenance dose 5 mg/kg/d Divided every 12 hours			Caution that effect of phenobarbital is heightened by systemic opioids

NAS, Neonatal abstinence syndrome.
From Kilpatrick SJ, Papile L, Macones GA. *Guidelines for perinatal care*. 8th ed. Elk Grove Village, IL: American Academy of Pediatrics and American College of Obstetricians and Gynecologists; 2017.

The extant literature does not identify the optimal initial drug or the drug regimen for the treatment of NAS. Published studies are few and generally report small sample sizes. Older studies are often marred by methodological flaws such as quasi-random patient allocation; substantial and often unexplained differences in allocation of patients to treatment groups; imbalances in group characteristics after randomization; failure to mask study treatments; and failure to mask outcome measurements. One recent single-center study showed that methadone compared to morphine treatment significantly reduced hospital length of stay.[20] Results of a larger multicenter study are pending (www.clinicaltrials.gov NCT01958476). With further study, it is possible that an accurate quantification of all prenatal drug exposures will allow specification of optimal pharmacologic treatment. In the future, genetic and epigenetic analyses may more clearly indicate the likelihood and severity of NAS in an exposed infant. In any case, standardization of a comprehensive treatment protocol within a center has been shown to reduce length of stay and length of drug treatment.[53]

Early discharge and subsequent outpatient management of infants with NAS occur in some areas of the country. Existing literature reports experience mainly from abroad and has documented successful but in some cases very prolonged outpatient treatment with both opioids and phenobarbital. Typically, families are carefully screened for eligibility for an outpatient management program. A recent retrospective study reported that 46 of 121 infants with NAS qualified for outpatient management with methadone. The infants with continuing outpatient care had shorter hospital stays and lower hospital costs than the inpatient group. The total duration of medication was higher in the outpatient group, but the total dose of medication was the same between the groups. Readmission rates were similar in the two groups.[115] The prolonged duration of drug exposure with outpatient management raises concerns. Certainly, to safely accomplish home management in these high-risk patients, a multidisciplinary team with frequent assessment of home safety is imperative.

Prevention of NAS

As with most diseases, prevention of NAS is preferable to treatment. Levels of prevention are shown in Box 46.2. The principal means of primary prevention, reducing the number of fetuses exposed to opioids, will require significant

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• BOX 46.2 Overview: Levels of Prevention of Neonatal Abstinence Syndrome

Primary Prevention

- Reduce the number of fetuses exposed to opioids
- Alter the nature, dose, and timing of opioid exposure

Secondary Prevention

- Improve the identification of mother–fetal dyads at risk for NAS
- Modify co-exposures that amplify signs of NAS

Tertiary Prevention

- Minimize postnatal drug exposure
- Promote family resiliency and successful home transition

progress toward reducing the national opioid epidemic; this will result in a parallel decrease in the number of women of reproductive age with opioid dependence. Use of implantable long-acting reversible contraceptives in women on opioids who wish to avoid pregnancy is very effective, but implementation has been stymied in many states by unfavorable Medicaid policies on payment. Finally, there is growing experience with medically supervised maternal opioid withdrawal treatment.[14] It appears promising that appropriate management and provision of intensive outpatient support can achieve detoxification that is safe for both the mother and the fetus and that minimizes maternal recidivism. Further careful research is needed about selection criteria, withdrawal regimen, and intensive supportive outpatient care to verify safety and efficacy.

Long-Term Outcomes

Relatively few studies that control adequately for confounding variables have followed drug-exposed children beyond the first few years of life. Nonetheless, there is emerging evidence for an increased risk of hyperactivity and attention-deficit problems in toddlers and school-age children and of abnormalities in memory and perception in older children. Data do not yet exist or are inconclusive with respect to the independent effect of opioids on intelligence, executive functioning, language, or academic achievement[13] (see Table 46.1). An Australian study has documented that children with a history of NAS are at increased risk for abuse, physical injury, and death during a subsequent hospitalization compared to control children.[111]

Benzodiazepines and Barbiturates

Infants with antenatal exposure to benzodiazepines or barbiturates (nonopioid hypnosedatives) may develop signs of drug withdrawal as late as 7-21 days of age. Usually, the mother has been on high doses of the drug for a long duration before birth. Rarely, infants develop signs of withdrawal when a mother has been exposed to therapeutic doses for a short time. As with the opioids, benzodiazepines with longer half-lives (e.g., diazepam) are associated with more severe signs and duration of withdrawal. Common signs include hypertonia or hypotonia; excessive or poor suck; and vomiting. If an infant has severe signs, these infants have typically been treated with phenobarbital. In such cases, outpatient weaning of phenobarbital has been reported to require weeks to months.

Cocaine

Cocaine (benzoylmethyl-ecgonine) is an alkaloid stimulant drug that is derived from *Erythroxylon coca* shrub leaves. Its derivative, cocaine hydrochloride, can be snorted as a powder as well as ingested orally or administered intravenously. In adults, cocaine can cause convulsions, myocardial infarction, and death. Smoking of "crack" cocaine, an alkaloid free-base form of nearly pure cocaine, became widespread in the 1980s and affected large numbers of women of childbearing age. Inner-city hospitals that provided obstetric and newborn care witnessed rising numbers of cocaine-exposed infants. Initially confined to the high-intensity, drug-trafficking areas, this epidemic subsequently spread to remote rural areas. Media attention focused on the fate of so-called "crack" babies and unfortunately resulted in dissemination of much information that was later proved to be untrue or misleading.

Cocaine alters the norepinephrine, dopamine, and serotonin neurotransmitter pathways. Cocaine inhibits norepinephrine reuptake so that norepinephrine concentration increases in the synaptic cleft and produces tachycardia, arrhythmias, hypertension, vasoconstriction, diaphoresis, and mild tremors through persistent stimulation of the postsynaptic norepinephrine receptors. Similarly, its ability to block dopamine reuptake stimulates dopamine neurotransmission and initially results in neurochemical amplification of the pleasure response, increased alertness, enhanced sense of well-being and self-esteem, and heightened energy and sexual excitement. However, compulsive users soon experience anxiety, depression, and exhaustion, and addicts may exhibit mood disorders, paranoid ideation, and sexual dysfunction. Acute tolerance, rebound mood swings, and cravings are explained by regulatory changes in presynaptic and postsynaptic dopaminergic receptors secondary to persistent use. Cocaine blocks the uptake of tryptophan, hence decreasing endogenous synthesis of serotonin and reducing the perceived need for sleep.

Cocaine readily crosses the placenta and is also excreted in breast milk. Metabolism of cocaine occurs primarily by plasma and hepatic cholinesterases that produce inactive compounds that are eliminated by the kidneys. In pregnant women, fetuses, and infants, plasma cholinesterase activity is diminished, increasing the half-life of cocaine. The degree to which an individual is susceptible to the effects of cocaine may be related to genetic polymorphisms of the cholinesterase enzyme. The term placenta may also provide a degree of protection for individual fetuses by converting cocaine

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into less active metabolites, presumably via cholinesterase activity.

Cocaine use during pregnancy impacts fetal oxygenation by reducing uterine and placental blood flow and impairing fetal oxygen transfer. Pregnant women who use cocaine are at increased risk for spontaneous abortions, abruptio placentae, premature rupture of the membranes, and death. Transient neonatal ventricular tachycardia has been associated with maternal cocaine use shortly before delivery. Higher arterial blood pressure and diminished cardiac output and stroke volume, presumably affected by increased norepinephrine levels, have also been reported in full-term, cocaine-exposed infants compared with drug-free infants on the first postnatal day.

Birth Defects

Animal studies of cocaine exposure show a wide variety of congenital anomalies, including exencephaly, anophthalmia, malformed or missing lenses, cryptorchidism, hydronephrosis, grossly distended bladder, limb reduction defects, ileal atresia, and cardiovascular anomalies. Nonetheless, no consistent teratogenic effect has been found in cocaine-exposed newborns. In the Sprague-Dawley rat model, cocaine causes structural anomalies in a dose-dependent manner during late organogenesis or during the post-organogenic period. Reduction deformities of the limbs and tail and genital tubercle defects occur as a result of hemorrhagic necrosis, disruption, and amputation of existing and developing structures.[7] The etiology of these structural defects may be related to alterations of fetal, placental, and uterine blood flow that cause fetal vascular disruption. Cocaine-induced ischemia may play a role in the development of intestinal atresia and necrotizing enterocolitis, which has been reported in a small series of term and preterm infants prenatally exposed to cocaine.

Growth

Cocaine independently reduces fetal growth.[4,11,30,43,94,121,122] A large single-site cohort study that controlled for potential confounders revealed an independent effect of antenatal cocaine exposure in term infants on birth weight, length, and head circumference.[10] Data from the NIH Maternal Lifestyles Study suggested that the impact of prenatal cocaine exposure on fetal growth may be more pronounced later in gestation, with a cocaine-associated deceleration in growth occurring after 32 weeks' gestation.[8,10] Catch-up growth in early childhood has been observed in some studies and may be a risk factor for later obesity.

Neurobehavior/Withdrawal

Neurobehavioral abnormalities[11,44] frequently occur in neonates with intrauterine cocaine exposure, most frequently on the second or third postnatal days.[25] These abnormalities may include irritability, hyperactivity, tremors, high-pitched cry, excessive sucking, and poor alertness and orientation.[42] Because cocaine or its metabolites may be detected in neonatal urine for as long as 7 days after delivery,[25] observed abnormalities in exposed infants may reflect drug effect rather than withdrawal. In an unmasked study, 6%, 14%, and 35% of infants exposed to cocaine only, heroin only, or cocaine plus heroin, respectively, qualified for treatment on the basis of scoring.[47] Several studies that used masked evaluators found that cocaine-exposed infants had either no[28,52] or minimal[70] withdrawal signs compared with cocaine-naïve infants (i.e., those never exposed). Eyler and colleagues conducted a prospective controlled study of three groups of infants: One group had no documented exposure to cocaine by history or by maternal and infant urine testing; a second group was cocaine exposed but had negative urine screening at birth; and a third group had cocaine metabolites detected in neonatal urine.[44] Observers masked to infant status performed assessments using the Brazelton Neonatal Behavioral Assessment Scale.[17] Infants who were positive for cocaine metabolites did not differ significantly from metabolite-negative infants with a history of exposure or from cocaine-naïve infants. These findings supported neither a withdrawal nor a drug toxicity syndrome. Cocaine-exposed infants have been described as having a higher incidence of abnormal auditory brainstem responses and EEGs compared with unexposed infants.[38,108] In another study, infants with heavy exposure to cocaine had similar Brazelton findings at 2-3 days of age, as did infants with light or no exposure; however, by 17 days of age, heavily exposed infants were more excitable and demonstrated poorer state regulation.[110]

An abstinence syndrome after intrauterine exposure to CNS stimulants such as cocaine and amphetamine has not been clearly defined. Many studies that have assessed behavior and neurologic signs in cocaine-exposed infants have used scoring systems that were designed to evaluate opioid withdrawal.

Long-Term Outcomes

Large prospective studies have begun to show converging evidence for significant, albeit relatively subtle, cocaine-associated deficits in a number of domains of neurobehavioral and neuropsychologic functioning, such as sustained attention, language functioning, and external behaviors. In many of the studies, the observed deficits appear to be statistically robust indicators of cocaine exposure, because they persist even after controlling for numerous environmental confounding variables. Furthermore, in some studies, the effects have been shown to be dose dependent, which lends credence to a teratogenic effect. The importance of cocaine-associated subtle deficits should not be overlooked, because they may be costly in terms of increased numbers of children qualifying for special services in the school system.[78]

Significant deficits in executive function may not become apparent until the child reaches late adolescence or young adulthood as complex frontal lobe neurons complete their

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developmental trajectory of maturation into adulthood. Thus "sleeper effects" of prenatal cocaine exposure may emerge later to affect real-life functionality as these children face increasing demands related to academics, social situations, and acceptance of responsibility for the well-being of themselves and others. Cocaine may have a subtle effect on language. Studies are inconsistent with respect to an effect of cocaine exposure on school achievement.

Mothers who use cocaine often use other drugs that independently or via drug–drug interactions can affect long-term outcomes of interest. Environmental risk factors (e.g., poverty and exposure to domestic violence or community violence) and caregiver attributes also modulate long-term outcomes. The presence of factors that can confer resiliency to the child may countermand any adverse effects of antenatal exposure.

Amphetamines

Methamphetamine abuse has been reported among pregnant women,[102] although overall rates are low compared with cocaine and appear to have decreased in the general population.[106] Methamphetamine is an extremely potent sympathomimetic agent that induces euphoria and increases alertness and self-confidence, because it produces a massive efflux of dopamine in the central nervous system. Pregnant women who abuse methamphetamine are at increased risk of preterm birth, placental abruption, fetal distress, and intrauterine growth restriction at rates similar to those for pregnant women who use cocaine. In one study, only 4% of infants exposed to methamphetamine were treated for drug withdrawal, but it was not possible to exclude concomitant abuse of other drugs as contributory in all cases.[102] There are reports of long-term adverse neurotoxic effects of antenatal methamphetamine exposure on behavior, cognitive skills, and physical dexterity.[16,22]

Key Points

- Antenatal substance exposure may act on a developing fetus as teratogens, inhibitors of somatic growth and organ maturation, and disruptors of central nervous system development; in addition, at or shortly after birth, infants may demonstrate signs of toxicity or withdrawal.
- Prenatal exposure to alcohol causes the greatest single drug-induced cumulative preventable intellectual deficit in children.
- Infants with prenatal exposure to opioids are at risk to develop a constellation of signs of withdrawal, known as neonatal abstinence syndrome (NAS), involving primarily the central and autonomic nervous systems and the gastrointestinal system; infants at highest risk at birth are those most recently exposed to long-acting opioids with co-exposures due to maternal smoking or use of selective serotonin reuptake inhibitors.
- All mothers should be interviewed during prenatal care for the use of drugs and substances so that appropriate treatment can be provided to minimize risks to mother and fetus.
- The primary treatment of NAS is intensive nonpharmacologic support and monitoring; infants with severe signs of NAS that significantly compromise feeding and growth, sleeping, and socialization respond to pharmacologic therapy.
- While significant prenatal exposure to alcohol may have devastating long-term effects, the long-term impact of marijuana, opioids, and cocaine on growth, behavior, intelligence, language, and achievement appear to range from no effect to mild effects and may be modifiable by subsequent environmental exposure and intrinsic resiliency.

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47

Developmental Immunology

JOHN T. BENJAMIN AND AKHIL MAHESHWARI

Birth represents a functional watershed in the developing immune system. In utero, the fetus is exposed to a constant barrage of "foreign" antigens that are derived mainly from the mother and must downregulate its immune responses to survive. However, after birth, the neonatal immune system is exposed to a new, more varied set of antigens and must evolve dichotomous responses to simultaneously "contain" microbial populations on various cutaneous and mucosal surfaces and also develop tolerance to commensal microbes and dietary macromolecules. While some components of the neonatal immune system perform adequately and on par with adults, immaturity of several major arms of immunity results in a developmentally regulated, transient state of immunodeficiency during early infancy. This chapter highlights major strengths and limitations of the neonatal immune system.

The immunologic system is broadly comprised of two major host defense mechanisms: innate, or nonspecific, immune mechanisms, and the acquired, or specific, immune mechanisms. By definition, *innate immunity* includes host defense mechanisms that operate effectively without prior exposure to a microorganism or its antigens. Some of these mechanisms include physical barriers, such as intact skin and mucous membranes, and chemical barriers, such as gastric acid and digestive enzymes. Beneath these important protective layers lie phagocytic cells, which constitute the first line of host defense against any microbes that breach the cutaneous and mucosal barriers. Soluble plasma and tissue proteins serve to amplify the function of the phagocytic cells as innate immune effectors. *Acquired,* or specific, *immunity* comprises primarily the cell-mediated (T lymphocyte) and the humoral (B lymphocyte and immunoglobulin) systems.

Both innate and acquired immune mechanisms are necessary for an individual to be fully immunocompetent. These systems are intimately interrelated and interdependent. Phagocytes such as neutrophils and the cells of the monocytes–macrophage lineage are important effectors of innate immunity, because these cells function to ingest and clear microbial pathogens from normal tissues. Monocytes and macrophages also process microbial antigenic material for presentation to T lymphocytes, a pivotal step in the initiation of the adaptive immune response.

Overview of Hematopoiesis

During fetal development, hematopoiesis first begins in the extra-embryonic mesoderm of the yolk sac and later shifts to the liver and then to the marrow. Yolk sac hematopoiesis continues from the 3rd through the 8th-10th week. Hepatic hematopoiesis begins in the 5th week and continues through 20-24 weeks and is mainly erythropoietic; although myeloid progenitors are abundant in the liver, mature neutrophils are not identifiable. Hematopoiesis is observed in the marrow by the 11th week, when committed granulocytic progenitors are first seen in the clavicular marrow. As gestation proceeds to the 20th week, the bone marrow becomes the major site of hematopoiesis and thereafter remains the primary reservoir for replenishing circulating populations of immune cells.

All the cellular components of the immunologic system have limited life spans, and the cells must be constantly replenished from a pool of undifferentiated precursor cells derived from a pluripotent stem cell.[50] Through mechanisms that are not well understood, pluripotent stem cells are stimulated to divide and differentiate into committed progenitor cells that mature into circulating blood cells. Progenitor expansion and differentiation is normally driven and regulated by a variety of growth factors supplied by fibroblasts, endothelial cells, and macrophages present in the microenvironment of the hematopoietic stem cells. Emerging evidence also indicates a role for the local extracellular matrix; specific matrix-associated glycoproteins may favor one cellular lineage over another.

Pluznick and Sachs[39] and Bradley and Metcalf[9] first cultured hematopoietic progenitor cells in semisolid media and named these progenitors *colony-forming units* (CFUs). CFUs producing a mixture of granulocytes, macrophages, and erythrocytes were called *CFU-MIX*, whereas the CFUs producing granulocytes, macrophages, erythrocytes, and megakaryocytes were called *CFU-GEMM*. Other CFUs gave rise to only 1-2 cell lineages: *CFU-G* produced only

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Abstract

The transition from fetal to neonatal life marks a critical watershed period in the developing immune system. In utero, the fetus is primarily exposed to maternal antigens and must downregulate its immune responses to survive. In contrast, after birth, the developing newborn is exposed to a greater diversity of antigens, including pathogenic and commensal microbes, dietary macromolecules, and self-antigens. The neonate must thus evolve dichotomous immune responses to simultaneously fight various pathogenic microorganisms while also developing immune-tolerance to self-antigens. Although some components of the neonatal immune system are functionally similar to adults, others are immature, leading to a developmentally regulated state of relative immunodeficiency in the neonate. This chapter highlights the major quantitative and qualitative changes occurring in the innate and adaptive arms of the immune system in the developing fetus and the neonate.

Keywords

innate immunity
adaptive immunity
development
leukocytes
phagocytes
immunoglobulins

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neutrophils, *CFU-M* produced monocytes, *CFU-GM* gave rise to both neutrophils and monocytes, and *CFU-Meg* produced only megakaryocytes. More recently, development of monoclonal antibodies that recognize cell surface molecules expressed on hematopoietic stem cells has permitted the isolation and characterization of these cells.

Innate Immunity

Cellular Components

The most primitive host defense mechanism involves the ingestion and killing of bacteria and other microorganisms by phagocytic cells. Polymorphonuclear neutrophils (PMNs), monocytes, and macrophages are the major cell types that accomplish this aspect of host defense. Natural killer (NK) cells are also important components of the innate immune system, but these cells kill invading pathogens by non-phagocytic mechanisms. All these cell types can eliminate pathogens from the host, but do so more efficiently when the pathogens are opsonized, or coated, by complement components and other soluble proteins of the innate immune system. Similarly, non-phagocytic methods such as lysis of infected cells by PMNs and macrophages are also augmented in the presence of specific antibody to the target organism. This section provides an overview of neutrophils and monocyte/macrophages, important phagocytic cells mediating the innate immune response.

Polymorphonuclear Neutrophil System

Kinetics of Production and Circulation

In the human fetus, granulocytopoiesis takes place almost exclusively in the bone marrow. The PMN system arises from two major hematopoietic progenitors, the CFU-mix and the CFU-GEMM. In the bone marrow, the neutrophil cell lineage includes early precursors, which have a capacity for 4-5 cell divisions (the neutrophil proliferating pool or the NPP), and the later, postmitotic stages that are in the process of differentiation (neutrophil storage pool or NSP). In adults, the NPP contains about 2×10^9 cells/kg body weight, and the NSP contains about 6×10^9 cells/kg body weight.[28] The NPP and NSP together contain nearly 90% of all neutrophils in the body. The NSP constitutes a reserve pool of mature cells, including metamyelocytes, band neutrophils, and segmented neutrophils that may be rapidly mobilized into the circulation in response to inflammation.[28]

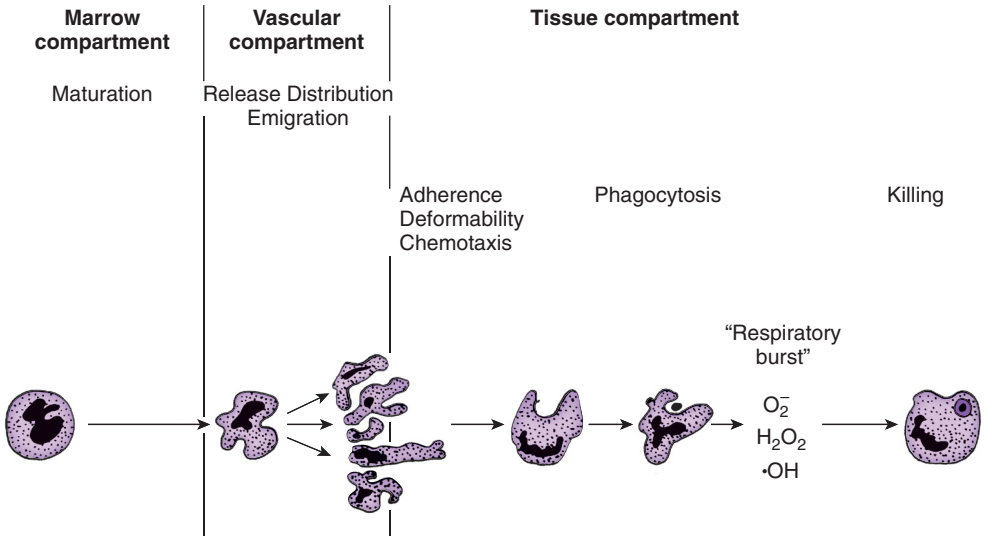
Positive and negative regulators of PMN production have been identified. Positive regulatory factors are interleukin (IL)-3, granulocyte-colony stimulating factor (G-CSF), and the granulocyte-macrophage colony-stimulating factor (GM-CSF). Several negative regulators of PMN production have also been identified, including the interferons (IFNs), transforming growth factor-α, macrophage inflammatory protein-1α (CC motif-ligand 3), prostaglandins, and lactoferrin and other iron-binding proteins. Although the mechanisms by which PMNs are released from the marrow under physiologic conditions are unclear, increasing evidence indicates an important role for the chemokine receptor CXCR4. During inflammation, IL-1, tumor necrosis factor (TNF), epinephrine, and complement fragments can stimulate PMN release from the bone marrow. Once released from the marrow, mature PMNs circulate for approximately 6-8 hours before migrating into tissues, where these cells survive for about an additional 24 hours. While in the bloodstream, half of the PMNs are attached to the microvascular endothelium, mainly in the lungs, and the other half are free in circulation. After PMNs emigrate from the blood vessels and enter a tissue, they do not reenter blood vessels but age and die in the tissue. Although the actual site of PMN clearance is unknown, macrophages may play an important role in ingestion and degradation of senescent apoptotic PMNs.

Mature PMNs are first identified in the fetal bone marrow at approximately 14 weeks of gestation.[28] By 22-23 weeks of gestation, the circulating PMN count increases but remains lower than in term newborns. The fetal blood contains 10- to 50-fold higher concentration of CFU-GM than adult blood, yet the fetus has a much smaller total pool of neutrophil progenitors. One explanation for the high concentration of circulating progenitors is that these stem cells may have left one hematopoietic environment (the liver) for another (the bone marrow).

In the mid-gestation fetus and preterm infant, the NSP is very small in size and can be readily exhausted during sepsis.[28] The NPP is also smaller, about one-tenth the size (per kg body weight) of adults. Interventions such as administration of recombinant granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and corticosteroids can release neutrophils from the NSP. Epinephrine can also rapidly release marginated neutrophils into circulation, and a mild demarginating response may also be observed in preterm infants after red cell transfusions.

Normal PMN Concentrations and Neutropenia. Circulating concentrations of PMNs increase dramatically at birth, peak at 12-24 hours, and then decline slowly by 72 hours to remain stable during the rest of the neonatal period. Blood PMN concentrations can be interpreted using one of several available reference ranges.[30,34,43] The absolute neutrophil count can be calculated from a routine complete blood count (CBC) by multiplying the white cell count with the sum of segmented and band neutrophil percentages on the differential count. Manroe et al. were the first to compile reference ranges for blood neutrophil concentrations in neonates using data from a cohort of 434 neonates born at 38.9 ± 2.4 weeks' gestation.[31] They showed that the neutrophil counts peaked at 12-24 hours with 95% confidence limits of 7,800-14,500/μL and then stabilized at a lower value of 1,750 by 72 hours of life. A stable upper limit was achieved at 6.6 days of age. Although these ranges were useful for term and late preterm neonates, these did not include many preterm infants. To address this deficiency, Mouzinho et al. compiled ANC values from 1,788 CBCs drawn from 63

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• **Fig. 47.1** Overview of polymorphonuclear neutrophil (PMN) functions. PMNs are produced and mature in the bone marrow over a 2-week period. On release from the marrow, PMNs circulate for 6-8 hours before emigrating into tissues. At sites of infection, chemotactic factors enhance PMN adhesion to and emigration through vascular endothelium, and PMNs migrate in a directed fashion (chemotaxis) toward the pathogens. Phagocytosis of the offending organisms stimulates an increase in production of oxygen metabolites (respiratory burst), which facilitates PMN killing of the ingested microbes.

neonates born at 29.9 ± 2.3 weeks' gestation.[34] Their revised charts were comparable to those from Manroe et al. near the upper limits of blood neutrophil concentrations but showed greater variation at the lower limit. In a more recent study, Schmutz et al. compiled a new set of reference ranges for ANCs using data from 30,354 CBCs from neonates born at 23-42 weeks' gestation.[43] Besides the large sample size, a major strength of this study was the use of automated blood counting instrumentation, which allowed greater consistency in identification of neutrophils. In the interval between 72 and 240 hours after birth, the ANC ranged between 2700-13,000/μL (5th-95th percentile) for infants >36 weeks' gestation, between 1000-12,500/μL at 28-36 weeks, and 1300-15,300/μL at <28 weeks' gestation. The upper limits of ANC in this data set were higher than ranges reported by both Manroe and Mouzinho, which may have been due to the high altitude at which the participating centers were located.

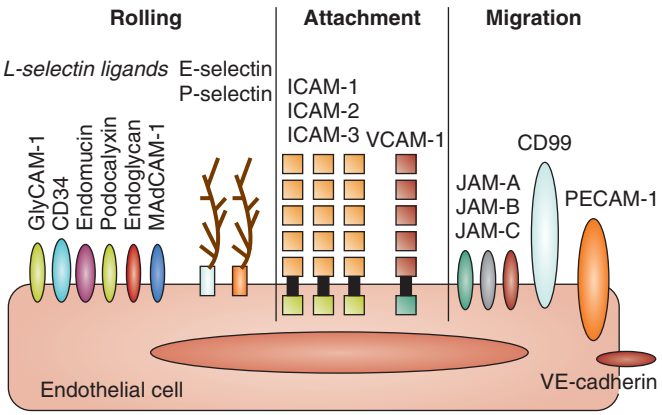
When searching for the cause of neutropenia (<1500 PMNs/mm^9) in infants, a strong suspicion of infection is warranted, although maternal preeclampsia, premature birth, birth depression, intraventricular hemorrhage, and hemolytic disease may result in low peripheral PMN counts. Persistent neutropenia is one feature that is frequently seen in patients who succumb to overwhelming sepsis. Neutropenia in these infants may be due to increased margination of activated circulating cells or to rapid depletion of circulating and bone marrow storage pool PMNs. Failure to provide adequate numbers of PMNs to the sites of microbial invasion may contribute to the risk of overwhelming sepsis in neonates.

Overview of Polymorphonuclear Neutrophil Function

The PMN is qualitatively and quantitatively the most effective killing phagocyte of host defense. Numerous coordinated steps are required to attract a large number of PMNs from the circulating blood into a tissue at the site of microbial invasion (Fig. 47.1). During acute inflammation, first mature neutrophils, and then progressively immature cells, are released from the bone marrow storage pool into the circulation. The circulating PMNs exit the intravascular compartment to enter tissue sites of inflammation in three steps: margination and rolling on vascular endothelium, attachment to the endothelial cells, and transendothelial migration. In the face of microbial translocation across cutaneous or mucosal barriers, a variety of chemoattractants recruit circulating PMNs, including microbial products such as *N*-formyl-methionyl-leucyl-phenylalanine (f-MLP), and host factors such as CXC chemokines (particularly those expressing the tripeptide sequence glutamic acid-leucine-arginine, such as IL-8), products of the complement system (C5a), lipids such as leukotrienes (LTB4) and hepoxilin-A3, collagen fragments containing the tripeptide sequence proline-glycine-proline, and nuclear matrix proteins (such as high-mobility group box-1) that are released during cell death.

Rolling and Adhesion. PMN adhesion to endothelial cells is a crucial step in the recruitment of these leukocytes to inflammatory sites. Although PMNs can adhere to normal or activated vascular endothelium, inflammation is associated with hemodynamic and biochemical changes in blood vessels that facilitate leukocyte adhesion to the vessel endothelial lining. PMNs flowing through an

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• **Fig. 47.2** Adhesion of white blood cells to endothelial cells is mediated by several receptor–ligand pair interactions. A distinct set of endothelial molecules are involved in each stage of leukocyte recruitment (rolling, attachment, and transendothelial migration). In the rolling phase, L-selectin receptors on neutrophils bind to one of several ligands on the endothelial cells. Similarly, in the attachment phase, neutrophil β-integrins bind to the ICAM 1-3 or VCAM-1 receptors.

inflamed venule may transiently adhere to the endothelium to "brake" their flow, causing the neutrophils to "tumble" or "roll" on the vascular surface. Leukocyte rolling is mediated via the interaction of L-selectin molecules on neutrophils with endothelial glycoproteins called addressins (Fig. 47.2): glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1), CD34/sgp90, endomucin, podocalyxin, endoglycan, and the mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1). Endothelial cells also express two selectin molecules, P-selectin/CD62P and E-selectin/CD62E, which interact with the P-selectin glycoprotein ligand-1 (PSGL-1) and L-selectin on leukocytes. Engagement of these selectins activates signaling pathways in neutrophils that initiate neutrophil rolling and activation.[1,29]

Circulating neutrophils usually roll along vascular endothelial cells with transient interactions between neutrophil selectins on the cell surface and counter-receptors on the endothelium. When endothelial cells are activated during inflammation, more selectin counter-receptors are expressed, and additional proteins (intercellular adhesion molecule [ICAM]-1 and ICAM-2) of the immunoglobulin supergene family, which serve as ligands for the neutrophil integrin family, are activated. Specific receptor-ligand interactions at the cell surface membrane facilitating neutrophil adhesion to vascular endothelium are shown in Fig. 47.2.

After a few rolling events, leukocytes slow down and rest on the endothelium. During this phase, the interaction of leukocyte integrins with endothelial receptors initiates signaling events in the endothelium leading to transendothelial migration of leukocytes. Integrins involved in neutrophil trafficking include three heterodimeric proteins, each of which consists of one immunologically distinct "α" subunit (leukocyte functional antigen-1; CD11a, Mac-1; CD11b, p150, 95; CD11c), along with a common "β" subunit (CD18). Monoclonal antibodies directed against CD11b/CD18 inhibit PMN aggregation, spread, chemotaxis, and adhesion to endothelial cells. CD11b/CD18 and CD11c/CD18 serve as complement receptors and mediate complement-coated (fragment iC3b) particle ingestion by PMNs. CD11a/CD18 has been shown to be important in PMN killing of target cells through antibody-dependent mechanisms. Patients with a heritable deficiency of these leukocyte cell surface glycoproteins have recurrent infections characterized by failure to accumulate granulocytes at sites of infection.

Increased interactions of neutrophil cell surface integrins with endothelial ICAM-1 and ICAM-2 results in firm neutrophil-endothelial adhesive interactions. After tight adhesion, the PMN begins a process of diapedesis through adjacent endothelial cells and the intact underlying basement membrane. Once the PMN has penetrated the basement membrane, the cell migrates from the blood vessel into the area of inflammation. In the tissues, initial random migration (chemokinesis) becomes progressively directed (chemotaxis) toward the nidus of microorganisms along concentration gradients of bacterial products or chemotactic factors.

Adhesion of PMNs to artificial surfaces in vitro is comparable for unstimulated PMNs isolated from neonatal or adult blood. When PMNs from term neonates are stimulated with chemotactic factors, adhesion is greatly diminished, however, compared with cells isolated from adults. More profound deficits are displayed by PMNs from preterm infants. Neonatal PMNs show lower selectin expression, defective shedding of L-selectin, and less stimulated mobilization and overall expression of CD11b/CD18 glycoproteins on the plasma membrane. Other causes of diminished stimulated adherence include impaired capacity to upregulate cell surface chemotactic receptors, lower granular content of lactoferrin, less fibronectin binding to the cell surface, and less shape change (failure to increase significantly overall cell surface area on chemotactic factor stimulation). Downregulation of L-selectin expression on term newborn cord blood granulocytes and monocytes during acute inflammation has been shown, although the pattern and level of shedding vary from neutrophils isolated from adult subjects.

Compared to neutrophils from adults, neutrophils from both term and preterm neonates adhere poorly to endothelium. Neonatal neutrophils have lower selectin and β-integrin expression. In neonates, L-selectin expression is lower at birth than in adults and decreases further during the first 24-72 hours. Neonatal "stress," as in perinatal asphyxia, may further reduce L-selectin expression on neutrophils. In addition, neonatal neutrophils display defective shedding of L-selectin. The combination of lower expression and impaired shedding of L-selectin reduces the frequency of neutrophil rolling events, which are a rate-limiting step in the tissue recruitment of neutrophils. Characteristics of preterm vascular endothelium such as lower *P*-selectin expression further contribute to these defects in neutrophil recruitment.

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Neonatal neutrophils have lower expression of Mac-1(CD11b/CD18), which correlates with lower neutrophil–endothelial adherence and transmigration. In addition, neutrophils from both preterm and term infants are unable to upregulate Mac-1 expression following stimulation by bacterial products.

Transendothelial migration of neutrophils is affected to some degree by deformability of neutrophils. Although initial studies reported conflicting data, deformability of mature resting neutrophils appears to be similar in healthy preterm neonates to their full-term counterparts and adults. However, the release of immature neutrophils from the NSP during sepsis is associated with an overall reduction in neutrophil deformability.

Interventions such as administration of recombinant G-CSF increase the expression of β_2-integrins but lower L-selectin expression on neonatal neutrophils (both term and preterm). In contrast, early dexamethasone administration decreases β_2 integrin expression on neutrophils.

Chemotaxis. Chemotaxis is defined as the directed cellular migration along the concentration gradient of a chemoattracting substance. This movement involves a series of orchestrated events, including the binding of the chemoattractant to cell surface receptors, generation of an intracellular second messenger that is coupled to the receptor-ligand binding, and remodeling of the plasma membrane and cytoskeleton to produce shape changes and proper orientation of the cellular contents toward the highest concentration of the chemoattractant. Morphologically, the PMN orients toward the chemoattractant with the formation of a lamellipodium along the leading edge. Most of the intracellular organelles remain at the posterior pole of the cell (uropod). As the cell moves, the leading edge adheres to available surfaces, and contraction of cytoskeletal microfilaments (actin and myosin) pulls along the rest of the cell. Many aspects of this process are poorly developed in PMNs isolated from neonatal blood. Some of the chemotactic defects of PMNs present during the neonatal period persist throughout early childhood.

Neutrophils from both term and preterm neonates have an impaired chemotactic response and migrate slowly compared to adult cells. Although neutrophils from term infants achieve normal chemotactic function by 2 weeks after birth, such postnatal neutrophil maturation begins 2-3 weeks after birth in immature preterm infants and proceeds very slowly. Neutrophils from preterm infants born at 34-36 weeks' gestation achieve normal chemotaxis by 40-42 weeks' postconceptional age (PCA). In more immature preterm infants (<34 weeks), neutrophil chemotaxis improves with time but remains impaired in comparison to adults, even at 42 weeks' PCA. The presence of various clinical confounders makes it difficult to separate the effects of clinical stress from the effects of prematurity on neutrophil function. Gram-negative sepsis may depress neutrophil chemotaxis whereas superficial infections are associated with enhanced chemotaxis.

Neonatal neutrophils bind various chemoattractants normally. However, chemoattractant-induced membrane depolarization, calcium transport, and sugar uptake are relatively less efficient. Neonatal neutrophils show an incremental chemotactic response to increasing chemokine concentrations, but these responses remain lower than adult neutrophils. The chemotactic defect in neonatal neutrophils may be multifactorial, affected by factors such as a larger, poorly motile neutrophil subpopulation; impaired calcium mobilization; and aberrations in intracellular signaling pathways such as NF-B activation. Lower Mac-1 expression can also impede chemotaxis due to impaired neutrophil interaction with the extracellular matrix.

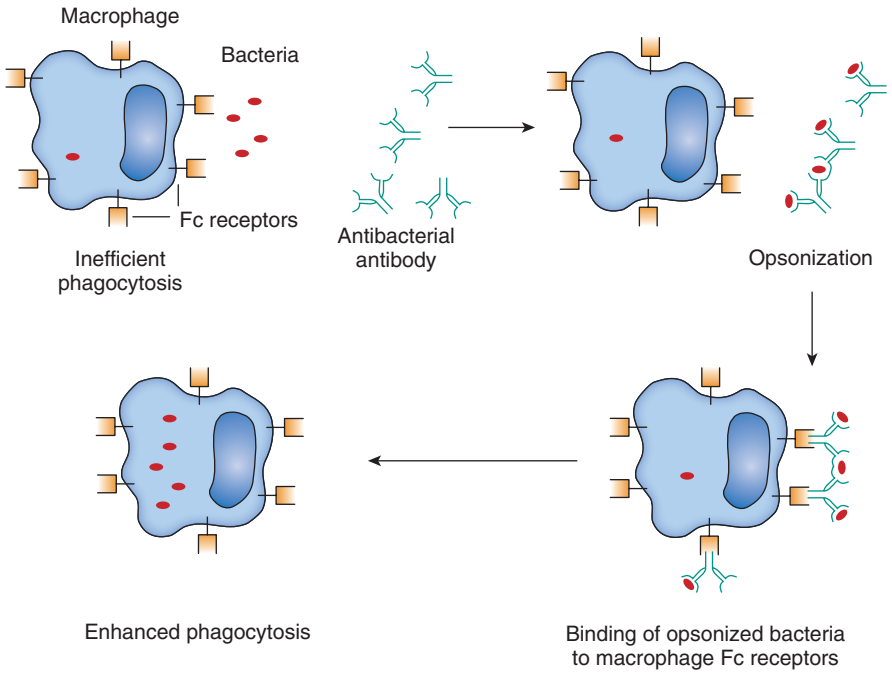
In preterm infants, intrapartum exposure to magnesium sulfate reduces both neutrophil chemotaxis and random motility. Theophylline concentrations in the high therapeutic range (84 μmol/L or 15 μg/mL) cause dose-dependent reductions in neutrophil chemotaxis. Cells from preterm infants are particularly sensitive to this effect. In contrast, theophylline concentrations in the low therapeutic range (28 μmol/L or 5 μg/mL) increase neutrophil activity. Indomethacin, too, has an adverse effect on neutrophil chemotaxis, which is more pronounced in preterm infants. Both G-CSF and GM-CSF increase neutrophil chemotactic responsiveness to other chemoattractants.

Phagocytosis. Phagocytosis is a process of particle ingestion. Most particulate matter must be opsonized (coated) with IgG, complement fragments C3b or iC3b, fibronectin, or other proteins before being recognized and engulfed by PMNs (Fig. 47.3). Neutrophils express IgG receptors such as Fcγ receptors I-III (or CD16, CD32, CD64), C3b (CR1), and iC3b (CR3). After binding of the opsonized microbe by an appropriate cell surface receptor, the PMN extends pseudopods to surround the particle and form a phagocytic vacuole. Microbes may also be ingested without opsonization through several interactions like lectin-carbohydrates on bacterial fimbriae that interact with neutrophil glycoproteins, protein–protein (such as filamentous hemagglutinin that express the argly-asp), and hydrophobic-protein (bacterial glycolipids and neutrophil integrins) interactions.

Neutrophils from preterm neonates show impaired phagocytosis, which corrects by late third trimester or term gestation to become comparable to adults. Preterm neutrophils ingest particles more slowly and ingest fewer bacteria. The lack of opsonic activity is an important consideration, as preterm infants often have lower concentrations of specific antibodies. Adult neutrophils lose their phagocytic efficiency if suspended in serum of preterm infants. Similarly, neutrophils of preterm neonates can increase their phagocytic function following exposure to adult serum or therapeutic immunoglobulin preparations.

Compared to term neonates and adults, preterm neutrophils have a lower expression of CD16 ($F_c\gamma$RIII) and CD32 ($F_c\gamma$RII), the two most abundant neutrophil IgG receptors. In "stressed" preterm neonates with severe RDS or sepsis, CD16 expression may be even lower. Whereas CD16

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• **Fig. 47.3** Antibody-dependent opsonization and phagocytosis of bacteria. Antibody binding to particles such as bacteria can markedly enhance the efficiency of phagocytosis. Enhancement of phagocytosis in macrophages involves increased attachment of the coated particle to the cell surface membrane and commensurate activation of the phagocyte, both of which are mediated through occupancy of Fc receptors. (From Abbas AK et al., eds. *Cellular and molecular immunology*. 2nd ed. Philadelphia: Saunders; 1994, with permission.)

expression normally increases to adult levels over the first 3 weeks of life, CD32 deficiency does not correct with time. CD32 is the high-affinity receptor for IgG_2 (important against encapsulated bacteria), and hence CD32 deficiency may represent an important immune defect in preterm neonates. Unlike CD16 and CD32, CD64 expression on neonatal neutrophils (both preterm and term) may be higher than neutrophils from adult subjects. CD64 is not affected by neonatal "stress" as in respiratory distress and/or prolonged rupture of membranes, and emerging data suggest that CD64 might be a useful early marker for bacterial infections.

Recombinant G-CSF and GM-CSF both activate neutrophil phagocytosis. The benefits of intravenous immunoglobulin (IVIG) as a source of opsonic activity remain uncertain. A major limitation may be in the formulation of current IVIG preparations, which may not have adequate concentrations of antibodies against neonatal pathogens.

Microbicidal Activity. The phagolysosome provides an enclosed space in which an ingested microbe is exposed to high concentrations of toxic substances while limiting the exposure of the phagocyte and other cells to these potentially injurious agents. The major killing mechanism in neutrophils involves the generation of highly reactive free oxygen radicals in a "respiratory burst." An NADPH-dependent respiratory burst oxidase localized on the cell membrane (and therefore, the phagosome membrane) reduces molecular oxygen (O_2) to superoxide anion ($O\bullet_2^-$). Subsequent generation of hydrogen peroxide (H_2O_2) and the hydroxyl radical (OH•, formed in the presence of iron) also contributes to the microbicidal capacity of neutrophils.[1]

These oxygen-dependent bactericidal mechanisms can be broadly divided into myeloperoxidase (MPO)-independent (such as hydrogen peroxide) and MPO-dependent (MPO catalyzes reactions between H_2O_2 and halides to form highly reactive products). H_2O_2 is a weak bactericidal agent per se, but the MPO-H_2O_2-halide system increases its efficacy by nearly 50-fold. The bactericidal effects of free oxygen radicals are due to oxidizing effects on various components of the bacterial cell wall.

Although preterm neutrophils have a higher oxygen consumption and normal/elevated release of superoxide and H_2O_2, the respiratory burst is, overall, depressed. This deficiency may be more marked in preterm infants with a high severity of sickness. Neutrophil oxidative burst remains impaired in preterm infants despite opsonization with IgG and complement.

Perinatal events can influence the respiratory burst in neonatal neutrophils. Labor and vaginal delivery activates the generation of free oxygen radicals in neonatal neutrophils. In contrast, perinatal distress can suppress the neutrophil respiratory burst. Both LPS and cytokines such as interferons and TNF can prime neutrophils for an accelerated respiratory burst in vitro, but prolonged exposure to these agents (during sepsis) can dampen their effect. Reduced respiratory burst activity in preterm infants

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correlates with impaired intracellular killing of *S. aureus* or *E. coli.* Whereas bacterial killing by neutrophils from term neonates has consistently been found to be normal, killing of staphylococci was impaired in preterm neonates.

The postnatal maturation of respiratory burst response varies according to gestational age. During the first week, infants born at 24–28 weeks have a lower respiratory burst than those born at 29-35 weeks. The differences between preterm infants born at different gestational ages disappear in about 2 months, but overall, neutrophils from preterm infants continue to have a weaker oxidative burst than adults. The postnatal maturation of the respiratory burst may not be seen at all in sick preterm infants receiving intensive care.

In "stressed" preterm infants receiving intensive care, recombinant GM-CSF can boost the neutrophil respiratory burst to levels seen in term neonates. Similarly, G-CSF can enhance neutrophil respiratory burst response in septic preterm infants. In adults, hypertonic saline may enhance host response to bacterial challenge by augmenting superoxide formation in neutrophils. Intracellular killing may also be augmented by fluoroquinolones such as ciprofloxacin, which have a potent intraphagosomal bactericidal activity against both gram-positive and gram-negative bacteria.

Neutrophils also contain additional elaborate nonoxidative killing mechanisms, including cationic proteins like defensins, bactericidal/permeability-increasing protein (BPI), and LL-37; proteolytic enzymes such as lysozyme, proteinase 3, and neutrophil elastase; and metal chelator proteins such as lactoferrin.[1] Defensins are broad-spectrum antimicrobial peptides with activity against gram-positive and gram-negative bacteria, fungi, and enveloped viruses. BPI binds lipopolysaccharide (LPS) and blocks its effects, can damage the outer membrane of gram-negative bacteria, and has some opsonic activity. Lactoferrin, an iron chelator, is bacteriostatic as it deprives bacteria of the iron required for growth. Lactoferrin is also involved in neutrophil degranulation, in oxygen radical production, and in granulocytopoiesis. Lysozyme hydrolyzes a glycoside bond in the bacterial cell wall peptidoglycan. Primary granules also contain other cationic antibacterial proteins such as azuricidin, indolicin, and cathelicidins.

Another elegant antimicrobial defense system demonstrated by neutrophils is their ability to form neutrophil extracellular traps (NETs). Upon activation, neutrophils can undergo a type of cell death in which chromatin is released from the cell in the form of NETs. These NETs also contain histones and other antimicrobial proteins that function to trap and kill microbes in the extracellular space. However, neonatal neutrophils are deficient in their ability to form NETs.[4] The mechanisms leading to NET formation and its ability to fight infectious agents is still not well understood and is an active area of investigation.[1]

Degranulation. Neutrophils contain three major types of granules: (1) the "azurophilic" granules (stain positive with the azure A dye), (2) "specific" granules (do not stain with azure A), and (3) "gelatinase" granules. Azurophilic granules contain myeloperoxidase (MPO); proteolytic enzymes such as cathepsin G, proteinase-3, and neutrophil elastase; and antimicrobial proteins such as defensins and the bactericidal permeability-increasing protein (BPI). These granules release their contents into the phagolysosomes and are involved in intracellular killing. The specific granules contain antibacterial agents such as lactoferrin and lysozyme, receptors for complement components, and bacterial products such as f-MLP. Specific granules fuse with the cell membrane to release their contents by exocytosis and also bring functionally important membrane proteins such as integrins, cytochrome-b_{558}, and receptors for chemotactic agents and opsonins to the cell surface. Specific granules play an important role in extracellular killing. Gelatinase granules contain fewer antimicrobial cargo but are storage sites for gelatinases and other metalloproteases.[1]

Neutrophils from term neonates have granule content and degranulation responses similar to adults. However, neutrophils from preterm infants have a lower capacity to release BPI, elastase, and lactoferrin than in adults and term infants. G-CSF activates mature neutrophils without degranulation of primary granules, whereas GM-CSF induces degranulation and exocytosis of granule contents. However, anti-inflammatory agents such as corticosteroids and indomethacin inhibit the degranulation of secondary granules.

Summary

PMNs of term and preterm infants are limited in chemotactic, phagocytic, and microbicidal activities. The physiologic rationale for the use of hematopoietic growth factors to improve neutrophil function qualitatively and quantitatively has been well established. The use of G-CSF and GM-CSF has been shown to increase the neutrophil storage pool, induce neutrophilia, and improve many neutrophil functions. In meta-analysis, G-CSF administration was shown to reduce mortality in neonates with sepsis.[5] However, when the nonrandomized studies were excluded, the analysis did not remain statistically adequate. G-CSF therapy is generally well tolerated in neonates, and many centers now use recombinant G-CSF in infants with severe neutropenia (absolute neutrophil counts <500 for 48 hours or between 500-1000 for more than 5-7 days).[16] However, based on current literature, a clear recommendation for the use of these growth factors to decrease the incidence of morbidity and mortality associated with sepsis in newborns cannot yet be made. Further studies are needed in high-risk neonatal subgroups with sepsis, as preliminary evidence suggests that such an approach may be more effective. The newer, longer-acting polyethylene glycol-conjugated or glycosylated forms of G-CSF also hold promise as viable therapeutic alternatives.

Mononuclear Phagocyte System

Production and Differentiation

The mononuclear phagocyte system comprises bone marrow monocyte precursors, circulating monocytes, and mature

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macrophages. As with the granulocyte lineage, mononuclear phagocytes are derived from CFU-GM progenitor cells. Several hematopoietic growth factors influence mononuclear phagocyte production. CSF-1 or macrophage CSF is the major hematopoietic growth factor influencing maturation and production of mononuclear phagocytes. Cells of this lineage seem to be unique in expressing cell surface receptors for CSF-1. On leaving the bone marrow, monocytes circulate for nearly 72 hours and then migrate into tissues, where the local extracellular milieu strongly influences monocyte-to-macrophage differentiation. Although the ultimate fate of macrophages is unclear, these cells have been observed to live for several months in many human tissues.

Embryonic macrophages are first seen in the yolk sac at 3-4 weeks of gestation. Unlike macrophages in the fetus and the adult that are derived from circulating monocytes, these large-sized histiocytic cells develop in the early embryonic period from yolk sac progenitors prior to the first appearance of monocytes. At 5 weeks of gestation, two distinct cell lineages with a dendritic/macrophage structure can be identified in the yolk sac, mesenchyme, and the fetal liver. The larger subgroup is MHC II–negative, and there is only a minor population that expresses these antigens. MHC II–negative cells also appear in the thymic cortex, in the marginal zones of lymph nodes, in the splenic red pulp, and in the bone marrow. A few MHC II–positive cells are seen in the liver at 7-8 weeks of gestation, the lymph nodes at 11-13 weeks of gestation, and the T-cell areas of the developing thymic medulla by 16 weeks of gestation. Subsequently, the numbers increase gradually, and MHC class II–positive cells are also seen in the skin and gastrointestinal tract.

During the second month of gestation, as hematopoiesis becomes established in the fetal liver, monocytes are seen in high proportions and constitute nearly 70% of all hematopoietic cells. Over the next 6 weeks, as the erythroid cells predominate, this proportion falls to 1%-2%. The first monocytes in circulation are not seen until about the fifth month of gestation and remain uncommon until the bone marrow becomes the predominant site of hematopoiesis. At 30 weeks, monocytes comprise 3%-7% of hematopoietic cells. Term cord blood studies show a relative monocytosis, which persists during the neonatal period. Although there is some disagreement between various reports on normal blood monocyte counts in neonates, recently normal ranges of absolute monocyte counts using data from more than 62,000 blood counts have been described, where it was shown that blood monocyte concentrations increase almost linearly between 22-42 weeks' gestation. Monocyte concentrations also increased during the first 2 postnatal weeks.[12] These data are consistent with previous kinetic studies in human fetuses, which show a similar maturational increase in monocyte precursors. In neonates, monocytosis has been associated with lower birth weight and gestational age, multiple transfusions, albumin infusions, and theophylline therapy. Monocytosis has also been described in infants with congenital infections, such as candidiasis and syphilis, and immune-mediated neutropenia.

Monocyte-to-macrophage differentiation has been well characterized, but the control mechanisms involved remain elusive. As monocytes develop into macrophages, certain morphologic changes occur. The cells increase in diameter more than threefold and acquire more cytoplasmic granules and vacuoles. Differentiation is also associated with increased expression of cell surface receptors, biosynthesis of numerous biologically active molecules, and improved phagocytic activity. Similar to PMNs, all mononuclear phagocytes have a well-developed cytoskeletal apparatus that is important in determining cell mobility and participation in many adhesion-related functions.

Information on tissue macrophage kinetics in the neonatal period is mainly from autopsy studies. The size of the macrophage pool varies in different organ systems. In the gastrointestinal tract, macrophages appear in the *lamina propria* as early as 10 weeks of gestation, and a sizable macrophage population can be seen during midgestation. In contrast, the alveolar macrophage population remains small in the fetus and expands during the early neonatal period.[6] This increase may result both from an influx of monocytes from the circulation as well as from clonal expansion in situ.

A lower proportion of cord blood macrophages stains for esterase, although there are no discernible differences in peroxidase activity. Neonatal monocytes have lower expression levels of the aforementioned surface markers, except for CD14. During infections, macrophages show an "activated" phenotype with enhanced phagocytic function, enhanced capacity to kill facultative intracellular microorganisms. These cells can be identified by unique morphologic features like larger diameter and greater number of pseudopods and pinocytotic vesicles.

Mononuclear Phagocyte Functions

Unlike neutrophils, the major host defense functions of monocytes in cord blood of term infants are intact. Cord blood monocytes show adherence, random migration, bactericidal activity, phagocytosis-associated chemiluminescence, production of superoxide anion ($O\bullet_2^-$), and generation of hydrogen peroxide at levels comparable to those of cells from healthy adult volunteers. One exception may be in the ability of cord monocytes to ingest group B streptococci (GBS). However, phagocytosis of GBS improved when neonatal monocytes were incubated with organisms preopsonized with fibronectin and IgG. The ability of fetal and neonatal monocytes to kill a variety of pathogens including *S. aureus*, *S. epidermidis*, *E. coli*, and *C. albicans* appears to be equivalent to that of adults.

Chemotaxis of cord blood monocytes is nearly normal, but monocytes isolated from the peripheral blood of newborns do not migrate normally. The chemotactic activity of these cells sequentially declines over the first week of life before slowly improving and achieving (by age 6 years) the chemotactic activity of monocytes isolated from the blood of adults. Impaired migration in response to

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chemoattractants may be a primary factor in the delayed influx of monocytes at inflammatory sites during the neonatal period.

Cytokine Production. Resident macrophages are often the first phagocytic cells of the innate immune system to encounter invading pathogens. These cells serve important host defense functions through phagocytosis and also as sentinel cells that regulate local inflammatory responses by producing various cytokines and chemokines. Most studies on monocyte/macrophage cell function have been done on cord blood, and fetal cells have not been studied to the same extent so far. Term cord-blood monocytes produce IL-1, IFN-α, and TNF in concentrations that are comparable to adults, but the levels of IFN-γ, IL-8, IL-10, and GM-CSF are lower. These cells also produce lower concentrations of extracellular proteins like fibronectin and bioreactive lipids like leukotriene B_4. Impaired monocyte function in neonates may be partially responsible for poorer cytokine responses of neonatal T cells.

Generally, mononuclear phagocyte recruitment and accumulation lag behind the brisk PMN influx by 6-12 hours, but the former process persists for several days. In addition to the host defense functions, mononuclear phagocytes also help regulate the process of tissue debridement and initiation of wound repair. During resolution of inflammation, the macrophage populations switch from a pro-inflammatory to an anti-inflammatory phenotype.[44] Emerging evidence indicates that macrophages are dynamic and heterogeneous cells, which are polarized into the classically activated M1 macrophages that express various inflammatory signals and the M2 macrophages that display an anti-inflammatory profile.[51] The effect of development on macrophage polarization is unclear.

Summary

The influx of mononuclear phagocytes to sites of inflammation is delayed and attenuated in newborns. This defect is most likely related to the impaired chemotactic activity displayed by the peripheral blood monocytes of these infants. Phagocytosis and microbicidal activity seem equivalent to the level displayed by mononuclear phagocytes of adults. In vivo studies of macrophage function at birth and during the neonatal period are limited, but pulmonary alveolar macrophages seem to function normally in the infants examined to date.

Humoral Components

Overview of Serum Opsonins

The role of humoral factors in the enhancement of leukocyte phagocytosis of bacterial pathogens has been known since the turn of the 20th century. These heat-labile and heat-stable plasma proteins, called opsonins, consist mainly of serum antibodies and components of the complement system, although several other proteins seem to play important roles (see later). The opsonic activity of plasma or serum from newborn term infants is equivalent to activity measured in sera from adults until the test concentrations of plasma or serum are reduced to less than 10%. At low serum concentrations, opsonic activity against various bacteria and fungi is diminished during the neonatal period. Opsonic activity is reduced even more in premature infants and persists at test concentrations of plasma or serum greater than 10%. These deficiencies in opsonic activity may be related partly to lower complement and IgG and IgM concentrations in newborns. The complement system is described in the following section. The opsonic role and other functions of immunoglobulins are reviewed later, when antibodies are discussed as humoral components of specific immunity.

Complement System

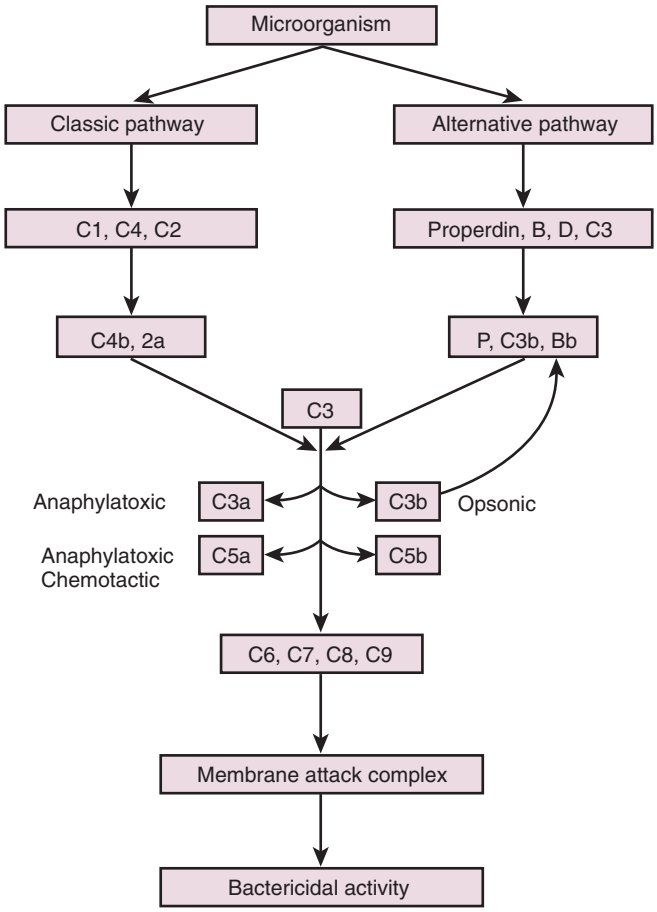
Activation Pathways and Overview of Functional Products

The complement system plays an important role as one of the principal humoral effector pathways of immunity. Its major function is to facilitate the neutralization of foreign substances either in the circulation or on mucous membranes. This function is accomplished by a series of plasma proteins that are involved in specific and nonspecific host defense mechanisms.

The classic pathway of complement activation requires the presence of specific antibodies against a particular antigen and the formation of immune complexes (Fig. 47.4). Two antibody molecules of the immune complex are bridged by the first component of complement, C1, which initiates a chain reaction in which one activated component serves as the enzyme that cleaves the next component in line. The order of component activation in the classic pathway is C1, C4, C2, and C3. Peptides with different biologic activities are created and either remain attached to the site of activation or diffuse into the milieu. C1 is itself a multimeric complex consisting of C1q, C1r, and C1s. When C1q binds the Fc portion of IgG or IgM immune complexes, C1 is activated. This cleaves C4, generating the C4a and C4b fragments. C4b then cleaves C2 into C2a and C2b. The C4b2a complex binds to microbial surfaces and acts as the C3 convertase, a protease that cleaves the third component of complement, C3, into membrane-bound C3b and the fluid-phase C3a. With the generation of C3b, the classic pathway merges with the other mode of complement activation, the alternative pathway.[11]

In contrast to the classic pathway, the alternative pathway may be activated by bacterial or mammalian cell surfaces in the absence of specific antibodies. This activation is possible because small amounts of C3 in the circulation are constantly being converted to C3b. This complement component can bind to cell surfaces, interact with the next alternative pathway components in sequence (factors B and D), and form a potent enzyme for further C3 activation (C3bBb). C3b originally generated by the classic pathway may involve this amplification loop of the alternative pathway and significantly enhance local C3 activation. The lectin pathway provides yet another mode of complement

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• **Fig. 47.4** Complement system activation cascade. Activation of the classic pathway (*left*) and the alternative pathway (*right*) causes generation of soluble factors that amplify phagocyte functions and produce a membrane-bound attack complex that damages cell membranes. (From McLean RH, et al: Genetically determined variation in the complement system: relationship to disease. *J Pediatr.* 1984;105:180, with permission.)

activation. This pathway is activated by binding of Mannose-binding lectins and ficolins with carbohydrate moieties on the surface of pathogens. These lectins are normally bound in complexes with MBL-associated serine proteases (MASP). Activation of MASP-2 results in cleavage of C4, forming C4a and C4b, which, as in the classical complement pathway, then cleaves C2 into C2a and C2b. The C4b2a complex that is then formed acts as the C3 convertase enzyme, resulting in C3 cleavage and activation.[11]

The central location of C3 in the complement pathway is important not only because the classic and alternative pathways converge at this point, but also because many biologic effects are determined by the interaction of this important molecule with various regulatory systems. The direction in which the complement pathway proceeds depends on the surface to which the C3b molecule is bound. Certain bacteria and other membranes offer a "protective surface" that favors the binding of C3b to factors B and D and the assembly of the enzyme that converts the next component in line, C5, into two biologically active fragments. The smaller product, C5a, acts as an anaphylatoxin to promote many aspects of acute inflammation, including chemoattraction of leukocytes and increasing vascular permeability. The larger fragment, C5b, remains attached to the C5 convertase on the membrane and assembles the components of the membrane attack complex: C5b, C6, C7, C8, and C9. Insertion of this complex into the cell membrane results in loss of membrane functions and cellular integrity.

In the absence of a protected site, C3b is exposed to factors I and H, which facilitate cleavage of C3b into iC3b and C3d. All these fragments of C3 can function as ligands for cellular receptors, which are located on erythrocytes and almost all immunocompetent cells. The C3b receptor (CR1) is known to mediate adherence of complement-coated complexes to erythrocytes, neutrophils, and mononuclear phagocytes and plays an important role in the clearance of immune complexes, bacteria, and cellular debris from the circulation. Other receptors also have been identified, such as the C3b binding protein, CR2, which is found on B lymphocytes and eosinophils. Its function awaits clarification, but there is evidence that adherence of the Epstein-Barr virus is mediated by this receptor. Finally, the iC3b receptor (CR3, CD11b/CD18) seems to be important for the ability of the host to overcome bacterial invasion. As previously mentioned, patients with a genetic deficiency of leukocyte cell surface CR3 experience severe recurrent bacterial infections. In addition to their roles in innate immunity, complement receptors may play important roles in adaptive immunity. Both CR1 and CR2 receptors are present on B-lymphocytes and play roles in B-cell differentiation and responses when presented with antigens. Similarly, T cells express receptors for the anaphylotoxins C3a and C5a, which maintain T-cell proliferation, viability, and differentiation.[41]

Ontogeny and Analysis of the Complement System in the Neonatal Period

Complement proteins are synthesized early in gestation. Synthesis of C2, C3, C4, and C5 can be confirmed between 8 and 14 weeks of gestation. Most evidence, derived through several methods, confirms that there is no transplacental passage of complement components. The components of the classic and alternate complement system and their functional activity (measured by total hemolytic complement assay) in full-term neonates are generally lower than normal adults (Table 47.1). Most serum alternative complement component values reach adult levels by 6-18 months of age. Proteins in the lectin pathway are also lower in neonates compared to adults and are decreased in preterm compared to term infants.[33]

Summary

Whether deficiencies in the complement system predispose a neonate to infection has not as yet been established. Defects in the complement system and in the alternative pathway, in particular, are likely to play a role in susceptibility to infection, especially in preterm infants. Newborns

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TABLE 47.1 Summary of Published Complement Levels in Neonates

Complement Component	Mean Percentage of Adult Levels	
	Term Neonate	Preterm Neonate
CH_{50}	52-81	32-78
AP_{50}	49-65	49-54
C1q	53-73	27-37
C4	54-80	42-59
C2	62-77	69
C3	50-97	39-60
C5	67-79	60-71
C6	44-58	35-39
C7	67-120	73-75
C8	36-38	29
C9	14-55	33-56
B	36-73	36-53
D	120-129	—
P	27-71	13-65
H	56-73	60
I	39-58	45

Adapted from McGreal EP, et al. Off to a slow start: under-development of the complement system in term newborns is more substantial following preterm births. *Immunobiology*. 2012;217:176-186.

have a limited spectrum of antibody transmitted across the placenta; they receive IgG, no IgM, and little antibody to the entire range of gram-negative bacteria. The classic pathway has relatively little value at and shortly after birth. It follows that, in the absence of specific antibody, activation of the biologically active fragments and complexes of the complement system through the alternative or lectin pathways becomes an extremely important defense mechanism for neonates during the first encounter with many bacteria. In most neonates, functional deficiencies in these pathways, in conjunction with impaired functioning of PMNs, is likely to be clinically relevant as suggested by lower levels of MBL and ficolin lectins in neonates with culture-proven sepsis.[42]

Fibronectin

Fibronectins are a class of multifunctional, high–molecular weight glycoproteins that serve to facilitate cell-to-cell and cell-to-substratum adhesion. Fibronectins play a key role in organogenesis and for hemostasis, hematopoiesis, inflammation, and wound healing. In many pathophysiologic conditions (e.g., sepsis, thrombosis, cancer, organ fibrosis), the normal structure, physiology, and function of fibronectins are altered in a way that contributes to the underlying tissue or organ dysfunction.

Structure and Function

Fibronectins exist as soluble and insoluble dimeric molecules. Soluble fibronectins have been identified in nearly every body fluid tested (synovial, ocular, pleural, amniotic, cerebrospinal, and others). Insoluble fibronectins are present in many connective tissues and extracellular matrices throughout the body. It is apparent that structural variants (isoforms) of fibronectin exist and that expression of these isoforms is highly regulated in a cell-specific and tissue-specific fashion.

All fibronectins are capable of binding to multiple ligands simultaneously. The modular design of these glycoproteins translates into a linear array of active globular functional domains. Fibronectins display individual binding sites for some molecules and multiple sites for others. Fibronectins bind certain bacteria, heparin, fibrin, IgG, and DNA in several separate domains, but other bacteria, matrix molecules, actin, complement component C1q, and gangliosides are bound at unique sites in individual domains. In this way, fibronectin facilitates the interaction of cells with other cells, bacteria, tissues, particles, and soluble proteins.

Circulating plasma fibronectin concentrations are reduced in fetal cord blood (120 fg/mL) and in term infants (220 fg/mL). Premature infants of 30-31 weeks' gestation have significantly lower plasma concentrations (152 fg/mL) than term infants. Lower plasma concentrations in neonates are correlated with decreased synthetic rates, but plasma clearance of fibronectin also is measurably slower. Plasma fibronectin concentrations are reduced further in infants with respiratory distress syndrome, birth depression, sepsis, and intrauterine growth restriction.

Role in Immune Responses

Fibronectin improves leukocyte function in vitro. Plasma fibronectin and proteolytic fragments of fibronectins promote human adult peripheral blood neutrophil and monocyte chemotaxis, adhesion, and random migration. In addition, fibronectin enhances phagocyte ingestion, reactive oxygen intermediate production, and killing of opsonized (complement or IgG) yeast and bacterial organisms. Fibronectin seems to play an important role as an enhancer of phagocyte function.

Summary

Circulating concentrations of fibronectin are decreased in the neonatal period and are correlated with gestational age. Even lower plasma concentrations are measured in infants who are ill. Plasma fibronectin increases phagocyte function in vitro. The role of fibronectin in host immune defense in neonates remains uncertain, but in vitro data suggest a potential role as an enhancer of phagocyte function.

Other Humoral Factors

Pentraxins

Pentraxins are a superfamily of proteins characterized by a 200–amino acid pentraxin domain at their C-terminal end.[8]

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They are broadly classified as short or long pentraxins depending on their primary structure. The classical short pentraxin, C-reactive protein (CRP), is an acute-phase reactant originally identified by its ability to bind to a pneumococcal polysaccharide antigen. It is primarily synthesized in the liver in response to inflammatory signaling, particularly IL-6. This protein has strong functional similarity to the complement component C1q-binding domain of IgG, and similar to IgG is able to activate the classic complement pathway by binding C1q. The polysaccharide antigen recognized by CRP is expressed by many bacteria and some fungi. When CRP binds to the antigen, and the complement system is activated, the organism is effectively opsonized, and rapid clearance occurs through neutrophil, monocyte, or macrophage phagocytosis.

CRP is synthesized by the fetus and the newborn. Serum concentrations seem equivalent in uninfected neonates and adults. CRP is one of the most rapidly responsive acute-phase proteins, with increases of 100-fold to 1000-fold (in adults) in the serum concentration detectable during an infection. In surveys of infants with proven infections, an elevation of CRP serum concentration has been observed in 50%-100% of patients. Normal values of CRP are less than 1.6 mg/dL on postnatal days 1-2 and less than 1 mg/dL thereafter. Diminished or absent increases in the CRP concentration have been observed during the first 12-24 hours of life in infected newborns, particularly in newborns infected with group B streptococci. CRP levels decrease rapidly in infants who clinically respond to antimicrobial therapy and return to normal in 5-6 days.

The long pentraxin, PTX3 (Pentraxin 3), is primarily produced by mononuclear phagocytes, dendritic cells, and neutrophils. Like CRP, surface-bound PTX3 can also activate the classical complement pathway by fixing complement component C1q on the surface of pathogens. In contrast, fluid-phase PTX3 can bind and sequester free C1q, thus inhibiting complement activation. Thus PTX 3 may play a dual role in regulation of the complement pathway. Normative levels of PTX 3 in term and preterm infants and its role in preserving innate immune defenses in the newborn remains to be determined.

Lactoferrin

Lactoferrin is a member of the transferrin family of iron-binding glycoproteins that is normally secreted at epithelial-lining mucosal surfaces and plays important roles in innate immune mechanisms in humans. High concentrations of lactoferrin are found in colostrum and breast milk.[17] Lactoferrin is also present in specific granules of neutrophils. It is released into the phagosome after particle ingestion and is deposited on the cell surface membrane during stimulated degranulation. By chelating iron, lactoferrin removes an important nutrient required for pathogen growth. It also destabilizes microbial membranes and prevents microbial adherence to host cells. Thus, it has potent antimicrobial actions. Lactoferrin also enhances neutrophil–endothelial adhesion interactions and neutrophil aggregation, reactive oxygen intermediate production, and chemotaxis.[26] Deficient neutrophil adherence and directed migration have been reported in studies of patients with a heritable deficiency of lactoferrin-containing, neutrophil-specific granules.

Neonatal cord blood neutrophils contain less lactoferrin when compared to adult neutrophils. Oral prophylaxis with bovine lactoferrin has been shown to reduce the incidence of late-onset sepsis in very low birth weight preterm infants, suggesting that quantitative deficiencies in lactoferrin may predispose to infections in the neonatal period.

Collectins

Collectins are soluble proteins that play a role in innate immunity. These molecules include mannose-binding lectin and surfactant proteins A (SP-A) and D (SP-D) in humans and the bovine molecules conglutinin, CL-43, and CL-1. Collectins share several structural features, including a collagen domain, a neck region, and a globular carboxyl-terminal C-type (calcium-dependent) lectin-binding domain. Collectins specifically recognize the patterns of carbohydrates on the outer walls of microorganisms. In essence, collectins function by binding to microorganisms and enhancing uptake and clearance by phagocytes. MBL can also function to activate the classic complement pathway in much the same fashion as the complement component C1q. MBL, SP-A, and SP-D bind to one or more receptors on phagocytes and stimulate chemotaxis, the respiratory burst, and the phagocytosis of a wide variety of microorganisms, including group B streptococci.

SP-A and SP-D are synthesized by type II alveolar epithelial cells and by nonciliated bronchiolar epithelial (club) cells. As with other components of surfactant, the biosynthesis and secretion of these collectins increases dramatically during the third trimester of pregnancy. Acute injury or inflammation results in rapid increases in SP-A and SP-D biosynthesis. While predominantly present in the lung, SP-A and SP-D are also found in other sites in the body. SP-A is present in small intestinal cells, and SP-D protein is also found in gastric mucosal cells. The important role for SP-A and SP-D in innate immunity is suggested by the increased susceptibility to bacterial and viral infections in mice deficient in either of these pulmonary collectins. In humans, genetic variations in SP-A and SP-D are associated with increased neonatal susceptibility to RSV-bronchiolitis.

Mannose-binding lectin (MBL) is synthesized in the liver and secreted into the circulation. MBL serum concentrations vary widely (1000-fold) in adult human subjects primarily related to inherited polymorphisms in the promoter region of the gene. Neonatal serum MBL concentrations generally are lower than the levels measured in adult serum. In addition, MBL levels are lower in the first week of life and lower in preterm compared to term infants. Polymorphisms in the MBL gene and low MBL serum levels are both associated with increased risk of neonatal sepsis, suggesting its possible role as an essential innate immune defense component in the newborn infant.

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Cytokines and Chemokines

Overview

Newborn infants have an increased susceptibility to infection because of various host defense impairments that exist during the neonatal period. The generation and maintenance of acquired immune responses are controlled by a network of regulatory glycoproteins and phospholipids that mediate the interactions between cells. These cytokines and chemokines are responsible for the generation of the immune response and differentiation of a wide variety of immune and nonimmune cells. The infant's ability to generate the right balance of proinflammatory and anti-inflammatory cytokines when challenged with an infectious agent allows recovery from the encounter with minimal residua. When the balance is not perfectly controlled, morbidity and mortality are increased. Unregulated production of cytokines in neonates may contribute to the development of necrotizing enterocolitis, bronchopulmonary dysplasia, and hypoxic-ischemic brain injury. The number of newly discovered cytokines is increasing on a yearly basis. This section focuses on the major cytokines involved in the immune responses to infectious agents and noninfectious stimuli, their developmental patterns in fetuses and newborns, and their coordinated role in neonatal sepsis.

Cytokine and Chemokine Biology

Interleukin-1 Superfamily. IL-1 family is a group of 11 immunoregulatory cytokines with complex pro- and anti-inflammatory effects[20] (Table 47.2). The three best-known members of this family are IL-1α, IL-1β, and IL-1 receptor antagonist [IL-1ra]). IL-1α and IL-1β are translated as precursor peptides. Pro-IL-1α is fully active and resides in the cytoplasm but can be transported to the cell surface where it has a role in cell–cell communication. IL-1α appears in the circulation only during severe disease. IL-1α and IL-1β share little sequence homology but bind to the same receptor and have the same tertiary structure. Pro-IL-1β (the main circulating member of this family) is inactive and must be cleaved by a cysteine protease (IL-1β-converting enzyme or caspase I) before it is secreted. IL-1ra is a competitive inhibitor of the other members of the family that has no agonist activity. There are two varieties of IL receptors: The type I receptor binds all members of the family; the type II receptor binds only IL-1β. Both receptors are members of the IL-1 receptor/TLR superfamily.

IL-1 is synthesized by a wide variety of immune and nonimmune cells, including monocytes, macrophages, neutrophils, endothelial cells, and epithelial cells. Synthesis of these ILs is triggered by microbial products of inflammation, and many of the features of the inflammatory response syndrome can be directly attributed to members of this family. IL-1 production by monocytes and macrophages from term and premature newborns is equivalent to that of adults. In preterm infants with sepsis, monocyte secretion may be diminished, however, during the acute phase of the disease.

Interleukin-6. IL-6 is secreted in a variety of different molecular forms as a result of post-translational modification. IL-6 synthesis is initiated by cytokines (including IL-1 and IL-6), platelet-derived growth factor, epidermal growth factor, viral and bacterial infections, double-stranded RNA, endotoxin, and cyclic adenosine monophosphate. The receptor for IL-6 consists of two subcomponents: (1) a ligand-binding molecule that is not responsible for signal transduction (IL-6R) and (2) a non-ligand-binding signal

TABLE 47.2 Members of the Interleukin-1 Family

Traditional Name	Family Name	Receptor	Coreceptor	Characteristics
IL-1α	IL1F1	IL-1RI	Interleukin-1 receptor accessory protein (IL-1RacP)	Proinflammatory
IL-1β	IL1F2	IL-1RI	IL-1RacP	Proinflammatory
IL-1Ra	IL1F3	IL-1RI	NA	Antagonist for IL-1α, IL-1β
IL-18	IL1F4	IL-18Rα	IL-18Rβ	Proinflammatory
IL-36Ra	IL1F5	IL-1 receptor related protein 2 (IL-1Rrp2)	NA	Antagonist for IL-36α, IL-36β, IL-36γ
IL-36α	IL1F6	IL-1Rrp2	IL-1RAcP	Proinflammatory
IL-37	IL1F7	Unknown	Unknown	Anti-inflammatory
IL-36β	IL1F8	IL-1Rrp2	IL-1RAcP	Proinflammatory
IL-36γ	IL1F9	IL-1Rrp2	IL-1RAcP	Proinflammatory
IL-38	IL1F10	Unknown	Unknown	Unknown
IL-33	IL1F11	ST2 (suppression of tumorigenicity 2)	IL-1RAcP	Th2 responses, proinflammatory

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TABLE 47.3 Members of the IL-10 Superfamily

Member	Receptor	Function
IL-10	IL10-R1/IL10-R2	Immune suppression, anti-inflammatory
IL-19	IL20-R1/IL20-R2	Skin development, immunoregulatory
IL-20	IL20-R1/IL20-R2, IL22-R1/ IL20-R2	Skin development and inflammation, hematopoiesis
IL-22	IL22-R1/IL10-R2	Acute-phase response, innate immunity
IL-24	IL20-R1/IL20-R2, IL22-R1/ IL20-R2 (skin only)	Pro-apoptosis, epidermal functions, inflammatory cascade
IL-26	IL20-R1/IL10-R2	Mucosal and cutaneous immunity
IL-28, IL-29	IFNLR1/IL10-R2	Antiviral immunity

transducer (gp130). A soluble form of the IL-6 receptor (sIL6Ra) also exists. sIL6Ra can bind to IL-6 and then interact with gp130 on cells that do not express the IL-6 receptor. IL-6 injected intravenously into human patients is less toxic than IL-1β and TNF but does result in chills and fever. IL-6 is known to activate T and B cells, stimulate maturation of megakaryocytes, increase the production of acute-phase response proteins, and enhance NK cell activities. Monocytes from term infants produce adequate amounts of IL-6 after stimulation with lipopolysaccharide (LPS) but not IL-1. Cells derived from preterm infants exhibit decreased production no matter what the stimuli. Circulating levels of IL-6 in newborns are lower than corresponding maternal values; however, the percentage of IL-6-positive monocytes (after stimulation with LPS) is higher in preterm and term neonates.

Interleukin-10 Superfamily. The IL-10 gene superfamily includes IL-10 and several other immunoregulatory cytokines, including IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29.[37] These cytokines, their cognate receptors, and the principal biological effects are summarized in Table 47.3. IL-10 is a potent anti-inflammatory/immunosuppressive polypeptide synthesized by monocytes, macrophages, T cells, and B cells in response to bacteria, bacterial products, viruses, fungi, and parasites. IL-10 decreases the synthesis of a wide variety of proinflammatory cytokines and increases the production of naturally occurring proinflammatory cytokine inhibitors (e.g., IL-1ra). The synthesis of IL-10 is enhanced by various other cytokines, including TNF, IL-1, IL-6, and IL-12. In contrast, IL-10 enhances B-cell function and promotes development of cytotoxic T cells. IL-10 receptors are members of the class II cytokine receptor family and consist of two subunits. IL-10 production in neonates is diminished.

Interleukin-12 and Interferon-γ. IL-12 is a heterodimer consisting of two subunits (p35 and p40) encoded by different genes.[47] The p40 subunit mediates binding to the IL-12 receptor, whereas the p35 subunit is needed for signal transduction. The p40 subunit can also form homodimers with itself that bind to the IL-12 receptor with equal affinity but without eliciting a cellular effect. The homodimers may help modulate the effects of IL-12. The synthesis of the p35 and p40 subunits is regulated independently. In response to a given stimulus, cells secrete 10-100 times more of the homodimer than the heterodimer. IL-12 is produced by phagocytic cells (e.g., monocytes and macrophages) in response to bacteria and bacterial products, intracellular pathogens, and viruses. The IL-12 receptor is a member of the gp130 cytokine receptor superfamily. The IL-12 receptor consists of two subunits, and both must be activated for signal transduction. The principal cellular targets of IL-12 are T cells and NK cells. IL-12 induces the production of interferon (IFN-γ), stimulates proliferation, and enhances cytotoxicity. The production of IL-12 by cord blood–derived mononuclear cells (in response to endotoxin) is diminished; however, normal IL-12 synthesis has been observed with heat-killed *S. aureus* as the stimulus.

IFN-γ is produced by NK cells, type 1 T-helper (Th) cells, and cytotoxic T cells in response to IL-12, TNF, IL-1, IL-15, and IL-18. The receptor for IFN-γ has two subunits; one is responsible for binding, and the other is responsible for signaling. IFN-γ induces class II histocompatibility antigens and activates macrophages and is important for host defenses against intracellular pathogens, among other functions (Box 47.1). Synthesis of IFN-γ is greatly diminished in neonates.

Tumor Necrosis Factor Superfamily. The TNF family has 18 members, which serve in a variety of developmental, inflammatory, and cytotoxic roles (Table 47.4).[15] The two best known members of this family are TNF (previously TNF-α, cachectin) and lympotoxin-α (LT-α, previously TNF-β). TNF exists as a transmembrane form (prohormone) and a smaller secreted form consisting of three monomers. The soluble form of TNF is formed by the cleavage of the prohormone by a matrix metalloproteinase disintegrin. The transmembrane and the secreted forms of TNF can be biologically active. Similar to IL-1, synthesis of TNF is triggered by microbial products of inflammation (and by IL-1 and TNF themselves). A wide variety of cells are capable of producing TNF; however, monocytes and macrophages represent the major sources of this circulating cytokine.

TNF-α and LT-α bind to two cognate receptors—TNF-RI and TNF-RII. Stimulation of TNF-RI reproduces many TNF functions, including cytotoxicity and upregulation of adhesion molecules. TNF-RI contains a cytoplasmic sequence of 80 amino acids that regulates programmed cell death. TNF-RII may facilitate binding of TNF to TNF-RI.

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The production of TNF by neonatal monocytes and macrophages is less than that in adults. Endotoxin-stimulated cord blood cells from preterm infants secrete significantly less TNF than cells derived from term infants or adults. The expression of TNF receptors may also be diminished.

• BOX 47.1 Functions of Interferon-γ

- Enhances macrophage microbicidal activity
- Promotes secretion of inflammatory mediators
- Enhances host cell resistance to nonviral intracellular pathogens
- Upregulates surface Fc receptors and class II major histocompatibility complex antigens on phagocytes
- Inhibits macrophage migration
- Promotes formation of giant cells
- Induces myelosuppression
- Augments functioning of mature neutrophils
- Enhances differentiation of cytolytic T cells, natural killer cells, and lymphocyte-activated killer cells
- Activates endothelial cells
- Suppresses host protein synthesis

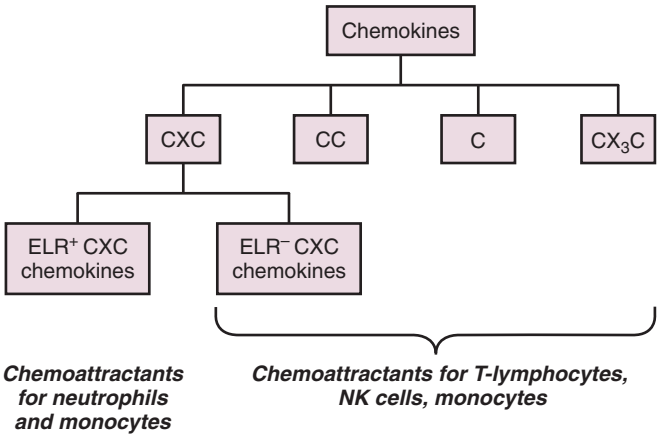
Platelet-Activating Factor. Platelet-activating factor (PAF) is a potent phospholipid inflammatory mediator that is rapidly degraded by acetylhydrolase. PAF is produced by many cell types; however, only macrophages and eosinophils exhibit regulated release. PAF primarily resides on the cell surface, where it acts as an intercellular messenger. Intravenous administration of PAF results in systemic hypotension, capillary leakage, pulmonary hypertension, neutropenia, thrombocytopenia, and ischemic intestinal necrosis in animals. At a cellular level, PAF is a potent activator of neutrophils. PAF production is increased by cellular exposure to lipopolysaccharide (LPS), hypoxia, hematopoietic growth factors, TNF, IL-1, thrombin, bradykinin, and leukotriene C4. PAF stimulates the production of other mediators, including TNF, complement, oxygen radicals, prostaglandins, thromboxane, and leukotrienes. There is a strong association (but not a proven etiologic relationship) between neonatal necrotizing enterocolitis and increased concentrations of PAF.

Chemokines. Chemokines are the largest cytokine family, comprised of approximately 50 chemokine ligands and 20 different signaling receptors involved in the

TABLE 47.4 Members of the Tumor Necrosis Factor Family of Cytokines

Traditional Name	Family Name	Receptor
Lymphotoxin-α	TNFSF1	TNF-RI/TNFRSF1A, TNF-RII/TNFRSF1B
Tumor necrosis factor	TNFSF2	TNF-RI/TNFRSF1A, TNF-RII/TNFRSF1B
Lymphotoxin-β	TNFSF3	TNFRSF3
Ox40 ligand	TNFSF4	Ox40LR/TNFRSF4
CD40 ligand	TNFSF5	TNFRSF5
Fas ligand	TNFSF6	Fas/CD95/TNFRSF6
CD27 ligand	TNFSF7	TNFRSF7
CD30 ligand	TNFSF8	TNFRSF8
4-1 BB ligand	TNFSF9	TNFRSF9
TRAIL (TNF-related apoptosis-inducing ligand)	TNFSF10	TRAIL-R1/TNFRSF10A, TRAIL-R2/TNFRSF10B, TRAIL-R3/TNFRSF10C, TRAIL-R4/TNFRSF10C
RANK ligand (receptor activator of nuclear factor kappa-B ligand)	TNFSF11	TNFRSF11A, TNFRSF11B
TWEAK (TNF-related weak inducer of apoptosis)	TNFSF12	TNFRSF12, TNFRSF12A
APRIL (a proliferation-inducing ligand)	TNFSF13	
BAFF (B-cell activating factor)	TNFSF13b	TNFRSF13B, TNFRSF13C
LIGHT (lymphotoxin-like, exhibits inducible expression and competes with HSV glycoprotein D for herpesvirus entry mediator, a receptor expressed by T lymphocytes)/CD258	TNFSF14	TNFRSF14, TNFRSF6B
TL1 (TNF-like cytokine 1)/TL1A	TNFSF15	TNFRSF12, TNFRSF6B
GITRL (glucocorticoid-induced TNFR-related protein ligand)	TNFSF18	
Nerve growth factor	-	NGFR/TNFRSF16

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• **Fig. 47.5** Chemokines are classified according to the position of conserved cysteine residues near the *N*-terminus. In CXC chemokines, two conserved cysteine (C) residues are separated by a variable amino acid (X). CC and C-chemokines have conserved cysteines, whereas the CX3C chemokine, fractalkine, has two cysteines separated by three variable amino acids.

activation and recruitment of a wide variety of cell types.[21] Chemokines are 8- to 12-kDa heparin-binding proteins ranging from 70-100 amino acids in length. All chemokines contain four cysteine motifs (forming double bonds) and are classified according to the arrangement of the cysteines at the amino-terminal end. Of the four subgroups (CXC, CC, C, and CX3C; Fig. 47.5), the CC and CXC are the largest (Table 47.5). Chemokine receptors belong to the seven transmembrane-spanning family of G-protein-coupled receptors. Chemokines are constitutively produced in organs where cell attraction is required for maintenance of local homeostasis. Most chemokines are inducible by inflammatory cytokines and endotoxin. In inflammatory states, chemokines are responsible for navigation and homing of effector leukocytes. In addition, chemokines induce a wide variety of leukocyte responses, including enzyme release from intracellular stores, oxygen radical formation, shape change through cytoskeletal rearrangement, generation of lipid mediators, and induction of adhesion to endothelium and extracellular matrix proteins. Chemokines are quite diverse in their target cell selectivity. CXC chemokines generally are more selective for neutrophils and T cells, whereas CC chemokines mainly attract monocytes and T lymphocytes. Considerable data suggest that chemotactic factor generation is deficient in newborn infants.

Coordinated Inflammatory Response in Neonatal Sepsis

In human bacterial sepsis, cytokines are released in a sequential manner, resulting in a cytokine cascade. After a challenge with a low dose of endotoxin, TNF peaks within 90 minutes. Other pro-inflammatory cytokines are released shortly afterward, and anti-inflammatory mediators follow in close sequence. The peak in IL-10 production may not occur for hours, however. In general, cytokines are not stored in intracellular compartments; they are synthesized and released in response to an inflammatory stimulus. Regulation of cytokine production occurs at the level of gene transcription. Specific transcription factors (e.g., NF-κB) bind to DNA response elements that either inhibit or promote gene transcription. Pro-inflammatory and anti-inflammatory cytokines or molecules are produced in response to an inflammatory stimulus. The anti-inflammatory molecules include soluble cytokine receptors (resulting from proteolytic cleavage of the extracellular binding domain), anti-inflammatory cytokines (e.g., IL-10), and cytokine receptor antagonists (e.g., IL-1ra).

Antigen-presenting cells (APCs) of the innate immune system (e.g., macrophages, NK cells, neutrophils, mucosal epithelial cells, endothelial cells, and dendritic cells [DCs]) play pivotal roles in the initiation of an inflammatory response to invading pathogens. As depicted in Fig. 47.6, the macrophage is activated by endotoxin (LPS) binding to the CD14 receptor (the main LPS binding receptor) by an LPS-binding protein. CD14 also exists in a soluble form that is shed from the macrophage cell surface through the action of serine proteases. Circulating LPS-CD14 complexes can attach to endothelial cells or epithelial cells. Through this mechanism, endothelial cells are activated to produce other cytokines and mediators (e.g., PAF, nitric oxide, and IL-6) that contribute to the pro-inflammatory response. CD14 is also required for the recognition of other bacterial products, including peptidoglycans and lipoteichoic acid from gram-positive bacteria. The formation of the CD14-LPS complex significantly reduces the concentration of LPS needed for activation.

CD14 lacks transmembrane and intracellular domains and cannot initiate a cellular response. Another pathway involving toll-like receptors (TLRs) is responsible for cell activation and signal transduction. CD14 seems to be able to discriminate between bacterial products and sort their signals to different TLRs. The TLRs are named from Toll, a plasma membrane receptor in Drosophila, which has a cytoplasmic domain homologous to the IL-1 receptor protein. Toll receptors induce signal transduction pathways that lead to the activation of the transcription factor NF-κB.[36] In mammalian species, there are at least 10 TLRs (Table 47.6), which represent type I transmembrane proteins characterized by an extracellular domain, a transmembrane domain, and an intracellular domain. TLRs are pattern recognition receptors that recognize pathogen-associated molecular patterns. Pathogen-associated molecular patterns are shared by many pathogens but are not expressed in host cells. TLR4 is responsible for the recognition of bacterial endotoxin. It is essential for signaling but requires a small protein (MD-2) to confer responsiveness. Other TLRs bind cell wall products from gram-positive bacteria and fungi.

When activated, TLRs initiate a signaling cascade that shares many of the same molecules used by the IL-1 receptor. Activated, macrophages synthesize and secrete the cascade of pro-inflammatory cytokines, chemokines, and mediators described earlier. Some of these cytokines activate neutrophils to release proteases and free radicals that have

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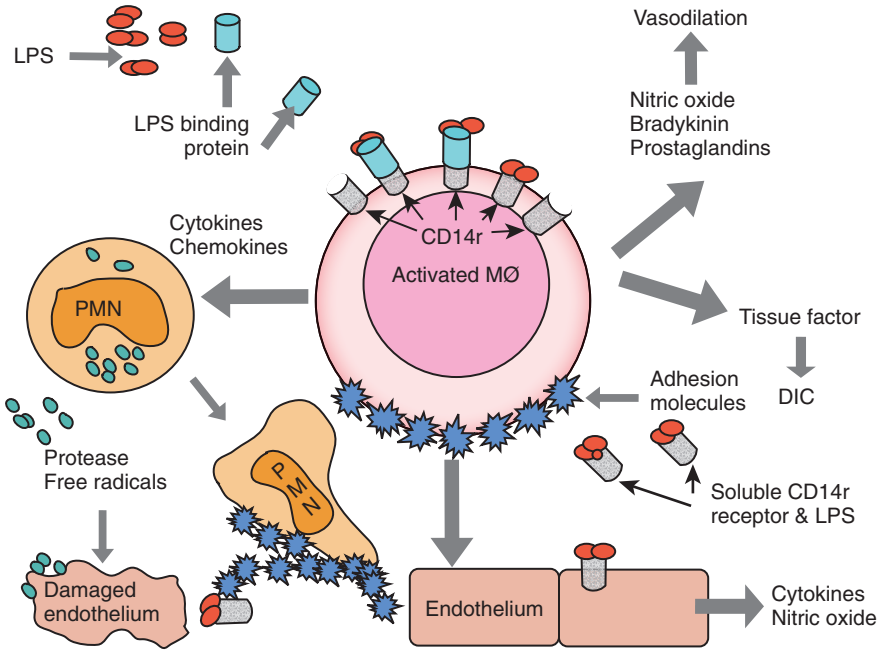
TABLE 47.5 Human CXC and CC Chemokines and Relative Receptors

Chemokines	Systematic Name	Chemokine Receptors
Growth-related oncoprotein (GRO)-α	CXC-motif ligand (CXCL)1	CXC receptor (CXCR) 2
GRO-β	CXCL2	CXCR2
GRO-γ	CXCL3	CXCR2
Epithelial neutrophil chemoattractant (ENA-78)	CXCL5	CXCR2
Granulocyte chemoattractant protein (GCP)-2	CXCL6	CXCR2, CXCR1
Neutrophil-activating peptide (NAP)-2	CXCL7	CXCR2
IL-8	CXCL8	CXCR2, CXCR1
Monokine induced by gamma interferon (MIG)	CXCL9	CXCR3
Interferon-gamma-inducible protein 10 (IP-10)	CXCL10	CXCR3
Interferon-inducible T-cell alpha chemoattractant (I-TAC)	CXCL11	CXCR3
Stromal cell-derived factor 1 (SDF-1)	CXCL12	CXCR4
B-cell chemoattractant (BCA-1)	CXCL13	CXCR5
Monocyte chemoattractant protein (MCP)-1	CCL2	CCR2
MCP-2	CCL8	CCR3
MCP-3	CCL7	CCR1, CCR2, CCR3
	CCL13	CCR2, CCR3
Macrophage inflammatory protein (MIP)-1α	CCL3	CCR1, CCR5
MIP-1β	CCL4	CCR5
RANTES (regulated upon activation, normally T-expressed, and presumably secreted)	CCL5	CCR1, CCR3, CCR5
Eotaxin	CCL11	CCR3
Eotaxin-2	CCL24	CCR3
Eotaxin-3	CCL26	CCR3
Liver and activation-regulated chemokine (LARC)	CCL20	CCR6
Thymus expressed chemokine (TECK)	CCL25	CCR9
Cutaneous T-cell-attracting chemokine (CTACK)	CCL27	CCR10
T-cell-directed CC chemokine (TARC)	CCL17	CCR4
Macrophage-derived chemokine (MDC)	CCL22	CCR4
Dendritic cell-specific chemokine (DC-CK1)	CCL18	?
Epstein-Barr virus–induced molecule 1 ligand chemokine (ELC)	CCL19	CCR7
Secondary lymphoid tissue chemokine (SLC)	CCL21	CCR7

Adapted from Manzo A, et al. Role of chemokines and chemokine receptors in regulating specific leukocyte trafficking in the immune/inflammatory response. *Clin Exp Rheumatol.* 2003;21:501.

the capacity to damage endothelium and promote capillary leak. Upregulation of adhesion molecules on the neutrophils allows them to bind to counter-receptors on the endothelial cells and migrate to sites of inflammation. The pro-inflammatory cascade is interrupted by the initiation of counter-regulatory mechanisms. Because most patients with life-threatening infections (i.e., systemic inflammatory response syndrome) are not admitted early in the course of their sepsis episode, pro-inflammatory cytokines are detected in only a subset of patients. Anti-inflammatory cytokines (which appear later in the cascade) are found in most of these infected individuals.

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• **Fig. 47.6** Role of macrophages in mediating the inflammatory response. Lipopolysaccharide (LPS) binding to the CD14 receptor (with or without LPS binding protein) activates the macrophage (MØ) to synthesize and secrete cytokines, chemokines, and other mediators. These soluble factors stimulate polymorphonuclear neutrophils (PMNs) to release proteases and oxygen-free radicals that are important for microbial killing but that also may injure endothelium and cause capillary leak. Binding of soluble LPS-CD14 complexes to endothelial cells promotes biosynthesis of other cytokines and small molecular mediators (e.g., nitric oxide, interleukin-6). Endothelial activation also results in upregulation of cell surface adhesive molecules that interact with neutrophil-adhesive molecules and promote neutrophil extravasation. DIC, disseminated intravascular coagulation.

TABLE 47.6 Role of Toll-Like Receptors (TLRs) in Pathogen Recognition and Pathophysiology of Human Disease

Toll-Like Receptor	Ligands	Pathogens or Disease State
TLR1	Signals as a dimer only when combined with TLR2 for all its ligands; recognizes Borrelia burgdorferi OspA; required for adaptive immune response	Lyme disease
	Tri-acyl lipopeptides (bacteria, e.g., Mycobacterium tuberculosis)	
	Soluble factors (Neisseria meningitidis)	N. meningitides
TLR2	Associates with CD11/CD18, CD14, MD-2, TLR1, TLR6, dectin 1; lipoprotein/lipopeptides (various microbial pathogens)	M. tuberculosis
	Peptidoglycan	Apoptosis of Schwann cells in leprosy
	Lipoteichoic acid	
	Lipoarabinomannan (mycobacteria)	
	Phenol-soluble modulin (Staphylococcus epidermidis)	
	Glycoinositolphospholipids (Trypanosoma cruzi)	Chagas disease
	Glycolipids (Treponema maltophilum)	Leptospirosis
	Porin (Neisseria)	
	Zymosan (fungi)	Fungal sepsis
	Atypical LPS (Leptospira interrogans)	
	Atypical LPS (Porphyromonas gingivalis)	Periodontal disease
	HSP70 (host)	
	CMV virions	CMV viremia
	Hemagglutinin protein of wild-type measles	Measles
	Bacterial fimbriae	
TLR3	Double-stranded RNA in viruses	Many

Continued

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TABLE 47.6 Role of Toll-Like Receptors (TLRs) in Pathogen Recognition and Pathophysiology of Human Disease—cont'd

Toll-Like Receptor	Ligands	Pathogens or Disease State
TLR4	Gram-negative enteric LPS (requires coreceptors MD-2 and CD14) Additional ligands Chlamydial HSP60 RSV F protein Taxol (plant) M. tuberculosis HSP65 Envelope proteins (MMTV) HSP60 (host) HSP70 (host) Type III repeat extra domain A of fibronectin (host) Oligosaccharides of hyaluronic acid (host) Polysaccharide fragments of heparan sulfate (host) Fibrinogen (host) B-defensin2	Gram-negative bacteria Septic shock Chlamydia trachomatis, Chlamydia pneumoniae Certain viruses (e.g., RSV) *M. tuberculosis* Smallpox (vaccinia) blocks TIR domain of TLR4 and others
TLR5	Flagellin (monomeric) from bacteria	Flagellated bacteria (e.g., Salmonella)
TLR6	See TLR2 (as dimers with TLR2) Phenol-soluble modulin Di-acyl lipopeptides (mycoplasma)	
TLR7	Responds to imidazoquinoline antiviral agents (synthetic compounds) Loxoribine (synthetic compounds) Bropirimine (synthetic compounds) Endogenous and exogenous ligands unknown Single-stranded RNA	May be useful as adjuvant for cancer therapy Viral infections
TLR8	Imidazoquinoline (synthetic compounds) Single-stranded RNA	Viral infections
TLR9	Bacterial DNA as "CpG" motifs	Viral infections Bacterial and viral infections (e.g., HSV) May be useful as adjuvant for vaccines and cancer therapy HSV type 2
TLR10	Unknown	Unknown

CMV, cytomegalovirus; HSP, heat-shock protein; HSV, herpes simplex virus; LPS, lipopolysaccharide; MMTV, mouse mammary tumor virus; RSV, respiratory syncytial virus; TIR, Toll/interleukin receptor.
From Abreu MT, Arditi M. Innate immunity and Toll-like receptors: clinical implications of basic science research. *J Pediatr.* 2004;144:421.

The concentration of anti-inflammatory substances (e.g., IL-1ra and soluble receptors) increases substantially with time and has been termed the compensatory anti-inflammatory response syndrome. This is a response of the host to limit the toxicity of proinflammatory substances. Shortly after the onset of an infectious episode, the mononuclear cell becomes refractory and is unable to respond to proinflammatory cytokines. In contrast, the capacity to produce anti-inflammatory substances such as IL-1ra and IL-10 is preserved. This phenomenon has been referred to as monocyte deactivation or immunoparalysis. Although the mechanism responsible for monocyte deactivation is unclear, it probably involves increased production of IL-10. The risk of infection is greatly increased during this period of hyporeactivity.

Acquired Immunity

Cell-Mediated and Antibody-Mediated Responses

Overview

Lymphocytes constitute almost 20% of blood leukocytes and specialize in the recognition of invading foreign antigens in the context of major histocompatibility antigens.

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Lymphocytes are of two major types: (1) B lymphocytes that are produced in the bone marrow, mature in secondary lymphoid organs, and subsequently differentiate into antibody-secreting plasma cells, and (2) T lymphocytes that mature and differentiate into CD4+ and CD8+ subsets in the thymus and subsequently seed the peripheral blood system, including the spleen and the lymph nodes. T-cell functions include helping B cells to make antibody; killing virally infected cells; regulating the level of the immune response; and stimulating the microbial and cytotoxic activity of the immune cells, including macrophages.

Each lymphocyte expresses a cell surface receptor that recognizes a particular antigen. In the case of T cells, it is called the T-cell receptor (TCR), and in the case of B cells, it is called the B-cell receptor (BCR). Each lymphocyte is engineered to express a receptor that is specific for only one antigen. In this way, the lymphocyte population as a whole can recognize a wide range of antigens. The antigen receptors are generated during development by a process known as somatic mutation and recombination involving a few germline genes. The antigen receptors used by B cells and T cells are different. The BCR is a surface immunoglobulin, a membrane-bound form of the antibody that eventually gets secreted. The TCR is generated from a different set of genes that encode only the cell-surface receptor.

T cells and B cells recognize antigens in different forms: B cells recognize an unmodified antigen molecule, either free in solution or on the surface of other cells. T cells recognize antigen only when it is presented to them in association with molecules encoded by the MHC. The functional consequence of these differences in antigen recognition is that T cells must be presented processed antigens in the form of short peptides by accessory cells such as macrophages or dendritic cells (DCs), whereas B cells can directly recognize antigens in tissue fluids.

The acquired immune response arises through the process of clonal recognition. An antigen selects the clones of B and T cells that express the cell surface receptors that recognize the antigen. Because the number of different lymphocyte antigen specificities is large, the number of lymphocytes available to recognize each antigen is relatively small—only a few hundred lymphocytes in an adult. In addition, because so few cells are insufficient to eradicate an invading pathogen, the first step toward the generation of a specific immune response involves a rapid expansion of antigen-specific lymphocytes. This step is followed by further differentiation of antigen-specific cells into effector cells. These events underlie the difference between primary and secondary immune responses. During the primary response, the small number of specific cells increases, and the cells undergo differentiation. If the antigen is encountered again (or persists), there is a larger population of specific cells to react with the antigen, and these cells are able to respond more quickly because they have already undergone several steps along their differentiation pathway. These lymphocytes that have been stimulated by antigen (primed) and their progeny either may differentiate fully into effector cells or may form the expanded pool of cells (memory cells) that can respond more efficiently to a future (secondary) challenge with the same antigen.

T Lymphocytes

Overview

T cells develop and differentiate in the thymus before seeding the secondary lymphoid tissues. T cells recognize both antigens and MHC molecules through the TCR. This receptor consists of an antigen-binding portion formed by two different polymorphic chains in association with CD3, a complex of proteins involved in signal transduction. The antigen-binding portion of the TCR is most commonly formed by the αβ polypeptide chain heterodimer. In humans, the markers CD2 and CD5 are also present on all T cells (Table 47.7). Activated T cells may also be induced to express CD25, which forms part of the high-affinity IL-2 receptor and is important in clonal expansion.

There are two main subpopulations of T cells, which are distinguished according to their expression of CD4+ or CD8+. These molecules act as receptors for class II (CD4+) and class I (CD8+) MHC molecules and contribute to T-cell immune recognition and cellular activation. The

TABLE 47.7 Cluster-Designated Molecules Found on Human T Cells

Antigen	Molecular Weight (kDa)	Comment
CD1a	49	Expressed on thymocytes
CD1b	45	Expressed on thymocytes
CD1c	43	Expressed on thymocytes
CD2	50	Sheep erythrocyte receptor
CD3	22	Part of T-cell antigen receptor complex
CD4	55	MHC class II immune recognition
CD5	67	
CD6	120	
CD7	40	Possibly IgM Fc receptor
CD8	32	MHC class I immune recognition
CD25	55	Low-affinity interleukin-2 receptor
CD45	180	Expressed on memory T cells (also known as UCHLI)
CD45R	200	Expressed on virgin T cells (also known as Leu-18)

MHC, major histocompatibility complex.

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CD4+ T-helper (Th) cells recognize antigens associated with class II MHC and participate in immune responses to extracellular pathogens by close coordination with other immune cells like macrophages, neutrophils, and B lymphocytes. However, CD8+ cytotoxic T cells recognize antigens associated with class I MHC and mount immune responses to intracellular pathogens leading to destruction of infected cells.

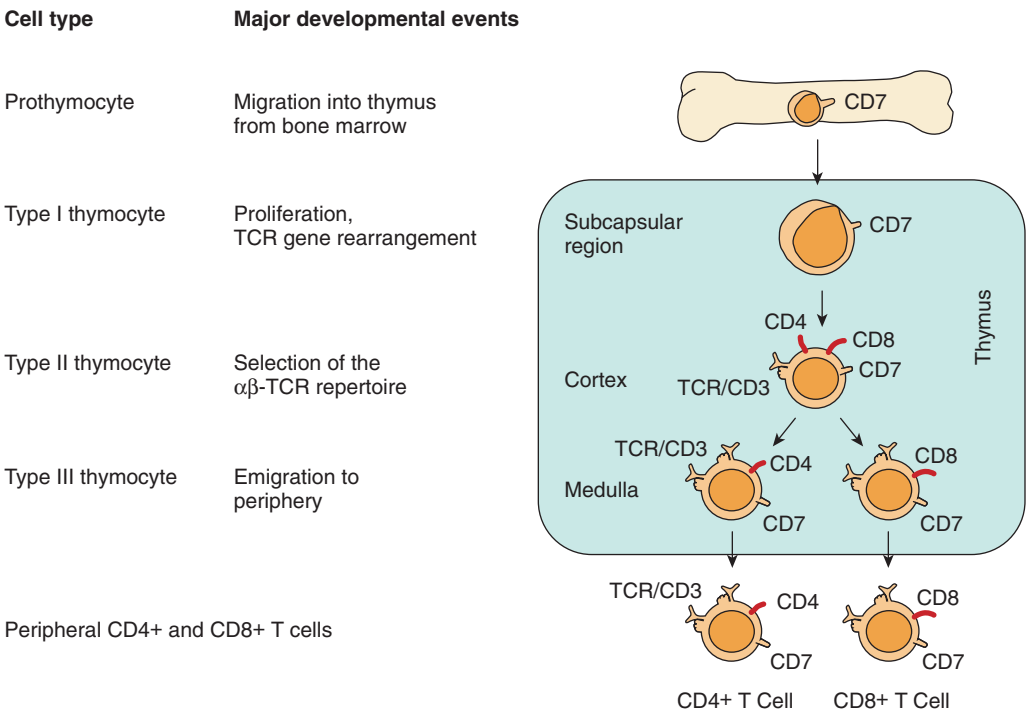
Clones of mature CD4+ T cells are functionally categorized into two major subgroups: Th1 cells that interact preferentially with mononuclear phagocytes, and Th2 cells that tend to promote B-cell division and differentiation. The balance of activity between these two subsets is related in part to how antigen is presented to the cells, and it ultimately determines the type of immune response that develops. Three other subgroups of CD4+ cells also exist, Th17 cells, T-regulatory cells (Treg), and T-follicular helper (Tfh) cells (discussed further below).[23]

Surface markers of T-cell populations change during T-cell development. In humans, naive T cells express the cell surface molecule CD45RA, whereas activated cells express the CD45RO isoform and higher levels of adhesion molecules, such as the β1 integrin (CD29). The mechanism resulting in the generation of activated T cells from resting memory T cells is still unclear.

T-Cell Development

Lymphocytes destined to become T cells must undergo several maturational steps in the thymus before they become mature effector T cells. In humans, the thymus develops embryologically as an outgrowth from the third and fourth pharyngeal pouches between weeks 6 and 7 of gestation. The cortex and medulla of the thymus begin to differentiate by the 10th week of gestation, and Hassall corpuscles appear by the 12th week of gestation.

The undifferentiated but committed lymphoid progenitor cells that first enter the thymus from the bone marrow (at approximately 7 weeks' gestation) are initially double-negative for both CD4 and the CD8 antigen but do express the T-cell markers CD7 and CD45 (CD7 may be the IgM Fc receptor, and CD45 is the common leukocyte antigen). With maturation, the thymocytes first become CD4+ CD8+ double-positive and appear in the thymic cortex at approximately 10 weeks' gestation (Fig. 47.7). At this stage, αβ TCRs are first expressed on their cell surface. Production of the T-cell α chain precedes production of the β chain. In the thymus, T-cell maturation is accompanied by the sequential appearance of surface phenotypic markers (see Table 47.7). CD1, CD2, and CD5 surface antigens appear soon after CD7 expression, whereas CD3 appears later. As gestation progresses, most cells leaving the thymus become



• **Fig. 47.7** Putative stages of human thymocyte development. Prothymocytes from the bone marrow enter the thymus and give rise to three major stages of αβ–T-cell receptor (αβ-TCR) lineage thymocytes. TCR-α and TCR-β chain genes are rearranged during stage I; thymic selection occurs mainly during stage II; and emigration of mature CD4+ and CD8+ cells occurs in stage III. (From Lewis DB, et al.: Developmental immunology and role of host defenses in neonatal susceptibility to infection. In: Remington JS, et al., eds. *Infectious diseases of the fetus and newborn infant*. 4th ed. Philadelphia: Saunders; 1995, with permission.)

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single-positive for either CD4+ or CD8+ surface antigen. Cells that lack both antigens (double-negative cells) retain stem cell function and possess a receptor (CD25, Tac antigen) for IL-2, which plays an essential role in T-cell proliferation. Mice lacking Notch-1 have blocked T-cell development with B cells developing in the thymus instead, suggesting that Notch signaling may play an important role in early T-cell commitment and differentiation.[45]

By the 12th week of gestation, occasional CD3+ cells can be identified in human fetal peripheral blood. As gestation progresses, the percentage of CD3+ cells in the peripheral blood increases, coming to represent more than 50% of T lymphocytes by 22 weeks' gestation. These CD3+ cells also express either CD4+ or CD8+ antigen. By 13 weeks of gestation, CD3+ T cells appear in the fetal liver and spleen, and these cells represent more than 50% of the T lymphocytes in those organs by the end of the second trimester.

Role of Cytokine Receptor Signaling in Lymphocyte Development

In humans, X-linked severe combined immunodeficiency (X-SCID) syndrome is characterized by defective T-cell development and function. Affected patients lack T cells but possess near normal numbers of B cells. B cells from patients with X-SCID tend to secrete predominantly IgM antibody. Altered B cell–mediated antibody production in patients with X-SCID has also been attributed to defective T-helper cells. The mapping of the gene that encodes the common subunit of cytokine receptors, including the IL-2 receptor, has been linked to the X-SCID locus. Patients with X-SCID possess mutations in the common subunit, establishing a correlation between defects in this gene and the cause of X-SCID. Based on these observations, it was predicted that lymphocytes deficient in the expression of the IL-2 receptor would mimic some of the phenotypic abnormalities associated with patients with X-SCID. However, deficiency of IL-2 or the IL-2 receptor does not result in any of the defects observed in patients with X-SCID. These observations have since been attributed to the presence of the common subunit in multiple other cytokine receptors as well, including the IL-4, IL-7, IL-9, and IL-15 receptors. All these receptors are expressed on T cells, and mutations in the common subunit in X-SCID are likely to affect the function of all these receptors, thus providing an explanation for the pathophysiologic process of this disease.

T-Lymphocyte Activation and Maturation

The T-cell receptor (TCR) is a multisubunit complex that consists of TCR-αβ chains noncovalently associated with the invariant CD3 chains and the TCR-ζ chains. Generally, interaction between the TCR and antigen-presenting cells (APC) results in the activation of Src homology (SH) 2 and SH3 domain containing signaling proteins that belong to the Src family of lymphocyte-specific tyrosine kinase (LCK). Activated LCK associates intracellularly with the TCR and with the CD8+ and CD4+ coreceptors. Once activated, LCK activates the cytoplasmic domain of CD3/ζ complex, which contains the ITAM motif. ITAM allows the binding of additional signaling molecules containing SH2 domains, such as the SYK kinase ZAP70. When recruited to ITAM, ZAP70 is phosphorylated and subsequently activates a major adapter protein in T-cell signaling termed linker for activation of T cells (LAT). Activation of LAT and several other signaling molecules downstream in this cascade results in the activation of nuclear proteins, including transcription factors such as nuclear factor of activated T cells and mitogen-activated protein kinases. This results in the transcription of important T cell–specific genes that are crucial for development, differentiation, and function of T cells.

T cells require two signals for activation: a signal provided through the TCR involving priming with an antigen by class I or II MHC complexes, and a second, costimulatory signal provided when the CD28 receptor on T cells binds to B7-1 (CD80) or B7-2 (CD86) on APCs.[23] A key feature of the costimulatory signal provided by CD28 is that, in conjunction with a TCR stimulus, it allows high-level IL-2 production and provides an essential survival signal for T cells. The combined costimulatory signal prevents T-cell apoptosis or the induction of anergy (unresponsiveness) that may occur in response to activation of either signal alone. In the case of CD4+ cells, a third signal provided by growth factors or cytokines is also needed for activation and subsequent differentiation into different subtypes.[23]

Naive CD4+ helper T cells can be divided into two main subsets based on the profile of cytokines they produce. Th1 cells produce IL-2, IFN, TNF, IL-3, and GM-CSF; Th2 cells produce IL-4, IL-5, IL-6, IL-10, 1L-12, and IL-13. This differential pattern of cytokine expression contributes to differences in the function of these two subsets of T cells. Th1 cells are inflammatory cells responsible for mediating cell-mediated immunity. In contrast, Th2 cells act to help B cells produce antibodies. Naive T cells generally do not express mRNA for cytokines such as IFN, IL-4, or TNF. The decision of a naive T cell to mature into either Th1 or Th2 is partly regulated by the interaction between growth factors/cytokines and their receptors and transcription factors. For Th1 differentiation, interaction between naive Th cells and APCs, especially dendritic cells (DC), results in the synthesis of IL-12. IL-12 in conjunction with transcription factors signals transducer and activator of transcription (STAT4), and T-bet drives the maturation of IFN-producing Th1 cells. Likewise, IL-4, STAT6, and the transcription factor GATA-3 are essential for the generation of Th2 cells. A balance between cytokines, signaling molecules, and transcription factors is thus essential for driving the differentiation of Th1 and Th2 cells from naive Th cells.[23]

Along with Th1 and Th2 cells, as previously stated, three other subsets of helper T cells have also been described. Th17 cells produce IL-17A, IL-17F, IL-21, IL-22, and IL26. Differentiation of these cells occurs with stimulation by TGF-β and IL-6 and requires the transcription factors

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RORγ, RORα, and STAT3. T-regulatory (Treg) cells are a subclass of CD4+ cells that play an important role in suppressing the effector activity of multiple T-helper subsets and mediating immune self-tolerance. Treg cells constitutively express the transcription factor forkhead/winged-helix family transcriptional repressor-p3 (Foxp3).[35] These cells can be thymically derived like other T-cell subsets or can be induced in the periphery. The transcription factors Foxp3 and STAT5 cooperate with TGF-β and control Treg differentiation. T-regulatory cells (Tregs) downregulate T-cell responses to both foreign and self-antigens. Although current knowledge about Tregs early in life is limited, recent studies suggest deficiencies in Treg function in both term and preterm infants when compared to adults.[40]

The T-follicular helper (Tfh) cells are a distinct class of helper T cells that are normally found in the B-cell follicles in secondary lymphoid organs. These cells are controlled by the Bcl-6 transcription factor and mediate B-cell activation and assist in germinal center formation.

Role of Cytokines in T-Cell Function

IL-2 was originally described as a T-cell growth factor, but it is now known to have activity on various other cell types, including NK cells, B cells, macrophages, and monocytes. The synthesis and secretion of this cytokine is triggered by the activation of mature T cells. Binding of IL-2 initiates clonal expansion of activated T cells. High-affinity IL-2 receptor expression is induced on B cells by exposure to IL-4 and immunoglobulin receptor binding. The activity of IL-2 on other cell types (NK cells, macrophages, neutrophils, and lymphokine-activated killer cells) is mainly through the intermediate-affinity IL-2 receptor. A key role of the IL-2 receptor γ chain (which is also found in the receptors for IL-4, IL-7, IL-9, and IL-13) in the immune response is highlighted by the consequences of its genetic malfunction. Mutations in the IL-2 receptor γ chain are responsible for X-SCID in humans.

IL-4 is produced by a subpopulation of T cells and by mast cells. Its production follows T-cell activation or cross-linkage of FcRI receptors on basophils or mast cells. IL-4 affects many cell types, promoting the growth of T cells, B cells, mast cells, myeloid cells, and erythroid cell progenitors. It promotes class switching in B cells to IgE and augments IgG1 production. The IL-4 effect on T-cell development is to drive T-cell differentiation toward a Th2 type at the expense of a Th1 response. In the neonatal Th1 cell, antigen presentation by APCs upregulates IL-13Rα, which forms a complex with IL-4Rα on the surface of Th1 cells. IL-4 produced by Th2 cells acts on the IL-4Rα/ IL-13Rα complex and induces Th1 cell apoptosis, skewing the T-helper cell response to a predominant Th2 response in neonates. IL-4 has also been shown to initiate cytotoxic responses against tumor cells. The pleiotropic activity of IL-4 is reflected in the range of cell types that express IL-4 receptor. This high-affinity receptor is found on T cells, B cells, mast cells, myeloid cells, fibroblasts, muscle cells, neuroblasts, stromal cells, endothelial cells, and monocytes.

IL-7 signaling promotes cell-cycle entry and proliferation of developing T-lymphocytes and B-lymphocytes. In thymocytes, IL-7 signaling has been implicated in the induction and maintenance of the antiapoptotic protein Bcl-2 and has been shown to inhibit the expression of the pro-apoptotic factor Bax. These results suggest that one of the principal functions of IL-7 signaling in developing thymocytes is to promote cell survival.

IL-12 is made by B cells, monocytes, and macrophages, and acts synergistically with IL-2 to induce IFN production by T cells and NK cells. In the absence of IL-12, cytotoxic CD8+ T cells can proliferate but fail to differentiate and do not produce important effector proteins such as IFN-γ and granzyme B. IL-12 thus enhances the cytotoxic activity of T cells.[32]

IL-10 has important biologic effects on T-cell function. Although initially described as a cytokine produced by Th2 cells capable of decreasing the activation of Th1 cells, it is now known to be produced by multiple immune cell types, including macrophages, monocytes, DC, T cells, and B cells. IL-10 primarily functions as an anti-inflammatory cytokine and may mediate some of the immunosuppressive effects of CD4+ CD25+ Treg cells.[19]

T-Cell Function in Neonates

T cells form an important component of the adaptive immune system in the neonate. While overall T-cell counts are higher in cord blood of term newborns compared to adults' blood,[48] both CD4+ and CD8+ lymphocyte counts decrease with gestational age and are lower at birth in preterm compared to term infants.[14] This deficiency in T-cell subsets could possibly contribute to the increased susceptibility to infections in the preterm infant. Treg cells are interestingly higher in cord blood of preterm compared to term infants or adults.[14] Given their important role in immune suppression, quantitative deficiencies in Tregs may be important in inflammatory diseases in neonates. Indeed, in infants with necrotizing enterocolitis, ileal Treg to CD4+ T-cell ratio or Treg to CD8+ T-cell ratio is lower than that in age-matched control infants.[49]

Along with quantitative differences, neonatal T cells are also functionally distinct from adult cells. Cord-blood T cells have reduced ability to proliferate and synthesize cytokines such as IL-2, IFN-γ, IL-4, and GM-CSF. Studies also suggested a greater propensity of neonatal naive Th cells to differentiate toward the Th2 phenotype rather than Th1 in the presence of endogenous neonatal APCs. Multiple factors contribute to this skewed Th2 phenotype in neonates. Th1 responses are dependent on IL-12 production by APCs like DC that are decreased in numbers and are functionally immature in neonates compared to adults (described below). In addition, the neonatal CD4+ cells are epigenetically poised to increase production of Th2 cytokines, such as IL-4 and IL-13. This results from a hypomethylated state in a key regulator element, CNS-1, at the Th2 cytokine locus in neonatal CD4+ cells. Thus with antigenic stimulation there is immediate release of Th2 cytokines and development of

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Th2 effector cells. In addition, as previously described, IL-4 elaborated from Th2 cells can act on the IL4Rα/IL13Rα heteroreceptor present on Th1 cells leading to Th1 cell apoptosis. The relative lack of Th1 differentiation from naive Th cells in neonates could thus result in impaired cell-mediated immunity.

While there is a bias toward a Th2 phenotype in neonatal CD4+ cells, an adult type Th1 response can be generated with the right inciting stimulus as demonstrated by responses in the human neonate to the mycobacterium bovis bacillus Calmette-Guerin (BCG). This is also observed in neonatal mouse studies, where altering the dose of the viral antigen or addition of costimulatory molecules leads to a deviation from the expected Th2 to an adult type Th1 response.[39] Thus although neonatal CD4+ cells are functionally distinct and manifest a Th2 skewed response, they have plasticity and retain the ability to mount an adult type Th1 response.

Compared with neonatal CD4+ cells, neonatal CD8+ cells have a normal frequency of precursors and are free of cytokine promoter modifications, such as the methylation changes that are commonly associated with neonatal CD4+ Th cells. Neonates show the presence of functional CD8+ cytotoxic T cells against congenital human CMV and Rous sarcoma virus. They also show the presence of functional memory CD8+ cells against congenital CMV. These results suggest that under certain conditions of stimulation, despite the absence of adequate CD4+ T-cell help, long-lived, functional memory CD8+ T cells can be generated by in utero CMV infection. This type of antiviral immunity in neonates persists partly because of persistent and prolonged viral secretion associated with some viral infections, such as CMV infection. This type of infection is likely to result in sustained and continuous stimulation of CD4+ and CMV-specific, long-lived memory CD8+ T cells in utero.

Studies have shown that neonatal T cells do not lack the ability to undergo proliferation and cytokine production when stimulated in a manner that does not require signaling through their TCR-CD3 complex. Studies comparing TCR-CD3-independent responses between adult and neonatal T cells have shown no differences in the ability of neonatal and adult T cells to synthesize IL-2 and undergo proliferation.

Other T-Cell Subgroups

Dendritic Cells. Efficient T-cell responses in vivo require the presence of mature and functional antigen-presenting cells (APCs). Dendritic cells (DC) are an important class of APCs stimulating naive T cells. DC populations have been grown from separated hematopoietic precursors, suggesting that there is a common granulocyte-monocyte-dendritic cell progenitor. Cells with a dendritic/macrophage morphology are present in the yolk sac, mesenchyme, and the liver at 4-6 weeks of age. DCs are detectable in skin by 6-7 weeks of gestation.

Human peripheral blood DCs include mainly two subgroups: (1) myeloid DCs (or mDCs) are $CD11c^+$ cells that express myeloid markers such as CD13, CD33, and CD11b; and (2) plasmacytoid DCs (or pDCs) are $CD11c^-$ and have a plasmacytoid morphology with well-developed rough endoplasmic reticulum and Golgi apparatus. Neonatal DCs have been shown to express low levels of costimulatory molecules, including CD40, CD80, and CD86, compared with adult DCs. The inability of neonatal DCs to deliver adequate levels of costimulatory signals to neonatal T cells is likely to be an important cause of neonatal tolerance, in addition to lack of adequate IL-12 production by APCs and IFN-γ by naive Th cells, preventing the differentiation of these cells into Th1 cells. In addition, the expression of MHC class II is also reduced on neonatal APCs. The reduced Th1 polarizing effect of fetal and neonatal APCs may help to reduce the risk of allo-immune reactions between the mother and the developing fetus. Similarly, recent studies indicate that while fetal DCs retain the ability to respond to immunostimulatory agents, at baseline they are programmed to suppress inflammation.[7] While this immunosuppresant tone in DCs may protect the neonate from a proinflammatory milieu on exposure to environmental antigens it also leaves the neonate susceptible to infections from viruses and other intracellular pathogens that need effective Th1 defenses for clearance.

Neonatal APCs also synthesize low levels of proinflammatory cytokines, including TNF, IL-1β, and IL-12, in response to LPS stimulation (i.e., TLR4 ligand) and in response to other TLR ligands. Upregulation of TLR4 and CD14 expression is not observed in neonatal APCs on LPS stimulation, and the expression of MyD88, a crucial adapter molecule in TLR signaling, is also reduced in neonatal APCs. TLR4 expression is further reduced on APCs derived from premature infants compared with full-term infants. It is conceivable that premature infants are more susceptible to infections because of impaired TLR expression.

Examples of additional complexity in this process have also been documented. Studies have shown a differential response to TLR ligands on neonatal APCs. TNF-α synthesis is reduced in neonatal monocytes that are stimulated with LPS, whereas this response seems to be normal when these same cells are stimulated with R-848, a ligand for TLR7 and TLR8. Neonatal APCs also show reduced IFN-γ responsiveness, which is associated with defects in phagocytosis. The ability of neonatal monocytes to differentiate into DCs is significantly modulated, as reflected by differences in the morphologic characteristics of cord blood–derived DCs compared with adult DCs. Taken together, studies so far implicate significant defects in TLR activation in neonatal monocyte/macrophage APCs.

Most studies related to neonatal DCs have been performed using in vitro–generated monocyte-derived DCs (mDCs). These cells have several defects relative to adult mDCs. They tend to be immature based on low-level expression of MHC class II and surface markers such as CD80, CD86, and CD40. Even on LPS stimulation, the phenotype of these cells remains immature as reflected by continued lack of upregulation of MHC and costimulatory molecules. The immaturity of neonatal DCs can be

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attributed to impaired TLR signaling, a phenomenon also observed in monocyte/macrophage-derived APCs discussed earlier. Neonatal cord blood–derived DCs produce reduced levels of IL-12p70 and INF-β, and less INF-β-inducible genes like CXCL9 and CXCL10 in response to LPS. The defect in IL-12p70 production can, however, be rescued by providing exogenous IFN-γ to cultures. Although the NF-κB pathway appears to be preserved in neonatal DCs with TLR agonist stimulation, TRIF-dependent signaling is decreased. Consistent with the above-described defects associated with neonatal DCs, these cells also show significant reduction in the priming of allogeneic cord blood–derived T cells relative to adult DCs. Neonatal DCs apparently require additional mechanisms of activation to achieve the activation status of adult DCs. When activated, they seem to be relatively competent, however.

In addition to monocyte-derived myeloid DCs, studies have suggested the presence of another group of DCs called plasmacytoid DCs (pDCs) that are characterized on the basis of lack of CD11c (a marker for myeloid DCs) expression and presence of CD123. Cord blood contains a higher frequency of pDCs compared with peripheral blood. An enhanced ratio of pDC to mDC (3:1) is also observed in neonatal cord blood compared with adult blood (1:3). Similar to mDCs, neonatal pDCs also show functional defects. They produce reduced levels of IFN-α and IFN-β in response to TLR7 and TLR9 agonists. Although cord blood pDCs respond to R-848 by upregulating the expression of CD40, CD80, CD86, and MHC antigens, the extent of upregulation is less in these cells compared with adult pDCs. Likewise, R-848-stimulated TNF-α synthesis in cord blood pDCs is also reduced compared with adult pDCs. In adults, Flt3 ligand treatment of cells results in significant growth of cultured mDCs and pDCs derived from peripheral blood. Treatment of hematopoietic progenitors from human fetal tissues and cord blood with Flt3 ligand induces differentiation of these cells into pDCs that synthesize significant amounts of IFN-α/β in response to viral stimulation. Flt3 ligand could likely be used clinically to induce the expression of IFN in neonatal pDCs.

Cytotoxic T-Lymphocytes (CTLs). CTLs are important in host defense against intracellular infections, in allograft rejection, and tumor cell surveillance. CTLs utilize two well-established mechanisms for cell lysis, one involving release of extracellular mediators (such as the pore-forming perforin/granzyme system), and a second fas/fas ligand–dependent pathway that leads to target cell apoptosis.

CTL cytotoxicity is evident by 18 weeks of gestation but is far less efficient that adult cells even at term (<20% of adult CTL activity). Perforin expression in neonatal CTLs is about 30% of adult levels. CD28, which is a T-cell activation marker, is also expressed to significantly lower levels. Similar results are also observed in other assays; neonatal cells showed only 33% of lectin/mitogen-dependent cytotoxicity of adult cells. Circulating inhibitors such as α-fetoprotein and prostaglandins may also lead to lower CTL activity in neonates.

γδ T cells. The γδ T cells represent a distinct functional subset, with a majority lacking surface expression of both CD4 and CD8. These cells are detectable in the fetal thymus and liver at 6-8 weeks of gestation and comprise nearly 10% of the peripheral blood T cells at 16 weeks. Subsequently, the numbers decline gradually to reach about 3% at term. These cells are mainly present on skin and mucosal surfaces and closely interact with αβ T and B cells and dendritic cells. Although the exact functions of γδ T cells are not well understood, they can lyse target cells with the perforin/granzyme system like the cytotoxic T cells and can secrete cytokines like interferon (IFN)-γ and tumor necrosis factor (TNF)-α upon activation. Subsets of γδ T cells, including those present in the intestinal lamina propria and in the dermis, also produce IL-17.[46] The cytotoxicity of neonatal γδ T cells is significantly less than adults.

Fetal γδ T cells have a more diverse repertoire but a more limited junctional diversity than adults. This diversity is retained throughout the first year of life and then decreases gradually over the first decade of life. Overall, however, γδ T cells have a relatively restricted repertoire in comparison to the αβ T or B cells.

Natural Killer T Cells. Natural killer (NK) T cells are a subset of T cells that express the T-cell receptor chains in addition to a variety of NK cell markers.[24] In the presence of MHC-like molecule CD1d, these cells recognize both exogenous and endogenous lipid antigens. NK T cells are classified into two main subtypes: type I or invariant NK T cells and type II or diverse NK T cells. Type I NK T cells are less than 1% of T cells in cord blood[27] and express the conserved αβ TCR. Type II NK T cells are more abundant and express a more diverse TCR α and β chain repertoire.

Summary

Neonatal T cells are impaired in producing a robust Th1 response and produce less IFN-γ and TNF under conditions of physiologic stimulation, including in response to TCR-CD3 stimulation. Neonatal T cells are not intrinsically incapable of mature function, however. Adult-level cytokine production can be elicited in human neonatal T cells by increasing the magnitude of Th1-promoting costimulatory signals. In contrast, neonatal cytotoxic T lymphocytes are capable of generating long-lasting memory effectors against several viral infections, including CMV and Rous sarcoma virus. These findings could be exploited in the future to generate vaccines for the treatment of viral infections.

Qualitative differences in neonatal T cells and APCs compared with adult cells might contribute to these deficient T cell–mediated responses of neonates. Compared with adult T cells, neonatal T cells seem to require more costimulation to achieve robust Th1 responses in vitro and in vivo. Neonatal APCs might be poorly functional in vivo and normally unable to promote vigorous Th1 responses. If APC function is augmented or supplemented, however, mature Th1 responses can be promoted.

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B Lymphocytes and Antibody Production

Overview of B-Cell Function and Phenotypic Appearance

B lymphocytes represent 5%-15% of circulating lymphocytes in the peripheral blood and are characterized by the presence of cell surface immunoglobulin. Most B lymphocytes simultaneously express endogenously synthesized IgM and IgD and various other cell surface receptors (Table 47.8). Relatively few cells express cell surface IgG, IgA, or IgE. Cell surface immunoglobulin is similar in structure to secreted antibody and consists of four polypeptide chains (two identical heavy chains and two identical light chains) joined by disulfide bonds. Surface immunoglobulin is inserted into the lymphocyte membrane at the constant region of the immunoglobulin molecule.

Immune responses to foreign antigens can be classified as primary or secondary (Table 47.9). The primary immune response results in an increase in the titer of antibody, which plateaus and then is catabolized. In the secondary immune response, the antibody titer is usually greater, appears more quickly, and consists almost entirely of IgG antibody (versus IgM in the primary immune response). Most important, after the primary response, the host acquires an immunologic memory of that foreign antigen by expanding the population of antigen-specific T cells and B cells. Memory B cells are prone to making IgG earlier and exhibit higher affinity antigen receptors. Although a few foreign antigens are considered T-cell independent (i.e., they do not require the help of T cells), the antibody response to most antigens requires the coordinated response of T cells, B cells, and APCs (B cells, macrophages, and DCs). Two kinds of signals are required to activate B cells. The first signal is provided by the interaction of the foreign antigen with surface immunoglobulin, and the second signal originates from Th cells, which are needed for amplification of the immune response.

TABLE 47.8 Cluster-Designated Molecules Found on Human B Cells*

Antigen	Molecular Weight (kDa)	Comment
CD5	67	B-cell subset marker
CD10	100	Pre-B-cell marker
CD19	95	
CD20	95	
CD21	35	Complement receptor CR2 (C3b receptor)
CD22	140	
CD23	45	IgE low-affinity receptor on activated B cells
CD25	55	Interleukin-2 receptor (low-affinity) chain
CDw32	40	Fc receptor (FcR11)
CD35	220	Complement receptor CR1 (C3d receptor)
CD45	180-220	Leukocyte common antigen
CD45R	220, 205	Restricted leukocyte common antigen

*All human B cells express surface immunoglobulin, and most B cells express class I and class II major histocompatibility antigens.

B-Cell Development

B-cell maturation occurs in two stages. In the first stage, undifferentiated stem cells mature into cells identifiable as B lymphocytes; this is an antigen-independent phase that occurs in the fetal liver and bone marrow in humans. The second stage of lymphoid differentiation is antigen dependent; during this phase, B lymphocytes are transformed into plasma cells.

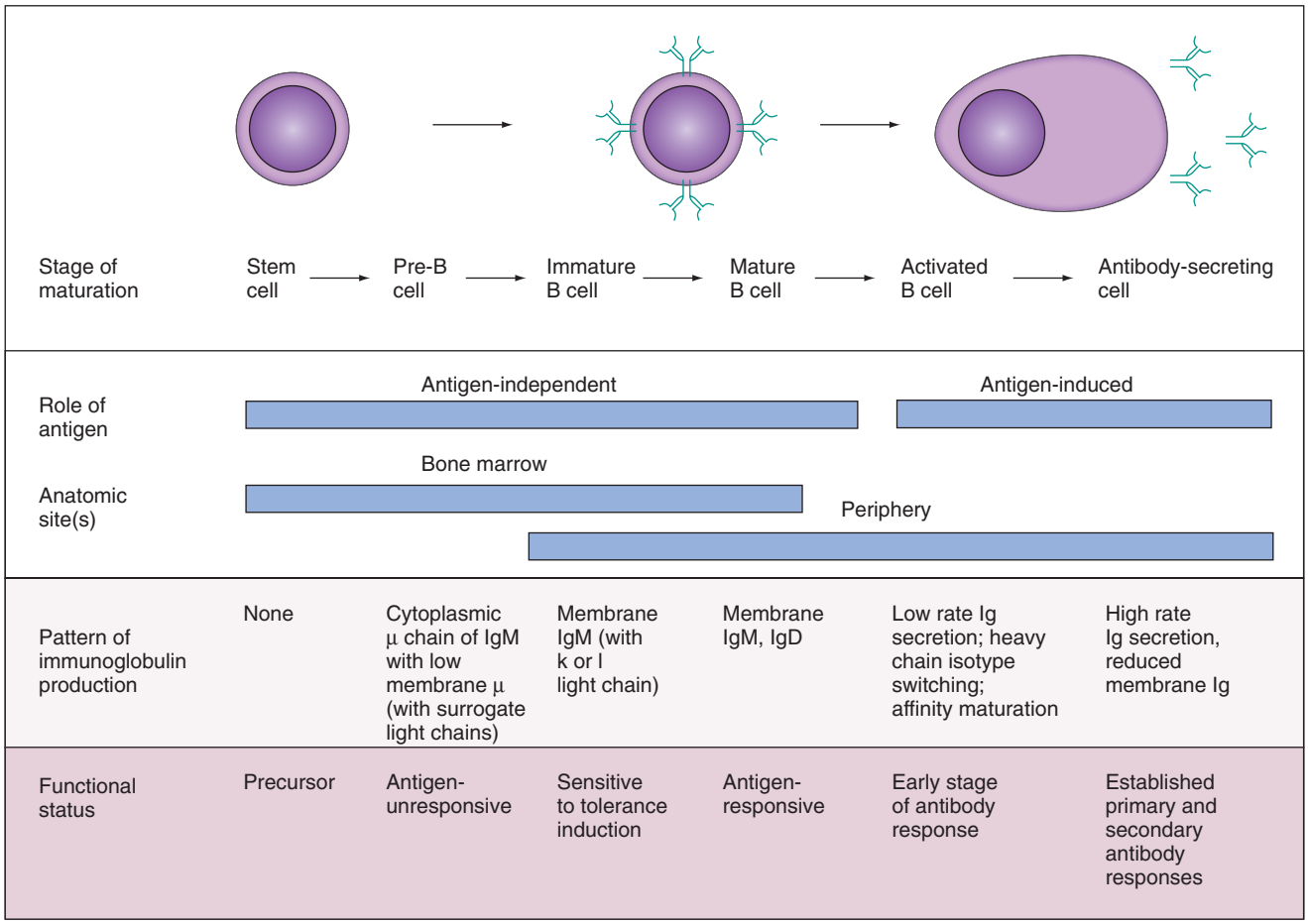
The first recognizable cell in the B-cell lineage is the pre–B cell (Fig. 47.8). This cell can be detected in fetal liver by 7-8 weeks of gestation and is characterized by cytoplasmic staining for the heavy chain of IgM (μ chain). As gestation progresses, pre–B cells can be detected in the fetal bone

TABLE 47.9 Features of Primary and Secondary Antibody Responses

Feature	Primary Response	Secondary Response
Lag after immunization	Usually 5-10 days	Usually 1-3 days
Peak response	Smaller	Larger
Antibody isotype	Usually IgM > IgG	Relative increase in IgG and, under certain circumstances, in IgA or IgE
Antibody affinity	Lower average affinity, more variable	Higher average affinity (“affinity maturation”)
Induced by	All immunogens	Only protein antigens
Required immunization	Relatively high doses of antigens, optimally with adjuvants	Low doses of antigens, with adjuvants usually not necessary

From Abbas AK, et al., eds. *Cellular and molecular immunology.* 2nd ed. Philadelphia: Saunders; 1994, p. 188.

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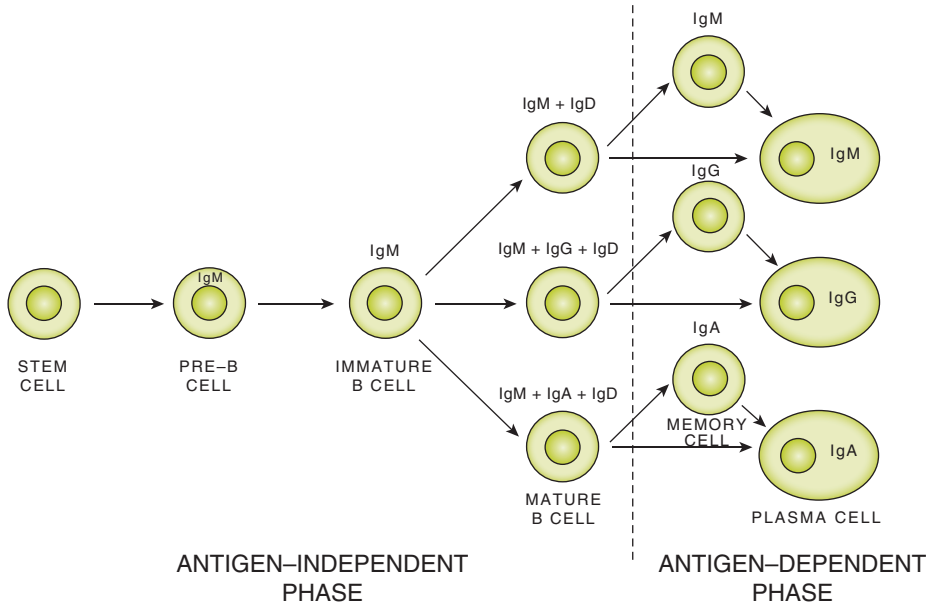
• **Fig. 47.8** Sequence of B-lymphocyte maturation and antigen-induced differentiation. Ig, immunoglobulin. (From Abbas AK, et al., eds. *Cellular and molecular immunology*. 2nd ed. Philadelphia: Saunders; 1994, with permission.)

marrow. Clonal diversity is generated at the pre–B cell stage of development. Intact immunoglobulin genes are formed by the rearrangement of gene segments composing each heavy-chain and light-chain family. Genes encoding the human heavy chain are located on chromosome 14; the κ light-chain genes are located on chromosome 2, and the λ light-chain genes are located on chromosome 22. The heavy-chain family consists of several hundred variable genes (VH), a smaller number of diversity genes (DH), and six joining genes (JH). The JH genes are linked to constant genes, which encode for the heavy-chain classes. The light-chain genes are similarly constructed. Antibody-variable regions are generated from multiple smaller gene segments; the potential number of different antigen-combining sites is the product of the number of VH, DH, and JH genes. Antibody diversity is additionally increased by the random addition of nucleotides at the splice site junctions of V, D, and J segments and by point mutations in variable-region gene segments.

Pre–B cells give rise to immature B lymphocytes, which express surface IgM and complement receptors but no other immunoglobulin classes. These cells can be detected in the fetal liver at 8-9 weeks of gestation. Immature B lymphocytes have a unique functional property; when exposed to an antigen or ligand in the absence of activated T cells, they are rendered tolerant to additional stimulation with the same antigen; this process, called clonal anergy, accounts for the tolerance of B lymphocytes to self-antigens. Immunoglobulin class diversity occurs by a process of isotype switching, during which cells that express surface IgM with a particular specificity generate daughter cells that express another immunoglobulin class (Fig. 47.9). Cells that express other membrane immunoglobulin isotypes (IgG, IgA) can be seen by the 12th week of gestation. These other immunoglobulin classes almost always appear on cells that express membrane IgM concurrently.

At a later stage (the mature B-cell stage), cells express membrane-bound IgG or IgA in association with membrane IgM and IgD. Cells that express surface IgD are incapable of being deactivated by antigen. In cells that express three heavy-chain classes, all three isotypes exhibit the same specificity and express the same variable-region genes. During the antigen-dependent phase of B-lymphocyte differentiation, most B lymphocytes express only a single isotype, and plasma cells do not express surface immunoglobulin (see Fig. 47.8). By the 15th week of gestation, a normal fetus has levels of circulating B lymphocytes that are equal to or higher than the levels of adults. Fetal

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• **Fig. 47.9** Development of B-cell surface immunoglobulin expression. Immunoglobulin class diversity occurs by a process of isotype switching. Immature B lymphocytes express surface IgM, but as cells mature, surface IgM and IgD in association with IgA or IgG are expressed. During the antigen-dependent phase of B-cell maturation, B cells express a single immunoglobulin isotype, and mature plasma cells are devoid of surface immunoglobulin.

B lymphocytes can be shown in highest proportions in the spleen (30%), blood (35%), and lymph nodes (13%).

B-Cell Activation by B-Cell Antigen Receptors and Coreceptors

The B-cell receptor (BCR) serves multiple functions on B cells that can differ substantially through various stages of their development. Proliferative expansion and differentiation are triggered through the pre-BCR and BCR complexes in pre–B cells and mature resting cells. At the opposite extreme, apoptosis is triggered in immature B cells on excessive clustering of newly expressed BCRs as a mechanism to eliminate autoreactive membrane IgM-expressing B cells. Strong BCR ligation in mature B cells has also been shown to inhibit V(D)J recombination at the membrane immunoglobulin locus, whereas weak ligation promotes recombination, presumably to generate higher affinity antibodies. Finally, the BCR serves as a specific receptor to internalize antigen efficiently for processing and peptide presentation to Th cells. The B cell has devised a complex network of BCR signaling cascades to perform such a diverse array of functions.

Role of Cytokines in B-Cell Function

The cytokines IL-1, IL-2, and IL-4 affect B-cell and T-cell function. IL-2 stimulates the growth and differentiation of B cells. The ability of IL-4 to induce class switching in B cells has been documented earlier. This section deals in more detail with other cytokines having more specific effects on B cells.

IL-5 is produced by activated T cells. On B cells, IL-5 functions as a late-acting B-cell differentiation factor, playing a major role in the production of IgA. IL-5 is perhaps better known, however, for its effect on eosinophil differentiation. It not only induces the generation of eosinophils from human bone marrow precursors but also upregulates expression of CD11b on human eosinophils and activates IgA-induced eosinophil degranulation. T-cell production of this cytokine is stimulated by parasitic infections.

IL-6 is a pleiotropic cytokine produced by many cell types, including T cells. Its effect on B cells is to promote growth and facilitate maturation of the B cells, causing immunoglobulin secretion. Resting B cells do not express the IL-6 receptor but are induced to express the IL-6 receptor after activation.

IL-7 has been described previously in the T-cell section, but this cytokine, which is secreted by stromal cells, has a great effect on the development of progenitor B cells. IL-10 also affects T cells and B cells, acting synergistically with other cytokines on the growth of hematopoietic lineages, including those giving rise to B cells. Antibody depletion of IL-10 in vivo results in a reduced IgM and IgA response with an increase in IgG2 and a depletion of certain B-cell subsets.

IL-13 is predominantly expressed in activated Th2 cells and regulates human B-cell and monocyte activity. It acts as a costimulant with CD40 receptor engagement of human B cells. Interaction between CD40 and CD40 ligand in the presence of IL-13 induces isotype switching and IgE synthesis, as does IL-4.

IL-14 is believed to play a role in the development of B-cell memory. IL-14 enhances the proliferation of activated B cells and inhibits the synthesis of immunoglobulin. It is produced by follicular DCs and activated T cells. IL-14

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expression in reactive lymph nodes suggests that, during a secondary immune response, surface IgD B cells migrating through the lymph node encounter antigen, become activated, and express IL-14 receptor; after binding of IL-14, the increased Bcl-2 expression prevents apoptosis and permits B-cell memory development.

B-Cell Responses in Neonates

Several distinctions between neonatal and adult splenic B cells have been identified. Neonatal B cells express reduced levels of costimulatory molecules CD40, CD80, and CD86, which results in defective T-cell responses via CD40 ligand (CD40L) and IL-10. Marginal zone B cells derived from spleens of neonates tend to express reduced levels of CD21. In addition, expression of a critical costimulatory receptor, TACI, is impaired in neonatal B cells, in particular in premature infants.

Although these cell-intrinsic factors contribute significantly to defects in antibody responses in neonates, B-cell responses in neonates are also affected by external factors. Maternal-derived antibodies can bind to vaccine antigens and inhibit neonatal B cells from recognizing them. Additionally, serum complement levels, in particular C3 levels, in neonates are reduced; this results in reduction in the formation of antigen-antibody complexes. The number of marginal zone macrophages in neonate spleens is also reduced compared with adults. These cells play an essential role in trapping antigens. Defects are also observed in the maturation of follicular DCs in neonates. Follicular DCs are crucial for attracting B cells and provide signals that result in somatic hypermutation and class switching of antibodies.

Additional defects include a lack of prolonged antibody response; this is due partly to impairment in the establishment and maintenance of antibody-secreting plasma cells in the bone marrow of neonates. Although plasma cells in neonates do migrate to the bone marrow, they are impaired in their ability to thrive as long-lasting cells largely because of lack of survival and differentiation signals from bone marrow–derived stromal elements. Finally, studies have also shown that in some instances administration of vaccines to neonates preferentially leads to the generation of memory B cells rather than plasma cells. This situation has been largely attributed to reduced overall B-cell receptor affinity of neonatal naive B cells for antigens resulting in an overall reduction in the strength of the intracellular signal, which may preferentially lead to the generation of memory B cells rather than plasma cells. In neonates, a significant number of B-cell intrinsic factors and microenvironmental factors cooperate to regulate the development and maintenance of antibody-producing plasma cells and the preferential generation of memory B cells.

CD5-Expressing B Cells

B cells with surface expression of CD5, which is a T-cell antigen, may represent a functionally and ontogenically distinct subset. Some believe that CD5 positivity defines a so-called "B-1" subset of cells, distinct from the conventional adult "B2" population by virtue of their earlier appearance in ontogeny, capacity for bone marrow–independent self-renewal, and constitutively expressing signal transducer and activator of transcription-3 (STAT3). B-1 cells express the B cell–lineage antigens CD19 and CD45R, although CD45R is present at lower levels on B-1 cells than on B-2 cells. B-1 cells in the peritoneal and pleural cavities can be identified by their unusual CD11b+ $sIgM^{hi}$ $sIgD^{low}$ phenotype and can be further subdivided on the basis of differential expression of the cell-surface antigen CD5, into CD5+ CD11b+ $sIgM^{hi}$ $sIgD^{low}$ B-1a cells and CD5- CD11b+ $sIgM^{hi}$ $sIgD^{low}$ B-1b cells.

These cells are the predominant B-cell type during fetal life and have a distinctive anatomic localization in the fetal spleen and the peritoneal cavity. They appear in the spleen at 15 weeks and are seen in the lymph node primary follicles at about 17 weeks of gestation. In adults, CD5 expression can be found on about 25%-35% of total B cells and 1%-7% of all the peripheral blood mononuclear cells. In contrast, CD5+ B cells represent approximately 90% of the total cord blood B cells. This number decreases to 75%-80% during infancy and reaches adult levels only by late adolescence.

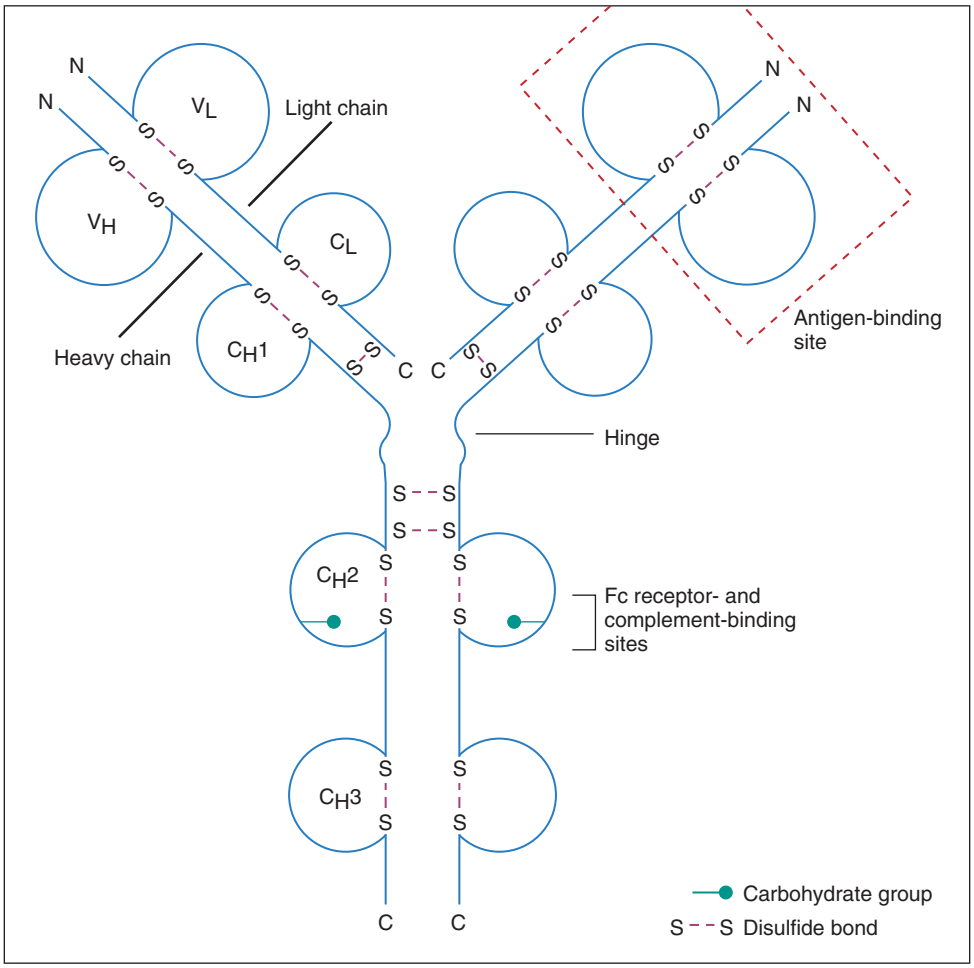
The exact function of B-1 cells in the fetus is still unclear. The functional characteristics of B-1 cells such as the unique localization, broad polyspecific specificities, and a restricted Ig repertoire have been considered to indicate a role of these cells in the innate rather than in adaptive immunity. Unlike follicular B-2 cells that respond to protein antigens, and with T-cell help undergo immunoglobulin heavy chain class-switching and affinity maturation, B-1 cells respond mainly to T cell–independent immunogens that include carbohydrate antigens. Observations indicate that the two types of B-1 cell, B-1a and B-1b, show functional differences during the immune response.[4] B-1a cells spontaneously secrete IgM, which provides a first line of defense against certain encapsulated bacteria, such as *Streptococcus pneumoniae*, whereas antibody production by B-1b cells is induced and has a role in the ultimate clearance of the pathogen and in providing long-term protection.

Immunoglobulin Structure and Function

Specific antibody may be produced in response to direct microbial exposure or through immunization by an almost infinite spectrum of antigens (e.g., proteins, carbohydrates, bacteria, viruses, fungi, and drugs). Antibodies are synthesized and secreted by B lymphocyte–derived plasma cells that reside in the lymph nodes, spleen, mucosal linings of the gastrointestinal and respiratory tracts, and bone marrow.

Antibodies comprise a unique family of glycoproteins called immunoglobulin, which in humans consists of five major classes: IgG, IgA, IgM, IgD, and IgE. The basic structure of the IgG molecule is depicted in Fig. 47.10. The IgG molecule is composed of four polypeptide chains—two heavy chains and two light chains—held together by covalent disulfide bonds and noncovalent forces. In a given IgG molecule, the two heavy chains and two light chains have

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• **Fig. 47.10** Schematic diagram of an immunoglobulin molecule. In this drawing of an IgG molecule, the antigen-binding sites are formed by the juxtaposition of light-chain (V_L) and heavy-chain (V_H) variable domains. The locations of complement-binding and Fc receptor-binding sites within the heavy-chain constant (C_H) regions are approximations. S-S refers to intrachain and interchain disulfide bonds; N and C refer to amino and carboxyl termini of the polypeptide chains. (From Abbas AK, et al., eds. *Cellular and molecular immunology*. 2nd ed. Philadelphia: Saunders; 1994, with permission.)

identical amino acid sequences. The different immunoglobulin classes are distinguished by antigenic and amino acid sequence differences in their heavy chains. Some of the immunoglobulin classes are composed of subclasses; IgG has four subclasses—IgG1, IgG2, IgG3, and IgG4—that arise from antigenic differences in the heavy chains. In addition to these differences between the immunoglobulin classes and subclasses, there are antigenic and amino acid sequence variations in the amino-terminal portions of the heavy chains and light chains in the so-called variable regions. The structural variability in this region permits different antibody molecules to react specifically with different antigens. In contrast, the amino acid sequences of the carboxyl-terminal portions of the heavy (Fc region) and light chains do not vary between molecules of the same immunoglobulin class or subclass; these are called the constant regions. The variable regions of immunoglobulin molecules confer the antigen-binding specificity, and the constant regions differ among the various immunoglobulin classes; these regions' biologic properties and functions vary as well. Only IgM and IgG activate the complement system through the classic pathway, and only IgG can be actively transported across the placenta.

The chemical characteristics and biologic properties of the immunoglobulin classes are summarized in Table 47.10. IgG is the major immunoglobulin in the serum and interstitial fluid and has a long half-life of approximately 21 days. It is responsible for immunity to bacteria (particularly gram-positive bacteria), bacterial toxins, and viral agents. IgG antibodies can neutralize viruses and toxins and facilitate the phagocytosis and destruction of bacteria and other particles to which they are bound. IgG can also activate the complement pathway and amplify the inflammatory response by increasing leukocyte chemotaxis and complement-mediated opsonization.

IgA is the second-most abundant immunoglobulin in serum, but it is the predominant one in the gastrointestinal and respiratory tracts and in human colostrum and breast milk. In secretions, IgA occurs as a dimer joined by a J chain and bears an additional polypeptide chain, called the

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TABLE 47.10 Chemical and Biologic Properties of Human Immunoglobulin Classes

Variable	IgG	IgA	IgM	IgD	IgE
Heavy chains	Γ	α	μ	δ	ε
Molecular weight (Da)	150,000	160,000 400,000*	900,000	180,000	190,000
Biologic half-life (days)	21	5	5	2	2
Adult serum concentration (mg/dL)	1000	250	100	2.3	0.01
Placental transfer	+	0	0	0	0
Binds complement (classic pathway)	+	0	+	0	0
Reaginic activity	0	0	0	0	+
Mucosal immunity	+	+++	+	0	++

*Secretory IgA.
0-+++ Indicates increasing ability to protect mucosal surfaces from pathogen invasion.

secretory component. This moiety endows the molecule with resistance against degradation by proteolytic enzymes. Secretory IgA is uniquely suited for functioning in the secretions of the respiratory and gastrointestinal tracts. IgA provides local mucosal immunity against viruses and limits bacterial overgrowth on mucosal surfaces. It also may limit absorption of antigenic dietary proteins. IgA does not activate the classic complement pathway but can activate the alternative pathway.

IgM antibodies exist in serum primarily as pentamers joined together by a J chain. IgM provides protection against blood-borne infection. It occurs only in small quantities in interstitial fluids and secretions. IgM antibodies are potent bacterial agglutinins and activate the classic complement pathway. Through activation of the complement system, IgM antibodies cause deposition of C3b on bacterial cell surfaces and facilitate phagocytosis. There are no phagocytosis-promoting receptors for IgM. Most serum antibodies to gram-negative bacteria are of the IgM type. Intrauterine and neonatal infections elicit the formation of predominantly IgM antibodies. Because IgM does not cross the placenta, the presence of specific IgM antibody in cord blood to spirochetes, rubella, CMV, or other microorganisms can be taken as reliable evidence of intrauterine infection with these agents. The absence of IgM does not exclude the possibility of congenital intrauterine infection, however.

IgE antibodies are present in extremely small quantities in serum and secretions. These antibodies play a major role in allergic reactions of the immediate hypersensitivity type. IgE antibodies bind to the cell membranes of basophils (mast cells) by a receptor for the carboxyl-terminal portion of the heavy chain. Binding of antigen (allergen) to the IgE fixed to the basophil results in the liberation of histamine, leukotrienes, and other pharmacologic mediators of immediate allergic reactions. IgD, which occurs in low concentration in serum, is present on the surface of B lymphocytes. The role of circulating IgD is unclear.

Antibody Production in Fetuses and Neonates

The fetus acquires the ability to produce serum immunoglobulins early in gestation. In vitro studies have shown the ability of fetal cells to produce antibody (IgM) by 8 weeks' gestation. IgG synthesis occur slightly later, and IgA synthesis begins at approximately 30 weeks' gestation. For numerous reasons (i.e., the sterile environment in utero, the inability of the fetus to respond to certain kinds of antibody, T-cell suppression of B-cell differentiation), the fetus makes little antibody before the time of birth. As discussed later, at the time of birth, most of the circulating antibodies are IgG antibodies that have been transported across the placenta from the maternal circulation. Low levels of "fetal" IgM (<10% of adult levels) are present at term gestation and reach adult levels by 1-2 years of age. The concentration of IgG decreases postnatally (because of the catabolism of maternal IgG) and reaches a nadir (physiologic hypogammaglobulinemia) at approximately 3-4 months of age. Adult concentrations of IgG are reached by 4-6 years of age, and adult levels of IgA are attained near puberty (Table 47.11).

Innate Lymphoid System

The innate lymphoid cells (ILC) include cytotoxic natural killer (NK) cells and noncytotoxic ILC populations.[2] These cells are characterized by a classic lymphoid cell morphology, but unlike adaptive T and B cells, they do not show antigen specificity and function as a part of the innate immune system.

Natural Killer Cells

Phenotypic and Functional Characteristics

Generally, NK cells are defined by their large granular morphology. These cells make up almost 15% of peripheral blood lymphocytes in adults and are found in several tissues, including liver, peritoneal cavity, placenta, and

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TABLE 47.11 Normal Values for Immunoglobulins at Various Ages

Age	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)
Newborn	600-1670	0-5	5-15
1-3 mo	218-610	20-53	11-51
4-6 mo	228-636	27-72	25-60
7-9 mo	292-816	27-73	12-124
10-18 mo	383-1070	27-169	28-113
2 y	423-1184	35-222	32-131
3 y	477-1334	40-251	28-113
4-5 y	540-1500	48-336	20-106
6-8 y	571-1700	52-535	28-112
14 y	570-1570	86-544	33-135
Adult	635-1775	106-668	37-154

From Buckley RH, et al. Serum immunoglobulins, I: levels in normal children and in uncomplicated childhood allergy. *Pediatrics.* 1968;41:600.

bone marrow. Human NK cells are defined by the expression of cell surface proteins CD56 and CD16.[25] NK cells share some T-cell markers but are not affected in many natural/experimental disruptions of the T-cell system. It is conceivable that the two lineages derive from a common progenitor. Morphologically, NK cells display characteristic surface markers including the CD56/neural cell adhesion molecule and CD16/Fcγ receptor IIIa (FcγRIIIa), a low affinity IgG receptor. They also express CD2, LFA-1, and cytokine receptors such as IL-2$R_{\beta\gamma c}$, IL-12R, IFN-γR, and IL-15R_{α}.

NK cells can be detected as early as 6 weeks of gestation, and the number then increases progressively until birth. In cord blood, 10%-15% of all lymphocytes are NK cells, which is comparable to adult peripheral blood. The phenotype of fetal NK cells, however, is different from that of adults' cells. NK cell numbers are highest in cord blood and in the newborn period and decline through childhood.[25] Fifty to eighty percent fetal NK cells express CD3γ, ε, λ, and σ proteins, unlike a much smaller number in term infants or in adults where only CD3σ is expressed. On the other hand, only 30%-50% of fetal NK cells express CD16 (compared with more than 90% of neonatal and adult NK cells). Similarly, CD56 and CD57 are expressed poorly on fetal or neonatal NK cells compared to nearly 50% positivity in adult NK cells.

NK cells recognize viral-infected and tumor cells by the absence or decreased expression of MHC class I molecules on the cell surface. Their MHC-unrestricted killing is mediated by perforin/granzyme apoptotic pathways. The other mechanism of cytolysis is antibody-dependent cell-mediated cytotoxicity (ADCC), where target cell-bound IgG1 or IgG3 triggers the FcγRIIIa receptor on the NK cell. NK cells are also believed to play a key role in maintaining immunologic tolerance at the maternal–fetal interface.

Fetal NK cells have a significantly lower cytolytic activity (including ADCC) against tumor cell target cell lines than adults, but it increases with gestational age parallel to increasing expression of CD56 and CD16. However, even at term, the cytolytic activity is only 50%-80% of adult levels.

NK cells should not be confused with the natural killer T cells, a heterogeneous group of T cells that are discussed elsewhere in the chapter, which express an αβ T-cell receptor along with some NK cell markers. Many of these cells recognize the nonpolymorphic CD1d molecule, an antigen-presenting molecule that binds self- and foreign lipids and glycolipids. NK T cells constitute only 0.2% of all peripheral blood T cells. These cells play an important role in mucosal immunity and in the pathogenesis of inflammatory/allergic conditions; the role during fetal life remains unclear.

Noncytotoxic ILC

Phenotypic and Functional Characteristics

Noncytotoxic ILCs and NK cells are thought to be derived from a common lymphoid progenitor that then differentiates into committed precursors. Recent studies have confirmed that NK cells and noncytotoxic ILCs belong to distinct cell lineages.[13,22] Noncytotoxic ILCs are characterized by a classic lymphoid cell morphology. While these cells express IL2 receptor-α and IL7 receptor-α, unlike adaptive T and B cells, they do not exhibit antigen specificity. ILCs are divided into 3 groups: group 1 ILCs (ILC1s), group 2 ILCs (ILC2s), and group 3 ILCs (ILC3s). This grouping is based on the differential requirement for specific transcription factors during development by these cells, their expression of specific cytokines, and their distinct effector functions.

Although the three ILC subsets demonstrate remarkable similarity with the T-helper cell subsets, Th1, Th2, and Th17 in relation to cytokine expression and effector function,[2] they can function in the absence of antigen specificity. ILC1s express the T-bet transcription factor and produce Th1-associated cytokines that protect against intracellular bacteria and parasites. ILC2s express GATA-binding protein 3 transcription factor, produce Th2-associated cytokines (including IL-4, IL-5, IL-9, and IL-13) and mediate type 2 inflammation seen during tissue repair and allergic disorders. ILC3s express the RAR-related orphan receptor-γT transcription factor. These cells have a cytokine profile similar to Th17 cells and produce IL-17A, IL-17F, IL-22, GM-CSF, and TNF. ILC3s are further subdivided into two distinct subsets based on their expression of the chemokine receptor CCR6.

While little is known about the role of ILCs in the fetus and neonate, this is currently an area of active investigation. ILC2 cells are present in cord blood and may be present in higher proportions in male than in female neonates. In a murine model of gastroschisis, organs exposed to amniotic

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fluid were shown to contain high numbers of ILC2 and ILC3.[18] In another recent study, ILC3s were identified as the source of increased IL-17 levels seen in patients with preeclampsia and gestational diabetes.[3]

Summary

The ability to mount cell-mediated or antibody-mediated immune responses to specific antigens is acquired sequentially during the course of embryonic development. Early in gestation, fetuses can respond to certain antigens, whereas other antigens elicit antibody production or cell-mediated immune reactions only after birth. The well-known inability of children younger than 18 months of age to induce antibodies to polysaccharides from Pneumococcus and Haemophilus organisms is a clinically important example of the sequential acquisition of antigen-specific immunocompetence in humans.

Antibody responses of fetuses and premature and full-term newborns differ from responses of children and adults. Fetuses and newborns do not respond to some antigens (e.g., pneumococcal polysaccharide), and the antibody responses to other antigens (e.g., rubella, CMV, Toxoplasma) are predominantly of the IgM type. T lymphocytes are less experienced in neonates and may tend to suppress rather than stimulate B-cell differentiation. In addition, B cells of newborns differentiate predominantly into IgM-secreting plasma cells, whereas activated adult B cells produce IgG-secreting and IgA-secreting plasma cells as well. The adult pattern of B-cell differentiation develops during the first year of life.

Passive Immunity

Passive immunity is the acquisition of specific antibody or sensitized lymphocytes from another individual, and it represents a means by which specific immunity can be acquired without previous exposure to antigen or the mounting of a specific immune response. Such immunity is transient but nonetheless may provide sufficient antimicrobial protection during a vulnerable period of life. The development of an antibody response to an antigen seen for the first time requires 7-14 days. Active antibody-mediated immunity is of little value during the crucial first few days of an infection with a new microorganism. The presence of circulating specific antibody to that organism (i.e., passive immunity) permits the mobilization of multiple host defense mechanisms (e.g., complement system, neutrophils) to eliminate the invading microorganism and limit its colonization. In humans, the major avenues for the acquisition of passive immunity are the transfer of IgG across the placenta and the transfer of secretory IgA through colostrum and breast milk.

Placental Transport of Antibodies

Although B lymphocytes are present in a fetus by the end of the first trimester, there is little active fetal immunoglobulin production, because this process depends on exposure to antigens. Serum immunoglobulin levels in fetuses are extremely low until 20-22 weeks of gestation, at which time an accelerated active transport of IgG across the placenta begins. Only maternal IgG is transported. The specificity of this transport process is due to the presence of specific placental receptors for the heavy chain (Fc region) of the IgG molecule. The transport of IgG is an active placental process. Prematurely delivered infants have lower IgG levels than infants delivered at term. Fetal IgG concentrations are estimated to be only 5%-10% of the maternal levels at 17-22 weeks of gestation. IgG acquisition by the fetus occurs predominantly during the last 4 weeks of pregnancy, and neonatal IgG concentrations may exceed maternal levels by 20%-30% at full term.[38] Infants who are small for gestational age have lower IgG levels than infants who are an appropriate size at any gestational age. The placental dysfunction that reduces the nutrient supply to these poorly growing infants may also limit transfer of IgG. This phenomenon is manifested further by the progressive decrease in IgG transport after 44 weeks of gestation, a period when the placenta is known to become increasingly dysfunctional.

Elevated levels of IgM or IgA in cord blood usually indicate that the infant has been exposed to antigen in utero and has synthesized antibody itself. Congenital infections with syphilis and rubella characteristically produce elevation of the cord blood IgM concentration, and specific fetal antibody of the IgM type directed against the infecting agent can be detected. Elevated levels of IgM and IgA also may be found if maternal-to-fetal transplacental bleeding has occurred.

Immunologic Properties of Human Breast Milk

Maternal transfer of immunity to the newborn infant is also possible through breast milk. Table 47.12 lists specific and nonspecific protective factors that are transferred to the neonate by breast milk. Although all immunoglobulin classes can be detected in colostrum, secretory IgA constitutes most of the immunoglobulin in human breast milk.[10] Secretory IgA consists of two "serum" IgA subunits, a J chain and a secretory component, which render it resistant to digestion by trypsin and pepsin and to hydrolysis by gastric acid. There is no evidence that immunoglobulins present in breast milk enter the systemic circulation of the human neonate.

The levels of IgA, IgM, and IgG have been studied serially in milk. The IgG concentration is relatively constant during the first 180 days of lactation, whereas IgM and IgA are highest in colostrum, decrease during the first 5 days of lactation, and remain relatively constant during the next 175 days. Breast milk contains antibodies to a broad spectrum of enteric bacteria and viruses (e.g., poliovirus, echovirus, coxsackievirus), and the antibody titers to these agents decrease in parallel to the decrease in concentrations of IgA in the milk.

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TABLE 47.12 Immunologically and Pharmacologically Active Components and Hormones Found in Human Colostrum and Milk

Soluble	Cellular	Hormones and Hormone-like Substances
• Immunologically specific • Immunoglobulin: secretory IgA (11S), 7S IgA, IgG, IgM • IgE, IgD, secretory component • T-cell products • Histocompatibility antigens • Nonspecific factors • Complement • Chemotactic factors • Properdin • Interferon • α-fetoprotein • Bifidus factor • Antistaphylococcal factors • Antiadherence substances • Epidermal growth factor • Folate uptake enhancer • Antiviral factors • Migration inhibition factor • Carrier proteins • Lactoferrin • Transferrin • Vitamin B_{12}-binding protein • Corticoid-binding protein • Enzymes • Lysozyme • Lipoprotein lipase • Leukocyte enzymes	• Immunologically specific • T lymphocytes • B lymphocytes • Accessory cells • Neutrophils • Macrophages • Epithelial cells	• Epidermal growth factor • Prostaglandins • Relaxin • Neurotensin • Somatostatin • Bombesin • Gonadotropins • Ovarian steroids • Thyroid-releasing hormone • Thyroid-stimulating hormone • Thyroxine and triiodothyronine • Adrenocorticotropic hormone • Corticosteroids • Prolactin • Erythropoietin • Insulin

From Ogra PL, et al. Human breast milk. In: Remington JS, et al., eds. *Infectious diseases of the fetus and newborn infant.* 4th ed. Philadelphia: Saunders; 1995, p. 114.

Most immunoglobulins present in human breast milk are believed to be produced by plasma cells located in the breast itself, and very little milk immunoglobulin is derived from maternal serum immunoglobulins. Milk antibodies are directed predominantly against enteric bacterial and viral antigens; the concentration of such antibodies is much higher in colostrum than in maternal serum. The antibody composition of breast milk compensates partly for the deficiency of antibodies directed against enteric antigens in placentally transferred IgG. This unique spectrum of antibody specificity is achieved by the "homing" of B lymphocytes, sensitized in the mother's gastrointestinal tract, to her mammary glands. B cells stimulated by enteric bacterial or viral antigens in the Peyer patches of the small intestine migrate to the mucosal linings of the lactating mammary gland, where they differentiate into plasma cells and secrete their antibodies. Antigens introduced into the gastrointestinal tract stimulate the development of antibodies in breast milk; however, antibodies to these antigens do not develop in the serum. A mother transfers antibodies specific for microbial agents present in her own gastrointestinal tract to her infant through breast milk. As the neonate is being freshly colonized by primarily maternal flora, these antibodies limit bacterial growth in the gastrointestinal tract and protect against overgrowth.

The cellular components of human breast milk consist of macrophages, T and B lymphocytes, neutrophils, and epithelial cells.[10] The cellular content of colostrum or early milk is higher than that of later milk and varies greatly among women. Neutrophils are present in significant numbers early in lactation, and their presence may be related to breast engorgement during the initial days of lactation. Although the function of the breast milk neutrophil is unclear, its presence does not imply infection. Epithelial cells occasionally present in milk may originate from the skin of the nipple.

Breast milk macrophages are mononuclear phagocytic cells that constitute approximately 80% of the leukocytes in milk. This is an active phagocytic cell that contains large amounts of intracytoplasmic lipid and IgA; bears cell surface receptors for IgG and C3b; and synthesizes several important host resistance factors, including lysozyme, C3 and C4 complement components, and lactoferrin. Milk macrophages are capable of phagocytizing and killing gram-positive and gram-negative bacteria and apparently interact with the lymphocytes present in breast milk.

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The host defense factors that the breast milk macrophage synthesizes provide important nonspecific antimicrobial protection for neonates. Lysozyme is capable of lysing the cell walls of many bacteria. This enzyme is synthesized by the milk macrophage, and its concentration in human milk is 300 times that found in cow milk. It is stable in an acid environment comparable with that of the gastric contents. Lactoferrin is synthesized by the milk macrophage, and its concentration in breast milk is higher than in any other body fluid. Lactoferrin antimicrobial activity derives from its ability to chelate iron, depriving bacteria of a cofactor important for their growth. The growth of Staphylococcus organisms and *E. coli* is limited by lactoferrin.

The C3 and C4 complement components are also actively synthesized by breast macrophages. The function of these proteins in milk is unclear, because there is little IgG and IgM or the early complement components, C1 and C2, which are necessary for activation of C3 to its biologically active forms. IgA may activate C3 through the alternative pathway; however, it is found in highest concentrations in the breast macrophage itself. This macrophage-associated IgA is not synthesized but rather is ingested by the macrophage. Viable in situ macrophages have been shown to release this IgA slowly, and this has led to the hypothesis that the breast milk macrophage may represent a vehicle for immunoglobulin transport down the neonate's gastrointestinal tract.

Viable T and B lymphocytes are present in human breast milk. T lymphocytes represent 50% of the milk lymphocytes early in lactation, declining to less than 20% as lactation progresses. The spectrum of responses of breast milk T cells differs from that of peripheral blood T cells from the same donor. Milk T cells are often unresponsive to C. albicans antigen, whereas peripheral blood T cells from the same donor are highly reactive. In contrast, milk T cells respond well to the K1 capsular antigen of *E. coli*, whereas peripheral blood lymphocytes exhibit minimal or no response to K1. This phenomenon may be related to the previously described homing of lymphocytes sensitized in the gastrointestinal tract to mammary glands.

The transfer of cell-mediated immunity from tuberculin-sensitive mothers to their breastfed infants has been reported. If these reports are substantiated, this form of passive transfer of cellular immunity could be of major clinical significance. It is unlikely that intact T lymphocytes are passing from the mother's milk across the mucous membranes of the infant's gastrointestinal tract. A soluble T-cell growth factor or lymphokine more likely is involved. The B lymphocytes present in milk have IgG, IgA, IgM, and IgD on their surfaces. These cells synthesize IgA almost exclusively, however. The contribution of B cells as passive immune effectors in breast milk is as yet unclear.

Summary

Maternal transfer of IgG antibodies across the placenta provides a newborn with a measure of immune protection. Antibodies to viral agents, diphtheria, and tetanus antitoxins, which are usually of the IgG class, are efficiently transported across the placenta and attain protective levels in the fetus. In contrast, antibodies to agents that evoke primarily IgA or IgM antibody responses are transported poorly or not at all, leaving the neonate unprotected against those organisms. An infant cannot be protected against agents to which the mother has not made significant amounts of antibody. Breast milk constituents may interact with the neonate's immune system in ways other than those already mentioned. A significant increase in the secretory IgA content of nasal and salivary secretions has been observed in breast-fed versus formula-fed newborns during the first few days of life. It is postulated that this increase may reflect the influence of a soluble factor in milk that acts to stimulate the mucosal immune system of breast-fed infants. Factors that enhance IgA synthesis by B cells and promote epithelial cell growth are also secreted by milk macrophages.

Evaluation of Host Defenses in Neonates

Some disorders of immunologic function may become clinically apparent in the neonatal period or first year of life. Because of differences in the developmental status of the newborn's host defense mechanisms and the lack of vast exposure to antigens, evaluation of the function of host defense mechanisms in the infant is different from the evaluation performed for older children and adults. Infants who have experienced two or more significant bacterial or fungal infections should be suspected of having a defect in host defense mechanisms. Patients with unusual infections (e.g., from Pneumocystis jiroveci) or infections that respond incompletely to therapy and recur are also suspect. Growth failure, chronic diarrhea, chronic dermatitis, hepatosplenomegaly, and recurrent abscesses commonly occur in infants with immunologic deficiency. Primary immunodeficiency disorders are relatively uncommon, however, and numerous other predisposing conditions should be considered that may be predisposing an infant to multiple infectious episodes.

In evaluating a patient for a possible host defense mechanism defect, natural (cellular and humoral components) and acquired (cellular and humoral components) immune mechanisms should be considered and investigated. The evaluation should be divided into initial screening tests and definitive tests that allow one to establish a specific diagnosis (Box 47.2).

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• BOX 47.2 Tests to Evaluate Neonatal Host Defense Mechanisms

Natural Immunity

Cellular Components

- White blood cell count and differential*
- Nitroblue tetrazolium (NBT) dye reduction test*
- Random mobility and chemotaxis assay
- Phagocytosis assay
- Quantitative bactericidal assay
- Flow cytometric analysis of cell surface receptor expression
- Analysis of oxidative metabolism and enzyme activity

Humoral Components (Complement)

- Total hemolytic complement assay (CH_{50})*
- Determination of C3 and C4 concentrations*
- Assay of individual components of classic and alternative pathways
- Functional measurement of alternative pathway
- Functional assay for C3a and C5a

Acquired Immunity

B Lymphocytes and Antibody Production

- Quantitation of serum IgG, IgA, and IgM*
- Measurement of specific antibodies after immunization*
- Isoagglutinin titer (anti-A and anti-B)*
- Determination of IgE and IgD concentrations
- Flow cytometric enumeration and analysis of B-cell phenotype
- Tests of B-cell-to-plasma-cell maturation and antibody production in vitro

T Lymphocytes

- Total lymphocyte count and morphology*
- Delayed hypersensitivity skin tests to common antigens*
- Chest radiograph for thymic size*
- Proliferative responses to mitogens, antigens, and allogeneic cells
- Flow cytometric enumeration and analysis of T-cell subsets
- Cytotoxicity assays
- Lymphokine production assays

*Considered one of the initial screening tests.

Key Points

- The ability to mount cell-mediated or antibody-mediated immune responses to specific antigens is acquired sequentially during the course of embryonic development.
- Maternal transfer of IgG antibodies across the placenta provides a newborn with a measure of immune protection.
- PMNs of term and preterm infants are limited in chemotactic, phagocytic, and microbicidal activities.
- The influx of mononuclear phagocytes to sites of inflammation is delayed and attenuated in newborns.
- Neonatal T cells are impaired in producing a robust Th1 response and produce less IFN-γ and TNF under conditions of physiologic stimulation.
- In evaluating a patient for a possible host defense mechanism defect, natural (cellular and humoral components) and acquired (cellular and humoral components) immune mechanisms should be considered and investigated.

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48

Postnatal Bacterial Infections

FRANK ESPER

Neonatal Sepsis

Newborns are extremely susceptible to infection, and sepsis is a significant cause of morbidity and mortality in this population. Neonatal sepsis is a systemic inflammatory response syndrome (SIRS) that is secondary to infection. Systemic inflammatory response syndrome is defined by the presence of two or more of the following variables: fever or hypothermia, tachycardia, tachypnea or hyperventilation, and an abnormally high or low white blood cell count. Although this chapter focuses on bacterial infections, it is important to also consider viral, fungal, and parasitic causes in the differential diagnosis of newborns with SIRS.

Epidemiology and Microbiology

Neonatal sepsis is categorized according to the infant's postnatal age at onset of disease. Although the definitions for early-onset and late-onset sepsis vary slightly, most reports define early-onset sepsis as that occurring at or before 72 hours of life and late onset occurring at greater than 72 hours to 7 days.[102] The categories are meant to reflect the different etiologies and pathophysiologic changes associated with timing of disease onset.

In early-onset sepsis, infants acquire infection by vertical transmission either through ascending amniotic fluid infection or through acquisition of bacterial flora from the mother's anogenital tract during vaginal delivery. Examples of bacteria that cross the placenta to cause fetal infection are *Treponema pallidum* and *Listeria monocytogenes*. Over the past decade, our understanding of the maternal vaginal and infant microbiome has substantially increased. Exposure of the neonate to maternal vaginal microbiota during delivery is essential for healthy development during the newborn period, providing the primary source for normal gut colonization, initiating host immune maturation, and metabolism.[55] However, these same bacteria are responsible for early-onset sepsis, including group B streptococci (GBS) and Gram-negative enteric bacilli. The development and makeup of the infant microbiome can be altered by cesarean section (C-section), perinatal antibiotics, and formula feeding.[72]

Factors that increase the risk for infection can be divided into those that are intrapartum and those related to the infant after delivery. Maternal intrapartum conditions that increase the risk of infection include maternal GBS colonization, maternal fever, chorioamnionitis, prolonged rupture of membranes (>18 hours), and inadequate intrapartum antibiotic administration before delivery. Newborn conditions that increase the risk of infection include the degree of prematurity and lower birth weight.[9,90]

The epidemiology of neonatal sepsis has changed significantly over the past several decades and continues to change. Universal antenatal screening for GBS colonization with intrapartum antibiotic prophylaxis for women colonized with GBS has significantly reduced the rate of early-onset GBS sepsis.[121] The overall incidence of early-onset sepsis in the United States is estimated to be 0.77 per 1000 live births, with the highest rates occurring among preterm, low birth weight, and African American infants.[124] For those infants with a birth weight less than 1500 g, the rate is 10.96 per 1000 live births, and for those with a birth weight between 1500 and 2500 g, the rate is 1.38. Mortality rates are also inversely proportional to gestational age. Although the case fatality rate among full-term infants has dramatically decreased over the past several decades to 2.5%-3%,[9,124] the mortality rates for early preterm infants remain high between 30%-54%.[113,124] The most common causative bacteria are GBS and *Escherichia coli*, accounting for 38% and 24% of early-onset cases, respectively.[101,113,124] *Staphylococcus aureus*, viridans group Streptococci, Enterococci, group A Streptococci, *Listeria monocytogenes*, Haemophilus, and other enteric Gram-negative organisms, including *Klebsiella*, *Enterobacter*, *Citrobacter*, *Acinetobacter*, and *Pseudomonas*, are also known pathogens associated with early-onset neonatal sepsis. Among preterm infants, *E. coli* was the most common infection with the highest case fatality ratio (32.1%).

In late-onset sepsis, acquisition of infection is predominantly through the infant's environment. The infant becomes colonized with pathogenic bacteria that are ubiquitous in their physical environments, including part of the flora of their caregivers. The gut microbiome is often involved in the pathogenesis of late-onset sepsis. While the agent can

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Abstract

Bacterial diseases of the newborn continue to cause significant morbidity and mortality in infants throughout the world. Many of these infections can be broadly categorized according to the infant's postnatal age at onset of disease. With early-onset infections, pathogens often originate through ascending amniotic fluid infection or through acquisition of bacterial flora during delivery. Conversely, in late-onset infections, acquisition of infection is predominantly through the infant's environment or caused by slow-growing organisms. Clinicians must maintain a low index of suspicion to diagnose and initiate potentially lifesaving empirical antibiotic therapy.

Keywords

newborn
infant
neonatal sepsis
group B streptococcus
GBS
congenital infection
perinatal transmission

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vary, the causative organism is usually found to be abundant in the infant's gastrointestinal tract.[108] Extreme prematurity is one of the greatest risk factors for late-onset sepsis. A 2010 National Institute of Child Health and Human Development Neonatal Research Network study of morbidity and mortality rates for extremely preterm infants showed that late-onset sepsis is a frequent complication for these patients. Among 9575 infants born between 22 and 28 weeks' gestation, 36% developed late-onset sepsis.[111] As compared with term infants, premature infants have more impaired innate and adaptive immune function and thus are more susceptible to invasive infections.[58]

As overall care and survival rates for premature and low birth weight infants continue to improve, long hospital stays and indwelling vascular catheters provide additional infectious risk factors for these infants.[9] Common causes of late-onset infection in this population of infants include coagulase-negative staphylococci and *S. aureus*, as well as invasive candidiasis. Group B streptococcus and *E. coli* are also commonly implicated in late-onset sepsis. *Escherichia coli* is frequently a cause of urosepsis in young infants. Although screening for maternal GBS colonization and intrapartum antibiotic prophylaxis have markedly decreased the incidence of early-onset GBS, it has not reduced the incidence of late-onset GBS disease in either term or preterm infants.[26] Similarly, improved surgical care and survival for neonates with congenital heart disease have led to prolonged hospitalizations with associated risk for sepsis. Coagulase-negative staphylococci, *S. aureus*, *E. coli*, and candidiasis are common causes of bloodstream infection in this population, which has been associated with an increased mortality risk compared with uninfected infants with congenital heart disease.[4] The use of histamine-2 blockers and proton pump inhibitors, as well as gastrointestinal tract pathology, have been associated with an increased risk for late-onset Gram-negative bloodstream infections.[40] Numerous efforts are under way to decrease the incidence of late-onset sepsis, including comprehensive catheter-care bundles and aggressive enteral feeding programs with early line removal.[19,50]

Clinical Presentation

The clinical signs of sepsis in a neonate are varied and often nonspecific. Detection requires that clinicians maintain a high index of suspicion. Familiarity with epidemiologic risk factors is crucial to determining the threshold index of suspicion. For early-onset infection, consider any perinatal risk factors that may be present, including maternal GBS status, chorioamnionitis, prolonged rupture of membranes, and gestational age. For late-onset infection, consider whether the patient has indwelling foreign bodies such as a central venous catheter or endotracheal tube, is dependent on parenteral nutrition, or receives proton-pump inhibitor or histamine-2 blocking therapy.

Clinical signs and symptoms are variable and nonspecific and can reflect noninfectious etiologies. These include, but are not limited to, findings of hyper- or hypothermia, lethargy or irritability, hypotonia, respiratory distress, cyanosis, apnea, feeding difficulties, poor perfusion, bleeding problems, and abdominal distention.[99] Lethargy or poor feeding may be the only symptoms initially. Metabolic changes may include hyperglycemia or hypoglycemia, acidosis, and jaundice. Meningismus is uncommon in neonates with central nervous system (CNS) infection. Full fontanelle, irritability, lethargy, and seizures may occur. Noninfectious etiologies that can mimic newborn sepsis are numerous and include respiratory distress syndrome, cardiogenic pulmonary edema, metabolic acidosis, and meconium aspiration syndrome. Lethargy, irritability, and seizures can also occur secondary to electrolyte, endocrine, or metabolic disturbances.

Diagnosis

Because signs and symptoms are nonspecific, the clinical diagnosis of neonatal sepsis is extremely challenging. A definitive diagnosis requires the isolation of a pathogen from a normally sterile body site, including blood, cerebrospinal fluid (CSF), and urine. Isolation of bacteria from blood is considered the gold standard for the diagnosis of sepsis.[39] A blood culture should be drawn in any infant with suspected sepsis. A collection volume of at least 1 mL is recommended for improved recovery of microorganisms in culture, particularly for those patients with low colony count bacteremia. A lumbar puncture should also be considered in any infant with suspected sepsis. (See Table 48.1 for normal values for CSF cell counts, protein, and glucose according to gestational age, postnatal age, and birth weight.) If the infant is critically ill with respiratory or hemodynamic instability, the procedure can be deferred until the patient is more stable. Studies have shown poor correlation between results of blood and CSF cultures, so blood culture results alone should not be used to determine which patients should receive a lumbar puncture. In infants with bacteremia, the incidence of meningitis has been shown to be as high as 23%. A study among very low birth weight infants with meningitis showed that one-third of them had negative blood cultures.[86,110]

For suspected early-onset sepsis, a urine culture is not part of the recommended work-up. In newborns, urinary tract infections are primarily caused by renal seeding during bacteremia, and thus urine cultures are of low yield in early-onset sepsis. In older infants, urinary tract infections increasingly result from ascending infection, so urine cultures should be part of the evaluation of late-onset sepsis.[86] Suprapubic aspiration or sterile catheterization are the preferred procedures to obtain cultures.

To date, no single blood cell index has been shown to be sensitive enough to safely exclude sepsis. Numerous indirect markers of infection have been studied. Although none of these tests can definitively confirm or exclude infection, they can be used to help identify infected infants and guide decisions on duration of antimicrobial therapy. A

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TABLE 48.1 Cerebrospinal Fluid Reference Values

Term Infants*			
Postnatal Age	**Median WBC/mm³ (IQR)**	**Median Protein mg/dL (IQR)**	**Median Glucose mg/dL (IQR)**
≤7 days	3 (1-6)	78 (60-100)	50 (44-56)
8 days to 6 months	2 (1-4)	57 (42-77)	52 (45-64)
Preterm Infants (<37 Weeks' Gestational Age)*			
Postnatal Age	**Median WBC/mm³ (IQR)**	**Median Protein mg/dL (IQR)**	**Median Glucose mg/dL (IQR)**
≤7 days	3 (1-7)	116 (93-138)	53 (43-65)
8 days to 6 months	3 (1-4)	93 (69-122)	47 (40-58)

Very Low Birth Weight (BW) Infants (24-33 Weeks' Gestational Age)**				
	Postnatal Age	**Median WBC/mm³ (range)**	**Median Protein mg/dL (range)**	**Median Glucose mg/dL (range)**
BW ≤1000 g	≤7 days	3 (1-8)	162 (115-222)	70 (41-89)
	8-28 days	4 (0-14)	159 (95-370)	68 (33-217)
BW 1001-1500 g	≤7 days	4 (1-10)	136 (85-176)	74 (50-96)
	8-28 days	7 (0-44)	137 (54-227)	59 (39-109)

IQR, Interquartile range; WBC, white blood cell count.
Adapted from data from *Srinivasan L, et al. Cerebrospinal fluid reference ranges in term and preterm infants in the neonatal intensive care unit. *J Pediatr*. 2012;161(4):729-734; and **Rodriguez AF, et al. Cerebrospinal fluid values in the very low birthweight infant. *J Pediatr*. 1990;116(6):971-974.

peripheral white blood cell (WBC) count with differential is commonly obtained with sepsis evaluations. It is recommended to wait 6-12 hours after birth before obtaining a WBC with differential, as later counts are more likely to reflect a pathologic inflammatory response compared with those obtained at birth.[75] Studies have shown leukopenia and a high percentage of immature to total white blood cells (>0.2) were associated with early-onset sepsis.[47] Late-onset sepsis has been associated with both high and low WBC, high absolute neutrophil count, and high percentage of immature to total white blood cells.[47,48] Newer technology allows automated calculation of the immature granulocyte, which accurately identifies sepsis.[77,79]

C-reactive protein (CRP) and procalcitonin are two acute-phase reactants that have been studied extensively in neonatal sepsis. C-reactive protein levels increase within 6-8 hours after infection and peak after 24 hours.[33] The sensitivity of CRP for neonatal sepsis is lowest early in infection and then increases over the next 10-12 hours after the onset of infection.[99] Serial determinations may be useful for identifying infants who do not have a bacterial infection or in monitoring response to treatment for infected infants.[46] The specificity and positive predictive value of CRP range from 93%-100%.[76,99] However, it is worth noting that preterm infants have lower CRP values and response which affect its predictive value.

Procalcitonin concentrations peak as early as 6-8 hours following infection, although there is a physiologic increase within the first 24 hours after birth. Also, unlike CRP, the serum procalcitonin concentration is not affected by gestational age.[99] Increased levels can be seen with noninfectious causes such as respiratory distress syndrome. Thus, procalcitonin appears to have better sensitivity but less specificity than CRP for identifying neonatal sepsis.[7] Given that neither CRP nor procalcitonin values have been shown to be entirely sensitive or specific, the most important information guiding clinical decisions continues to be the patient's overall clinical status and culture data.

Specific cytokines have also been evaluated for potential roles in the diagnosis of neonatal sepsis. Serum concentrations of interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α, interleukin-2 soluble receptor (sIL2R), and granulocyte colony-stimulating factor all increase in newborns with bacterial infection.[99] Several have been shown to rise early in the course of infection, often before clinical findings become apparent.[7] Newer technologies using cytometry to accurately identify immature granulocytes have also shown to be as effective, with faster turnaround time and less operator variability than manual differentials. While cytokine and cytometry assays may be helpful in diagnosis or in guiding decisions regarding therapy, their use is not widely employed related to issues of cost, the need for specialized equipment, and the processing time.[93,99] These tests hold promise for the future.

Real time online/mobile applications are now available that predict the probability of early-onset sepsis based on objective maternal risk factors available at the time of birth. In early studies, these algorithms perform better than those

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based on risk-factor threshold values. These have allowed improved recognition as well as reduced use of unnecessary antibiotics by 50%[59,90] and separation of mother and infant.[64]

Management

Ampicillin and an aminoglycoside are recommended as empiric therapy for early-onset sepsis. This combination provides coverage against GBS and *E. coli*, the most common causative pathogens, as well as *Listeria monocytogenes*. Empiric use of third-generation cephalosporins is not recommended because of concerns for development of resistance and the increased risk for invasive candidiasis with prolonged administration. However, if Gram-negative meningitis is suspected, then it is recommended to add cefotaxime to the empiric regimen, given its excellent CNS penetration. Cefotaxime is preferred over ceftriaxone for use in neonates because of ceftriaxone's potential to displace bilirubin and increase the risk for kernicterus and its association with biliary sludging. However, recent shortages of cefotaxime have required the use of alternative agents in infants with invasive Gram-negative disease, including ceftriaxone (in term infants with normal bilirubin) or cefipime.

Empiric therapy for late-onset sepsis usually consists of ampicillin and an aminoglycoside or cefotaxime, providing coverage for common pathogens like group B streptococci and Gram-negative organisms. As with early-onset disease, if Gram-negative meningitis is suspected, consider adding a third-generation cephalosporin. In preterm infants or infants with complex medical problems necessitating surgeries or prolonged indwelling central catheters, vancomycin should be given in lieu of ampicillin if suspected of having coagulase-negative Staphylococci or *S. aureus* disease. Carbapenems may be considered depending on local resistance patterns or if the patient had previously received therapy with a third-generation cephalosporin.[101] It is also important to consider empiric antifungal coverage for invasive candidiasis for severe sepsis unresponsive to antibiotics, infants on chronic TPN, or those with unexplained cytopenias. Experience with fungal biomarkers including beta-D-glucan assays for the diagnosis of candidemia in infants is limited.[23,92]

Once a pathogen is identified, therapy should be tailored to the species and antimicrobial susceptibilities. Duration will be determined by the site of infection and the patient's clinical response. There is little evidence from randomized, controlled trials on the appropriate duration of treatment for culture-proven sepsis, especially in preterm and low birth weight infants. Bacteremia without a focus of infection is usually treated for 10 days.[86] It is reasonable to expect that early preterm infants (<32 weeks' gestational age) may require slightly longer treatment courses of 10-14 days.[104,118] In addition, Gram-negative bacteremia tends to be treated with longer courses of 10-14 days. In general, uncomplicated GBS meningitis is treated for 14-21 days. Longer courses are needed for other focal complications of GBS infection (see Specific Pathogens). For Gram-negative bacterial meningitis, treatment is for 21 days, or 2 weeks beyond the first negative CSF culture, whichever is longer.[94,117] The use of systemic ciprofloxacin is indicated in those infants with multidrug-resistant Gram-negative disease when alternative antibiotics are not available.[53]

It is often difficult to determine an appropriate duration of antibiotic therapy for suspected sepsis when cultures are negative. In well-appearing infants without clinical or hematologic evidence for infection, standard practice is to discontinue antibiotics if cultures have been negative after 36-48 hours. Management decisions are much more challenging for those infants in whom sepsis is highly suspected but cultures are negative, which is often the case for preterm infants. Infants whose mothers received antibiotics during labor may have false negative blood cultures because of antibiotic suppression. Cerebrospinal fluid culture data may be lacking in infants who are not clinically stable enough to tolerate a lumbar puncture. Noninfectious conditions mimicking sepsis can also complicate the clinical picture. Still, studies have shown potential harm associated with longer duration (>5 days) of empiric antibiotics, including increased risk for necrotizing enterocolitis, candidemia, and mortality among premature infants.[20,86] There is also concern that early antibiotic exposure may permanently alter the microbiome and predispose to obesity.[5] There is little available evidence on when it is safe to discontinue antimicrobials in such cases, and clinicians must consider each patient's clinical course as well as the risks associated with longer courses of antibiotics.[104] The CDC has led efforts to decrease antibiotic exposure in a campaign entitled "Choosing Wisely."[44] These efforts have championed use of sepsis risk calculators and early stopping rules.[64]

Prevention

As mentioned, universal antenatal screening for GBS colonization and intrapartum antibiotic prophylaxis for the prevention of early onset GBS disease has been highly successful, although it has not had an effect on the incidence of late-onset GBS.[121] Details of the current recommendations for antenatal GBS screening and intrapartum antibiotic prophylaxis are included in a later section. Preventive efforts to reduce the risk of late-onset sepsis have focused on infection control in the postnatal environment. Successful measures include hand hygiene, proper management of central venous catheters, appropriate use of antibiotics, and limited use of histamine-2 blockers and proton pump inhibitors.[40,114] A Cochrane review on oral lactoferrin prophylaxis in preterm infants showed a reduced incidence of late-onset sepsis in infants weighing less than 1500 g. The roles of exclusive maternal milk feeding and probiotic prophylaxis in prevention of late-onset sepsis require further study.[83,84]

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Bacterial Infections by Organ System

Meningitis

Bacterial meningitis is more common in the first month of life than at any other age.[63] Incidence of neonatal bacterial meningitis varies across the globe. While the incidence is estimated to be 0.3 per 1000 live births in developed countries, neonatal meningitis is much higher (0.8-6.1 per 1000 live births) in developing nations.[63] As with neonatal sepsis, neonatal meningitis can be categorized into two patterns of disease: early onset and late onset. Infants with early-onset meningitis present within the first week of life, usually within 72 hours of birth. These infections are vertically transmitted and are associated with the complications of labor and delivery. Late-onset disease occurs after the first week of life and reflects community or nosocomial transmission. Among infants with bacteremia, as many as 25% of them will also have meningitis.[86]

The causative pathogens for neonatal meningitis are similar to those for neonatal sepsis with group B streptococcus and *E. coli* predominant. Group B streptococcus is the most common cause of neonatal meningitis and occurs in up to 40% of infants with early onset meningitis. Gram-negative enteric bacilli cause 30%-40% of cases of neonatal meningitis, and *E. coli* accounts for approximately 50% of the Gram-negative isolates.[63,87,113] *E. coli* is now recognized as the most common cause of early-onset meningitis among very low birth weight (<1500 g birth weight) infants.[63,112] The majority of *E. coli* strains causing meningitis contain the K1 polysaccharide capsular antigen, which assists the organism in evading host defenses. Other important Gram-negative organisms include *Klebsiella*, *Enterobacter*, *Citrobacter*, and *Serratia* species. A known complication of *Citrobacter koseri* and *Enterobacter sakazakii* meningitis in neonates and young infants is the formation of brain abscesses, so it is important to obtain brain imaging whenever these species are isolated from the CSF.[11,27,122] Although *Listeria monocytogenes* is a relatively uncommon cause of neonatal meningitis, it can lead to significant morbidity and mortality because of its association with rhombencephalitis. It has been estimated to cause 5%-20% of neonatal meningitis cases.[49,87] Nosocomial pathogens include coagulase-negative *Staphylococci*, *Candida*, and resistant Gram-negative organisms, particularly *Pseudomonas*, are more prominent in late-onset meningitis.[63]

The clinical presentation of neonatal meningitis is often nonspecific and is similar to that of neonatal sepsis. The most common finding is temperature instability, which occurs in approximately 60% of infants with meningitis. Common neurologic signs include irritability, emesis, lethargy, poor tone, and seizures. Most infants present with a full, but not bulging, fontanelle without meningeal signs. Other signs include poor feeding, respiratory distress, apnea, and diarrhea.

Neonates with suspected bacterial meningitis should undergo a complete sepsis evaluation—including blood culture, complete blood count with differential, urine culture if greater than 6 days of age, and lumbar puncture for CSF Gram stain and culture—cell count with differential, glucose, and protein in order of priority. For clinically stable infants, the lumbar puncture should be performed before administration of antibiotics.

Cerebrospinal fluid studies need to be interpreted based on the infant's gestational age, postnatal age, and birth weight (see Table 48.1). A CSF WBC count of greater than 20-30 cells/μL is consistent with meningeal inflammation. However, neonatal meningitis has been shown to occur with normal CSF parameters, and there is some overlap in CSF WBC values between neonates with and without meningitis.[35] If CSF findings are not definitive in an infant whose clinical picture is otherwise suspicious for meningitis, a repeat lumbar puncture obtained 24-48 hours later will still show pleocytosis if true meningeal inflammation is present even with use of antibiotics. Cerebrospinal fluid protein and glucose values are highly variable in neonates with and without meningitis. Cerebrospinal fluid Gram stain may be helpful in providing an early presumptive etiologic diagnosis, although a negative Gram stain certainly does not exclude the diagnosis. If the lumbar puncture is traumatic, it is not recommended to adjust the CSF white blood cell count based on the red blood cell counts, as this does not improve the diagnostic utility for neonates.[41] Ultrasound to guide lumbar puncture may reduce the incidence of traumatic taps.[82] Infants who have had a traumatic lumbar puncture may be treated presumptively for meningitis pending CSF culture results. Increasingly, PCR against common newborn pathogens has been utilized as a diagnostic in situations where the CSF is uninterpretable.[18] Automated systems are now commercially available and may reduce antibiotic exposure.[65]

Empiric therapy for early-onset meningitis includes ampicillin and an aminoglycoside. If infection with a Gram-negative organism is suspected, the regimen may be expanded to include cefotaxime or higher generation cephalosporin in addition to ampicillin. Aminoglycosides are not used as monotherapy because of their poor CNS penetration. Once a pathogen is identified, therapy should be tailored according to the causative organism.

Group B streptococcus meningitis is treated initially with ampicillin (or penicillin) plus an aminoglycoside. Group B streptococcus has thus far been shown to be uniformly susceptible to penicillins while resistance to clindamycin and erythromycin is reported.[15,43] Combination therapy is used because synergy is seen in vitro and animal studies have shown improved outcomes with combination therapy versus penicillin alone.[115,119] When the patient shows clinical improvement and the CSF is sterilized, therapy can be narrowed to ampicillin or penicillin monotherapy to continue for 14 days after the first negative culture. Although not all patients with GBS meningitis require a lumbar puncture at the end of therapy to confirm treatment response, it should be considered in patients with a complicated clinical course, including seizures, abnormal neuroimaging,

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prolonged positive CSF cultures, or slow clinical response to therapy.

Gram-negative meningitis is treated with a third-generation cephalosporin (cefotaxime) for at least 21 days or for 14 days after the first negative CSF culture. An aminoglycoside is added until CSF sterilization, which usually takes longer for meningitis caused by Gram-negative organisms than for GBS meningitis. A fourth-generation cephalosporin (cefepime) or a carbapenem (meropenem) in combination with an aminoglycoside may be considered for infection with members of the *Enterobacteriaceae* family with inducible beta-lactamase resistance (e.g., *Citrobacter*, *Enterobacter*, *Serratia*) and for *Pseudomonas.* Studies have shown that recommended meningitic doses of meropenem may be toxic at lower gestational ages and may produce seizures.[105] A lumbar puncture may be considered before discontinuation of antibiotics to confirm response to treatment.

Listeria monocytogenes is not susceptible to cephalosporins and should be treated with ampicillin and an aminoglycoside until CSF sterilization, followed by ampicillin monotherapy for 14 days after first negative culture. The same therapy is recommended for infection with *Enterococcus.* Vancomycin should be avoided, if able, in patients with infection by *Listeria monocytogenes* as treatment failures are reported.[45] Meningitis with coagulase-negative *Staphylococci* is seen in preterm infants and is often associated with the presence of a foreign body in the CNS. Most of these organisms are resistant to penicillin, and treatment with vancomycin is often required. Duration is generally 14-21 days after CSF sterilization, with removal of any foreign body if feasible. Adjunctive use of corticosteroids has not shown improvement in the outcome for neonatal bacterial meningitis other than tuberculosis meningitis.[25]

Mortality from neonatal meningitis has decreased dramatically over the past several decades, although substantial neurologic morbidity continues to be seen among affected patients. Mortality rates were estimated at almost 50% in the 1970s and have decreased to current estimates of 10%-15%,[36,63,87] with higher mortality rates among preterm infants and those in developing countries. Neurologic sequelae include developmental delay, seizures, hydrocephalus, cerebral palsy, blindness, and hearing loss. Studies estimate that among survivors, 21%-38% will have mild deficits and 24%-29% will have severe neurologic sequelae.[32,63] Predictors of poor neurologic outcomes include seizures lasting >72 hours, presence of coma, hypotension requiring the use of inotropes, leukopenia (<5.0), and abnormal electroencephalogram findings.[61,63]

Pneumonia

Pneumonia is a significant cause of morbidity and mortality in neonates, especially in developing countries where it is a leading cause of death for all children under 5 years of age.[52] The incidence of lower respiratory tract infection in developed countries is estimated at less than 1% among full-term infants, but may be as high as 10% in low birth weight infants. In developed countries, the morbidity and mortality from neonatal pneumonia depend largely on the gestational age of the patient, severity of disease, and underlying medical conditions, especially chronic lung disease. Neonatal pneumonia is also categorized into two patterns of disease according to timing and route of acquisition. Early-onset pneumonia is usually acquired within the first 3 days of life via vertical transmission, including aspiration of infected amniotic fluid and transplacental transmission. Late-onset pneumonia occurs after the first week of life, and infection arises from pathogenic organisms in the infant's environment. The risk for late-onset pneumonia is highest among infants who require mechanical ventilation. Other risk factors include extreme prematurity, prolonged hospitalization, and previous bloodstream infection.[2]

The most common cause of early-onset pneumonia in developed countries is GBS. Other common causes include *S. pneumoniae*, nontypable *H. influenzae*, *S. aureus*, *E. coli*, *Klebsiella*, and atypical organisms. *Ureaplasma urealyticum* has been potentially linked to the development of chronic lung disease in colonized infants. However, the significance of this association is unknown, and the efficacy of antimicrobial therapy for those colonized infants is also uncertain.[123] *Chlamydia trachomatis* pneumonia can occur in the first week of life but more typically presents between 2 and 4 weeks of age, given its long incubation. *Chlamydia trachomatis* pneumonia and ophthalmia neonatorum are discussed in more detail elsewhere. While syphilis, *Listeria monocytogenes,* and *Mycobacterium tuberculosis* can be transmitted across the placenta, these pathogens are uncommon causes of neonatal pneumonia.

Definitive culture data are often lacking for cases of late-onset, community-acquired neonatal pneumonia. *Streptococcus pneumoniae* is considered a predominant causative pathogen in this population. Other important pathogens include *S. aureus*, *S. pyogenes*, nontypable *H. influenza*, and Gram-negative enteric organisms. *Staphylococcus aureus*, *Streptococci*, *Klebsiella pneumoniae*, *Citrobacter*, *Enterobacter*, *Serratia*, and *Pseudomonas* have all been shown to have the potential to cause extensive lung injury, including abscess formation, empyema, and pneumatoceles.[38,60,100] Although it generally causes self-limiting illness in older children and adults, *Bordetella pertussis* infection in young infants can lead to respiratory failure and death. The Centers for Disease Control and Prevention (CDC) updated their vaccination guidelines in January 2013 to include a recommendation that all pregnant women get a dose of the tetanus, diphtheria, and pertussis (Tdap) vaccine during each pregnancy. Receipt of Tdap vaccine during pregnancy allows for increased maternal pertussis antibody transfer to the neonate. This provides added protection for infants from birth to the time of infant pertussis vaccination at 2 months.[88]

The clinical presentation of early-onset pneumonia often includes respiratory distress within the first few hours of life, with tachypnea, retractions, nasal flaring, or grunting.

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Other associated signs are apnea, lethargy, poor feeding, temperature instability, abdominal distention, poor perfusion, and metabolic acidosis. None of these signs is specific for pneumonia, and any infant with these symptoms should undergo a complete sepsis evaluation. Copious or purulent tracheal secretions may also be present.

The diagnosis of neonatal pneumonia can be difficult. The differential diagnosis is broad and includes many noninfectious causes such as transient tachypnea of the newborn, respiratory distress syndrome, meconium aspiration, pulmonary hemorrhage, pneumothorax, hypoglycemia, and metabolic acidosis. Anatomic abnormalities that can cause respiratory distress include primary pulmonary hypoplasia, tracheoesophageal fistula, choanal atresia, congenital diaphragmatic hernia, and congenital heart disease, among many others. Causative pathogens are rarely obtained and identified from the lower respiratory tract. Blood and CSF cultures should be obtained from any neonate with suspected pneumonia. Chest radiographs can be helpful in making the clinical diagnosis, although there is significant radiologic overlap between pneumonia and other respiratory disorders of the newborn. In pneumonia, radiographs often reveal bilateral alveolar densities with air bronchograms, or irregular, patchy pulmonary infiltrates. Pleural effusions are seen in up to two-thirds of pneumonia cases and are almost never seen in uncomplicated respiratory distress syndrome. The chest radiograph may appear normal in up to 15% of pneumonia cases.[70] Tracheal aspirate Gram stain and culture results must be interpreted with caution. These specimens may be of some value if obtained immediately following intubation. If an infant has been intubated for several days, the endotracheal tube will invariably become colonized and will be of little value in the evaluation for sepsis.[86]

Like most early-onset newborn infections, empiric antibiotic treatment includes ampicillin and an aminoglycoside. Therapy can then be tailored to susceptibility results if a causative organism is identified. Empiric antibiotic therapy for late-onset pneumonia will depend on local bacterial resistance patterns in both the hospital and the community. Vancomycin and a cephalosporin, often cefotaxime, are commonly used as empiric therapy to provide coverage against newborn pathogens as well as coagulase-negative Staphylococci and methicillin-resistant *S. aureus* (MRSA). If *Pseudomonas* is suspected, an aminoglycoside plus an antipseudomonal beta-lactam, such as ceftazidime, cefipime, or piperacillin-tazobactam, should be given. Recommended duration of therapy for uncomplicated pneumonia is 7-10 days.

Urinary Tract Infections

The incidence of bacteriuria in term newborns is estimated to be 0.1%-1%. The incidence is higher in preterm infants and is thought to be around 2%. In the neonatal period, urinary tract infection (UTI) is more common among males than females. Over the first 6 months of life, the incidence of UTI in males decreases, whereas in females it increases. By 1 year of age or older, girls are more likely than boys to have UTIs.[54,95] Uncircumcised males are at higher risk for UTI than are circumcised males. This is owing to enhanced bacterial adherence to the foreskin and increased bacterial colonization in the urogenital tract.[103] It is rare for a UTI to occur in the first 3 days of life; therefore, urine cultures are not recommended as part of the routine early-onset sepsis evaluation.

Infection of the urinary tract in neonates is thought to be acquired either through hematogenous spread or by ascending infection, often associated with anatomic abnormalities. Hematogenous spread is thought to be the cause for many young infants with UTI, because bacteremia with the same organism is seen in approximately one-third of neonates with upper tract infection.[95] Preterm infants are at higher risk for UTI with concordant bacteremia. Associated meningitis is also seen in 1%-2% of these cases.[28,116] Urinary tract abnormalities are seen in approximately 20%-50% of infants with UTI.[51,95] The most common abnormality seen is vesicoureteral reflux (VUR). Other abnormalities that may increase the risk for UTI include ectopic ureter, duplicated collecting system, renal dysplasia, and causes of obstruction, such as posterior urethral valves and ureteropelvic junction stricture. An additional risk factor for UTI is the presence of an indwelling urinary catheter.

The most common causative pathogen for neonatal UTI is *E. coli*, which has been isolated in approximately 80% of cases in some large series.[51,95] *E. coli* has several virulence factors that confer an increased ability to cause UTI. Uropathogenic *E. coli*, the causative organism in most UTIs, can invade and replicate within uroepithelial cells. Adhesins on the bacterial surface allow for increased adhesion to urogenital tract cells, and fimbriae are important in promoting persistence of infection. Other common causative organisms include other Enterobacteriaceae: *Klebsiella*, *Enterobacter*, *Proteus*, *Citrobacter*, *Salmonella*, and *Serratia*. Gram-positive organisms are isolated much less frequently than Gram-negative organisms, although Enterococci, *S. aureus*, and coagulase-negative Staphylococci are also known to cause UTI in newborns.

The signs of neonatal UTI are nonspecific and may include fever, lethargy, failure to thrive, poor feeding, abdominal distention, vomiting, tachypnea, and cyanosis. The clinical presentation of preterm infants is similar to that of term infants, although preterm infants may also have hypoxia or apnea with bradycardia. Definitive diagnosis must be made by urine culture with specimens obtained by catheterization or suprapubic bladder aspiration. Samples collected into a bag are less helpful, because they are frequently contaminated. Any growth of a urinary pathogen from bladder aspirate is considered significant. Catheterization cultures with greater than 1000 colony-forming units per milliliter are considered meaningful. Urinalysis lacks specificity and sensitivity for diagnosis of UTI in neonates and is not recommended as part of the evaluation. Blood cultures should be obtained for all infants with suspected

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UTI, as one-third with UTI will have bacteremia with the same organism.[37] Clinicians should have a very low threshold for performing a lumbar puncture in neonates with UTI, because the risk for concomitant meningitis is 1%-2%.[28,116]

Empiric antibiotic treatment for neonatal UTI includes ampicillin and an aminoglycoside. Hospitalized infants with late-onset infections should be given vancomycin and an aminoglycoside to provide coverage for hospital-associated infections with coagulase-negative Staphylococci and MRSA. If the infection is caused by a highly resistant pathogen, or if there is a known anatomical abnormality, a urine culture may be repeated 2-3 days after start of treatment to confirm sterilization of the urine. If cultures remain positive despite adequate therapy, the infant should be further evaluated for a potential reservoir of infection. The duration of therapy is generally 7-14 days for uncomplicated bacterial UTI in a newborn.[95] Neonates and newborns with delayed clinical response, prematurity, bacteremia, or presence of anatomic abnormalities are usually given intravenous antibiotics for the entire course. Older infants with uncomplicated disease may be switched to oral antibiotics after demonstration of clinical improvement. The use of systemic ciprofloxacin is indicated in those infants with multidrug-resistant, Gram-negative disease or orally when alternative oral antibiotics are not available.[53,91] Reviews of use of ciprofloxacin in children show the risk of arthropathy is low and reversible.[1]

All neonates with UTI should undergo imaging evaluation because of the high prevalence of urinary tract abnormalities. If prenatal ultrasound data are not available, a renal ultrasound should be performed after the infant has clinically stabilized. Ultrasound can detect structural abnormalities, although it cannot detect vesicoureteral reflux or renal scarring. Voiding cystourethrogram is performed to detect vesicoureteral reflux, and this is usually done 3-6 weeks after completion of antibiotic treatment. Long-term outcomes of UTI can include renal scarring with subsequent hypertension and chronic kidney disease. If renal damage is suggested by ultrasound, renal cortical scintigraphy can be performed to better assess for renal scarring.[95]

Osteomyelitis and Septic Arthritis

Osteomyelitis and septic arthritis are uncommon infections in neonates, and can be difficult to diagnose in this population. In neonates, the most common route for infection to the bone or joint is by hematogenous spread. There are important differences in the pathophysiology of musculoskeletal infections in neonates compared with older children and adults. In all ages, metaphyses are susceptible to hematogenous seeding of infection because of the reduced rate of blood flow within metaphyseal blood vessels. In infants, secondary ossification centers have not yet formed, and their cartilaginous epiphyses are supplied with blood directly from transphyseal vessels from the bone metaphysis.[97] Therefore, osteomyelitis in infants commonly leads to epiphyseal damage and joint infections. This contiguous infection rarely occurs in older children and adults with osteomyelitis, because the epiphyses and metaphyses have separate blood supplies. Similarly, anatomic differences in the blood supply to the spinal column render neonates more susceptible to discitis than to vertebral body osteomyelitis.[81]

The most common causative organisms are *S. aureus*, *E. coli*, and GBS.[81] Less common pathogens include group A Streptococcus, *N. gonorrhoeae*, other enteric Gram-negative bacilli and Candida. The signs and symptoms of osteomyelitis and joint infections in neonates are often subtle and similar to signs of sepsis. Infants may present with irritability, poor feeding, or fever. Some will show positional preference, lack of use of the involved extremity (pseudoparalysis), joint or limb swelling, or pain with passive motion as with diaper changes. Infections are often multifocal. If left untreated, septic arthritis of the hip can lead to spontaneous drainage along the internal obturator muscle, resulting in a lower abdominal mass just above the inguinal canal.

Imaging studies should be obtained for any patient with suspected osteomyelitis or septic arthritis. The radiologic investigation usually starts with plain radiographs. Findings can include deep soft tissue swelling, widening of the joint space or joint dislocation, osteoporosis, periosteal new bone formation, and bony destruction.[81] Soft tissue swelling is the earliest finding and can be detected as early as 48 hours after onset of infection. Bony changes, however, are not apparent until 7-10 days after onset of infection. For this reason, further imaging is often required for patients in whom there is a high index of suspicion. Ultrasound can detect subperiosteal collections and joint effusions, so it is very useful in cases of suspected septic arthritis. Ultrasound can also detect findings of subperiosteal abscesses and fluid collections, although this is highly dependent on the duration of infection as well as operator experience. Bone scintigraphy is more sensitive than plain films for detecting osteomyelitis early on, and it is useful for detecting multiple foci of infection.[96] Magnetic resonance imaging (MRI) is extremely useful in the evaluation for osteomyelitis. Bony changes can be detected within 24-48 hours after onset of symptoms. Magnetic resonance imaging provides excellent anatomic detail without exposing infants to ionizing radiation. It also provides better information on growth plate involvement than does bone scintigraphy. However, careful interpretation of bone scans and MRI is necessary to distinguish physiologic from pathologic increased uptake owing to increased vascularity of the metaphyseal region in neonates.[120]

Fluid collections in soft tissue or bone should be aspirated and sent for Gram stain and culture. Patients with joint involvement should have synovial fluid sent for Gram stain and culture. Blood cultures yield the causative organism in approximately 50% of cases.[10] Lumbar puncture should be performed on ill-appearing infants or those with positive blood cultures.

Recommended empiric antibiotic treatment includes vancomycin for broad Gram-positive coverage and an

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aminoglycoside or third-generation cephalosporin for Gram-negative coverage. Therapy can be narrowed once the causative organism is isolated. Most patients with osteomyelitis can be managed with conservative, or nonsurgical, treatment. Joint infections and bony abscesses require surgical drainage. The total duration of therapy is 4-6 weeks for uncomplicated cases. Therapy should be 8 weeks for osteomyelitis caused by MRSA and 6-12 months for infants with fungal disease caused by candida.[34,67] Parenteral therapy should be continued at least until the patient demonstrates clinical improvement and the inflammatory markers have normalized.

Significant morbidity may be associated with neonatal musculoskeletal infections, and prompt diagnosis and treatment are needed to minimize complications. Septic arthritis of the hip in particular is associated with serious long-term sequelae. Complications include growth plate damage, avascular necrosis, limb length discrepancies, and angular joint deformities, among many others.[81] These patients should be followed for the development of long-term complications, as many will require surgical intervention.

Ophthalmia Neonatorum

Ophthalmia neonatorum is conjunctivitis occurring in the first month of life. Bacterial causes include *S. aureus*, nontypable *H. influenzae*, *S. pneumoniae*, enteric Gram-negative bacilli, GBS, *N. gonorrhoeae*, and *Chlamydia trachomatis.* The differential also includes viral causes, particularly herpes simplex virus, and noninfectious causes, such as chemical conjunctivitis. Conjunctivitis in neonates is managed aggressively because of the high risk for associated systemic illness and complications. Prophylactic administration of ophthalmic antibiotic agents shortly after birth greatly reduces the risk of gonococcal conjunctivitis but not chlamydial disease.

In the United States, it is recommended that prophylaxis is provided to all newborns.[30] Regimens with equal efficacy include 0.5% erythromycin ointment, 1% tetracycline ointment, and silver nitrate solution, although the latter two are not commercially available in the United States. Chemical conjunctivitis is usually seen soon after birth and improves over 48 hours.

The clinical presentation of bacterial conjunctivitis in neonates is similar to that in older patients. Typical signs include purulent ocular discharge, erythema and edema of the eyelids, and injection of the conjunctivae. Gonococcal infection in the newborn is typically acquired during delivery, with perinatal transmission occurring in 30%-40% of cases of maternal cervical infection.[126] Infants usually show signs of infection 2-5 days after birth, with profuse, purulent ocular discharge and swelling of the eyelids. Untreated, infection can spread into the subconjunctival connective tissue and cornea, leading to ulceration, scarring, and visual loss. In addition to conjunctivitis, infection of other mucosal surfaces can occur, and scalp abscess may be associated with the use of fetal monitoring electrodes. Disseminated infection can lead to septic arthritis or, less commonly, bacteremia or meningitis.

Chlamydia trachomatis is usually transmitted to the neonate during vaginal delivery, and approximately 20% of infants born to mothers with cervical infection will develop conjunctivitis.[6] Chlamydial conjunctivitis is also known as inclusion conjunctivitis. The serovariants of *C. trachomatis* causing infection in neonates (D through K) reflect the primary serotypes causing genital disease in adults. The onset of conjunctivitis is often 5-14 days after birth. Findings may range from mild eyelid swelling with minimal discharge to mucopurulent discharge; significant swelling; and red, thickened conjunctivae. If the exudate adheres to the conjunctivae, a pseudomembrane may form. Bloody discharge may also be noted with intense inflammation. Without treatment, infection may lead to corneal and conjunctival scarring or progression toward pneumonia 2-8 weeks after birth. Approximately half of the infants with chlamydia pneumonia have a history of conjunctivitis.

All newborns who develop conjunctivitis after the first days of life should have laboratory testing performed to determine the etiology, because there is significant overlap in clinical presentation among the causative pathogens. If gonococcal infection is suspected, CSF and blood cultures are obtained to determine if dissemination occurred.[94] Purulent ocular discharge is sent for Gram stain and culture. Culture on selective media (e.g., Thayer-Martin) is needed to evaluate for gonococcal infection. Additionally, conjunctival specimens should be sent for *C. trachomatis* testing. These are obtained from an everted eyelid using a Dacron-tipped swab. *Chlamydia trachomatis* is an obligate intracellular organism, so specimens must contain conjunctival epithelial cells; ocular exudates are not adequate specimens for testing. Culture of the organism is the gold standard for diagnosis of *C. trachomatis* infection in infants. Nucleic acid amplification tests may also be considered because they have been found to have high specificity and sensitivity, although none has been approved by the Food and Drug Administration for use on conjunctival specimens.[22] In infants with signs of pneumonia, testing for *C. trachomatis* can be sent from nasopharyngeal specimens. Any infant with signs of systemic illness should have blood and CSF cultures obtained.

Systemic antibiotics are required to treat conjunctivitis resulting from *N. gonorrhoeae* and *C. trachomatis.* For other causes of bacterial conjunctivitis, topical antibiotic ointment or solution given for 7-10 days provides adequate therapy. Infants with gonococcal eye disease should be hospitalized and monitored for response to treatment as well as for signs of disseminated disease. Recommended treatment for conjunctivitis is a single dose of intramuscular or intravenous ceftriaxone. Note that infants, especially preterm, with hyperbilirubinemia should not be treated with ceftriaxone. The eyes should also be irrigated frequently with sterile saline until the discharge has resolved. Recommended treatment for either chlamydial conjunctivitis or pneumonia is

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oral erythromycin for 14 days or with azithromycin for 3 days.[94]

Omphalitis

Omphalitis is an infection of the umbilicus or surrounding tissues. Newborns are predisposed to umbilical infections following colonization of the umbilicus by a wide array of microorganisms shortly after birth as devitalized tissues of the cord stump provide for excellent bacterial growth. Bacteria can reach the bloodstream through patent vessels of the newly cut cord and lead to systemic infection and severe complications. The incidence of omphalitis in developed countries is low and is estimated to be less than 1%.[109] Although complete data are lacking from developing countries, the incidence is expected to be much higher. The risk may be six times greater for infants delivered at home than for hospital births. Other risk factors include low birth weight, prolonged rupture of membranes, umbilical catheterization, and improper cord care. Cord care varies according to accepted practices and culture. In many parts of the world, unhygienic substances are applied to speed up cord separation and result in increased risk for infection.

Organisms that colonize the umbilicus or surrounding skin can produce omphalitis. Common pathogens include *S. aureus*, group A Streptococci, GBS, and Gram-negative bacilli, including *E. coli*, *Klebsiella*, and *Pseudomonas*. Polymicrobial infections may occur. Anaerobic bacteria can contribute to infection, especially in infants born to mothers with chorioamnionitis.

The clinical presentation is characterized by purulent drainage from the umbilical stump (or from the navel after the cord has separated), with surrounding erythema, induration, and tenderness. The drainage may be foul smelling, which is suggestive of infection with anaerobic bacteria. Infants with more severe infection will display systemic signs of illness, including fever, lethargy, poor feeding, and irritability. Involvement of the abdominal wall or extensive edema should prompt consideration for necrotizing fasciitis as a complication. Other complications of omphalitis include peritonitis, intra-abdominal abscess, suppurative thrombophlebitis of portal or umbilical veins, and umbilical hernia with bowel ischemia.

Purulent discharge should be sent for Gram stain and culture. Blood and CSF cultures should be obtained from infants with signs of systemic illness, including fever, lethargy, and irritability. Treatment consists of broad-spectrum parenteral antibiotics. Typically, an anti-staphylococcal penicillin and an aminoglycoside are given to provide Gram-positive and Gram-negative coverage. If the community prevalence of methicillin-resistant *S. aureus* is high, vancomycin should be used instead of anti-staphylococcal penicillin. The addition of clindamycin or metronidazole may be considered if there is suspicion for anaerobic involvement, especially for infants with foul-smelling discharge or if there is a history of maternal chorioamnionitis. For uncomplicated cases, duration of treatment is typically 10 days. A switch to oral therapy for completion of the course of treatment may be considered, depending on the patient's age, culture results, and clinical response.

Prevention of omphalitis involves both clean delivery services and hygienic cord care. It is generally agreed upon that the umbilical cord should be cut with clean hands using a sterile blade or scissors. This helps to prevent both omphalitis and neonatal tetanus. However, optimal care of the cord stump after the cord has been cut is an area of active research and some debate. A 2004 Cochrane review of 21 studies, most of them performed in high-income countries, showed no difference in risk for omphalitis among cords treated with antiseptics (such as alcohol, iodine, and chlorhexidine) compared with dry cord care or placebo.[129] Application of antiseptics may be beneficial for infants in resource-poor countries where the risk for omphalitis and associated complications is high and some traditional unhygienic cord practices continue. Two randomized studies from Nepal and Pakistan showed that application of chlorhexidine significantly reduced the risk of omphalitis compared with dry cord care.[73,106]

Specific Pathogens

Group B Streptococcus

Group B Streptococcus (GBS), or *Streptococcus agalactiae*, is the most common cause of early-onset sepsis in the United States. The primary risk factor for early-onset disease in the neonate is maternal intrapartum GBS colonization of the genitourinary or gastrointestinal tract leading to vertical acquisition of GBS during passage through the birth canal. The introduction of universal screening for maternal GBS colonization and use of intrapartum antibiotic prophylaxis has led to 80% reduction in the burden of early-onset GBS disease, yet has had no impact on late-onset disease.[14,74]

Following several clinical trials and observational studies, which demonstrated that early-onset GBS disease in neonates could be prevented by administering intravenous antibiotics during labor to women at risk for transmitting GBS, the Centers for Disease Control and Prevention (CDC) published the first set of guidelines for the prevention of perinatal GBS disease. The guidelines, most recently revised in 2010, recommended the use of either a risk-based approach or a culture-based screening approach to prevention.[56] The risk-based prevention method identified candidates for intrapartum antibiotic prophylaxis according to the presence of known intrapartum risk factors for early-onset disease (delivery before 37 weeks' gestation, intrapartum temperature 38° C or higher, or rupture of membranes for 18 hours or longer). The screening-based prevention method involved screening all pregnant women for vaginal and rectal GBS colonization between 35 and 37 weeks' gestation. All colonized women were then offered intrapartum antibiotic prophylaxis at the time of labor. Both the risk- and screening-based prevention methods offered

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intrapartum antibiotic prophylaxis to women with a history of GBS bacteriuria during the current pregnancy or with previous delivery of an infant with early-onset GBS disease. Continued active surveillance of GBS disease showed that the screening-based approach was superior to the risk-based approach.

Current recommendations include universal screening for rectal and vaginal GBS colonization of pregnant women between 35 and 37 weeks' gestation. All women with positive cultures, a history of GBS bacteriuria during the current pregnancy, or a history of having a previous infant with invasive GBS disease, should receive intrapartum antibiotic prophylaxis. Women with GBS colonization who have cesarean delivery performed before onset of labor or rupture of membranes do not require intrapartum antibiotic prophylaxis. The guidelines also contain recommendations for management of women with unknown GBS status at onset of labor, expanded recommendations for laboratory identification of GBS, a change in the recommended dose of penicillin G prophylaxis, and recommendations for women with penicillin allergy. Algorithms are included to assist in management of women with preterm labor, women with preterm, premature rupture of membranes, and newborns at risk for early-onset GBS disease.

Before the initiation of active prevention with intrapartum antibiotic prophylaxis, the estimated incidence of invasive neonatal GBS disease in the United States was 1.8 cases per 1000 live births (1.5/1000 for early onset and 0.35/1000 for late onset).[128] Following implementation of the CDC guidelines in the mid-1990s, the incidence of early-onset disease had decreased by 80% to 0.3-0.4 cases per 1000 live births after 2002.[56]

Despite the dramatic decrease in the incidence of newborn GBS disease, GBS disease remains the leading infectious cause of morbidity and mortality among newborns in the United States.[99] Rates of maternal GBS colonization are unchanged since the 1970s.[56] The use of intrapartum antibiotic prophylaxis has had no effect on the incidence rate of late-onset GBS disease, which has remained approximately 0.30 cases per 1000 live births.[8] Continued monitoring is needed to evaluate for potential adverse consequences of intrapartum antibiotic prophylaxis, including the emergence of drug resistance and a possible increase in incidence of non-GBS neonatal pathogens. Clinical trials are underway to evaluate administration of conjugate GBS vaccines in pregnant women.[80] Maternal vaccination has the potential to provide a simpler strategy for prevention, without the concerns about antibiotic resistance and emergence of non-GBS pathogens associated with intrapartum antibiotic prophylaxis.[98] However, licensing of GBS vaccines remains problematic due to the low incidence of neonatal diseases.

Early-onset GBS disease most commonly presents within the first day of life. Invasive early-onset disease may lead to bacteremia, pneumonia, meningitis, or bone or joint involvement. Late-onset GBS disease occurs after the first week of life, and patients commonly present with bacteremia and meningitis.[62] Recommended definitive antibiotic therapy for GBS disease is penicillin G, given its narrow spectrum and excellent in vitro activity. GBS is consistently susceptible to penicillin, ampicillin, first- and second-generation cephalosporins, and vancomycin. Approximately 30% of GBS isolates are resistant to erythromycin, and approximately 20% are resistant to clindamycin.[15] Duration of therapy depends on location of disease involvement. Therapy should be continued for 7-10 days for bacteremia without a focus, 14-21 days for meningitis, 14-21 days for septic arthritis, and 4-6 weeks for osteomyelitis.

The widespread use of intrapartum antibiotic prophylaxis has led to a substantial decrease in mortality associated with all causes of early-onset neonatal sepsis. In the period just before implementation of intrapartum antibiotic prophylaxis (1985-1991), mortality from early-onset sepsis was 24.9 per 100,000 cases. In the years following implementation of intrapartum antibiotic prophylaxis (1995-1999), mortality rates had decreased to 15.6 per 100,000.[68] As with all pathogens causing neonatal sepsis, mortality from GBS disease is higher among preterm and low birth weight infants. Data published in 2008 showed mortality rates from early-onset GBS disease of 20% in preterm infants and 2%-3% in term infants. Late-onset GBS mortality was 5%-6% in preterm infants and 1%-2% in term infants.[85]

Staphylococcus aureus

Staphylococcus aureus is a facultative anaerobic Gram-positive coccus, and it is frequently found as a commensal organism in the respiratory tract and on the skin. Although it is not always pathogenic, it is a common cause of infection, leading to diseases that range from mild to severe and life threatening.

In neonates, *S. aureus* is more often seen as a cause of late-onset infection and does not commonly occur within the first 72 hours of life. It is a common cause of hospital-acquired infection among neonates in the intensive care unit. Bloodstream infections are often associated with umbilical or central venous catheters. Other frequent manifestations include pneumonia, conjunctivitis, and skin and soft tissue infections. The spread of drug-resistant *S. aureus* is a continuing problem that affects patients of all ages. There are increasing reports of methicillin-resistant *S. aureus* (MRSA) outbreaks in neonatal intensive care units (NICUs) across the United States. Data from the Emerging Infections Program Network Report on Methicillin-Resistant *Staphylococcus aureus* shows African Americans have nearly twice the rate of invasive disease than Caucasians (29.9 vs. 17.7 per 100,000 population).[16] The incidence of MRSA infections in NICUs has increased, stressing the importance of continued efforts at infection control and prevention.[66]

Community-acquired *S. aureus* infections among previously healthy neonates have a wide variety of clinical manifestations. These include pustulosis, cellulitis, skin abscess, and mastitis, as well as invasive disease with bacteremia,

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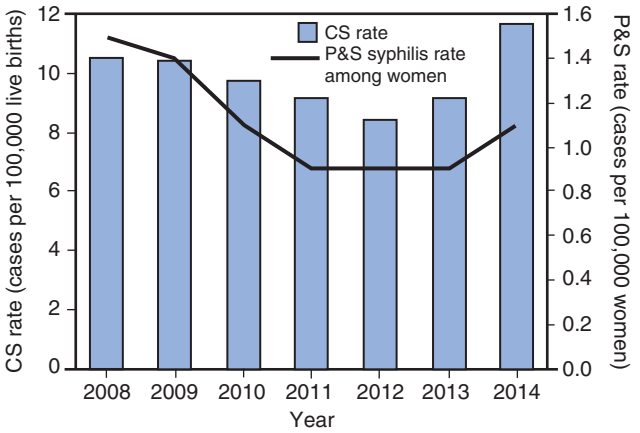
urinary tract infection, pneumonia, and musculoskeletal infections. Symptoms often begin after the first week of life. Neonatal infection may be associated with recent or current maternal infection, such as mastitis, cellulitis, abscess, or cesarean wound infection. As with hospital-acquired infection, drug resistance is increasing among community-acquired *S. aureus* isolates, with rates of MRSA among neonates reflecting increasing rates among the general population in the community.[31]

Initial diagnostic evaluation and empiric antibiotic therapy depend on the extent and severity of illness at presentation. In any infant with systemic signs of illness, or in whom invasive disease is suspected, a full sepsis evaluation with blood, urine, and CSF cultures should be obtained. Empiric *S. aureus* coverage with vancomycin and nafcillin should be given until final susceptibility results are available. Completion of therapy with nafcillin alone is appropriate for infections caused by methicillin-susceptible *S. aureus*. Vancomycin is the preferred therapy for MRSA infections in neonates. At this time there is little data on the use of intravenous Daptomycin in infants. Clindamycin or linezolid may provide an alternative to vancomycin therapy. However, clindamycin is bacteriostatic rather than bactericidal against *S. aureus*, so it should not be used to treat bacteremia or severe infections. For bloodstream infections associated with central venous or umbilical catheters, the catheter should be removed if possible and antibiotics administered for at least 14 days, given the high virulence of *S. aureus* and its propensity to colonize foreign material and create biofilms.[71] A common conundrum is the lack of vascular access in a critically ill neonate that may prevent removal of the affected line.

There is little evidence available to guide clinicians in the treatment and evaluation of otherwise healthy, full-term neonates with mild, localized *S. aureus* skin infections. Localized pustulosis and omphalitis without associated cellulitis or systemic symptoms can be treated with topical antibiotics such as mupirocin, whereas localized disease in premature or very low-birth-weight infants is treated with IV medication.[67] A more thorough evaluation (including blood and CSF cultures) and parenteral antibiotics should be given to infants with systemic symptoms, premature or low birth weight infants, or infants with more widespread infection. Empiric treatment options for staphylococcal skin and soft tissue infections (SSTI) include vancomycin, clindamycin, and linezolid. Infants initially started on parenteral therapy who have shown clinical improvement and have negative blood and CSF cultures can often be switched to oral therapy. Oral antibiotic options for staphylococcal SSTI include cephalexin, clindamycin, linezolid, and amoxicillin-clavulanate. A total duration of 7-14 days of therapy is recommended.

Syphilis

Syphilis is caused by *Treponema pallidum*, a thin, motile spirochete. Syphilis is generally acquired through sexual contact, in which the spirochete enters through breaches in squamous or columnar epithelium. Transmission of congenital syphilis is most frequently transplacental, although infection is rarely acquired by contact with genital lesions during delivery. The incidence of congenital syphilis parallels that of primary and secondary disease in women. In the late 1980s and early 1990s, the incidence of acquired and congenital syphilis increased dramatically in the United States. Decreasing incidence was seen in the late 1990s, but since 2001, the rates of primary and secondary syphilis have increased. From 2004-2007, a 38% increase in rates of primary and secondary syphilis was seen among females. This was associated with a subsequent 23% increase in the rate of congenital syphilis (8.2 cases per 100,000 live births in 2005 to 10.1 during 2008).[17] The number of congenital syphilis cases declined in 2008-2012, followed by another sharp increase from 2012-2014, representing an increase in rate from 8.4-11.6 cases per 100,000 live births (Fig. 48.1). Rates of infection are highest in large urban areas and the southern United States with rate among blacks remaining approximately 10 times the rate among whites.[12]



• **Fig. 48.1** Congenital syphilis (CS) rate* among infants aged <1 year and rate of primary and secondary (P&S) syphilis among women† — United States, 2008-2014§. *CS rates during 2008-2013 were calculated by using annual live birth data as denominators. (Available at http://wonder.cdc.gov/natality-current.html.) †P&S syphilis rates during 2008-2013 were calculated by using bridged race U.S. census population estimates as denominators. (Available at http://wonder. cdc.gov/bridged-race-v2013.html.) §The CS rate and P&S syphilis rate for 2014 were calculated by using 2014 case counts and 2013 denominators. (From Centers for Disease Control and Prevention. Morbidity and mortality weekly report. November 13, 2015; 64[44].)

Transplacental transmission can occur at any time during pregnancy and at any stage of maternal disease. Rates of transmission are higher during primary and secondary maternal syphilis than with later stages of disease (early latent and late latent). Intrauterine infection may result in spontaneous abortion, hydrops fetalis, or stillbirth. Infection also increases the risk for preterm birth, low birth weight, and perinatal death. Clinical manifestations in infected infants within the first 1-2 months of age include hepatosplenomegaly, lymphadenopathy, rash, mucocutaneous lesions, copious nasal secretions (snuffles), pneumonia,

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• BOX 48.1 Clinical Findings of Early Congenital Syphilis*

Nonimmune hydrops fetalis
Intrauterine growth restriction
Failure to thrive
Generalized lymphadenopathy
Bone abnormalities
- Periostitis
- Osteochondritis (Wimberger sign)
- Osteitis

Hepatosplenomegaly (with or without elevated aminotransferases, jaundice)
Mucocutaneous lesions
- Pemphigus syphiliticus (vesiculobullous eruption, contagious)
- Maculopapular eruption
- Mucous patches of palate, perineum, intertriginous areas
- Condyloma latum

Persistent rhinitis (snuffles, contagious)
Pneumonitis (pneumonia alba)
Nephrotic syndrome
Neurologic abnormalities
Syphilitic leptomeningitis
Hematologic abnormalities
- Leukocytosis
- Leukopenia
- Anemia, Coombs-negative hemolytic
- Thrombocytopenia

Ocular abnormalities
- Chorioretinitis
- Uveitis

*Defined as age <2 years.

• BOX 48.2 Clinical Manifestations of Late Congenital Syphilis*

Dental
- Hutchinson teeth (notched, peg-shaped upper central incisors)†
- Mulberry molars (multiple small cusps)

Bone
- Frontal bossae of Parrot
- Saddle nose deformity
- Short maxillae
- High-arched palate
- Higoumenakía sign (sternoclavicular thickening)
- Flaring scapulae
- Saber shins (anterior bowing of tibia)
- Clutton joints (painless synovitis, hydrarthrosis)

Cutaneous
- Rhagades (linear scars radiating from mouth, nares, and anus)

Ocular
- Interstitial keratitis†

Neurologic
- Eighth cranial nerve deafness†
- Mental retardation
- Hydrocephalus
- Cranial nerve palsies
- Seizure disorder

*Defined as age >2 years.
†Features of Hutchinson triad.

hemolytic anemia, thrombocytopenia, and skeletal involvement (osteochondritis, periostitis, and osteitis) (Box 48.1). The nasal secretions and skin lesions in untreated infants are highly infectious. Infected infants may also be completely asymptomatic.

Treatment of early-stage infection can prevent late manifestations of infection. Left untreated, late-stage findings usually appear after 2 years of age and include CNS, skeletal, dental, ocular, and skin involvement (Box 48.2). Several of these findings may not occur until many years later. The Hutchinson triad refers to interstitial keratitis, eighth cranial nerve deafness, and notched central incisors (Hutchinson teeth). Other manifestations include frontal bossing, saddle nose deformity, and anterior bowing of the shins.

All women should be screened for syphilis with serologic testing early in pregnancy and again at delivery.[125] Initial screening should be done with a nontreponemal test (e.g., RPR, rapid plasma regain; VDRL, Venereal Diseases Research Laboratory). The result of a positive nontreponemal test should be confirmed with a treponemal antibody test (e.g., FTA-ABS, fluorescent treponemal antibody absorption; TP-EIA, *T. pallidum* enzyme immunoassay; MHA-TP, microhemagglutination test for antibodies to *T. pallidum*; TP-PA, *T. pallidum* particle agglutination). Any woman treated for syphilis during pregnancy should have follow-up testing with a nontreponemal titer to assess response to therapy. Penicillin is the recommended treatment for pregnant women. Admission for desensitization to penicillin is recommended for women with penicillin allergies.

Low-titer, false-positive nontreponemal test results do sometimes occur during pregnancy. A false-positive nontreponemal test result is confirmed if a woman has a reactive nontreponemal test but a consistently negative treponemal test result. Some laboratories screen pregnant women using a treponemal TP-EIA test. If a woman has a reactive TP-EIA, she should have confirmatory testing done with an RPR or VDRL. Subsequent evaluation of the infant should be based on the infant's RPR or VDRL titer results as compared with the mother's.

An infant should be fully evaluated for congenital syphilis if the maternal RPR/VDRL titer has increased fourfold, the infant's RPR/VDRL titer is fourfold greater than the mother's, or the infant is symptomatic or has an abnormal exam. If an infant is born to a mother adequately treated for syphilis with penicillin before the pregnancy with a stable low titer and has a normal physical examination, the infant does not require further evaluation or treatment. If the mother was adequately treated with penicillin during pregnancy more than 4 weeks before delivery, the infant has

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a normal examination, and the infant's RPR/VDRL is the same as or less than fourfold the maternal titer, then the infant may be treated with penicillin without further evaluation. If a mother has untreated or inadequately treated syphilis (received no treatment or treatment is not documented, treatment was 4 weeks or less before delivery, or treatment was with a non-penicillin drug), then the infant requires full evaluation and treatment.

Full evaluation for congenital syphilis includes RPR/VDRL; complete blood count; and CSF examination for cell count, protein, and quantitative VDRL. Other tests should be done as clinically indicated, including long bone radiographs, eye examination, liver function tests, neuroimaging, hearing tests, and chest radiographs. A definite or highly probable diagnosis of congenital syphilis is based on presence of any of the following: physical, laboratory, or radiographic evidence of active infection; a positive CSF VDRL; an infant RPR/VDRL titer fourfold or more than that of the mother; or a positive specific treponemal stain of the placenta or umbilical cord.

The recommended treatment for definite or probable congenital syphilis is intravenous penicillin G. The dose is based on chronologic rather than gestational age. The recommended dose is 50,000 U/kg every 12 hours if 1 week of age or younger, or every 8 hours if older than 1 week, for a total duration of 10 days. If more than 1 day of therapy is missed, the entire course should be restarted.

All infants with reactive RPR/VDRL or those who were seroreactive at delivery require careful follow-up during the first year of life. Nontreponemal tests should be performed every 2-3 months until the test becomes nonreactive or the titer has decreased at least fourfold. If the infant was adequately treated in the neonatal period, the nontreponemal titer should be nonreactive by 6 months of age. Infants with increasing or persistently stable titers 6-12 months after treatment should be re-evaluated (including CSF VDRL) and treated with a 10-day course of intravenous penicillin G. Infants diagnosed with congenital neurosyphilis should have a repeat clinical evaluation with CSF examination every 6 months until the CSF is normal. If the CSF VDRL is positive 6 months after initial treatment course, the infant should be retreated with another 10-day course of penicillin.[94]

Listeriosis

Listeriosis is caused by *Listeria monocytogenes*, a non-spore-forming, short, Gram-positive bacillus. It is an intracellular pathogen that is able to survive and multiply within host phagocytic cells. Listeriosis primarily affects older adults, pregnant women, neonates, and immunocompromised hosts. Listeria is found in soil and decaying vegetable matter. It is also found in the intestinal tracts of several mammals, birds, fish, and crustaceans. In adults, most infections are thought to arise from oral ingestion of contaminated material, leading to intestinal mucosal penetration and systemic infection. Impaired cell-mediated immunity and macrophage function are associated with increased susceptibility to infection with Listeria.[107] In pregnant women, the bacterium is able to cross the placenta during maternal bacteremia and infect the fetus. Infection in pregnant women can lead to spontanous abortion, stillbirth, preterm labor, or neonatal infection.

In a systematic review of peer-reviewed literature, the WHO estimated that listeriosis resulted in 23,150 illnesses worldwide in 2010 leading to 5463 deaths. In this review of listeriosis cases, 20.7% were perinatal infections with septicemia occurring in 30.7% of infected neonates.[24] Most cases of listeriosis occur as sporadic illnesses, likely after ingestion of contaminated food. Several foodborne outbreaks have also been reported and are associated with a variety of foods. The most common foods implicated in infections are delicatessen meats, hot dogs, soft cheeses, smoked seafood, and pâtés.

Among all organisms causing neonatal sepsis, *L. monocytogenes* is a relatively uncommon cause. Listeria infection in neonates is classified as early onset or late onset. The signs and symptoms of listeriosis in neonates are indistinguishable from the signs and symptoms of other postnatal bacterial infections. Early-onset disease is most often acquired by transplacental transmission, and affected infants are symptomatic soon after birth. Meconium passage is often associated with intrauterine Listeria infection. Common manifestations of early-onset infection include neonatal sepsis and pneumonia. Late-onset infection may be acquired by vertical transmission from a colonized mother during passage through the birth canal or by transmission from other colonized or infected caregivers. Symptoms usually arise after the first week or two of life. The most common manifestation of late-onset listeriosis is meningitis, often with insidious onset.

As for any neonate with suspected sepsis, blood and CSF cultures should be obtained. In addition, isolation of *L. monocytogenes* from cultures of amniotic fluid or placental tissue may support the diagnosis of early-onset disease. Recommended empiric antibiotic treatment for neonatal sepsis includes ampicillin and an aminoglycoside. This regimen provides important coverage for listeriosis, as cephalosporins have no activity against *L. monocytogenes*. When infection with Listeria has been confirmed, the antibiotic of choice is ampicillin. The addition of gentamicin is recommended to provide synergy. After the patient demonstrates clinical improvement, gentamicin can be discontinued and ampicillin given alone to complete the remainder of treatment. For all cases of Listeria meningitis, a repeat lumbar puncture should be performed 1-2 days after the start of treatment to confirm sterilization of the CSF. Treatment duration of 10-14 days is recommended for uncomplicated bacteremia. For meningitis, treatment should be continued for 14-21 days. All patients with Listeria meningitis should have neuroimaging obtained near the anticipated end of treatment to determine whether there is parenchymal involvement and whether the patient may require a more prolonged course of treatment.

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TABLE 48.2 Perinatal Transmission of Tuberculosis

Maternal Focus of Infection	Mode of Spread	Timing	Relative Frequency
Pneumonia with cavitary lesion*	Inhalation of infected droplets	Postnatal	Most common
Amniotic infection after rupture of placental caseous lesion	Aspiration or ingestion of infected fluid	Congenital or intrapartum	Less common
Placentitis after miliary or endometrial tuberculosis	Hematogenous through umbilical vein	Congenital	Rare
Cervicitis	Direct contact, aspiration, or ingestion	Intrapartum	Rare
Mastitis	Ingestion of infected milk	Postnatal	Extremely rare

*Any caregiver with cavitary pulmonary tuberculosis can transmit infection to the infant.

Tuberculosis

Although perinatal tuberculosis (TB) is rare in the United States, the burden of tuberculosis, especially worldwide, among women of childbearing age is quite high.[29] The risk for perinatal TB is much higher in areas with high prevalence for both TB and HIV infection among young women.[69] Perinatal TB includes both congenital and neonatal TB (Table 48.2). Mother-to-child transmission of congenital TB may occur in utero by hematogenous dissemination via the umbilical vein or by intrapartum aspiration of infected amniotic fluid or genital secretions. Tuberculosis during pregnancy is also associated with increased risk for preterm labor, low birth weight, and fetal and perinatal death. Clinical manifestations of congenital TB are often nonspecific and include respiratory distress, lethargy, irritability, fever, low birth weight, hepatosplenomegaly, and poor feeding.

Neonatal TB, which is somewhat more common than congenital TB, is transmitted through inhalation or ingestion of respiratory droplets or through ingestion of infected breast milk. Clinical manifestations include failure to thrive, fever, vomiting, cough, and tachypnea. Because perinatal disease is very rare, there are little data on mortality rates and outcomes. Without prompt evaluation and treatment, mortality rates are quite high and are estimated at 50%.[42]

Any neonate with suspected TB disease should undergo a complete evaluation for both TB and bacterial sepsis. A tuberculin skin test (TST) should be placed, although newborns may have a nonreactive TST in the presence of active disease. Interferon-gamma release assays (IGRA) are not reliable in children younger than 4 years and should not be used in the diagnostic work-up of either latent or active TB infection in infants. A chest radiograph should be obtained. Mycobacterial stains and cultures should be obtained from three consecutive, early-morning gastric aspirates to evaluate for pulmonary TB. Mycobacterial stains and cultures can also be obtained from other sites if extrapulmonary TB is suspected. Cerebrospinal fluid obtained for evaluation of routine bacterial meningitis should also be sent for mycobacterial stains and cultures.

Regardless of the initial TST result and while other studies are pending, the infant should be promptly started on antituberculosis therapy with isoniazid, rifampin, pyrazinamide, and either ethambutol or an aminoglycoside such as amikacin, kanamycin, or streptomycin. The infant's mother should undergo a full evaluation for pulmonary and extrapulmonary TB (including uterine infection). The placenta should be examined for the presence of granulomas and sent for mycobacterial stains and culture. If the infant's physical examination and diagnostic work-up are consistent with TB, a full treatment regimen should be administered. This should consist of 2 months of the described four-drug regimen, followed by at least 4 months of isoniazid and rifampin. If TB meningitis is confirmed, corticosteroids should be added.[94]

Management of the asymptomatic newborn whose mother or another household contact has TB will depend on whether the contact has latent TB infection or active disease. If the mother has a positive TST or IGRA, a normal chest radiograph, and is asymptomatic, no separation between mother and baby is required. The infant needs no special evaluation or therapy. The mother is a candidate for latent TB infection treatment after the initial postpartum period. Breastfeeding is not contraindicated.

If the mother (or household contact) has a positive TST/IGRA along with clinical symptoms or an abnormal chest radiograph consistent with active TB disease, the infant and mother should be separated until the mother has been fully evaluated, including testing for HIV. The infant should be evaluated for congenital TB, and all household contacts should be evaluated for TB infection. If the mother is diagnosed with active TB, separation from the infant is only required until the mother is on antituberculosis treatment and the infant is receiving isoniazid. Continued separation is necessary if the mother has suspected multidrug-resistant TB or has poor adherence to therapy. The mother may breastfeed if she has been on therapy for at least 2 weeks and is not considered contagious. If congenital TB is excluded, the infant should be given isoniazid until 3 or 4 months of age, when a repeat TST is performed. If the TST

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is positive, repeat evaluation for TB disease is required. If the TST is negative, the infant should receive a total of 9 months of isoniazid.[94]

Botulism

Infant botulism is caused by *Clostridium botulinum*, a heterogeneous group of ubiquitous, spore-forming, obligate anaerobic, Gram-positive bacilli. The spores are found across the globe in soil, water, agricultural products, and honey. When appropriate environmental conditions are present, the spores germinate and grow into toxin-producing bacteria. Eight serologically distinct types of *C. botulinum* toxin have been described. Toxin types A, B, E, and rarely F and G cause disease in humans.[78] After entry into the body, the toxin disperses widely throughout the body and binds to a specific receptor on peripheral cholinergic synapses of ganglia and neuromuscular junctions.[57] Binding of the toxin leads to irreversible disruption of acetylcholine release by the presynaptic nerve terminal, which in turn leads to a severe neuroparalytic syndrome. Different types of botulism infection are classified according to the mode of acquisition. Foodborne botulism occurs after ingestion of preformed botulinum toxin in contaminated food. Infant botulism occurs after ingestion of the spores, which then colonize the host's GI tract and release toxin produced in vivo.

Infant botulism was first recognized as a distinct entity in 1976. On average, 100-150 cases of botulism are reported each year in the United States. Of these, approximately 75% are cases of infant botulism.[89] Incidence is highest in California (which accounts for over 50% of cases), Texas, and Pennsylvania. Although infant botulism has long been associated with the ingestion of raw honey, most cases likely result from ingestion of environmental dust containing *C. botulinum* spores. The spores have been isolated from several types of environmental samples, including yard soil and vacuum dust.

Clinical manifestations of infant botulism range from mild disease to sudden death, and onset may be insidious or fulminant. The diagnosis must be considered in any infant presenting with hypotonia, constipation, and poor feeding. In the United States, the median age of affected infants is approximately 17 weeks, ranging from 1-60 weeks of age.[89] Presenting symptoms often include lethargy, poor feeding, drooling, constipation, and progressive, symmetric weakness. The weakness may involve descending or global hypotonia. Patients are typically afebrile. Early in the course, the physical examination may be normal. As the infection progresses, cranial nerve palsies, poor head control, and weak cry develop. Loss of gag, swallow, and suck reflexes can lead to airway compromise. Initially, deep tendon reflexes may be normal, although these become diminished or absent as the descending, symmetric, flaccid paralysis progresses.

Because confirmatory stool studies and electrophysiologic studies can be nonspecific and may require several days to obtain results, a presumptive diagnosis should be made based on clinical presentation, and therapy should be administered as soon as possible. For assistance with management of any suspected case of infant botulism in the United States, the California Department of Health Services, Infant Botulism Treatment and Prevention Program may be contacted (www.infantbotulism.org, [510] 231-7600) to discuss with an on-call physician.

The diagnosis is supported by isolation of *C. botulinum* spores from the stool and confirmed by identification of the botulinum toxin in the stool. Stool sample collection is often difficult because most patients are constipated, and it takes several days to obtain results from these stool studies (which must be sent out to reference laboratories at state health departments or the CDC). While stool study results are pending, electromyography (EMG) may be obtained. Electromyography findings that are consistent with infant botulism include short-duration, low-amplitude motor unit potentials, as well as abnormal incremental response to repetitive nerve stimulation.[21]

Treatment includes supportive care and very close monitoring for signs of respiratory failure. All suspected cases should receive botulism immune globulin intravenous (BIG-IV or BabyBIG) as early as possible. Botulism immune globulin intravenous is a human-derived botulinum antitoxin, and it has been shown to be safe and effective treatment for infant botulism. A randomized, placebo-controlled trial showed that patients who received BIG-IV had reduced duration of hospital stay, intensive care, mechanical ventilation, and tube or intravenous feedings. Botulism immune globulin intravenous was not associated with any serious adverse events.[3] Antibiotics are not recommended for infant botulism because lysis of *C. botulinum* organisms within the gastrointestinal lumen could increase the amount of toxin available for absorption.[13]

Recovery often requires several weeks, although most patients are expected to achieve complete recovery. Botulinum toxin does not cross the blood–brain barrier and thus does not affect the CNS. The case fatality rate for infant botulism is currently less than 1%.[89]

Tetanus

Neonatal tetanus is very rare in developed countries because of widespread hygienic birth conditions and maternal immunization, although it remains a significant cause of morbidity and mortality in developing countries. Tetanus is acquired through exposure to the spores of *Clostridium tetani*, a slender, anaerobic, Gram-positive bacillus. When the spores germinate, the bacteria produce the tetanospasmin toxin (also known as tetanus toxin). The toxin reaches the spinal cord and brainstem and binds tightly and irreversibly to receptors at the neuromuscular synapse. Its effects occur through disinhibition of neurons that modulate excitatory impulses from the motor cortex. This results in increased muscle tone, spasms, and autonomic instability.

Clostridium tetani is present in the soil and can be found in human and animal feces. Because it is impossible to eliminate the bacteria or its spores from the environment,

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control of the disease relies on widespread immunization and proper wound care. The World Health Organization (WHO) reports that neonatal tetanus resulted in approximately 34,019 deaths in 2015, representing a 96% reduction in deaths since the late 1980s.[127] Neonatal tetanus remains a problem in several countries because of inadequate maternal immunization coverage and unhygienic birth practices leading to infection of the umbilical stump.

Disease onset typically occurs at 1 week of age, with incubation periods ranging from 1 day to 1 month. Clinical manifestations include irritability, poor suck, fever, rigidity, muscle spasms, and seizures. Spasms are exacerbated by stimulation. On examination, infants usually have hyperreflexia and extreme flexion of the toes. Although trismus is commonly seen in generalized tetanus in adults, it is seen less often in infants. Other signs include tachycardia, tachypnea, and apnea. Laryngospasm may lead to aspiration pneumonia, and pulmonary processes are a frequent cause of death in neonatal tetanus.

The diagnosis is based strictly on clinical presentation. Treatment is largely supportive. Intramuscular human tetanus immune globulin is given to neutralize unbound toxin, and metronidazole is given to reduce the number of toxin-producing bacteria. Airway management and maintaining adequate ventilation are essential, although unfortunately, critical care services are often not available in resource-poor settings where most neonatal tetanus occurs. Benzodiazepines and baclofen can be given to help control muscle spasms. Because stimulation can precipitate spasms and seizures, efforts should be made to reduce environmental stimulation as much as possible. Magnesium sulfate and beta-blockers can help control autonomic dysfunction.

Since the introduction of mechanical ventilation and benzodiazepines in the 1960s and 1970s, the morbidity and mortality of tetanus patients of all ages has significantly decreased. If modern critical care services are available, mortality rates may be less than 20%. If basic medications and high-quality nursing care are provided, mortality rates can be reduced to under 50%. Survivors may have full recovery or varying degrees of neurologic sequelae, ranging from minor deficits to cerebral palsy.

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Key Points

- Newborns are extremely susceptible to infection.
- Current recommendations include universal screening for rectal and vaginal GBS colonization of pregnant women between 35 and 37 weeks' gestation. Antibiotics should be given to those mothers identified at risk.
- The introduction of universal screening for maternal GBS colonization and use of intrapartum antibiotic prophylaxis has led to 80% reduction in the burden of early-onset GBS disease yet has had no impact on late-onset disease.
- The use of ciprofloxacin is indicated in those infants with multidrug-resistant Gram-negative disease when alternative antibiotics are not available.
- There are increasing reports of methicillin-resistant *S. aureus* (MRSA) disease in newborns across the United States, paralleling the spread of drug-resistant *S. aureus* in the community.

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49

Fungal and Protozoal Infections of the Neonate

DAVID A. KAUFMAN AND PAOLO MANZONI

Fungal infections in the neonatal intensive care unit (NICU) remain an important health problem associated with substantial morbidity and mortality. Invasive fungal infections encompass infections largely caused by *Candida* species and with a small portion caused by *Aspergillus*, *Zygomycetes*, *Malassezia*, *and Trichosporin*. Invasive *Candida* infections occur in two main patient groups in the NICU: (1) the extremely premature infant and (2) NICU patients with complex gastrointestinal disease such as necrotizing enterocolitis (NEC), gastroschisis, and spontaneous bowel perforation.[26,33,49,54,62] Strategies for prevention and management of invasive *Candida* infections are paramount for improving outcomes for neonates (Fig. 49.1).

The incidence of candidiasis correlates with advances in medical therapy and increased survival of extremely low birth weight and gestational age preterm neonates. In developed countries, increases occurred in the 1980s and 1990s, then began to fall after 2001, primarily in infants less than 1000 g, owing to various factors including antifungal prophylaxis, antibiotic and medication stewardship, and central line–associated bloodstream infection (CLABSI) bundles.[24,38,52]

Definitions

Invasive *Candida* infections (ICI) in neonates include: congenital cutaneous candidiasis (CCC) and late-onset cutaneous candidiasis, bloodstream infections (BSIs), urinary tract infections (UTIs), meningitis, peritonitis, and infection of other sterile sites (bone and joint infections). These infections are often classified similar to other neonatal infections into early-onset (<72 hours after birth) and likely vertically transmitted and late onset (≥72 hours after birth) and potentially horizontally transmitted infections. This is a worthy system to standardize definitions, recognizing that *Candida* species are slow-growing organisms and some infections in the first weeks of life have been shown by molecular studies to be vertically transmitted.

Microbiology

Candida albicans and *C. parapsilosis* account for 80%-90% of invasive *Candida* infections in centers not using antifungal prophylaxis. Less-common *Candida* species include *C. glabrata* and *C. tropicalis*, and a smaller percentage of infections are caused by *C. lusitaniae*, *C. guilliermondii,* and *C. dubliniensis. C. parapsilosis* isolates have been found to be genetically heterogeneous, with 10% being identified as two different species: *C. metapsilosis* and *C. orthopsilosis*. These three species are phenotypically indistinguishable, and molecular methods are needed for their detection. Centers using antifungal prophylaxis have a very low incidence of infections, and the few that occur are primarily by non-*albicans* species in NICUs using fluconazole prophylaxis. The change in epidemiology of *Candida* species with antifungal prophylaxis is important because fluconazole prophylaxis has virtually eliminated the more virulent *C. albicans* infections.

Pathogenesis and Pathophysiology

Most *Candida* species are commensal organisms and part of the normal human microbiome in the skin and gastrointestinal tract. They may exist primarily as budding yeast cells, filamentous hyphal structures, or both. Adherence and colonization are normal, and fungi become pathogenic owing to fungal and host factors (Fig. 49.2).

The slow-growing nature of *Candida* facilitates its ability to progress from colonization to dissemination into the bloodstream and body tissues before clinical signs and symptoms of infection become apparent. In preterm neonates, similar to other hosts, four major steps can be identified in infected infants after exposure to *Candida* spp.: (1) adhesion, (2) colonization, (3) dissemination, and (4) abscess formation (see Fig. 49.2). These steps are related to the size of the inoculum (e.g., the number of fungal organisms), their virulence, and the characteristics of the host response.

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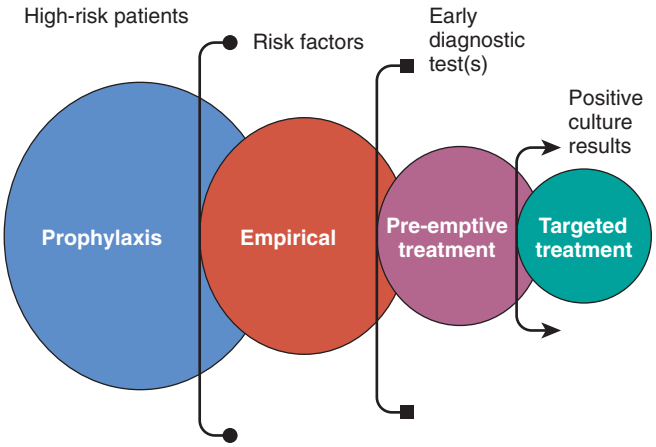
Abstract

Invasive *Candida* infection is associated with significant mortality and morbidity with extremely preterm infants comprising the highest risk patients. NICU patients are at risk due to their developing skin, gastrointestinal tract and immune system; need for intensive care, catheters, and tubes that breech important protective barriers; and exposure to antibiotics and certain medications that can favor fungal growth. Standardization of treatment regimens is key to improving outcomes including appropriate dosing and prompt central catheter removal with *Candida* bloodstream infections. Cutaneous manifestations of *Candida* and molds such as aspergillosis warrant prompt recognition, culturing of the skin in addition to other sites, and systemic empiric treatment at the time of rash presentation. Empiric antifungal treatment when invasive *Candida* infection is suspected should also be given in high-risk patients. The majority of infected infants despite empiric and optimal treatment still have significant sequelae or do not survive making prevention critical for every NICU. Prevention in high-risk patients is highly effective and recommended by pediatric infection control groups using a combination of antifungal prophylaxis, central catheter infection prevention measures, and antibiotic and medication stewardship. Targeted antifungal prophylaxis with infection control practices administered to infants with birth weights less than 1000 g and/or less than 28 weeks' gestational age can significantly reduce invasive *Candida* infections, their associated neurodevelopmental impairment, and *Candida*-related mortality. Both nystatin and fluconazole prophylaxis have level A-I evidence demonstrating efficacy in the prevention of invasive *Candida* infection with fluconazole having the better efficacy in extremely low birth weight infants.

Keywords

candida
fungal
preterm infants
antifungal prophylaxis
fluconazole prophylaxis

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• **Fig. 49.1** Approaches to invasive *Candida* infections.

- Exposure
- Adherence
- Colonization/biofilm
- Infection
  - BSI, UTI, meningitis, peritonitis, cutaneous candidiasis
- End-organ dissemination
  - Heart, kidneys, central nervous system, eyes, lungs, subcutaneous tissues, liver, spleen, joints, bone, intravascular thrombus, intra-abdominal abscess

- Number of organisms
- Host immunity/response
- Compromise of physical defense barriers
  - Skin, gastrointestinal or respiratory tracts
- *Candida* virulence

• **Fig. 49.2** Pathogenesis of invasive *Candida* infections.

Adhesion is the key step in colonization. Candidal species can adhere to epithelial and endothelial cells as well as catheters. Biofilm formation limits penetration of antifungals and shielding *Candida* from the host response. Surface glycoproteins such as INT1p, which binds to beta-integrins present on the endothelium and white blood cells, facilitate fungal adherence. The absence of a functional *INT1* gene diminishes adherence in yeast cells.[40]

The preterm infant has an immature immune system and is frequently exposed to broad-spectrum antibacterial and other medications that can suppress their immune response. Studies examining the effect of steroids and antibiotics have been performed in mice orally inoculated with *C. albicans* to mimic conditions in the preterm infant.[12] Antibiotic treatment alone led to increased *Candida* colonization but did not affect dissemination. When dexamethasone was added to the antibiotic regimen, both colonization and dissemination increased in these animal models. Additionally, dexamethasone plus antibiotics led to an increase in the percentage of filamentous forms in the gastrointestinal tract compared with antibiotics alone. These studies also showed that *C. albicans* strains with two functional copies of the *INT1* gene increased the number of fungi colonizing the cecum and disseminating to extraintestinal sites.

Studies consistently demonstrate higher associated mortality in preterm infants with *C. albicans* compared with non-*albicans* BSIs.[16,103] Its virulence encompasses a combination of factors involving adhesion, cytotoxicity, hydrolytic enzymes (aspartyl proteinases, phospholipases, lipases, and hemolysins), morphologic switching, and genes. In addition to the adhesion factors discussed, *C. albicans* produces higher concentration of hydrolytic enzymes compared to non-*albicans* species.

C. albicans can alternate its morphology in response to specific environmental cues, has an obligate diploid genome, lacking a complete sexual cycle, and has several genes important for virulence. Studies have found a strong correlation between virulence and the ability to alternate among three morphological forms—yeasts, hyphae, and pseudohyphae. The morphologic switch is a complex process involving changes in cellular shape, mechanical properties, interactions with other cells, and differential expression of multiple genes. Because of their size and shape, filamentous forms increase virulence of *C. albicans* in part by escaping phagocytosis.

To further examine the role of yeast and filamentous forms, three strains of *C. albicans* were studied: (1) a wild-type strain that had both yeast cell and filamentous forms, (2) a strain only producing yeast cells, and (3) a strain that was constitutively filamentous.[11] The mortality rate was significantly greater in both the wild-type (92%) and yeast-cell (56%) strains compared with the filamentous strain alone (0%). The filamentous strain had no dissemination, and cecal colonization was significantly less than that of the other two strains. The wild-type strain had diffuse hyphal invasion with increased tissue necrosis compared with the yeast-cell strain. The researchers speculated that the yeast forms are critically important for adherence and tissue dissemination and that hyphal formation in the tissues contributes to parenchymal destruction.

Prematurity

The immature lymphocyte and antibody system predisposes preterm infants to skin and mucosal fungal adherence and colonization, whereas deficient innate host defense mechanisms predispose them to dissemination and overwhelming infection.[54] With compromise of the barrier defense system, invasive *Candida* infections may occur, owing to deficient neutrophil function and when neutropenia is present. Neutrophils provide the major role in antifungal defense, ingesting and killing *Candida* in a process requiring production of oxygen metabolites, antibodies, cytokines, and activation of the C3 complement component, all of which are decreased in preterm infants compared with term infants and adults. Also deficient are neutrophil granules and cytokines that play a critical role in the

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lysis of *Candida* hyphae and pseudohyphae, which are too large to be engulfed by phagocytosis. Macrophages have impaired adherence, phagocytosis, and oxidative killing in preterm infants, affecting their ability to contain fungal colonization and infection. In addition, dysregulation of the cytokine response of the innate immunity against fungal infection impairs cytokine enhancement of cell-mediated fungicidal activity. Pulmonary host defense is also diminished by immature or deficient alveolar macrophages, cilia and mucous, and surfactant in preterm infants.

Additionally, studies in animal models showed that the hypoxic insult effect on cellular function and tissues that can be common in preterm infants around delivery or with apnea events is associated with increased gut fungal colonization and dissemination to mesenteric lymph nodes.[60]

Candida species produce proteases that may be lytic for the thin keratin layer produced by the immature stratum corneum in the first weeks after birth and phospholipases against lipid membranes that both may facilitate epithelial invasion.[54] Recently the first cytolytic peptide toxin of *C. albicans* that can directly damage epithelial membranes was identified.[78] Increased transepidermal water loss from preterm skin creates a moist environment that facilitates fungal colonization and growth. Because of the increased permeability of the preterm skin, substrates such as glucose may diffuse to the epithelial surface, facilitating *Candida* growth. *Candida* may alter its surface structure in the presence of high glucose, increasing its adherence and proliferative properties. Skin maturation occurs by 2 weeks of life in extremely preterm infants, after which new fungal skin colonization occurs less frequently.

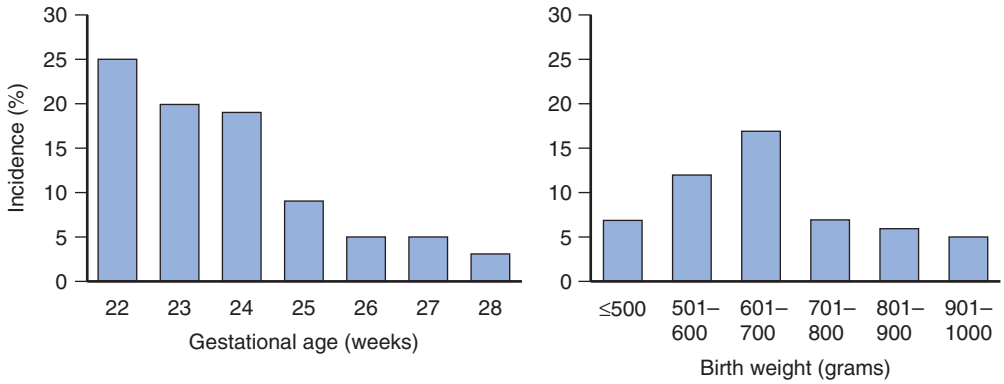
Incidence

There is variation between rates in different NICUs and the incidence reported in the literature. These differences reflect a wide range of factors and are not a mere indicator of the overall quality of care. Based on patient demographics; use of antifungal prophylaxis; surgical population; resuscitation of extremely preterm infants; and practices related to feeding, medication, and antibiotic usage of individual NICUs, considerable variation exists between rates and risk for invasive *Candida* infections. Fridkin et al. reported the rate of *Candida* BSIs ranged between 3% and more than 23% among NICUs in infants less than 1000 g, and other studies have reported similar findings[17,30,38] (Fig. 49.3). Centers that care for infants with gastroschisis, NEC, and other complex gastrointestinal diseases have an increased risk for invasive *Candida* infections.[33] Resuscitation practices may be the most significant area of practice variation affecting invasive *Candida* infection rates; NICUs that do not resuscitate infants less than 25 weeks, for example, would have a lower rate of invasive *Candida* infections in infants less than 1000 grams compared with centers caring for 23- and 24-week-gestation infants.

The literature has limitations owing to definitions of incidence. Studies including all invasive *Candida* infections in both preterm and full-term infants are limited, and most studies of incidence or risk factors focus on only *Candida* BSIs. The burden of all invasive *Candida* infections is nearly twice as high as BSI rates (Figs. 49.4 and 49.5).

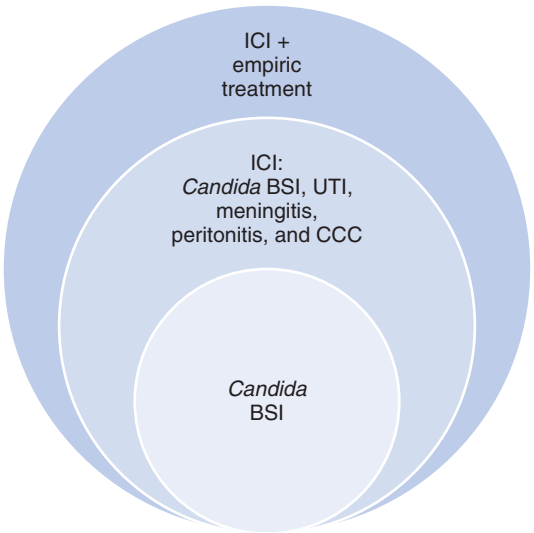
The incidence of invasive *Candida* infections in extremely low birth weight (ELBW, <1000 grams at birth) infants, not including congenital cutaneous candidiasis, is around 10% in the absence of antifungal prophylaxis.[17] The highest incidence of invasive *Candida* infections occurs in the most extremely preterm infants and is greater than 20% for infants less than 25 weeks' gestation (see Fig. 49.3). Many studies only report BSI incidence, but *Candida* UTIs account for an additional 3%-4% of invasive *Candida* infections in ELBW infants.[17,52,117] Multicenter studies have reported that *Candida* UTIs have a high associated mortality similar to *Candida* BSIs in ELBW infants, confirming their invasive nature in neonates.[17] Finally, meningitis and peritonitis contribute an additional 1%-2% to the incidence of invasive *Candida* infections in ELBW infants.[26]

Examining candidemia alone, the largest is a report from 128 US NICUs using US National Nosocomial Infections

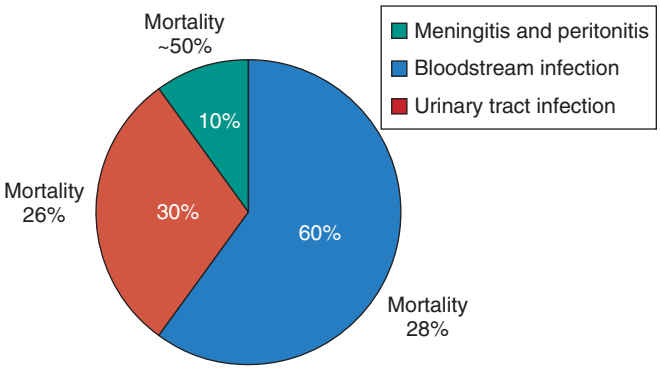


• **Fig. 49.3** Incidence of invasive *Candida* infection (ICI) by gestational age and birth weight groups in infants less than 1000 grams birth weight not receiving antifungal prophylaxis. Gestational age has a linear relationship to ICI compared to birth weight and aids in defining the highest-risk patients. Data from 137 infections in 1515 infants less than 1000 grams from 19 centers of the NICHD Neonatal Research Network.

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• **Fig. 49.4** Burden of invasive *Candida* infections (ICI). BSI, Bloodstream infection; CCC, congenital cutaneous candidiasis; UTI, urinary tract infection.



• **Fig. 49.5** Invasive *Candida* infections by site and mortality in extremely low birth weight infants. Although 60% were bloodstream infections, urinary tract infections and other sites accounted for an additional 40% and had similar or higher all-cause mortality. All-cause mortality at ≥2 sites was 57%. (Data from Benjamin DK Jr, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics.* 2010;126(4):e865-e873.)

Surveillance (NNIS) system data from 1995-2004 (N = 130,523 neonates).[38] For infants less than 1000 g, the median infection rate was 7.5%, whereas 25% of NICUs had rates 13.5% or higher. The incidence decreases significantly for infants greater than 1000 g. Candidemia rates for infants of birth weights 1001-1500 g is 1.32%, for 1501-2500 g is 0.36%, and for those greater than 2501 g is 0.29%. The incidence increases in an inverse linear pattern when examining rates by gestational age. The rate of invasive *Candida* infections increases from around 3% at 28 weeks' gestation to 24% at 23 weeks' gestation (see Fig. 49.3).

Since 2001, several epidemiologic studies have tracked the incidence of *Candida* blood and cerebrospinal infections and have correlated a decrease in these infections with an increased use of fluconazole prophylaxis, decrease in broad spectrum antibiotics, and initiation of CLASBI prevention interventions.[2,24]

Complex Gastrointestinal Disease

Complex gastrointestinal diseases can be complicated by invasive *Candida* infections. Feja et al. found that candidemia was increased in patients with gastrointestinal pathology (OR = 4.57; 95% CI = 1.62-12.92).[33] Gastrointestinal pathology was defined in their study as tracheoesophageal fistula, gastroschisis, omphalocele, Hirschsprung disease, intestinal atresia, or episodes of NEC. The incidence of candidemia has been reported between 10 and 16.5% in patients with NEC.[20,23,81] Peritoneal cultures isolating *Candida* species have been found in ~50% of focal bowel perforations and 15% of surgical NEC cases.[26,91] In a study of the pathology from 66 surgical NEC cases, 7.5% had intestinal candidiasis with *C. albicans*.[85]

Congenital Heart Disease

Congenital heart disease is an emerging patient population that may develop invasive *Candida* infections. Candidemia accounts for 9% of BSIs in patients with congenital heart disease cared for in NICUs in the first 4 months of life.[4] *Candida* BSI occurred at a rate of 6.3 per 1000 admissions and had an overall mortality rate of 21%.

Extracorporeal Membrane Oxygenation

Candida species are the second most common cause of infection in neonates on extracorporeal membrane oxygenation (ECMO), responsible for 10% of infections.[19] Compared with the first 7 days on ECMO, *Candida* infections are twofold and fourfold more common between 8 and 14 days and more than 14 days on ECMO, respectively.

Outcomes

For preterm infants, invasive *Candida* infections are associated with neurodevelopmental impairment and high mortality.

Neurodevelopmental Impairment

Invasive *Candida* infections may lead to significant neurodevelopmental impairment even in the absence of documented fungal meningitis. Neurodevelopmental impairment in most studies is the presence of one or more of the following: low mental and motor development using Bayley Scales of Infant Development II, cerebral palsy, deafness, and/or blindness. Using these criteria, the incidence of neurodevelopmental impairment is 57% with candidemia versus 29% in noninfected ELBW infants.[16] The incidence is similar for *Candida* meningitis as well as with candiduria.[16,119] In another study demonstrating similar neurodevelopment impairment of 59% of *Candida*-infected patients, earlier

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treatment within 2.1 ± 1.3 days of the blood culture was associated with normal or mildly impaired cases compared with later antifungal therapy (5.1 ± 3.0 days after blood culture was drawn), which was associated with severe disability or death ($p < .0001$).[39]

Survival

Candida-Related Mortality

Identifying *Candida*-related mortality is difficult to determine and in the literature may include attributable mortality, death within a specified number of days from onset of infection (3, 7, 14, or 30 days) or review of each death using predetermined definitions. Many studies simply report overall mortality. In infants less than 1000 g with invasive *Candida* infections, these rates range from an attributable mortality of 13% to 20% to overall mortality rates of 23% to 66% when examining overall mortality rates of patients in the placebo or control groups in the prophylaxis studies.[17,55,120] Mortality increases at lower gestational ages, and variation of mortality rates by NICU, similar to infection rates, is influenced by admission rates of these extremely preterm infants. Additionally, a standardized approach with prompt treatment with appropriate drug dosing and line removal with BSIs decreases *Candida*-related mortality rates.

Mortality is high with all types of invasive *Candida* infections in ELBW infants. In a multicenter epidemiologic study of patients less than 1000 grams, all-cause mortality rates were 28% for *Candida* BSI, 26% for *Candida* UTI, 50% for other sterile sites (meningitis and peritonitis), and if two or more culture sites were involved (BSI + UTI or UTI + meningitis), the mortality rate was 57% (see Fig. 49.5).[17] In this study, the overall mortality was 34% for infants with invasive *Candida* infections compared with 14% without infections.

There is a marked difference in overall and attributable mortality between infants less than 1000 grams and larger and more mature infants with invasive *Candida* infections. In infants less than 1000 g with infections, all-cause mortality rate was 26% compared with 13% in infants without candidiasis. For infants greater than 1000 g with invasive *Candida* infections versus those without, mortality was 2% compared with 0.4%.[120]

The *Candida* species causing the infection also affects survival. *C. albicans* is more virulent than nonalbicans species. In infants less than 1000 grams, *Candida*-associated mortality was 43% in infants with *C. albicans* candidemia compared with 19% with *C. parapsilosis* sepsis.[17]

Hospital Costs

The financial costs of invasive fungal infections are high. Two case control studies have examined the effect of these infections on cost of hospitalization and length of hospital stay.[102,120] They are limited, because they were based on ICD-9 codes, which may not have captured all invasive *Candida* infections. The mean increase in hospital costs was $39,045 for infants less than 1000 g with no difference in length of stay, and for infants ≥1000 g, there was an increase of $122,302 with an additional length of stay of 16 days.

Risk Factors

As neonatal candidiasis can be fatal among premature infants, an understanding of the risk factors that lead to infection is critical (Table 49.1). Conditions that facilitate fungal colonization and proliferation increase the risk for invasive infection and include gastrointestinal dysmotility, ileus, antibiotics, acid inhibition, steroids, and the immaturity of the patient's immune system. Several risk factors have been identified, with gestational age having the strongest effect. This correlates with the degree of underdevelopment of the immune system and immaturity of the skin and gastrointestinal and respiratory tracts in these infants.

The extremely preterm infant has the unique combination of being immune compromised, requiring prolonged intensive care (parenteral nutrition, mechanical ventilation/endotracheal tube, central venous access), being exposed to medications that promote fungal growth (H_2 blocking agents, proton pump inhibiting agents, postnatal corticosteroids,

TABLE 49.1 Patient-Related Risk Factors for Progression to Invasive *Candida* Infections in Colonized Patients in the NICU

Immunity	Medications That Facilitate Fungal Growth	Medications That Suppress Immune Defense	Diseases	Conditions
Undeveloped immune system Immunosuppression Neutropenia	Cephalosporins Carbapenems Postnatal steroids	Acid suppression (H_2 antagonists and proton pump inhibitors) Postnatal steroids	Necrotizing enterocolitis Focal bowel perforation Complicated gastrointestinal diseases (e.g., gastroschisis) Prior blood stream infection	Extreme prematurity Maternal vaginal colonization Vaginal delivery Male Central venous catheter Intubated Lack of enteral feedings Hyperglycemia

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and broad-spectrum antibiotics), and being predisposed to gastrointestinal dysmicrobism, dysmotility, and disease (NEC and focal bowel perforation).[17,33,99] Infants, both term and preterm, with complicated gastrointestinal diseases such as gastroschisis or NEC also have multiple risk factors of prolonged ileus, central venous access, parenteral nutrition, surgery, and exposure to prolonged and/or broad-spectrum antibiotics.[33]

Medications such as broad-spectrum antibiotics and third- and fourth-generation cephalosporin and carbapenem antibiotics and the lack of feeding are associated with increased risk for candidemia.[13,30,99] It is hypothesized that these medications accumulate in high concentrations in bile and alter the balanced gastrointestinal microflora, eradicating competitive gram-negative and anaerobic bacteria, thus facilitating proliferation and dissemination of fungal organisms. Other classes of drugs found to be risk factors for neonatal fungal infection are H_2 antagonists and postnatal corticosteroids.[99,105] In examining risk factors present at 3 days after birth in infants less than 1000 g, lack of enteral feedings and third-generation cephalosporin use increased risk for infecion.[16] For infants not feeding by day of life 3, 8.7% developed *Candida* BSI or meningitis, compared with 3.4% of those receiving enteral feedings by day of life 3.

A few multivariate analyses have examined risk factors, finding that central venous catheter use, previous bacterial BSIs, broad spectrum antibiotics, presence of an endotracheal tube, and gastrointestinal pathology were significantly associated with candidemia.[33,99] Gastrointestinal pathology was defined in the study as tracheoesophageal fistula, gastroschisis, omphalocele, Hirschsprung disease, intestinal atresia, or episodes of NEC.[33]

The microflora of the oral mucosa and gastrointestinal tract play an important role in fungal colonization and infection. A normal bacterial flora inhibits *Candida* growth by competing for both adhesion sites and nutrients as well as various anticandidal actions. The commensal gut microflora can also enhance immunomodulatory activities against the most common pathogens, including *Candida* spp. This may explain, in part, the protective role of enteral feeding in the absence of antibiotics. In athymic compared to euthymic adult neonatal mice exposed to *Candida* spp., probiotics (*Lactobacillus acidophilus*, *L. reuteri*, *L.casei GG*, or *Bifidobacterium animalis*) decreased the incidence of systemic candidiasis and were associated with prolonged survival.[112] Probiotic bacteria also affected antibody- and cell-mediated immune responses to *C. albicans*. This highlights the fact that the intestinal microflora may be as important as a mature immune system in preventing fungal colonization and infection.

There are some differences in risk factors for infection by species. Risk factors for *C. albicans* and *C. parapsilosis* include exposure to third-generation cephalosporins, central vascular catheters, parental nutrition and lipid emulsions, and high acuity while, additionally, vaginal delivery increases risk for *C. albicans* and H_2 antagonists for *C. parapsilosis* infection.[99] Risk for *C. glabrata* infection is increased with gastrointestinal disease, exposure to fluconazole or antibiotics, prolonged hospitalization, and prior infection with other fungi. *C. tropicalis* infections are associated with gastrointestinal mucosal injury, antibiotic suppression of bacterial flora, neutropenia, and parenteral nutrition.[54]

Colonization

Colonization is the key step in the pathway that leads from exposure to disseminated infection. Colonization may occur via vertical (maternal) or horizontal (nosocomial) transmission. Most fungal colonization occurs by 2-3 weeks of life. Fungal colonization of the skin and respiratory or gastrointestinal tract occurs in 10% of full-term infants compared with 26.7%-62.5% of very low birth weight (VLBW, <1500 grams at birth) infants in the first weeks of life.[54] Fungal colonization and subsequent infection depend on exposure, size of inoculum, host susceptibility, and properties of the pathogen (see Fig. 49.2).

Vertical transmission leading to colonization is common and has been confirmed in studies using genotyping techniques. *Candida* yeast cells adhere preferentially to intermediate layers of the vaginal tract that are increased during pregnancy, increasing maternal fungal colonization and exposure of vaginally delivered infants. Maternal risk factors include gestational diabetes and need for steroid treatment outside of antenatal steroids. The incidence of vaginal fungal colonization during pregnancy has been reported to be between 25% and 50%, with up to 90% due to *C. albicans* and the remainder predominantly *C. glabrata* and *C. tropicalis*.[54] Despite the frequent fungal colonization, chorioamnionitis caused by *Candida* occurs less frequently, with almost all vertical transmission occurring when the infant passes through the birth canal via mucocutaneous contact, swallowing, or aspiration of fungi. Treatment of maternal *Candida* vaginosis and UTIs during pregnancy may decrease the inoculum the infant is exposed to and potentially prevent vertical transmission. However, maternal exposure during pregnancy to repeated courses of antifungal products (mainly topical azoles) may alter yeast susceptibility and if maternal symptoms persist, follow-up cultures to confirm clearance and/or identify resistance should be performed.[37]

Candida colonization may also be acquired horizontally, primarily from the hands of health care workers. In a multicenter trial examining fungal colonization in six NICUs, *Candida* species were isolated on the hands of 29% of health care workers.[62] Whereas *C. albicans* was the more common fungal isolate in all NICU patients (14% versus 7%), *C. parapsilosis* was the most common species isolated from the hands of NICU staff. *C. parapsilosis* was isolated from 19% and *C. albicans* from 5% of the cultures from health care personnel ($p < .001$). *C. lusitaniae* (2%), *C. guilliermondii* (1%), *C. tropicalis* (<1%), and *C. glabrata* (<1%) were also recovered from hand cultures. Increased handling required by sicker preterm infants increases the risk of acquiring

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fungal colonization, because there is an average of 32 direct infant touches during a 12-hour shift.[27,62]

Candida species causing invasive infection rarely colonize environmental sources. Despite the tendency of fungus to grow in moist environments, studies have not isolated fungi from incubators, wash basins, water faucets, chest tubes, intravenous drug pumps, ventilators, inanimate objects, or radiant warmers.

Colonization by Site

Risk factors for *Candida* colonization and sepsis are similar, as adhesion and colonization of the skin, mucosal membranes, and/or vascular catheters occur prior to most infections.[98,99] Colonization is inversely proportional to gestational age and birth weight. Both *C. albicans* and *C. parapsilosis* colonize multiple sites in the majority of infants, whereas colonization at three or more sites occurs more frequently with *C. albicans*.[59]

Biofilm formation on catheters inhibits the host's defense mechanisms and the penetration of antifungal agents. Elements of catheter care related to sterile placement; hub and dressing care; sterile preparation of parenteral nutrition, intravenous fluids, and medications; and line changes at the bedside are critical infection control practices.[24] Infusates may also become contaminated and directly seed the bloodstream. In vitro growth curves demonstrate that *Candida* species have a selective growth advantage compared with bacteria in parenteral nutrition fluid.[61]

Candida colonization characteristics aid in identifying which colonized infants have the highest odds to progress toward invasive *Candida* infections (Table 49.2). Although skin and gastrointestinal colonization are more common and precede respiratory tract colonization, endotracheal colonization has a higher risk for infection.[52,59,95] The highest risks for progression are from colonization of indwelling devices (endotracheal tubes and central catheters) and when more than one site is colonized.[65,66] Rowen et al. demonstrated that with endotracheal fungal colonization, candidemia was 15.4 times more likely to occur compared with infants without any fungal colonization.[95] Controlling for fungal colonization at other sites, endotracheal colonization alone increased the risk for fungal sepsis nearly six-fold.

TABLE 49.2 Odds of Progression From *Candida* Colonization to Infection

	Odds Ratio	Reference
Endotracheal tube	15.4	Rowen et al., 1994
Respiratory tract colonization	35.5	Kaufman et al., 2001
Colonization in multiple sites	6.2 (3 or more) 3.0 (for each additional site)	Manzoni et al., 2006 Kaufman et al., 2001
Urine	11.6	Manzoni et al., 2006
Colonization of central venous catheter	10.8	Manzoni et al., 2006

Diagnosis

Evaluation and Diagnosis

Cultures

Cultures of blood, urine, cerebrospinal, and peritoneal fluid or other sterile body fluids remain the best method for diagnosing invasive *Candida* infections (Fig. 49.6). Focus on obtaining sufficient blood culture volumes (≥1 mL) and performing urine and cerebrospinal fluid cultures at the time of evaluation for sepsis remains critical to making prompt diagnoses. One study of neonates demonstrated that isolation of fungus in blood cultures occurred at 37 ± 14 hours, and 97% of blood cultures were positive by 72 hours.[101] Laboratory capabilities to culture fungi, identify *Candida* species, and perform susceptibility testing are critical to diagnosis and management.

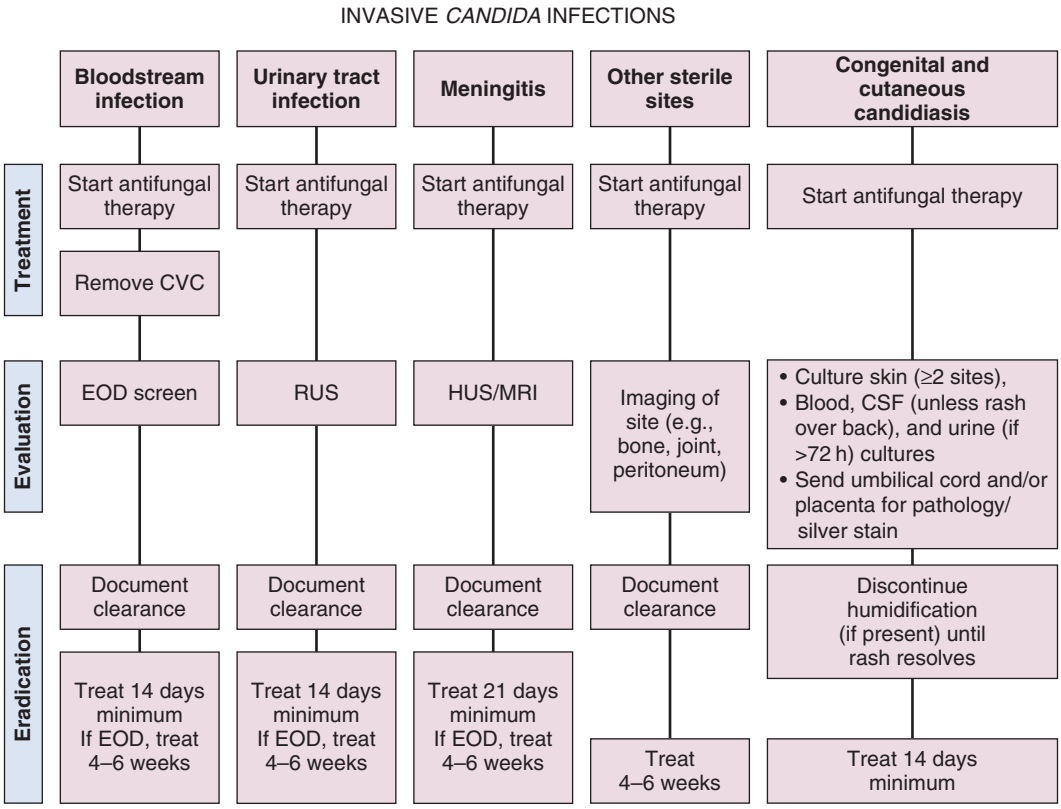
End-Organ Dissemination

Most commonly, with bloodstream infections, an initial end-organ dissemination (EOD) screen including an echocardiogram, liver and renal ultrasound, cranial ultrasound, and ophthalmologic examination should be performed. This could be performed at presentation or after 5-7 days of antifungal therapy. If there is significant bowel pathology such as NEC or focal bowel perforation, a complete abdominal ultrasound should be performed to rule out peritoneal, liver, or splenic involvement. If signs and symptoms of septic arthritis (joint swelling) or osteomyelitis (swelling or immobility) are present, a clinical diagnosis can be made, and evaluation with joint aspiration, bone scan, or magnetic resonance image (MRI) may help define the extent of involvement but should not be used to rule out joint or bone involvement in neonates. If candidemia persists, end-organ dissemination is even more likely, and surveillance after 5-7 days should also include: (1) ultrasound at location of the tip of any previous or current central catheters for infected thrombus, (2) complete abdominal ultrasound for abscesses (laparotomy is sometimes considered if high clinical suspicion), and (3) cranial ultrasound/MRI to detect brain dissemination. Abscesses that are amenable to drainage should be drained.

Molecular Techniques and (1-3)-Beta-D-Glucan (BDG)

Laboratory adjunctive tests have not been able to replace cultures but can be useful in identifying high-risk patients who would benefit from early empiric antifungal therapy (pending culture results) and to follow response to antifungal therapy. Polymerase chain reaction (PCR) and fungal cell wall polysaccharides such as (1-3)-beta-D-glucan (BDG) and mannan can be extremely helpful in high-risk patients in determining the need for early empiric antifungal therapy while cultures are pending, detecting infections

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• **Fig. 49.6** Algorithm for evaluation and treatment of invasive *Candida* infections in neonates. Initiate therapy pending susceptibilities (see Table 49.5). Initial end-organ dissemination screening should be performed at presentation or after 5-7 days of appropriate antifungal treatment. With end-organ dissemination (EOD) meningitis, persistent candidemia greater than 7 days, combination therapy with a second antifungal is recommended based on susceptibilities (fluconazole is most commonly selected due to water solubility and CSF penetration). EOD screen includes surveillance for cardiac, renal, eye, and brain involvement. If bowel disease such as necrotizing enterocolitis or focal bowel perforation is present, complete abdominal ultrasound for abscess should be performed. BSI, Bloodstream infection; CCC, congenital cutaneous candidiasis; CVC, central venous catheter; HUS, head ultrasound; ICI, invasive *Candida* infections; MRI, magnetic resonance imaging; RUS, renal ultrasound; UTI, urinary tract infection.

when there is a high suspicion for infection that is not in the bloodstream (e.g., urine, peritoneal cavity, abscesses), and determining if length of treatment needs to be extended.

Molecular techniques to identify fungi and their antifungal susceptibilities more rapidly and with higher sensitivity than with blood cultures are being studied. Examples include polymerase chain reaction (PCR) and DNA microarray technology. One challenge is that these tests are mainly compared only with blood culture results, but often detect infection or only colonization at other sites. Fungal PCR to detect the gene for 18S ribosomal RNA in VLBW infants has yielded promising results but requires additional study. Results of PCR tests showed a broader number of infections, because they not only detect patients with candidemia but are also positive in those with *Candida* peritonitis, candiduria, previous candidal infections, and endotracheal colonization.

BDG levels are helpful if there is uncertainty in deciding need for empiric antifungal therapy and in following response to therapy as levels decrease over time with antifungal therapy. Various cut-off points have been recommended for interpreting BDG levels in neonates. A recent neonatal study of BDG found higher levels in infants with ICI (364 pg/mL vs. 89 pg/mL in non-infected neonates), and levels decreased significantly with antifungal therapy to 58 pg/mL (28-81).[43] They suggested the cut-off for BDG be higher (>125 pg/mL) for neonates than adults (>80 pg/mL) due to the effect colonization and other infections (Gram-negative and coagulase-negative *Staphylococcus* [CoNS]) can have on BDG levels. The BDG levels in infants infected with CoNS were 116 pg/mL (46-128) and 118 pg/mL (52-304) in patients without bacteremia. One challenge is that BDG can be elevated to the same degree with fungal colonization as with ICI, and studies have not critically examined this effect.[29] As several studies have demonstrated there are high-risk sites that when colonized (e.g., the respiratory tract) may benefit from empiric treatment.[89,109] One study used endotracheal lavage aspirates with mannan levels ≥0.5 ng/mL to decide on preemptive treatment and significantly decreased ICI.[89] Further study of preemptive treatment at certain BDG levels may be beneficial.

BDG may also give false-positive results following transfusion of blood products in adults and neonates.[42] A study

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of 133 VLBWs found BDG to be higher in transfused (red blood cells or fresh frozen plasma) neonates (170 pg/mL, 65-317) compared to nontransfused infants (57 pg/mL, 34-108; $p < 0.001$).

Another method that may help with the decision to start early empiric therapy is direct fluorescent assay in buffy coat.[47] This test is a fluorescent stain that binds to structures containing cellulose and chitin. This diagnostic test has been successfully used for identifying hyphae and spores, and results are obtained after only 1-2 hours. Other markers of fungal disease being studied include anti-*Candida* antibodies, D-arabinitol (candidal metabolite), and fungal chitin synthase. These markers have some of the same challenges, because they may be present with bloodstream infections, nonbloodstream infections, previous infections, or with colonization alone.

Clinical Manifestations

Invasive *Candida* Infections

Skin-Invasive Infections

Congenital Cutaneous Candidiasis

Congenital cutaneous candidiasis (CCC) (Table 49.3, Fig. 49.7) presents most commonly at birth but can occur within the first week. Dermatologic findings include desquamating maculopapular, papulopustular, and/or erythematous rashes. The most common finding from a recent study included desquamation alone (scaling, peeling, flaking, or exfoliation) or with other rash presentations.[57] CCC usually occurs only as a rash but dissemination such as pneumonia or bloodstream infection may also be present. Without prompt identification and systemic treatment, dissemination to the blood, urine, or CSF can occur in infants with CCC ranging from 11% in term infants to 33% in infants 1000-2500 grams and highest at 66% in infants <1000 grams.[31] A study examining the pathology and pathogenesis of CCC demonstrate a high burden of yeast with invasion into the epidermis and dermis with inflammation and injury including granulomas, focal necrosis, and hemorrhage.[94] These data from biopsies give insight into the invasive nature of the cutaneous involvement. For these reasons, preterm and term infants should be treated promptly at the time of rash presentation with systemic antifungal therapy and for a minimum of 14 days similarly to other invasive fungal infections. Delaying systemic treatment, solitary use of topical therapy (nystatin), and treating for <10 days is associated with *Candida* dissemination to the bloodstream.[57]

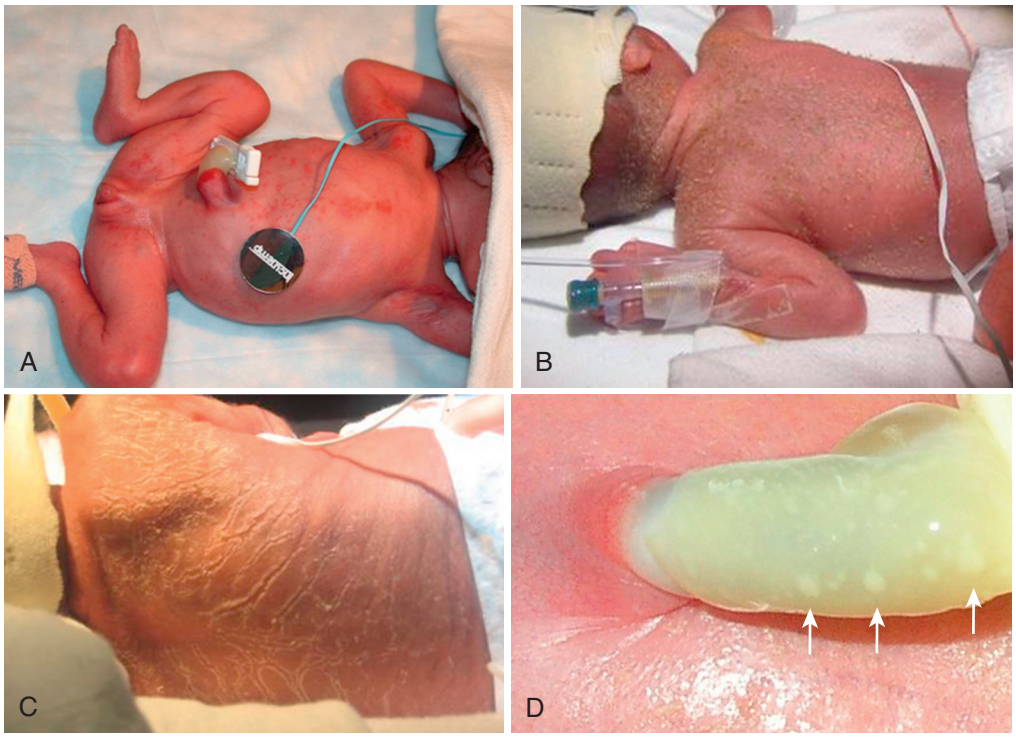
By culturing for both fungal and bacterial organisms by performing aerobic skin cultures of the rash, the source of infection can be confirmed in a timely fashion, but empiric therapy should be administered at time of rash presentation. Differential diagnosis includes staphylococcal as well as other bacterial and fungal skin infections. Pathology with fungal staining of the umbilical cord and placenta can also aid in diagnosis.

TABLE 49.3 Cutaneous Candidiasis Definition

Presentation	**Extensive Candida Skin Rash** • Covering 2 or more affected areas (see below) OR • Covering 1 affected area (see below) PLUS umbilical plaques or placental pathology (silver or H&E) would count as 1 affected area
Affected Areas	**Skin** • Chest • Abdomen • Back • Extremity • Groin or perineal area • Neck • Face or scalp **Umbilical Cord and Placenta** • White plaques on umbilical cord • Placenta with yeast invasion
Skin Rash	• Erythematous maculopapular • Papulopustular • Scaly • Dry, flaking • Desquamating • Burnlike erythematous
Timing	**Congenital Cutaneous Candidiasis** • Presenting in the 1 week after birth—most commonly present at birth to 3 days **Cutaneous Candidiasis** • Presenting after 7 days of life
Evaluation	**Congenital Cutaneous Candidiasis** • Culture skin rash (≥2 sites) (aerobic culture) • Blood, CSF (unless rash over back), and urine (if >72 h) cultures • Send umbilical cord and/or placenta for pathology/silver stain **Cutaneous Candidiasis** • Skin rash sites, blood, urine, CSF (unless rash over back)
Diagnosis	**Skin Findings and 1 or More of the Following:** • Surface culture isolating *Candida* species • Placental or cord identification (culture or silver stain) of yeast or *Candida* species for congenital cutaneous candidiasis • Positive blood, urine, CSF cultures for *Candida* species
Treatment	• 14-day course of systemic antifungal therapy

CSF, Cerebrospinal fluid.

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• **Fig. 49.7** Congenital cutaneous candidiasis. **A,** Macular papular rash. **B,** Dry, flaky rash. **C,** Dry, cracking scaly rash. **D,** White plaques of the umbilical cord. (From Kaufman DA, Coggins SA, Zanelli SA, Weitkamp JH. Congenital cutaneous candidiasis: prompt systemic treatment is associated with improved outcomes in neonates. *Clin Infect Dis*. 2017;64:1387–1395.)

Cutaneous Candidiasis

Cutaneous candidiasis, referred to in past literature as mucocutaneous infection, presents with similar skin manifestations to CCC but occurs later than CCC. In the era prior to antifungal prophylaxis, the incidence was reported to be as high as 8% in VLBW infants. Risk factors include extreme prematurity, vaginal birth, postnatal steroids, and hyperglycemia. The importance of candida-like dermatitis often goes unrecognized prior to dissemination to the blood.[17] Cutaneous candidiasis, similar to CCC, is an invasive infection of the skin; empiric therapy should be started at the time of rash presentation and needs treatment for a minimum of 14 days in preterm infants.

Bloodstream Infection

Candidemia

Clinical signs and symptoms of candidemia are similar to bacteremia[54] (Table 49.4). Most importantly, candidemia can be associated with disseminated disease (see End-Organ Dissemination). Evaluation of cardiac, liver, renal, ophthalmologic, and central nervous systems is warranted and discussed in the following.

TABLE 49.4 Presenting Signs and Symptoms of Candidemia in Very Low Birth Weight Infants

Common (>50%)	Frequent (~33%)
Thrombocytopenia <100,000/μL (84%)	Lethargy and/or hypotonia
Immature-to-Total Neutrophil Ratio ≥0.2 (77%)	Gastrointestinal symptoms (e.g., gastric aspirates, distention, bloody stools)
↑C-reactive protein (CRP)	
(1-3)-Beta-D-glucan >125 pg/dL	
↑Apnea and/or bradycardia	
↑Oxygen requirement	
↑Assisted ventilation	
Less Common (10–15%)	**Can Occur (3%)**
Hypotension	Absolute neutrophil count <1500/μL
Hyperglycemia	
Elevated white blood cell count >20,000/μL	
Metabolic acidosis	

Renal Candidiasis

Candida infection of the kidney may occur because of an ascending urinary tract infection or via hematogenous spread. Studies demonstrate that *Candida* UTIs without bloodstream involvement are more common than with a BSI, suggesting that the ascending route via the urinary tract is more common than hematogenous spread. *Candida* can attach to human uroepithelial cells. Colonization and proliferation is augmented by proteinuria, nitrogenous compounds, acidic pH, hydrophobic *Candida* cells, and the presence of Enterobacteriaceae such as *Escherichia coli*. Signal-activated phospholipases (SAPs) and phospholipases

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play a role in the renal system as well, attacking structural and immunologic defenses leading to tissue injury and invasion.[34] Risk factors for candiduria include vaginal birth, lower birth weight and gestational age, male gender, and prolonged antibiotic therapy.[119]

Urinary Tract Infection

Evaluation of late-onset sepsis should include a urine culture obtained via sterile catheterization or suprapubic bladder aspiration. Infection is defined as growth of 10,000 or more colony-forming units (CFU)/mL from a sterile catheterization or 1000 or more CFU/mL for bladder aspiration. Many neonatal studies have used lower CFUs as well. Lower CFUs, while likely not infection, indicate colonization at a high-risk site in which a follow-up urine culture should be obtained and empiric antifungal therapy started pending culture results. Preemptive treatment for 14 days would be appropriate as well for lower CFUs. Additionally, empiric antifungal therapy should be used with subsequent sepsis evaluations.

Signs and symptoms of urinary tract infections can be similar to sepsis and near-term and term infants may also present with fever.[92] Additionally, an elevated creatinine value in the absence of other pathology should prompt evaluation for a urinary tract infection. If the urine culture is positive for fungus, renal ultrasonography is needed to evaluate for abscess formation. In the absence of antifungal prophylaxis, candiduria occurs in approximately 2% of VLBW infants and up to 6% of ELBW infants.[17,52] Mortality is similar in infants with *Candida* UTI alone (26%) compared with *Candida* BSIs (28%) in ELBWs and older infants and studies showing increased neurodevelopmental impairment as well.[17,92,119] These findings emphasize the need for prompt treatment for a minimum duration of 14 days.

Renal Abscess

Renal abscess formation may occur by dissemination of candidemia or as an ascending infection with candiduria.[34] Two studies of candiduria from 1982-1993 and 2001-2003 found that renal abscesses developed in 42% (36 screened) and 12% (26 screened) of infants with candiduria (±candidemia), while a more recent study during 2004-2007 found the incidence to be 0% (0 of 23 evaluated) with candiduria alone and 22% (2 of 9) with concordant *Candida* infection.[92,119] One study found ultrasound examinations were normal in one-third of patients who later developed renal abscesses 8-39 days later, which may have been related to antifungal dosing used or delay in treatment. Between these two study periods, antifungal prophylaxis, pharmacokinetic and safety studies of appropriate initial antifungal dosing (e.g., amphotericin B deoxycholate at 1 mg/kg compared with 0.25 mg/kg in the previous era), and increased empiric antifungal therapy may be attenuating the formation of renal abscesses. These studies have small numbers but suggest that in infants with candiduria, prompt initial antifungal therapy has improved outcomes, and renal imaging should be performed at presentation and repeated in cases with persistent candiduria.

Central Nervous System Candidiasis

Meningitis and Meningoencephalitis

Central nervous system fungal infection may involve meningitis, ventriculitis, or abscess formation in infants. Studies have found around 50% of meningitis cases occur in the absence of candidemia, pointing to the importance of CSF evaluation when performing sepsis evaluations.[16,28] Culture of the CSF is important in diagnosing fungal meningitis prior to the initiation of antifungal therapy, because CSF cell counts and chemistries often are not abnormal.[28] This may be because of the number of organisms in the CSF or difficulty of interpretation caused by blood contaminating the lumbar puncture, the location of the central nervous system infection (brain tissue versus spinal fluid), and host response of the preterm or term infant.

Central Nervous System Abscess

Fungal abscesses of the central nervous system have been reported to be microscopic and not readily detectable by ultrasonography. In a study of 46 ELBW patients with fungal sepsis and/or meningoencephalitis, only 6 of 13 cases with fungal central nervous system abscesses (detected by neuroimaging or on autopsy) had abnormal results on lumbar puncture.[39] Studies have found an association between invasive fungal infection and periventricular leukomalacia in preterm infants, possibly related to release of cytokines, which may damage the periventricular white matter. These findings and animal studies demonstrate the need for central nervous system imaging (ultrasonography or MRI) in all patients with fungal sepsis regardless of the results of CSF studies in addition to meningitis cases.

Gastrointestinal Disease

Peritonitis

In patients presenting with NEC or focal bowel perforation, invasive *Candida* infections can complicate these gastrointestinal diseases. Peritonitis with bowel perforation owing to NEC or focal bowel perforation often presents with abdominal distention with or without erythema. *Candida* species are the predominant organism causing peritonitis in 15% of the perforated NEC cases and 44% of focal bowel perforation patients.[26] Radiographs help confirm perforation, but at times ultrasound or an exploratory laparotomy may be needed if clinically indicated. Persistent leukopenia, severe thrombocytopenia, hypotension, or low urine output (<1 mL/kg/hr) after 48 hours of treatment even if radiographs and ultrasound are negative should also prompt consideration for an exploratory laparotomy to evaluation for perforation(s) and/or abscesses. When exploratory laparotomy is performed or drains are placed, cultures should be obtained to determine organisms associated with bowel perforation, peritonitis, and potential abscesses.

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Necrotizing enterocolitis can be complicated by fungal infections, and associated bloodstream infections occur in up to 16.5% cases of NEC.[23,81] Screening the gastrointestinal tract for the presence of *Candida* species (by culture of rectum, stool, or oral flora) should prompt the addition of a systemic antifungal to the antimicrobials selected as part of the treatment of NEC. If *Candida* is not detected on screening, antifungal prophylaxis should be considered while treating NEC until full enteral feedings are reached.

Respiratory Disease

Pneumonia

The diagnosis of pneumonia remains difficult in ventilated preterm and term infants with chronic lung disease, as atelectasis, fluid, scar tissue, and infection have similar radiologic findings. *Candida* colonization of the respiratory tract occurs after colonization of the skin and gastrointestinal tract. Respiratory colonization is a high-risk site for invasive *Candida* infections (see Table 49.2). Pre-emptive treatment when *Candida* species are isolated in the lungs by culture, polymerase chain reaction (PCR), or *Candida* mannan antigen have been shown to prevent dissemination.[89]

End-Organ Dissemination

At the time fungal infection is clinically apparent, the organisms have often disseminated from the blood, urine, or CSF to adhere and proliferate in body fluids, tissues, and organs. *Candida* species can cause endocarditis, endophthalmitis, dermatitis, peritonitis, osteomyelitis, and septic arthritis, and fungal abscesses may form in the central nervous system, kidneys, liver, spleen, skin, bowel, and peritoneum (see Fig. 49.2). Fungal end-organ dissemination has been noted since the earliest reports of *Candida* sepsis in neonates, being as high as 66% in the 1970s, reflecting prolonged periods of fungemia, uncertainty of significance of positive fungal cultures, underdosing of antifungals, and poor diagnostics, as many infections were diagnosed late or at the time of autopsy. A meta-analysis of studies reporting fungal end-organ dissemination in neonates spanning various practices from 1979-2002 found median prevalence of cardiac vegetations or thrombi was 5%, endophthalmitis 3%, renal involvement 5%, and central nervous system abscesses 4%.[15] Dissemination may be higher in the more extremely preterm infant.[63]

Persistent candidemia of 5-7 days was associated with increased end-organ dissemination, as each day of candidemia increases the risk by 10%.[63,81] When amphotericin B was administered and central vascular catheters removed within 2 days of the first positive blood culture, outcomes such as end-organ dissemination and mortality were decreased.[81]

Endocarditis and Infected Vascular Thrombi

Candida endocarditis or infected vascular thrombi have been reported in 5.5%-15.2% of cases of fungal sepsis, with equal prevalence for *C. albicans* and *C. parapsilosis*. Fungal endocarditis may be associated with higher mortality than fungemia alone.[23,81] Central vascular catheters place neonates at increased risk. Catheters can cause local trauma to valvular, endocardial, or endothelial tissue, creating a nidus for thrombus and infection at insertion and while in situ. When antifungal therapy alone is unsuccessful in resolution of the endocarditis or thrombus, thrombolytic or anticoagulation therapy may be indicated in some cases, depending on infant's gestational age and accompanying conditions.

Endophthalmitis and Retinopathy of Prematurity

Endophthalmitis represents intraocular dissemination from the bloodstream. Exogenous infection can also occur secondary to retinopathy of prematurity (ROP) surgery or trauma. Endophthalmitis begins as a chorioretinal lesion that gradually elevates and breaks free in the vitreous, appearing as a white fluffy ball. The infection appears as solitary or multiple yellow-white elevated lesions with indistinct borders that are most often seen in the posterior retina and vitreous.[10] The clear cell-free vitreous becomes hazy, owing to an influx of inflammatory cells. This vitreous reaction is more difficult to recognize in preterm infants because of the vitreous haze that is present in the first weeks of life. The most immature infants appear to be at highest risk for fungal endophthalmitis. The incidence of retinal endophthalmitis with candidemia has decreased over the years, likely because of more rapid diagnosis, treatment, and prevention of invasive *Candida* infections. Incidence may be affected by timing of screening, as antifungal treatment effectively treats this infection. The incidence has decreased from 6% to 0.8% of preterm infants with candidemia who had indirect ophthalmoscopic examination.[35,81]

Even in the absence of visible retinal abscesses or chorioretinitis, there is some epidemiologic evidence that *Candida* sepsis may predispose preterm infants to severe ROP. Noyola and colleagues, in a case control study of VLBW infants less than 28 weeks' gestation, found that 52% (24 of 46) of infants with candidemia developed threshold ROP compared with 24% (11 of 46) of controls without candidemia (p = .008).[80] Although this has been shown only as an association between fungal sepsis and ROP, early and frequent screening for retinal pathology is recommended in preterm infants with candidemia.

Treatment

Adequate dosing of antifungal therapy has been understudied in neonates and remains a critical issue (Table 49.5). Most of the literature lacks good data on dosing and outcomes. As more data are emerging, it has been learned that underdosing and delaying optimal therapy occurred, which may have contributed to delayed clearance, treatment failures, and increased dissemination, morbidity, and mortality. In the NICU, most *Candida* species have favorable susceptibility to amphotericin B, fluconazole and the

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TABLE 49.5 Antifungals

Treatment	Dose	Interval	Comments
Invasive *Candida* Infection			
Amphotericin B deoxycholate	1.0-1.5 mg/kg	Every 24 hours	Monitor electrolytes; 4 mEq/kg/day NaCl recommended.
Amphotericin B lipid formulations	5-7 mg/kg	Every 24 hours	
Fluconazole	12 mg/kg	Every 24 hours	Monitor liver function tests during therapy.
Caspofungin	2.5-3 mg/kg	Every 24 hours	Monitor electrolytes, calcium, phosphorus, and liver function tests during therapy.
Micafungin	10 mg/kg	Every 24 hours	Monitor liver function tests during therapy.
Anidulafungin	3 mg/kg, followed by 1.5 mg/kg	Every 24 hours	Monitor liver function tests during therapy. Dosing still being studied.
Invasive *Aspergillosis*			
Voriconazole	6 mg/kg x 2, then 4 mg/kg	Every 12 hours	Monitor levels in neonates if feasible.
Micafungin	10 mg/kg	Every 24 hours	Monitor liver function tests during therapy.
Caspofungin	3 mg/kg	Every 24 hours	Monitor liver function tests during therapy.
Prevention			
Invasive *Candida* Infection			
Fluconazole	3 mg/kg	Twice a week	IV while central or peripheral access present
Nystatin	1 mL (100,000 units)	Every 6-8 hours	Oral and/or enteral (1 mL to stomach OR 0.5 mL to oral mucosa and 0.5 mL to stomach)

echinocandins. Susceptibilities should be confirmed with all clinical isolates. Antifungal resistance is associated with inferior clinical outcomes.[86] *C. parapsilosis* and *C. glabrata* isolates can have resistance to both azole and echinocandin antifungal agents.[87]

In addition to dosing, prompt central line removal with *Candida* bloodstream infection is needed for clearance and to improve outcomes. Information on central line removal is often lacking in studies of antifungal efficacy, making it difficult to assess the efficacy of the agents being studied. In the area of pharmacokinetics, premature neonates, full-term neonates, pediatric patients, and adults often have different plasma clearance rates and drug half-lives, which affect dosing decisions as well as drug efficacy, safety, and toxicity for each of those groups.

Amphotericin B Preparations

Amphotericin B deoxycholate is often chosen for treatment because of its excellent coverage for almost all *Candida* species causing infections in neonates due to its efficacy, low cost compared with other antifungals, safety, and possible better renal penetration compared with lipid amphotericin preparations. Resistance to amphotericin B is rare, making it a good initial choice pending speciation.[86] When fluconazole is being used for prophylaxis in a NICU for any patient, a different antifungal should be used for treatment of invasive *Candida* infections in that NICU to decrease antifungal pressure that may lead to azole resistance.

Amphotericin B deoxycholate binds to the sterol component (ergosterol) of the cell membrane, creating pores that lead to cell death. Amphotericin B is combined with deoxycholate to make it soluble in water. In the bloodstream, it dissociates from deoxycholate, and 90% of it binds with lipoproteins. The drug distributes and binds to most tissues, with higher accumulation in the reticuloendothelial system.

There are three lipid preparations of amphotericin B. Liposomal amphotericin B is produced by incorporation of amphotericin B into tiny unilamellar liposomes (<100 nm in diameter). Liposomal amphotericin B is small in size and has a negative charge, which prevents significant uptake with the mononuclear phagocyte system. Its properties lead to high peak plasma levels and a larger area under the concentration-time curve. Tissue concentrations are highest in the liver and spleen and lower in the kidney and lungs. In the amphotericin B lipid complex, the drug is complexed in a 1:1 ratio with two lipids in a sheetlike formation (500-5000 nm). Its size facilitates rapid uptake by the mononuclear phagocyte system and sequestration in tissues such as the lung, liver, and spleen. This increased volume of distribution is associated with lower serum levels. Amphotericin B colloidal dispersion is a complex with cholesteryl sulfate in a 1:1 ratio with amphotericin

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B in a disclike structure (100 nm). These lipid complexes remain intact and are rapidly taken up by the macrophage phagocyte system. Lipases at the sites of infection then aid in the release of the drug. Liposomes can also bind to the fungal cell membrane, with fungal phospholipases aiding in its release. It is theorized that there are fewer side adverse effects if there is more targeted release of drug at the sites of infection.

Amphotericin B deoxycholate should be started at 1 mg/kg and lipid preparations at 5 mg/kg.[84] Serum electrolytes and urine output should be monitored, as additional sodium and potassium supplementation is often required. Fluids and enteral feedings should be adjusted to maintain urine output of 2 mL/kg/hour.

Several studies in the past decade have demonstrated no adverse renal or systemic effects of daily amphotericin B deoxycholate at 1 mg/kg. Linder et al. demonstrated that dosing of 1 mg/kg of amphotericin B deoxycholate (N = 34) did not affect renal function.[64] Creatinine levels (mg/dL) remained unchanged from the start of treatment (0.8 ± 0.4), at 24 hours after beginning treatment (0.8 ± 0.4), and through the end of therapy (0.6 ± 0.2). This is an important difference compared to older children and adults for whom infusion-related reactions and nephrotoxicity are frequent concerns with amphotericin B deoxycholate. Lower "test" dosages of amphotericin B deoxycholate are not needed in neonates,[64] as renal and other adverse effects commonly seen in older patients do not occur in neonates. Moreover, lower dosages in neonates only delay the time to achieve optimal therapy and may contribute to morbidity and mortality by delaying clearance of *Candida* species. If the initial treatment is ineffective, studies have demonstrated safety with increasing the dosing of amphotericin B deoxycholate to 1.5 mg/kg per day.[50]

Lipid preparations starting with doses of 5-7 mg/kg are effective and safe with an eradication rate of 95%.[51,67] Juster-Reicher et al. reported that eradication was achieved more rapidly when liposomal amphotericin B was started at the target dose of 5-7 mg/kg per day.

A few retrospective studies have examined whether lipid formulations are better than amphotericin B deoxycholate, but none has shown superiority.[5,64] Some studies help guide treatment, whereas other studies may raise questions. Antifungal studies in which the dosing and specific antifungal were known have not found a difference in mortality between lipid preparations of amphotericin B and other antifungals, whereas one study from an administrative database found higher mortality when examining all amphotericin B lipid products grouped together compared with amphotericin B deoxycholate or fluconazole.[5,64] It is probable that the lipid preparations were underdosed in the later study. Without knowing dosing and the specific antifungal used, as well as controlling for line removal, the data are difficult to interpret, as these factors affect mortality. Additionally, the three lipid products may be associated with different outcomes and should not necessarily be combined into one group.

Other major differences that still need to be evaluated in prospective studies include risk for phlebitis when given via peripheral IV, and whether amphotericin B deoxycholate has an advantage in treating UTIs and renal abscesses. Animal studies have demonstrated significantly higher renal concentrations of deoxycholate, which has led most experts to recommend preference over lipid formulations for UTIs and renal candidiasis. None of the studies have compared optimal dosing of 1-1.5 mg/kg of amphotericin deoxycholate with 5-7 mg/kg of lipid preparations of amphotericin B. A rodent study examining 1 mg/kg of both amphotericin B deoxycholate and liposomal amphotericin B found kidney tissue concentrations of 735 ng/gram compared with 298 ng/gram, respectively. With dosing having a linear concentration for liposomal amphotericin B, a fivefold increase would be expected with dosing of 5 mg/kg, and kidney concentrations would be equivalent or even higher.[114] Studies examining efficacy for the treatment of UTIs are needed, because many treatment studies have focused only on bloodstream infections.[64]

Azole Agents

Fluconazole

Fluconazole, an azole that inhibits the enzyme C-14 lanosterol demethylase in the formation of ergosterol, has demonstrated similar efficacy to amphotericin B deoxycholate. Fluconazole is readily bioavailable and has excellent tissue penetration. As mentioned above, fluconazole should be reserved and used for prophylaxis primarily and added when combination therapy is desired. Enteral systemic fluconazole treatment is also a good selection when the *Candida* species is susceptible, infant is tolerating feedings, and IV access is not needed for other reasons.

Susceptibility information is important to know when using fluconazole. Clinical outcomes are significantly improved at lower MICs.[86] Resistance to azoles can occur from a change in the quantity or binding of the target enzyme (lanosterol), an increase in MDR (multidrug resistance) or CDR (*Candida* drug resistance) efflux pump activity pumping more drug out of the fungus, leading to reduced drug concentrations in the fungus, or a combination of these mechanisms.

Population pharmacokinetic study of fluconazole in 23- to 40-week-gestation infants demonstrated that dosing at the higher end of the recommended range (12 mg/kg/day) may yield better efficacy, although the safety of this dosing awaits further clinical study.[111] Standard dosing of fluconazole for treatment of invasive *Candida* infections had been 6 mg/kg with every 48- to 72-hour dosing until daily dosing began at 4 weeks of age. A loading dose of 25 mg/kg has been studied in a small number (n = 8) of mature neonates (median 37 weeks' gestation) to achieve higher levels (>8 mcg/mL) within 24 hours, but safety, side effects, and improved efficacy have not been evaluated.[88] For patients on ECMO, a higher dose may be needed due to the increased volume of distribution added with the ECMO

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circuit.[115] Most *Candida* species have minimum inhibitory concentration (MIC) values less than 1-2 mcg/mL, so rarely levels of more than 8 mcg/mL are needed, which explains why 6 mg/kg dosing was associated with similar efficacy as other antifungals in the past. With higher dosing, safety in relation to liver function, drug–drug interactions, and effect on fungal resistance needs to be monitored and studied further.

Voriconazole

Voriconazole, another azole, has a broader spectrum of antifungal activity, and it is the first-line treatment option in cases of Aspergillus infection. Unlike fluconazole, it is mostly protein bound and also tends to accumulate in infants with renal insufficiency; drug levels should be monitored. From a few case reports in the neonatal literature and the adult and pediatric data, suggested dosing is 6 mg/kg every 12 hours (for 24 hours), followed by 4 mg/kg every 12 hours, with monitoring of serum hepatic enzymes weekly and drug levels obtained if there is oliguria or renal impairment.[36,79]

Echinocandin Agents

The newest class of antifungals is the echinocandins, which include caspofungin, micafungin, and anidulafungin. Echinocandins are noncompetitive inhibitors of (1,3)-b-D-glucan synthase, a fungus-specific enzyme crucial to the biosynthesis of the cell wall component glucan and, therefore, compromise fungal cell wall integrity, causing fungal cell death. Echinocandins have a broad-spectrum *Candida* coverage, activity against Aspergillus, and a high degree of antifungal activity against both developing and well-organized biofilms. Acquired resistance of *Candida* species to echinocandins can occur via acquisition of point mutations of the major subunit of the target enzyme (1,3)-b-D-glucan synthase. Susceptibility patterns to common neonatal *Candida* species such as *C. parapsilosis* will be important to follow as their use increases.[87]

Micafungin is currently the only echinocandin licensed for neonatal use in Europe. It has good activity against biofilms and most nonalbican *Candida* species. Neonatal pharmacokinetic data and animal models demonstrate that 10 mg/kg is needed in neonates for effective central nervous system penetration and clearance of meningitis, and two small neonatal studies have confirmed its safety and efficacy at this dose.[6,18,48,73] A randomized controlled trial comparing micafungin and amphotericin B deoxycholate found similar efficacy and safety of 10 mg/kg of micafungin compared to 1 mg/kg of amphotericin B deoxycholate.[18]

Caspofungin and anidulafungin are other echinocandins with potent activity against *Candida* species. Caspofungin pharmacokinetic data in neonates points to dosing of 2.5-3 mg/kg or of 25-30 mg/m^2.[97] Anidulafungin dosing is still being studied with a loading dose of 3 mg/kg, followed by 1.5 mg/kg/day. A much higher dose appears to be needed from preliminary animal models of central nervous system infection, suggesting that the current regimen is suboptimal, but safety of higher dosing needs further study.[113]

Combination Therapy

The selection of a second antifungal may aid in treatment when there is central nervous system disease, disseminated infection, or persistent candidemia after 7 days of antifungal therapy. Susceptibility testing is important to help guide the selection of a second antifungal drug. Some experts would use the second agent for the entire treatment course, whereas others change back to monotherapy after resolution of abscess or persistent candidemia.

Linder et al. reported on outcomes with combination therapy.[64] A second antifungal agent, most commonly fluconazole, was administered if candidemia was associated with the presence of any abscess, a positive urine culture, or after 10 days of persistent culture-positive infection. Patients were treated for 14 days after negative culture or more until radiographic resolution of any abscess. Central catheters were removed at onset of infection. Sterilization occurred in 67% with monotherapy and increased to 96% with polytherapy.

Central Venous Catheter Removal With Bloodstream Infections

The removal of central venous catheters with *Candida* BSIs when culture results become positive improves outcomes. Several studies have demonstrated that prompt removal is associated with lower mortality rates, a shorter duration of infection, and reduced end-organ dissemination.[16,23,81] National Institute of Child Health and Human Development (NICHD) Neonatal Research Network data showed that mortality was reduced from 37% to 21% ($p < .024$) when catheters were removed promptly (<24 hours) compared with delayed removal.[16] The combined outcome of neurodevelopmental impairment and death were associated with delayed removal/replacement of catheters; although there was a trend, no difference in neurodevelopmental impairment alone was observed (45% for prompt removal versus 63% for delayed removal; $p = .08$). The strongest effect of prompt catheter removal and mortality was with *C. parapsilosis*; prompt removal was associated with a 10% mortality compared with 31% when catheter removal was delayed.

It is important to note that catheter removal, not simply catheter replacement, is recommended.[81] *Candida* can quickly form resilient biofilms on catheters and prevent the penetration of antifungal agents. A new central catheter can be placed after documentation of clearance of *Candida* infection from the blood with three or more negative cultures in the first 3 days of therapy or two or more after 4 days of antifungal treatment. Further study of catheter replacement at a different site while still candidemic is needed but may be an option when peripheral IV access cannot be maintained or central access is needed. It is better

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to immediately remove and replace rather than delay removal if IV access is a major concern.

Time to Clearance of Blood and Persistent Candidemia

Another crucial management issue regarding neonatal candidiasis is how to determine that a patient's bloodstream is clear of infection. Antifungal dosing and line removal also play a role in the length of persistent candidemia. Time to clear *Candida* from the blood is on average 2 days less with prompt catheter removal from the first positive blood culture.[16] Complete clearance of BSI has a median of 3 days after antifungal therapy is started. Of note is that in 21% of cases of infants with *Candida* BSI, intermittent negative cultures occurred between positive cultures. In this epidemiologic study, only 30% of catheters were promptly removed, which may have contributed to persistent candidemia and intermittent release of *Candida* from catheter biofilms. Similarly, it is possible all infections have undetectable microabscesses that may be slowly dissolving. Based on this high incidence of false negatives, daily blood cultures of 1 mL or more should be drawn until three negative cultures are documented in the first 3 days of treatment to confirm sterilization of the bloodstream; then a (new) central access device can be placed if needed for treatment. Another approach would be to obtain two or more negative blood cultures after 4 days from both the initiation of antifungal therapy and line removal. Treatment is recommended for 14 days after the bloodstream is clear of *Candida*.[64] Persistent candidemia >5-7 days as discussed previously should prompt re-evaluation of end-organ dissemination and addition of a second antifungal.

Adjunctive Therapies

Infection is affected by fungal load, virulence, and host factors, with neutrophil function being critical for *Candida* killing and clearance. Neutropenia should be corrected if it persists after receiving 48 hours of antifungal therapy. As an adjunctive therapy for invasive *Candida* infections, granulocyte colony-stimulating factor (in the absence of neutropenia), other colony-stimulating factors, and immunoglobulin therapy have not improved the efficacy of treatment.[54]

Treatment Summary

In summary, several measures are proving to be critical with regard to the effective treatment of neonatal candidiasis: (1) prompt and appropriate antifungal dosing, (2) central line removal if present with BSI, and (3) screening for end-organ dissemination. Amphotericin B deoxycholate starting at 1 mg/kg/day is a good choice for initial treatment based on efficacy, cost, and safety, but the liposomal amphotericin antifungals and echinocandins such as micafungin are also appropriate choices. The optimal doses of some new and older antifungal agents without adverse effects in neonates are still being studied. When faced with persistent candidemia, consultation with pediatric infectious disease specialists is beneficial. The addition of a second agent is one area of ongoing investigation. Comparison studies to determine the best choice of antifungal for each type of invasive infection, when combined with prompt central catheter removal, hopefully will serve to lower the high rate of mortality and morbidity caused by invasive *Candida* infections in these infants. Preventing these infections with antifungal prophylaxis as discussed below not only decreases these infections significantly but removes invasive *Candida* infections as a cause of neurodevelopmental impairment and *Candida*-related mortality.

Empiric Therapy

The value of empiric therapy and its ability to improve outcomes in neonatal candidiasis continue to be investigated. Antibacterial agents are routinely prescribed when clinicians are concerned about late-onset sepsis in neonates, and perhaps in certain cases antifungals also should be added pending culture results. A few retrospective studies have demonstrated inconclusive data, as they were unable to control for important variables that would affect survival, such as timing of empiric therapy, dose and antifungal used, central line removal with BSIs, and standardization of protocols for patient selection for empiric antifungal therapy.[44]

One prospective study using a specified protocol for empiric antifungal therapy in neonates less than 1500 g, as well as older critically ill infants in the NICU, demonstrated a decrease in mortality.[90] This NICU did not use antifungal prophylaxis. Empiric antifungal therapy was started in high-risk patients who had received vancomycin plus third-generation cephalosporin for 7 days and had one or more of the following infection risk factors: total parenteral nutrition, mechanical ventilation, corticosteroids, H_2 blocking agents, or signs of a *Candida* rash or thrush. The *Candida*-related mortality was 61% (11 of 18) in patients who did not receive empiric therapy compared with no deaths (0 of 6) from invasive *Candida* infections in infants receiving empiric therapy.

Although empiric or prompt standardized treatment may reduce *Candida*-related deaths, neurodevelopmental impairment may still occur in almost 60% of the survivors, particularly those with birth weights less than 1000 grams. More prospective studies controlled for timing, antifungal type, dose and duration, antifungal prophylaxis, and central line removal need to be performed.

Pre-Emptive Treatment

Pre-emptive treatment has been proposed in a few neonatal studies following early detection of *Candida* colonization by culture or mannan antigen from the endotracheal tube in infants 28 weeks' or less gestation.[89,108] Respiratory colonization, as discussed, is a high-risk site in preterm infants.[52,95] With this approach of early identification from

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tracheal aspirates followed by 14 days of antifungal treatment, invasive *Candida* infections were reduced from 75% (12 of 16 with positive growth of *Candida* in culture) to 0% (0 of 16 with *Candida* mannan detected) of these patients with *Candida* species identified in their respiratory tracts.[108] Both approaches eliminated all *Candida*-associated mortality. This may be an approach to be studied in patients with NEC in whom *Candida* is isolated in their gastrointestinal tract.

Prevention

The NICUs successful in eliminating infections view infections as preventable and focus on prevention instead of early detection and treatment. As with other infectious diseases, prevention is vital to achieving the best clinical outcomes. Mortality and morbidity are high, and for extremely low birth weight infants, 73% either do not survive or survive with neurodevelopmental delay.[16,104] To date, antifungal prophylaxis is the only intervention that has been subjected to evidence-based randomized controlled trials for the prevention of invasive *Candida* infections. Prophylactic antifungal therapy has been shown to reduce both colonization and invasive *Candida* infections in high-risk preterm infants. A summary of neonatal fluconazole and nystatin prophylaxis studies has been recently reviewed in detail.[7,25,32,55]

Prophylaxis prevents invasive *Candida* infections by decreasing *Candida* colonization of the skin, gastrointestinal and respiratory tracts, and central venous catheter, as well as colonization at multiple (two or more) sites.[8,52,72] At birth, most infants are not colonized or have low colony counts of yeast, making them ideal candidates for antifungal prophylaxis. In the absence of antifungal prophylaxis, up to 60% of ELBW infants become colonized in the first 2-3 weeks after birth.[52] In addition to the effect on fungi with therapeutic concentrations, subinhibitory concentrations of fluconazole improve white blood cell phagocytosis and killing of *C. albicans* from 50%-90%.[45]

Fluconazole

Currently, there are more than 20 studies examining fluconazole prophylaxis for the prevention of invasive *Candida* infections in more than 6400 neonates and consistently demonstrating efficacy, with an overall reduction in invasive *Candida* infections of 80% and a greater than 90% decrease in *Candida*-related mortality.[55] The overall incidence of invasive *Candida* infections in the placebo or control (untreated) groups was 9.1% compared with 1.3% in the fluconazole prophylaxis groups ($p < .0001$). Efficacy is highest in the smallest infants (<1000 g) and youngest infants (≤27 weeks) when prophylaxis is started shortly after birth and given while there is central or peripheral IV access. All of the studies have demonstrated the safety of fluconazole prophylaxis and lack of emergence of resistance over several-year periods.[52,53,68]

The first study of fluconazole prophylaxis against fungal colonization and infection in preterm infants was a prospective, randomized, double-blind clinical trial involving 100 high-risk preterm infants weighing less than 1000 g.[52] Infants were randomly assigned during the first 5 days of life to receive either 3 mg/kg fluconazole IV or placebo for up to 6 weeks. Results demonstrated that fluconazole prophylaxis significantly decreased invasive fungal infection. None of the infants in the treatment group developed infection compared with 20% of infants in the placebo group ($p = .008$). A subanalysis of infants less than 24 weeks' gestational age, approximately 10% of the cohort, revealed that fluconazole treatment was efficacious even in the most immature of infants.

From a systems viewpoint, the dosing schedule, while effective and safe in the first study, was complicated and changed every 2 weeks. Therefore, the efficacy of a twice-weekly dosing regimen was studied as a simplified schedule in a randomized controlled trial and was as effective in preventing invasive *Candida* infections compared to the more frequent dosing schedule used in the previous study.[53] This dosing has been confirmed in several other studies.[14,55] Twice-weekly dosing can occur on the same two days (e.g., Tuesday and Friday) and a specific time, reducing pharmacy preparation time as well as administration and drug costs over the prophylaxis period. Twice-weekly administration of 3 mg/kg is also associated with a decreased risk for development of azole resistance among fungi.[52,53]

Fluconazole prophylaxis has similar efficacy with either 3-mg/kg or 6-mg/kg dosing. A multicenter, randomized, placebo-controlled trial investigating two different fluconazole doses (3 mg/kg and 6 mg/kg) was compared with a placebo group in 322 infants less than 1500 g.[72] Fungal colonization was significantly decreased for both doses from 29.2% in the placebo patients to 7.7% and 9.8% in the 3- and 6-mg/kg groups, respectively. Invasive *Candida* infections were significantly decreased with either dose from 13.2% in the placebo patients to 3.8% and 2.7% in the 3- and 6-mg/kg groups, respectively. The results also showed a significant effect in infants less than 1000 g as well as infants less than 27 weeks.

Healy and colleagues also demonstrated that by targeting fluconazole prophylaxis to infants less than 1000 g, *Candida*-related mortality can be eliminated in the NICU for all patients.[46] Their study examined IV fluconazole prophylaxis over the course of 4 years and found the incidence of invasive candidiasis in infants less than 1000 g decreased from 7.3% to 2% ($p = .003$) with mortality related to *Candida* infection decreasing to 0 ($p = .01$). This demonstrated that *Candida*-related mortality for the entire NICU can be eliminated by targeting antifungal prophylaxis in high-risk patients less than 1000 grams.

Safety of Fluconazole Prophylaxis

No significant adverse effects have been reported in randomized trials in infants treated with fluconazole prophylaxis compared to control patients.[55] Preventing invasive

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Candida infections has not led to an increased incidence in other infections. The incidence of bacterial infections and necrotizing enterocolitis is similar in all studies between treatment and control groups. Focal bowel perforation was also similar in infants less than 1000 g (4% in fluconazole compared with 10% in placebo patients).[52] Fluconazole-related cholestasis has been examined closely in several studies. No cholestasis was seen between groups in the randomized controlled trials. Retrospective studies have shown by multivariate analysis that cholestasis is related to other factors such as NEC and bacterial infections and not fluconazole prophylaxis.[46] Cholestasis is also not associated with increasing doses or days of fluconazole. In addition, dosing of 3 mg/kg twice a week compared with more frequent dosing is associated with less cholestasis.[9]

Fluconazole prophylaxis has also been evaluated in two studies demonstrating long-term neurodevelopmental safety. At 18-22 months, neurodevelopmental impairment using the Bayley III cognition composite scores did not differ (31% in the fluconazole-treated patients and 27% in the placebo group).[14] At 8-10 years old, neurodevelopmental status and quality of life of survivors from the first randomized controlled trial were evaluated.[58] There were no differences in the Vineland Adaptive Behavior Scales-II scores for the fluconazole-treated compared with the placebo group. Patients scored well in the four domains: communication (95 versus 93), daily living skills (88 versus 87), socialization (97 versus 94), and motor skills (92 versus 95). There were also no differences between groups regarding emotional difficulties or behavioral problems. Regarding quality of life, self-esteem scores were 87 versus 90. Survivors were happy or satisfied with school (90% versus 100%), friendships (90% versus 88%), and life (95% versus 100%).

Azole Resistance

Studies of MIC values have demonstrated no significant resistance among fungal strains causing colonization or infection over 4- to 13-year time periods in various NICUs.[46,52,53,56,68] These studies have also shown a relationship with frequency of dosing and fungal resistance. Twice-weekly dosing of 3 mg/kg of fluconazole prophylaxis compared with more frequent dosing is associated with colonization with fungal isolates with lower MICs.[52,53]

A retrospective evaluation of all clinical and surveillance fungal isolates obtained from infants during a 10-year period (1997-2006) revealed no significant evidence of colonization or infection with *C. glabrata* or *C. krusei* strains.[68] A comparison was made between the 6-year prophylaxis period (2001-2006) and a 4-year period prior to the start of fluconazole prophylaxis. The rate of *C. glabrata* or *C. krusei* colonization remained approximately 4% and the rate of infection 1%, with no significant differences detected comparing the two study periods. It is important to note that in these studies invasive *Candida* infections were treated with amphotericin B preparations, which decrease the overall exposure to fluconazole and may intermittently eliminate resistant organisms.

Dosing may play a role in resistance. Sarvikivi et al. used fluconazole prophylaxis over a 12-year period (1991-2002) in infants less than 1000 g and less than 30 weeks and reported minimal resistance.[100] They found no *C. albicans* BSIs or resistance and no *C. glabrata* or *C. krusei* BSIs. After 10 years of targeted prophylaxis in preterm infants, the NICU expanded its protocol to the entire NICU and increased the daily dose to 6-12 mg/kg. In the 2 years following that change, it reported two infants who developed a fluconazole-resistant strain of *C. parapsilosis*. Further investigation revealed that a single strain with decreasing susceptibility was responsible for these BSIs in their NICU over the entire 12-year study period. This study and others have revealed a higher risk of emergence of resistance with higher (≥6 mg/kg) and more frequent (daily) dosing of fluconazole.[100,118] This study illustrated two important points. First, it is important to use a different antifungal agent for treatment than the one used for prophylaxis, so that if an infection by a resistant organism occurs, treatment will be with an effective antifungal agent. Second, although a rare occurrence, high doses and total NICU exposure to fluconazole may have led to the resistant strains. By using fluconazole for both prophylaxis and treatment, patients in the NICU were exposed to higher doses for longer periods of time. It is important to note that higher doses of daily fluconazole over longer time periods are associated with resistance in adult HIV patients. These mechanisms of resistance include increases in efflux pumps, point mutations, and gene overexpression.[118]

Systematic Reviews of Fluconazole Prophylaxis

Fluconazole prophylaxis has been the subject of several meta-analyses, all demonstrating safety and efficacy. One systematic review of randomized and nonrandomized trials investigated the effect of fluconazole prophylaxis on invasive *Candida* infections and analyzed all-cause mortality, *Candida*-related mortality, combined outcomes, adverse drug reactions, and fluconazole sensitivities.[25,55] Fluconazole prophylaxis decreased the incidence of invasive *Candida* infections in infants less than 1000 g by 91% (OR, 0.09; 95% CI, 0.04-0.24; $p = .0004$) and in all infants less than 1500 g by 85% (OR, 0.15; 95% CI, 0.080.26; $p < .0001$). The all-cause mortality was 11% for the fluconazole-treated group compared to 16.3% for controls (OR, 0.74; 95% CI, 0.58-0.95; $p = .017$). *Candida*-related mortality was virtually eliminated (OR, 0.04; 95% CI, 0.01-0.31, $p = .006$), and a 96% decrease in mortality was found.

In a high-level analysis using patient-level data from available randomized trials in premature infants performed in the United States, fluconazole prophylaxis reduced the odds of invasive *Candida* infections or death by 52%, invasive *Candida* infections by 80%, and *Candida* colonization by 72% during the drug exposure period compared with infants given placebo.[32] The majority of patients were <750 grams (73%), which makes this analysis particularly important as these are the infants at highest risk for infection, mortality from infection, and long-term impairment. This

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study provided the most complete analysis of the safety of fluconazole prophylaxis for premature infants and found no difference in the number of infants with abnormal ALT, AST, alkaline phosphatase, or conjugated bilirubin levels. Resistance was also evaluated, and no difference was found in azole susceptibility testing between the fluconazole and placebo groups, and no emergence of resistance.

Cochrane review of these trials has also demonstrated efficacy of this treatment.[25] They examined invasive infections during the entire hospitalization compared to while on prophylaxis used in the other analyses. The number needed to treat varies depending on incidence of invasive *Candida* infections in individual NICUs but should not be the only factor used to determine high-risk patients. Our approach to prevention should not be restricted to an arbitrary number needed to treat. Patients at risk for mortality and neurodevelopmental impairment from invasive *Candida* infections are at high risk and should be protected from the harm of invasive *Candida* infections.

Nystatin Prophylaxis

Nystatin, an enteral and/or orally administered nonabsorbable antifungal agent, was the first antifungal studied for prophylaxis in preterm infants and has been the subject of randomized, quasi-randomized, retrospective, and epidemiologic studies. These studies have added to our understanding of antifungal prophylaxis by demonstrating its efficacy and use in NICUs with low rates of infection,[49] demonstrating the greater efficacy of prophylaxis when it is started early (by 72 hours after birth) versus later when colonization is detected,[83] and a decrease in all-cause mortality.

Antifungal prophylaxis started after colonization is detected is not as effective as starting shortly after birth in preventing infections. Ozturk et al. examined the efficacy of starting antifungal prophylaxis within 72 hours after birth compared with starting later and targeting only colonized infants once colonization was detected by surveillance cultures.[83] In their multigroup study, they demonstrated that nystatin prophylaxis was more effective in reducing *Candida* BSI when started in the first 72 hours after birth compared with identifying colonization first prior to instituting prophylaxis. Three groups were studied: (1) patients who received prophylactic therapy within the first 72 hours following birth ($n = 475$), (2) infants who, if they became colonized, were started on prophylaxis at the time colonization was detected ($n = 115$), and (3) control patients who did not receive antifungal prophylaxis ($n = 358$).[83] Fungal BSI was decreased by 90% when nystatin prophylaxis was started in the first 72 hours (47 ± 12 hours, mean ± SD) compared to only 62% when started after colonization was detected (12.6 ± 2.4 days). The rates of candidemia decreased significantly with oral nystatin prophylaxis in both ELBW and VLBW infants. There was no benefit for infants greater than 1500 grams.

Two large retrospective studies of nystatin prophylaxis demonstrated the use of antifungal prophylaxis even in NICUs with low *Candida* bloodstream rates.[41,49] In the largest multicenter epidemiologic study to date ($n = 14,778$), comparing preterm infants who received nystatin prophylaxis to those who did not receive antifungal prophylaxis (1993-2006; Australia and New Zealand), oral nystatin prophylaxis was associated with a decrease in BSI or meningitis in infants less than 1500 g (1.23% to 0.54%, $p < .0001$) and in less than 1000-g infants (2.67% to 1.23%, $p < .0001$).[49] Rates did not include *Candida* UTIs, which may occur alone without BSI in 3% of infants less than 1000 grams.[17]

Another large retrospective study of nystatin (1459 infants in the United Kingdom) demonstrated similar efficacy of nystatin prophylaxis in reducing invasive *Candida* infections in preterm infants less than 33 weeks. The study compared invasive *Candida* infection rates before (1998-2000) and after starting nystatin prophylaxis (2000-2003). There was a 56% decrease in invasive *Candida* infections in infants less than 33 weeks, from 4.1% to 1.8%, and a 54% decrease in those infants less than 1500 grams (5.5% to 2.5%) with nystatin prophylaxis. This study also found that all-cause mortality was lower in the nystatin prophylaxis group (11.8%) compared to patients not receiving prophylaxis (17.8%) ($p < .0001$).[41]

While effective for most preterm patients, study data are still sparse with the use and efficacy of nystatin prophylaxis for infants at the lower extremes of prematurity and with gastrointestinal diseases. Limitations of the nystatin studies are that few infants less than 25 weeks' gestation and less than 750 grams have been studied and that nystatin can be given to the oral mucosa but may not always be able to be administered enterally or effective when there is an ileus, gastrointestinal disease, feeding intolerance, or hemodynamic instability.

Fluconazole Versus Nystatin Prophylaxis

Antifungal prophylaxis with parenteral fluconazole is effective in preventing colonization of the skin, gastrointestinal and respiratory tracts, central venous catheter, and dissemination to multisite colonization (Table 49.6), as well as eradicating colonization with *Candida albicans*, the most virulent yeast for preterm infants. Aydemir has demonstrated that nystatin (given 0.5 mL to the oral cavity and 0.5 mL via the feeding tube every 8 hours) decreases skin, gastrointestinal, and respiratory fungal colonization but not at other sites.[8]

Some questions regarding fluconazole and nystatin prophylaxis remain unanswered, but there are two studies that have compared both agents. Nystatin is less efficacious compared to fluconazole and in one nystatin study a third of the eligible patients were excluded because of hemodynamic instability or gastrointestinal concerns. Additionally, the oral suspension of nystatin has a very high osmolarity of 3002 mOsm/L, and there is a concern with the use of hyperosmolar medications and NEC.

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TABLE 49.6 Antifungal Prophylaxis

	Fluconazole	Nystatin
Effect on colonization	Decreased CVC, skin, GI, and respiratory colonization	Decreased skin, GI, and respiratory colonization
Level of evidence	Level A-1 RCT data	Level A-1 RCT data
Efficacy	80% in all studies >90% in <1000 g	50%-60%
Evidence in extremely preterm infants	Efficacy in the most extreme preterm infants (<25 weeks' gestation and <750 grams)	Fewer infants <750 g or <25 weeks' gestation have been studied
Effect on mortality	*Candida*-related mortality decreased by 96%	Lower mortality in one study
Administration with GI disease or ileus	Can be given in infants with NEC, ileus, or GI disease	Cannot be given if GI disease or ileus
Resistance	No resistance	Lack of data on resistance
Dosing	Twice-a-week dosing	Dosing 3-4 times/day
Route of administration	Given IV*	Oral/enteral administration
Osmolarity	300 mOsm/L	3002 mOsm/L
Start prophylaxis	Soon after birth	Soon after birth
End prophylaxis	No longer need IV access	Full enteral feedings
Cost	Cost effective	Cost effective Costs more in U.S. compared to fluconazole

CVC, Central venous catheter; GI, gastrointestinal; NEC, necrotizing enterocolitis; RCT, randomized controlled trial.
*Some studies gave drug orally after IV access removed to complete 4 weeks (for infants 1000-1500 grams) and 6 weeks (for infants <1000 grams) of prophylaxis.

Aydemir et al., in a three-arm RCT of antifungal prophylaxis, compared intravenous fluconazole (n = 93) and oral/enteral nystatin (n = 94) with placebo (n = 91) in infants less than 1500 grams.[8] Patients were randomized (1:1:1) to fluconazole, nystatin, or placebo. This study demonstrated that nystatin prophylaxis resulted in decreased *Candida* colonization of the gastrointestinal tract, skin, and respiratory tract. Invasive *Candida* infections were significantly lower in both the fluconazole (3.2%) and nystatin (4.3%) groups compared with the placebo (16.5%) patients ($p < .0001$). Although a previous study had raised concerns regarding nystatin use and NEC and all-cause mortality,[110] this study demonstrated no difference between both groups regarding NEC (fluconazole 8.6%, nystatin 9.6%, placebo 9.9%) or mortality (fluconazole 8.6%, nystatin 8.5%, placebo 12.1%).

Whereas oral fluconazole for prophylaxis was used in one of the above studies, almost all other fluconazole prophylaxis studies have used intravenous administration in the first weeks. Although enteral fluconazole is 90% absorbed, absorption characteristics in preterm infants are variable and not well studied. Additionally, as discussed above, oral mucosa can be treated but enteral prophylaxis may not always be able to be given if patients have an ileus, NEC, intestinal perforation, or hemodynamic instability. It is during these patient conditions that fungal colonization, proliferation, and dissemination are likely to occur. For these reasons and to prevent colonization of central venous catheters, the intravenous route is recommended for fluconazole prophylaxis in preterm infants while peripheral or central intravenous catheters are present. In some studies, fluconazole was changed to enteral administration when patients achieved full enteral feedings, and intravenous access was discontinued in order to complete 4-6 weeks of prophylaxis.

For antifungal prophylaxis, the evidence favors fluconazole for prophylaxis owing to A-I evidence, greater efficacy compared with nystatin prophylaxis (80%-90% compared with 50-60%), safety in infants less than 1000 grams, lower cost in some NICUs, twice-weekly administration, and ability to administer to all high-risk infants less than 1000 grams, even in the face of gastrointestinal disease or hemodynamic instability (see Table 49.6). Some studies state nystatin is less expensive, based on comparing one dose of each medication, but for a complete course of prophylaxis, because nystatin is dosed 3-4 times a day compared with only twice a week for fluconazole, nystatin is approximately twice as expensive in the United States. Cost of the medications may vary by country and NICU.

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Timing of Prophylaxis

Targeted antifungal prophylaxis has been aimed at the time period when high-risk patients have additional risk factors for invasive *Candida* infections and when these *Candida* infections most commonly occur in preterm infants. All studies have targeted high-risk patients whether defined by birth weight, gestational age, or a combination birth weight and gestational age with additional risk factors (e.g., central venous catheter, prolonged antibiotics, NEC). Studies can also be defined by starting prophylaxis early (in the first 3 days) compared with later (after a week).

The most effective approach is to define a high-risk group and begin antifungal prophylaxis in the first day after birth and continue until the additional risk factors (other than birth weight and gestational age) are no longer present. For example, the initial fluconazole study targeted high-risk infants less than 1000 grams who were intubated or had a central venous catheter.[52] Prophylaxis was continued until intravenous access was no longer needed, which correlates with risk factors of receiving parenteral nutrition, antibiotics, gastrointestinal diseases, or having a central venous catheter. If a 26-week infant does well, achieves full enteral feedings at 3 weeks of life, and has IV (central or peripheral) access removed, the patient would require only 6 doses of fluconazole prophylaxis. Comparatively, if a 24-week infant takes 8 weeks to reach full enteral feedings, 16 doses of fluconazole prophylaxis would be administered. If a patient needs intravenous access after a period of being on full enteral feedings (e.g., treatment of an infection or NEC), then antifungal prophylaxis would be restarted until intravenous access is no longer needed again. Targeting prophylaxis to an individual patient's risk factors limits drug exposure to the patient and fungi and reduces drug toxicity, costs, and the emergence of fungal resistance.

Starting prophylaxis later, during prolonged antibiotic courses for more than 2-3 days, or after colonization is detected, has been examined in retrospective studies. The goal of these studies was to prevent invasive *Candida* infections but further limit drug exposure, cost, and potential fungal resistance. Some of these studies targeting late risk factors were 30% less effective.[74,83] There were also no significant differences in the number of prophylaxis drug doses with this approach. From a system's standpoint, it is more effective to identify patients on admission compared to successful initiation with daily assessment. One study demonstrated only 75% compliance when identifying patients based on several risk factors that need to be evaluated daily.[74]

The other major factor is that when starting prophylaxis later, colonization has likely occurred in high-risk patients. When prophylaxis is started after 5 days, it has been found to be less effective, especially if colonization has occurred at high-risk sites. Delaying antifungal prophylaxis until after colonization has been detected is 30% less effective compared with starting within 72 hours after birth.[83] Manzoni et al. also reported decreased efficacy of antifungal prophylaxis in infants who were colonized later.[69] If colonization of high-risk sites is detected, a pre-emptive approach should be considered as discussed above.

Cost Effectiveness of Antifungal Prophylaxis

There are several ways to examine costs, including financial costs, cost of life, and cost of disability. Fluconazole prophylaxis provides a financial cost advantage across most invasive *Candida* infection rates seen in the youngest premature infants. In a cost-analysis study using cost of fluconazole prophylaxis related to costs associated with infection, it was found the average cost per patient attributed to invasive *Candida* infection in patients receiving fluconazole prophylaxis was $785 versus $2617 in those not receiving fluconazole prophylaxis.[106] Invasive infection rates would need to be <2.8% for fluconazole prophylaxis to lose its cost benefit. In Monte Carlo simulation, targeting infants <1000 g would lead to $50,304,333 in cost savings per year in the United States.

When examining financial costs, it is important to realize that treating one invasive *Candida* infection costs approximately the same as the cost of antifungal prophylaxis for a NICU for 1 year. Several studies have examined the use and cost of antifungals after the institution of fluconazole prophylaxis in their NICUs. Rueda et al. examined the expense of antifungals during the year before and after instituting fluconazole prophylaxis. In their NICU, there was a cost savings of approximately $31,500. The cost of antifungals was $56,826 in the year prior and decreased to $25,397 after fluconazole prophylaxis was started.[96] Uko and colleagues reported a significant cost benefit of $516,702 over 18 months in their institution's NICU after instituting fluconazole prophylaxis.[107] In the United States, the pharmacy cost of a single dose of fluconazole is $18; the cost of a 4- to 6-week course (at twice-weekly dosing = 8-12 doses) is $144-$216 per patient. Comparatively, nystatin prophylaxis would cost twice as much. Nystatin costs $3.75 per dose; dosing at 3 times daily for 4-6 weeks would cost $315-$473 per patient. Nystatin dosing at 4 times daily would cost $420-$630 for a 4- to 6-week course.

Conclusions

Infection Control and Prevention Group Recommendations

According to Centers for Disease Control and Prevention, there are an estimated 30,000 preterm infants less than 1000 g or less than 28 weeks' gestation born each year in the United States. Instituting antifungal prophylaxis would prevent up to 2700 infections, 400 *Candida*-related deaths, and 570 infants with neurodevelopmental impairment yearly. A unified, dedicated approach similar to group B *Streptococcus* prophylaxis in all NICUs could achieve the largest impact on the prevention of invasive *Candida* infections. For group B *Streptococcus*, the number needed to

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treat to prevent one infection is 135. Using the National Nosocomial Infections Surveillance System (NNIS) data, the overall number needed to treat would be 13 for each *Candida* BSI prevented. Including all invasive *Candida* infections, bloodstream, urine, cerebrospinal, and peritoneal infections, the number needed to treat is closer to 10 for infants less than 1000 grams. Because of the severity of these infections, with 73% of infants less than 1000 grams dying or having neurodevelopmental impairment, prevention is critical.

The Red Book 2015 released guidelines regarding antifungal prophylaxis for preterm infants less than 1000 grams.[21] This report states that: "On the basis of current data, fluconazole is the preferred agent for prophylaxis, because it has been shown to be effective and safe. Fluconazole prophylaxis is recommended for extremely low birth weight infants cared for in neonatal intensive care units with moderate (5%-10%) or high (≥10%) rates of invasive candidiasis. The recommended regimen for extremely low birth weight neonates is to initiate fluconazole treatment intravenously during the first 48 to 72 hours after birth at a dose of 3 mg/kg, and administer it twice a week for 4-6 weeks, or until intravenous access no longer is required for care. This chemoprophylaxis dosage, dosing interval, and duration has not been associated with emergence of fluconazole-resistant *Candida* species." The Infectious Disease Society of America has similar recommendations.

Preterm infants in each 100-gram birth weight group less than 1000 grams and each gestational week less than 28 weeks' gestation average invasive *Candida* infection rates ≥5% (see Fig. 49.3). For NICUs with rates less than 5% in preterm infants less than 1000 grams, invasive *Candida* infection rates should be analyzed by both gestational age and 100-gram birth weight groups in those infants to find the break point where the rate falls below 5%. Invasive *Candida* infection rates should be determined including BSIs, UTI, meningitis, and peritonitis *Candida* cases over a period of a few years. It is advisable to consider criteria for antifungal prophylaxis to include both birth weight and gestational age because gestational age has a more linear relationship compared to birth weight to both incidence and mortality. Some very extremely preterm infants may be excluded if birth weight is solely used to establish a different cutoff for prophylaxis. For example, a 24-week-gestation infant can weigh between 468 and 940 g (between the 3rd and 97th percentile).

Those NICUs transitioning to resuscitate infants at younger gestational ages need to develop an infection prevention and control guideline. Decisions to resuscitate and manage extremely preterm infants should include antifungal prophylaxis in the care of these patients, as prophylaxis would contribute to decreasing mortality and neurodevelopmental impairment in these extremely preterm infants. Improving outcomes for these infants is multifactorial and needs to include all beneficial approaches as a "bundle" to have the largest effect, and antifungal prophylaxis should be included.

For NICUs with significant rates of invasive *Candida* infections in infants 1000-1500 g, some retrospective studies have proposed either presence of a central venous catheter or treatment with antibiotics for greater than 3 days as guidelines for the use of antifungal prophylaxis. A retrospective study by Bertini and colleagues reported that 10% of infants 1000-1500 grams had central venous catheters and were treated with fluconazole prophylaxis.[55] Another study targeted fluconazole prophylaxis (3 mg/kg) to infants in whom a decision was made to give broad-spectrum antibiotics for greater than 3 days. In this study, 40% of 1000- to 1500-gram infants in their NICU were targeted for prophylaxis.[107] Data from nystatin trials and a multicenter fluconazole study indicate that approaches starting prophylaxis after the first week of life would be more effective if fungal colonization has not already occurred.[18,32]

Antifungal Prophylaxis Summary

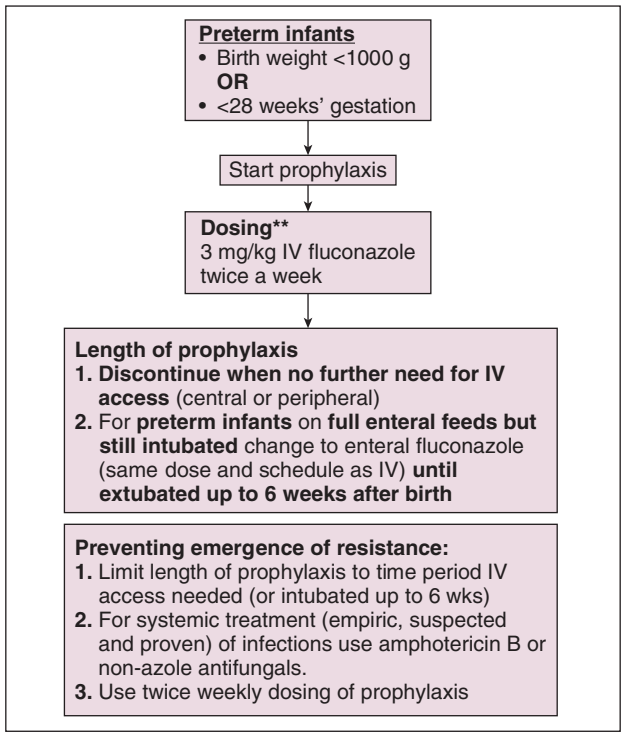
Targeted Prophylaxis in High-Risk Patients

Although individualizing NICUs to base antifungal prophylaxis is one method, a standardized approach for high-risk infants in every NICU may be more effective in preventing harm from and eliminating invasive *Candida* infections (Fig. 49.8). High-risk patients for targeted prophylaxis should be defined as NICU patients with a significant incidence, mortality, or neurodevelopmental morbidity from invasive *Candida* infections. Preterm infants less than 1000 grams at birth and less than 28 weeks' gestation have substantial *Candida*-associated mortality and neurodevelopmental impairment irrespective of specific rates. High-risk infants greater than 1000 g in the NICU who also have invasive *Candida* infections rates ≥5% or substantial *Candida*-associated mortality and morbidity include those with gastrointestinal diseases, including NEC and gastroschisis, and infants with Gram-negative infections being treated with broad spectrum antibiotics (third- or fourth-generation cephalosporins, carbapenems).

Fluconazole Prophylaxis Dosing Recommendation

Taking into consideration the issue of emerging antifungal resistance, a dosage of 3 mg/kg fluconazole administered intravenously twice weekly appears to be the safest and most effective schedule. This provides similar efficacy with less risk for resistance compared with higher and more frequent doses of treatment. Administering fluconazole prophylaxis (3 mg/kg) twice weekly on the same days, every Tuesday and Friday, at a specified time, also reduces pharmacy costs and may limit medication errors. With drug shortages this also reduces waste as one bag can be utilized for all the NICU patients needing prophylaxis that day.

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• **Fig. 49.8** Targeted antifungal prophylaxis (AP) for high-risk neonates. *Other high-risk patients in which to consider antifungal prophylaxis:* 1. **Treatment of infection requiring third- or fourth-generation cephalosporins or carbapenems**. Cover with AP while the patient is receiving these antibiotics. **2. Acquired complicated gastrointestinal disease**. Cover patients with necrotizing enterocolitis or spontaneous intestinal perforation until no longer needing IV access (central or peripheral). Consider evaluating for gastrointestinal colonization at time of presentation for fungal colonization and, if present, treat empirically with nonazole antifungal for 14 days. If laparotomy performed, send peritoneal cultures and treat peritonitis if present. **3. Congenital gastrointestinal diseases** with expected NPO period >7 days and/or need for prolonged antibiotics use >7 days. Examples would be gastroschisis or Hirschsprung disease. Start AP on day of birth and continue until no longer a need for IV access. ***Dosing notes:* First dose on day of birth, then twice a week (e.g., Tuesdays, Fridays at 10 AM); give over 60 min; if central line present, give via central line; 3 or 6 mg/kg dosing has similar efficacy in clinical trials.

This schedule continues until IV access (central or peripheral) is no longer required. Additionally, a different antifungal (amphotericin B) is selected for treatment or empiric therapy.

Infection Control Measures to Prevent Invasive *Candida* Infections

Prenatal Detection and Eradication of Maternal Vaginal Candidiasis

In pregnancies complicated by preterm labor or prolonged rupture of membranes, screening and treatment of vaginal candidiasis may be beneficial in preventing candidal colonization and subsequent infection in the newborn.[37,57] Vulvovaginal fungal colonization is more common during pregnancy, occurring in up to 30%. During pregnancy, correct diagnosis of maternal vulvovaginal candidiasis followed by appropriate treatment with confirmation of clearance if symptoms persist or in high risk cases may help prevent neonatal candidiasis.[37,76] Infection is increased in pregnancies complicated by preterm labor, premature rupture of membranes, cervical cerclage, history and/or presence of intrauterine contraceptive device, or broad spectrum antibiotic use. Germany screens many pregnant women for vaginal candidiasis during the third trimester.[77] Some data suggest that vaginal candidiasis in pregnancy may be associated with increased risk of pregnancy complications, such as premature rupture of membranes, preterm labor, and chorioamnionitis, and vaginal treatment may decrease preterm birth within the first trimester.[1]

Medication and Feeding Stewardship

Practices reducing medications that increase the risk for invasive *Candida* infections should be avoided if possible and instituted with stewardship, guidelines, tracking/auditing, and accountability. Medications that increase risk for invasive *Candida* infections as discussed previously include: broad-spectrum antibiotics (third- or fourth-generation cephalosporins or carbapenems), gastric acid inhibitors (H_2 blockers and proton pump inhibitors), and postnatal dexamethasone. Data from a multicenter study of postnatal hydrocortisone in infants less than 1000 grams did not demonstrate an increase with hydrocortisone, with both treated and placebo groups having an incidence of *Candida* BSIs of 10%.[116] One small retrospective study of VLBWs demonstrated a decrease in *Candida* BSI with a bundled reduction in antibiotics days, H_2 blocker, carbapenem, and third-generation cephalosporin use (replaced cephalosporin with gentamicin in early-onset antibiotic coverage).[22] Development of using feeding protocols (starting early and trophic and slow feed advances) and the promotion of practices that can lower NEC rates, such as breast milk feedings, may aid in decreasing the risk for invasive *Candida* infections as well.

Central Line–Associated Bloodstream Infection Bundles

Standardized protocols for insertion and management of central venous catheters, attention to sterile practices, hub and dressing care, and closed medication delivery systems may reduce CLABSIs, including *Candida*-related BSIs.[3,24] Aly et al. reported significant reduction in all CLABSIs and elimination of *Candida* infection using a "bundled approach," which included antifungal prophylaxis in addition to line placement and maintenance interventions.[3]

Candida CLABSIs among NICUs between 1999-2009 have decreased from 0.92 to 0.2 per 1000 line days.[24] These data represent preterm and term NICU patients, with infants less than 1000 grams representing nearly 70% of these infections. This fall is attributed to multiple factors, including antifungal prophylaxis, CLABSI bundles, and antibiotic stewardship.

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Lactoferrin

In a randomized controlled trial of bovine lactoferrin (bLF) in infants less than 1500 grams, subanalysis found that invasive fungal infections were also significantly less common with lactoferrin alone compared with placebo.[71] One limitation of the study was that there were only 9-18 infants ≤750 g in each group. Confirmation of the findings in extremely preterm infants is needed.

Probiotics

Microbes begin to colonize the neonate around birth, as the offspring ingests microorganisms from the normal commensal flora of the maternal genitourinary tract. Probiotics have immunomodulating and anti-infective activities that compete for adhesion to gut cells, displacing the pathogens, and influence intestinal permeability. Among all probiotics, *L. rhamnosus GG* and *L. reuterii* proved effective in preventing gut colonization by *Candida* species, a process that often precedes fungal sepsis (Table 49.7).[70,93] Whether prevention of fungal colonization in the gut might translate into prevention of fungal systemic disease in such patients still needs further study.

Invasive *Candida* Infection Summary

Invasive *Candida* infection is a major problem for preterm infants. Strategies to reduce invasive *Candida* infection and its morbidity and mortality in NICU patients are summarized in Box 49.1. Standardization of treatment regimens (appropriate dosing with prompt central catheter removal for documented candidal BSI) has been shown to decrease invasive *Candida* infection mortality, but it may not reduce the risk of neurodevelopmental impairment and other morbidities associated with these infections. Empiric antifungal treatment when invasive *Candida* infection is suspected should be given and may decrease mortality but needs further study. Infection control practices are likely to contribute to reducing the rate of invasive *Candida* infections, but this has not yet been shown in prospective studies. Both nystatin and fluconazole prophylaxis have level A-I evidence demonstrating efficacy in the prevention of invasive *Candida* infection. Prevention with fluconazole prophylaxis in extremely preterm infants is favorable and recommended by pediatric infection control groups. Antifungal prophylaxis with infection control practices administered to infants with birth weights less than 1000 g and/or less than 28 weeks' gestational age can reduce and potentially eliminate invasive *Candida* infections, their contribution to neurodevelopmental impairment, and *Candida*-related mortality.

Aspergillus, Mucormycosis, Malassezia, and Trichosporin Infections in the Neonatal Intensive Care Unit

Aspergillus and Mucormycosis (formerly Zygomycosis) are filamentous fungi, and while they rarely cause infections in neonates, these infections can be severe in preterm infants. *Aspergillus* may present as cutaneous, pulmonary, or disseminated disease. The major host defense against aspergillosis is macrophage chemotaxis and phagocytosis, both of which are diminished in the preterm infant. Infections are generally the result of environmental contamination such as dust from hospital construction or faulty cleaning practices that can carry spores that may settle in wounds or be inhaled. Regular cleaning of the ventilation systems in the NICU to avoid buildup of dust contaminated with spores, as well as appropriate containment of dust during hospital renovation and construction, can help to prevent aspergillosis infection in the high-risk neonate. Voriconazole as a first-line agent would be indicated in neonatal aspergillosis cases (see Table 49.5). The cutaneous manifestations in a preterm infant are shown in Fig. 49.9.

Mucormycosis initially present as a black eschar at the site of local trauma, intravenous catheter, or infiltrate, progressing to necrotizing soft tissue infections. *Rhizopus* and *Mucor* species most commonly cause infections in neonates and importantly are resistant to azoles. These fungi may contaminate adhesive tape, monitor leads, and wooden tongue blades used for splints in the NICU. Early diagnosis, amphotericin B, and surgical debridement are needed to prevent ulceration, necrosis, and rapid fatal dissemination. A high degree of suspicion is needed, and a tissue biopsy must be obtained to diagnose these right angle–branched,

TABLE 49.7 Probiotics and Colonization by *Candida* Species in Preterm Infants

	Probiotic Used	Primary Outcome	Incidence		*P*-Value
			Probiotic Group	Placebo Group	
Manzoni et al., 2006[79]	Lactobacillus rhamnosus GG	*Candida* gut colonization in <1500-g neonates	23.1%	48.8%	.01
Romeo et al., 2011[9]	Lactobacillus reuterii	*Candida* gut colonization in <2500-g neonates	7.1%	22.9%	.01
Romeo et al., 2011[9]	Lactobacillus rhamnosus GG	*Candida* gut colonization in <2500-g neonates	10.7%	22.9%	.01

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• BOX 49.1 Strategies to Reduce Invasive *Candida* Infections and Their Morbidity and Mortality in NICU Patients

- Use antifungal prophylaxis with IV fluconazole starting after birth and while requiring IV access (central or peripheral) for infants with birth weight less than 1000 grams and/or less than 28 weeks' gestational age (A-I).
  - There is also A-I evidence for antifungal prophylaxis with nystatin. Data are limited for infants less than 750 g and less than 26 weeks' gestation. Because fluconazole prophylaxis has greater efficacy compared to nystatin, efficacy in the most immature patients, and can be given to infants not feeding, current evidence would favor fluconazole prophylaxis in preterm infants less than 1000 grams.
- Start treatment of documented infections with appropriate antifungal dosing and prompt catheter removal for candidal BSI (A-II).
  - Promptly treat congenital cutaneous candidiasis with presentation of rash.
  - Consider starting empiric antifungal therapy if ICI is suspected.
- Decrease broad-spectrum antibiotic use (B-II).
  - Restrict third- and fourth-generation cephalosporins and carbapenems to treatment of proven Gram-negative infections.
  - Use antifungal prophylaxis while patients are receiving these agents.
- Decrease H_2 blocker and proton-pump inhibitor use (B-II).
  - Use only for proven gastritis, and restrict use to 3 days or until symptoms resolve.
- Decrease postnatal dexamethasone use (B-II).
  - Use only for severe lung disease.
- Institute central line–associated bloodstream infection reduction bundles (B-II).
- Monitor rates of ICI, including BSI, UTI, meningitis, and peritonitis infections, and provide feedback to staff (B-II).
- Probiotic supplementation (Lactobacillus rhamnosus GG or Lactobacillus reuterii) to decrease enteric fungal colonization (C-I).
- Bovine lactoferrin supplementation to decrease candidal bloodstream infections and to decrease the progression from enteric fungal colonization to systemic infection (B-I).

Level of Evidence: US Public Health Service Grading System for ranking recommendations in clinical guidelines: Strength of recommendation and levels of evidence. A, Good evidence; B, moderate evidence; C, poor evidence; I, at least one randomized clinical trial; II, at least one well-designed but nonrandomized trial; III, expert opinions based on experience or limited clinical reports.

BSI, Bloodstream infection; ICI, invasive *Candida* infection; IV, intravenous; UTI, urinary tract infection.

nonseptated hyphae. Mortality from the infection is reported as 61% (11 of 18) of infants.[82]

Malassezia furfur and *M. pachydermatis* are not highly virulent but have been associated with nosocomial infections in preterm infants. *M. furfur* is a lipid-dependent fungus that can colonize the skin, gastrointestinal tract, and intralipid solutions of NICU patients and can be spread from patient to patient via hands of health care workers or family members. Bloodstream infection with *M. furfur* is more common in infants of lower birth weight, gestational age, and longer NICU stays. The infection may clear simply with discontinuation of intralipid infusion and/or removal of central vascular catheters. Amphotericin B should be used for treatment until a clinical response and negative blood culture are documented. However, in preterm infants with significant symptomatology and documented *M. furfur* fungemia, treatment with systemic antifungal therapy is warranted. *M. pachydermatis* invasive infections have also been described in neonates, including an outbreak that may point to infection control strategies. *M. pachydermatis* infections should prompt infection control measures and potential screening as the source may be other infants, health care workers, and dogs. *Trichosporin* infections can occur in outbreaks and have high mortality in ELBW infants. They are susceptible to amphotericin. For both *Malassezia* and *Trichosporin* outbreaks, education on hand washing and treatment of infections is successful in eradicating this organism from the NICU.

Other Fungal Infections

Coccidioidomycosis

Incidence

Coccidioidomycosis is endemic in the San Joaquin Valley in California and in other areas of the southwestern United States, Mexico, Argentina, Venezuela, and Paraguay. Most susceptible individuals living in endemic areas acquire asymptomatic infection within 5 years. Disease can occur in any geographic location after reactivation of infection. Despite the high incidence of infection in endemic areas, perinatal coccidioidomycosis rarely occurs.

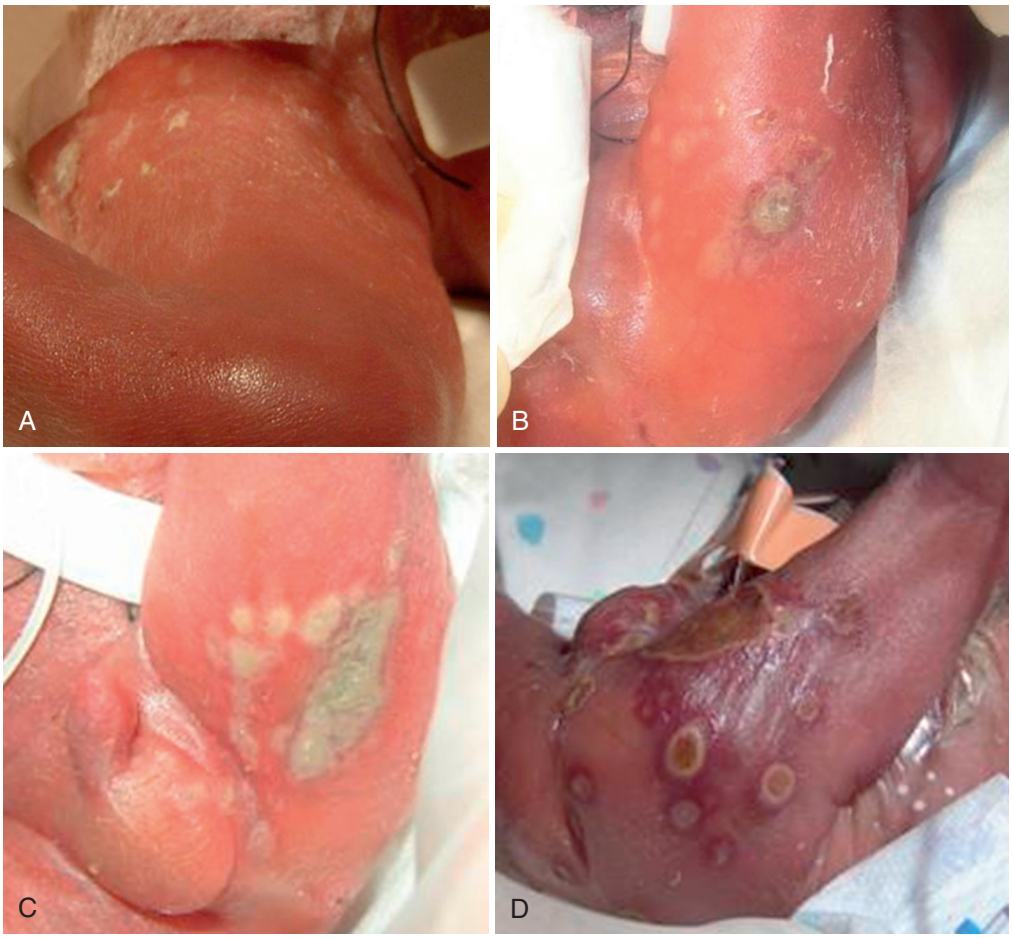
Microbiology

Coccidioides immitis, the causative agent of coccidioidomycosis, is a biphasic fungus. Highly contagious mycelia grow on culture media and soil, whereas the less infectious spherules grow in tissues. The spherule contains hundreds of endospores that, when released, can become spherules.

Pathogenesis

The infectious arthrospores can become airborne or can be transferred from inanimate objects contaminated with dust. Infection is acquired from inhalation of arthrospores and less commonly from direct inoculation into cutaneous lacerations or abrasions. The incubation period is 7-21 days. Infection occurring in infants younger than 1 week of age has been described, suggesting vertical transmission. Despite

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• **Fig. 49.9** Cutaneous aspergillosis. **A,** Cutaneous findings initially presented as small dry, flaky white lesions on day of life 3. **B,** Three days later, lesions had evolved into flat yellow-white target and nontarget lesions with dermal penetration. **C,** Five days into infection there was progression to deeper invasion with yellow-white ulceration **D,** Eight days after presentation there were multiple target lesions and surrounding erythema.

several reports of disseminated infection during pregnancy, placental and perinatal infections are rare.

After arthrospore inhalation, mature spherules develop within several days. Granuloma formation with tracheobronchial lymph node involvement can follow. In extensive disease polymorphonuclear leukocytes infiltrate the lung, similar to the process seen with bacterial pneumonia. Hematogenous dissemination occurs frequently in infants.

Clinical Manifestations

In contrast to older children and adults whose primary infection is often asymptomatic, pneumonia is usually present in most infants with recognized infection. Chest radiographs can show focal consolidation or diffuse nodular infiltrates, hilar adenopathy, and pleural effusions. Fever, anorexia, and respiratory distress often accompany neonatal coccidioidomycosis. If the disease becomes disseminated, lesions can develop in the skin, bone, lymph nodes, liver, spleen, and meninges.

Diagnosis

Clinical and radiographic features of coccidioidomycosis can resemble features seen with histoplasmosis, pulmonary tuberculosis, and viral pneumonitis. If meningitis develops, an elevated protein concentration and hypoglycorrhachia can be seen on CSF examination. Early in the course, a neutrophilic pleocytosis can be seen, but this quickly progresses to a lymphocytic predominance.

The diagnosis is best established using serologic and histologic methods. An IgM response is usually detectable 1-3 weeks after the onset of symptoms. A high IgG titer indicates severe disease, and decreasing titers suggest improvement. Transplacental passage of complement-fixing antibody occurs, so an increase in the infant's titer must be shown to document neonatal infection. Antibodies are detectable in CSF in patients with meningitis. Spherules occasionally can be observed on silver-stained tissue samples. Culture of the organism is feasible but is potentially hazardous to laboratory personnel. Coccidioidin skin tests are not helpful in

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the neonatal period, and these skin tests are not currently available in the United States.

Treatment

In older children and adults, primary infection is often self-limited and requires no therapy. The frequency of disseminated disease in young infants and the high case-fatality rate warrant treatment of all neonatal infections, however. Amphotericin B is the drug of choice for the initial treatment of infection. The duration of therapy is prolonged, and anecdotal therapy suggests that fluconazole administered orally can be given to complete the course of treatment.

Cryptococcosis

Incidence

Cryptococcosis occurs worldwide. Many infections are likely to be asymptomatic, and most symptomatic infections occur in individuals older than 30 years. Infection can occur in otherwise healthy individuals but is more common in immunocompromised hosts, including patients with acquired immunodeficiency syndrome (AIDS), malignancies, and diabetes mellitus. Cryptococcal infection in the newborn period is an extremely rare disease.

Microbiology

Cryptococcus neoformans is an encapsulated yeast that reproduces by budding. Its natural habitat is soil, and it has been commonly found in soil contaminated with pigeon excreta.

Pathogenesis and Pathology

Cryptococcosis is acquired from inhalation of the yeast with resulting primary pulmonary infection. Ingestion or cutaneous inoculation is possible; a central venous catheter may have been the source of cryptococcemia in one neonate. Case reports of disease with onset shortly after birth suggest that in utero or intrapartum transmission is possible. Otherwise, there has been no evidence of human-to-human transmission. Pulmonary infection can remain localized or can disseminate hematogenously to any organ, with the meninges most commonly affected. In adults, the infection is usually subacute or chronic, with large, solitary pulmonary nodules frequently observed. Diffuse pulmonary infiltration or miliary disease with dissemination is more common in infants.

Pathologic findings vary from minor inflammatory responses to abscess formation. Noncaseating granulomas, hepatitis, and cirrhosis of the liver are common findings. Meningitis frequently leads to obstructive hydrocephalus. Granulomas of the brain have been reported.

Clinical Manifestations

Infantile cryptococcosis is a multisystemic infection. The signs and symptoms are similar to congenital infection caused by *T. pallidum*, *Toxoplasma*, cytomegalovirus, and rubella, and include failure to thrive, jaundice, hepatosplenomegaly, chorioretinitis, rash, and intracranial calcifications. Other symptoms suggestive of a central nervous system process, such as lethargy, irritability, vomiting, and seizures, can be observed. Respiratory symptoms are minimal, but occasionally interstitial pneumonitis can be present. Infants with meningeal involvement can show a pleocytosis ranging from 40-1000 leukocytes/mm^3 with a lymphocytic predominance, elevated protein, and slightly decreased glucose concentrations on CSF examination.

Diagnosis

Definitive diagnosis of cryptococcosis requires isolation of the organism from body fluids or tissue specimens. Fungal cultures of CSF, blood, sputum or tracheal aspirates, material from abscess cavities, and bone marrow can yield growth of *Cryptococcus*. The presence of encapsulated, budding yeast on India ink–stained CSF or respiratory tract samples is usually indicative of cryptococcal disease. Serologic investigation includes antibody and antigen detection tests, but antigen detection is the preferred technique. Latex agglutination and enzyme immunoassay for detection of cryptococcal antigen in serum or CSF are excellent rapid diagnostic tests.

Treatment

In healthy adults, pulmonary cryptococcosis is usually self-limited and requires no therapy. Pulmonary disease frequently disseminates in immunocompromised patients if left untreated, however. Before the introduction of amphotericin B, cryptococcosis was almost uniformly fatal. The case-fatality rate has significantly decreased with amphotericin B therapy, but at least one-third of adults fail to respond to therapy and another one-fourth have relapse after discontinuation of therapy. The combination of amphotericin B and flucytosine or fluconazole is indicated as initial therapy for patients with meningeal and other serious manifestations of cryptococcal infection. Because only six cases have been reported in neonates, only anecdotal data exist for treatment. One infant with VLBW survived cryptococcemia after receiving a 6-week course of therapy with amphotericin B.

Histoplasmosis

Incidence

Histoplasmosis is one of the most common pulmonary fungal infections in immunocompetent humans. It occurs worldwide in temperate climates and is endemic in the Ohio and Mississippi river valleys of the United States. In older children and adults, most infections are asymptomatic; however, in young infants, infections are often apparent and frequently disseminate. Despite the high incidence of infection in endemic areas, neonatal histoplasmosis is rare.

Microbiology

Histoplasma capsulatum is the causative agent. It is not encapsulated, but artifacts resembling a capsule can be seen

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with some staining techniques. It is a thermally dimorphic fungus, growing as mycelia (mold) with microconidia and macroconidia (spores) in soil and converting to yeast form at human body temperatures. Soil is its natural habitat, and it thrives in moist soil contaminated with avian or bat excreta.

Pathogenesis

Inhalation of conidia is the most common mode of transmission. Other routes, such as ingestion or cutaneous inoculation, occur rarely. Human-to-human transmission, if possible, has not been well described. Several days after inhalation, the spores germinate in the alveoli, releasing yeast forms. An inflammatory response, initially neutrophilic, followed by an influx of lymphocytes and macrophages, ensues. The yeasts are phagocytosed, but not killed, and begin to proliferate within macrophages and can spread hematogenously to the liver, spleen, and other organs or to regional lymph nodes through the lymphatics. The inflammatory response can result in discrete granulomas resembling sarcoid, or caseating, lesions that frequently calcify during resolution.

Clinical Manifestations

The clinical spectrum of histoplasmosis in children includes asymptomatic infection, pulmonary disease that can be complicated by mediastinal lymphadenopathy and subsequent tracheobronchial obstruction, primary cutaneous infection, and disseminated infection. Asymptomatic infection occurs mostly in older children and adults, whereas acute disseminated infection with pulmonary disease is most common in young infants. The most frequently observed signs and symptoms in disseminated disease are prolonged fever, hepatosplenomegaly, anemia, and thrombocytopenia. Because the infection can disseminate to the lymph nodes, adrenal glands, gastrointestinal tract, bone marrow, central nervous system, kidneys, heart, and bones, many other signs and symptoms can be present.

Diagnosis

Fungal cultures from patients with acute, self-limited pulmonary infection rarely yield the organism but frequently are positive from patients with disseminated disease. *Histoplasma* can be isolated from lower respiratory tract specimens, blood, bone marrow, hepatic and splenic biopsy specimens, and CSF, but growth may not be detected for 8-12 weeks. Lysis-centrifugation of blood samples submitted for fungal culture has increased the sensitivity and reduced the interval until cultures become positive. Demonstration of intracellular yeast forms supports the diagnosis when the clinical picture is compatible. Detection of *H. capsulatum* polysaccharide antigen in serum, urine, or bronchoalveolar lavage specimens is a rapid and specific diagnostic method. Complement fixation titers greater than 1:32 or a fourfold increase in yeast-phase or mycelial-phase titers suggest acute infection.

Chest radiographs in pulmonary histoplasmosis often are negative or reveal nodular infiltrates with mediastinal and hilar adenopathy. In disseminated disease, chest radiographs most frequently are negative, but hilar adenopathy, bronchopneumonia, or miliary nodules can be present. Pulmonary and splenic calcifications can be seen on subsequent radiographs after recovery from infection. Findings common in adult disease, including pleural effusions or cavitary formation associated with chronic pulmonary infection, are not seen in infantile disease.

Treatment

Primary pulmonary histoplasmosis in a healthy child usually does not require treatment. Therapy is recommended for disease in infancy, because the risk of dissemination is higher, and untreated disseminated disease is almost uniformly fatal. Amphotericin B is effective for initial treatment of disseminated disease and other serious infections. In patients older than neonates, itraconazole is effective, either as initial treatment or after clinical improvement has been observed.

Other Fungi

Blastomyces dermatitidis is a dimorphic fungus endemic to the midwestern, southeastern, and Appalachian areas of the United States. Blastomycosis occurs more commonly in adults than in children and is rare in neonates. Infections can be asymptomatic, limited to the respiratory tract, or disseminated. Cutaneous and skeletal lesions are the most common extrapulmonary sites of infection. Cutaneous and genital diseases have been documented during pregnancy and, if inadequately treated, can result in neonatal blastomycosis. The diagnosis should be considered in infants with reticulonodular pneumonia born to mothers with chronic skin infections who live in endemic areas.

Dermatophyte infections, caused by *Microsporum*, *Trichophyton*, or *Epidermophyton*, are acquired postnatally from contact with contaminated soil, infected animals, or household members. Because lesions associated with dermatophytosis can resemble the lesions seen with psoriasis, seborrhea, or impetigo, they can easily be misdiagnosed.

Protozoal Infections

Malaria

Incidence

Worldwide, there are 300-500 million cases of malaria annually and greater than 2 million deaths, most of which occur in children. Malaria remains an important cause of abortion, stillbirth, and neonatal death in many parts of the world. Congenital malaria cases in the United States occur almost exclusively in infants of foreign-born women who were exposed within the year before the infant's delivery.

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Microbiology

Malaria is caused by an obligate, intracellular protozoan of the genus *Plasmodium*. Congenital malaria has been recorded with each species, including *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium falciparum.* Most congenital cases have been caused by *P. vivax* and *P. falciparum*.

Pathology and Pathogenesis

Malaria is transmitted by the bite of infected female *Anopheles* mosquitoes or from transfusions (maternal–fetal, blood products, or contaminated needles) of infected blood. Anemia is the result of hemolysis. Parasites can be found in other organs of the body, including the intestinal tract, liver, spleen, lung, and brain. Because *P. falciparum* and *P. malariae* have no persistent exoerythrocytic phase, relapses do not occur. *P. vivax* and *P. ovale* are associated with relapses from dormant exoerythrocytic organisms. Transfusion-related malaria and congenital malaria have no exoerythrocytic phase.

The placenta is involved in most women who acquire malaria during pregnancy. It is unclear whether transmission to the infant is transplacental or from direct contact with maternal blood during labor or parturition. Most pregnancies resulting in congenital malaria are associated with a malaria attack during pregnancy; however, congenital infection has been described after uncomplicated asymptomatic pregnancies.

Host factors that can decrease the risk of malarial infections include abnormal hemoglobin and malaria-specific antibodies. Erythrocytes with fetal hemoglobin or hemoglobin S are less likely to become infected than erythrocytes with hemoglobin A. Women living in endemic areas are continuously exposed to malaria and develop antimalarial antibodies. Maternal antibody is believed to exhibit a protective effect for the fetus. One survey found that 7% of infants born to women evaluated at seven African sites had congenital malaria.

Clinical Manifestations

Most infants with congenital malaria have onset of symptoms by the eighth week of life, with an average age at onset of 10-28 days. Occasionally, onset has been documented at several months of age. The most common clinical findings are fever, anemia, and splenomegaly. Approximately one-third of infants have jaundice and direct or indirect hyperbilirubinemia. Hepatomegaly can be present. Nonspecific symptoms include irritability, failure to thrive, loose stools, and reluctance to feed. Congenital malaria often is complicated by bacterial illnesses in developing countries. In rare cases, malaria can be complicated by hypoglycemia, central nervous system infection, splenic rupture, renal failure, and, in *P. falciparum* infections, blackwater fever (severe hemolysis, hemoglobinuria, and renal failure). Untreated *P. falciparum* infection is associated with a high case-fatality rate.

Diagnosis

Although a maternal history of a febrile illness during pregnancy can be elicited in most cases, congenital disease after an asymptomatic pregnancy in women has been reported. The diagnosis of congenital malaria should be considered in any infant presenting with fever, anemia, and hepatosplenomegaly born to a mother who at any time resided in an endemic area. The diagnosis depends on demonstration of parasites in the bloodstream. Thin and thick smears should be prepared and examined on several different occasions to maximize the possibility of parasite detection.

Treatment

Several types of antimalarial drugs act at different stages of the *Plasmodium* life cycle. Tissue schizonticides such as primaquine are effective against exoerythrocytic forms, whereas blood schizonticides such as chloroquine, quinine, and quinidine act only on parasites in the erythrocytic phase. Because transfusion-acquired disease, including congenital infection, does not have an exoerythrocytic phase, primaquine is not required. Chloroquine, given in an initial dose of 10 mg of chloroquine base per kilogram of body weight administered orally, followed by doses of 5 mg base/kg at 6, 24, and 48 hours after the initial dose, is frequently used. For treatment of congenital disease caused by chloroquine-resistant *P. falciparum,* quinidine gluconate or the combination of quinine administered orally and clindamycin has been suggested. Mefloquine is effective against most *P. falciparum* strains but is not approved for use in infants. Experience with newer treatment options in young infants, such as artemisinin derivatives, is limited. Severe congenital malaria can require intensive care, and exchange transfusion can be necessary for high-grade parasitemia. Current recommendations regarding treatment of congenital malaria can be obtained from the malaria branch of the Centers for Disease Control and Prevention in Atlanta, Georgia.

Pneumocystis

Incidence

Pneumocystis pneumonia occurs in patients with congenital immune defects or hematologic malignancies or patients receiving immunosuppressive medications for organ transplantation. *Pneumocystis* is an unusual cause of pneumonia in the first year of life, but it can be observed as epidemic disease, first recognized during World War II and presumed to be related to malnutrition, and as sporadic disease associated with congenital immunodeficiency or AIDS. Some surveys suggest that rare cases can develop in healthy infants.

Microbiology

Because of difficulties in laboratory cultivation, the taxonomy of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) is inconclusive; it has features in common with protozoan parasites and fungi. *Pneumocystis* is a unicellular organism

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that can be found in three forms: a thick-walled cyst, a thin-walled trophozoite, and an intracystic sporozoite. Each cyst can contain up to eight sporozoites. Organisms can be detected on tissue samples stained with Grocott-Gomori methenamine silver nitrate.

Pathology and Pathogenesis

Serologic studies suggest that asymptomatic infection with *Pneumocystis* is widespread and commonly occurs in the first years of life. The organisms are believed to persist in a latent stage until impairment in host defense mechanisms permits their reactivation. Disease associated with *Pneumocystis* usually is limited to the lungs. There is now evidence that person-to-person transmission is the most likely mode of acquiring new infections. Airborne transmission from mother to infant has been proposed.

Postmortem examination reveals a diffuse process, with the posterior and dependent regions of the lung most significantly affected. Microscopic examination reveals an eosinophilic, foamy, honeycombed intra-alveolar exudate composed of cysts. In epidemic infantile disease, a plasma cellular infiltrate is observed (hence the name interstitial plasma cell pneumonia), whereas in sporadic disease associated with immunodeficiency or immunosuppression, there is hyperplasia of the cells lining the alveoli and minimal cellular infiltrate with a paucity of lymphocytes.

Clinical Manifestations

The clinical characteristics of sporadic *Pneumocystis* pneumonia are different from the characteristics observed in epidemic infantile disease. In sporadic cases associated with congenital or acquired immunodeficiency, there is an abrupt onset of high fever, coryza, nonproductive cough, and tachypnea. There is a quick progression to dyspnea and cyanosis. Radiographic findings most commonly reveal diffuse infiltrative disease. Concurrent infections, most commonly with cytomegalovirus, occur in more than 50% of immunocompromised infants with *Pneumocystis* pneumonia.

In epidemic infantile *Pneumocystis* pneumonia, a rare disease in developed countries, the onset is slow and insidious, with nonspecific symptoms such as anorexia, diarrhea, and restlessness. Cough is not prominent initially, and fever is absent. In the subsequent weeks, infants become tachypneic, cyanotic, and dyspneic, with sternal retractions and flaring of the nasal alae. Auscultatory findings are minimal, consisting of fine, crepitant rales on deep inspiration. The chest radiograph can be negative early in the course or can reveal a perihilar or diffuse haziness that progresses to a finely granular, interstitial pattern. Coalescent nodules can form in the periphery. Pneumothorax with interstitial and subcutaneous emphysema and pneumomediastinum can occur.

Diagnosis

Typical findings on radiographic studies can suggest *P. jiroveci* pneumonia but are not diagnostic. Demonstration of *Pneumocystis* cysts or extracystic trophozoite forms establishes the diagnosis. *P. jiroveci* can be detected in induced sputum or in tracheal or gastric aspirates, but the yield is low, and detection does not imply disease. Bronchoalveolar lavage or open lung biopsy can yield the organism. Serologic tests are not useful.

Treatment

Trimethoprim-sulfamethoxazole is the drug of choice for treatment of *P. jiroveci* pneumonia in infants. It must be used with caution in young infants because of its potential for displacement of bilirubin from albumin-binding sites. The therapeutic dose is 15-20 mg/kg per day of the trimethoprim component in divided doses every 6-8 hours. The intravenous route of administration is preferable in infants with moderate or severe disease. Treatment is usually continued for 3 weeks. In infants who do not respond to trimethoprim-sulfamethoxazole or in whom adverse reactions develop, pentamidine isethionate, 4 mg/kg given parenterally as a single daily dose for 14 days, can be used.

Although radiographic improvement can take several weeks, clinical improvement is usually seen within 4-6 days after beginning therapy. Local reactions at the injection site, tachycardia, hypotension, pruritus, hypoglycemia, and nephrotoxicity have been associated with pentamidine administration. Trimethoprim-sulfamethoxazole is the standard for prophylaxis against *Pneumocystis* pneumonia and has been used for that purpose in infants 2 months old and older with HIV infection.

Toxoplasmosis

Incidence

Among 22,845 pregnant women analyzed by the Collaborative Perinatal Research Study in the United States, 38% had *Toxoplasma* IgG antibodies, reflecting past infection, and the incidence of acute maternal infection during pregnancy was estimated to be 1.1 per 1000 women. A higher incidence is seen in women born in Cambodia or Laos. In the United States, 1-3 infants per 1000 live births have *Toxoplasma*-specific IgM antibody. Worldwide, 3-8 infants per 1000 live births are infected in utero. An estimated 400-4000 cases of congenital toxoplasmosis occur in the United States each year.

Microbiology

Toxoplasmosis is caused by *Toxoplasma gondii,* an obligate intracellular protozoan parasite. This ubiquitous organism exists in three forms: an oocyst excreted by infected cats that produces sporozoites, a proliferative form (trophozoite or tachyzoite), and a cyst (cystozoite) found in tissues of infected animals. *Toxoplasma* can be propagated in tissue cell cultures or by animal inoculation in research laboratories.

Transmission and Pathogenesis

The cat is the only definitive host, but other mammals can be infected incidentally. Farm animals (cattle, pigs, sheep) can acquire infection after ingestion of food or water

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contaminated with infected cat feces that contain oocysts. Humans can acquire infection by ingestion of raw or poorly cooked meat containing the *Toxoplasma* cysts or by ingestion of food or water contaminated with oocysts. Risk factors include any exposure to cat feces, such as changing cat litter boxes, playing in sandboxes, or gardening in areas used by cats.

Congenital toxoplasmosis occurs almost exclusively as a result of primary maternal infection during pregnancy. Rarely, reactivation of infection in immunocompromised women during pregnancy can result in congenital toxoplasmosis. Most maternal infections are asymptomatic or result in mild illnesses. Fatigue and lymphadenopathy involving only a single posterior cervical node or generalized lymphadenopathy may be the only manifestation. Less commonly, acute maternal infection can manifest as an infectious mononucleosis-like syndrome with fever, nonsuppurative lymphadenopathy, headache, fatigue, sore throat, and myalgias. The general risk of transmission of acute infection from mother to fetus is estimated to be 40%; however, the actual risk and the severity of congenital infection vary with gestational age. The risk of transmission increases with increasing gestational age, but the earlier during pregnancy that fetal infection is acquired, the more severe the manifestations of congenital disease.

Clinical Manifestations

The classic clinical presentation of congenital toxoplasmosis is the triad of hydrocephalus, chorioretinitis, and intracranial calcifications, but there is a wide spectrum of manifestations, and more than 75% of infected newborns are asymptomatic in early infancy. As described by McAuley and colleagues, the four most common presentations include (1) a healthy-appearing term infant with subclinical infection in whom symptoms develop later in childhood, (2) a healthy-appearing term infant in whom clinical evidence of disease develops in the first few months of life, (3) an infant with generalized disease at birth, and (4) an infant with predominantly neurologic involvement at birth.

Many infants with subclinical infection who were believed to be normal at birth have evidence of infection on closer evaluation, including CSF abnormalities such as lymphocytic pleocytosis, hypoglycorrhachia, and elevated protein concentrations. Continued parasite proliferation may actually occur in the fetal brain despite maternal immunologic control in other tissues.

If the disease goes unrecognized and untreated, these infants can present with chorioretinitis, late-onset seizures, mental retardation, developmental delay, and hearing loss later in infancy or childhood. The second group of healthy-appearing, infected infants present with hydrocephalus and chorioretinitis in the first few months of life. Manifestations of generalized infection at birth include prematurity and intrauterine growth restriction, jaundice, hepatosplenomegaly, pneumonitis, temperature instability, lymphadenopathy, and cutaneous lesions (e.g., exfoliative dermatitis, petechiae, ecchymoses, and maculopapular lesions). Other signs of generalized infection include myocarditis; nephrotic syndrome; and gastrointestinal symptoms, such as vomiting, diarrhea, or feeding difficulties. The fourth group of infected infants has predominantly neurologic disease but can have systemic manifestations as well. Subtle neurologic deficits, obstructive hydrocephalus, or acute encephalopathy can be seen. Unilateral or bilateral macular chorioretinitis frequently occurs, and infants often have rash, hepatosplenomegaly, thrombocytopenia, granulocytopenia, and typical CSF findings.

Diagnosis

Maternal infection occurring during gestation can lead to fetal infection. Most infants with congenital toxoplasmosis have normal results on physical examination at birth. Visual and neurologic impairment results when the infection is not diagnosed and adequately treated. Generally, all suspected maternal, fetal, and neonatal infections should have confirmatory diagnostic testing performed in an experienced reference laboratory. Screening for IgG antibody in pregnancy is usually performed by indirect fluorescent antibody test or enzyme-linked immunosorbent assay and confirmed by the Sabin-Feldman dye test. Several tests are available to determine the duration of maternal infection when IgG and IgM antibodies are positive. Fetal infection is best determined using amniotic fluid polymerase chain reaction amplification of the *Toxoplasma* gene *B1*.

Infection of an infant is best established definitively by intraperitoneal inoculation of placental tissue into laboratory mice, yielding cultivation of *Toxoplasma* organisms. When this is not feasible, strong evidence for the diagnosis is provided by the presence of *Toxoplasma*-specific IgM, IgA, or IgE antibody. Infants with suspected toxoplasmosis should undergo MRI, evaluation of CSF, and indirect ophthalmologic examination.

Treatment

Pyrimethamine combined with sulfadiazine and supplemented with folinic acid is recommended for treatment of symptomatic and asymptomatic congenital infection. Therapy is continued for 1 year. Consultation with appropriate specialists should be sought when treating congenital toxoplasmosis.

Prognosis

A comprehensive maternal–fetal and infant strategy is needed to improve the outcomes of congenital toxoplasma infection. French experiences show that adoption of a scheduled, monthly prenatal screening strategy decreases the transmission rate and improves the clinical outcome at the age of 3 years in the offspring.

McLeod and colleagues published the results of the national collaborative Chicago-based treatment trial for 120 infants with congenital toxoplasmosis.[75] The duration of follow-up was a mean of 10.5 ± 4.8 years. A normal outcome was documented for 100% of infants treated with pyrimethamine and sulfadiazine for 1 year when there was

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no evidence of substantial neurologic disease at birth. Cognitive, neurologic, and auditory outcomes all were normal for these children. Normal neurologic or cognitive outcomes were also observed in greater than 72% of infants who did have moderate or severe neurologic disease at birth. None had sensorineural hearing loss, and most children in each group did not develop new eye lesions. These outcomes in patients treated for 1 year were markedly better than the outcomes in earlier years for infants who were untreated and infants who received only a 1-month course of therapy. There is a low but significant risk of late ocular manifestation because up to 12.6% of patients may develop ocular lesions during follow-up, mostly peripheral, with a first ocular lesion possibly occurring as late as 12 years after birth. Vaccine development to prevent feline oocyst shedding is ongoing, mostly with live vaccines.

The Society of Obstetricians and Gynecologists has developed an excellent clinical practice guideline that is available online at http://sogc.org/wp-content/uploads/2013/02/gui285CPG1301E-Toxoplasmosis.pdf (accessed December 21, 2017).

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Key Points

- *Candida* pathogenesis involves exposure, adherence, and colonization, followed by infection/dissemination.
- The prevention bundle of "antifungal prophylaxis, antibiotic stewardship of broad spectrum antibiotics, and CLABSI prevention measures" has contributed to lowering invasive *Candida* infections in high-risk patients.
- The highest risk patients are infants <1000 grams where infection is associated with high mortality and neurodevelopmental impairment.
- Starting appropriate dosing, adding antifungals to empiric therapy in high-risk patients, and prompt central venous catheter removal improve infection-related outcomes of survival and development.
- Cutaneous candidiasis is an invasive infection needing prompt recognition, evaluation, and systemic treatment for 14 days.
- Future prevention may involve lactoferrin, probiotics, and broader antenatal screening and treatment.

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Viral Infections in the Neonate

JILL E. BALEY AND BLANCA E. GONZALEZ

Certain viruses seem to have a predilection for the fetus and may cause abortion, stillbirth, intrauterine infection, congenital malformations, acute disease during the neonatal period, or chronic infection with subtle manifestations that may be recognized only after a prolonged period. It is important to recognize the manifestations of viral infections in the neonatal period not only to diagnose the acute infection but also to anticipate the potential abnormal growth and development of the infant.

Herpesvirus Family

The herpesvirus family consists of numerous closely related viruses. They all have a DNA core and are enveloped in an icosahedral (20-sided) nucleocapsid. Eight viruses in the family infect infants: herpes simplex virus (HSV) types 1 and 2; cytomegalovirus (CMV); varicella-zoster virus (VZV); Epstein-Barr virus (EBV); and human herpesviruses (HHV) 6, 7, and 8. These viruses are also characterized by the development of latent states after the primary infection.

Herpes Simplex Virus

Neonatal HSV infections are being diagnosed with increasing frequency, at a rate of 1 in every 3200 live births per year in the United States, resulting in an estimated 1500 new cases per year. The primary source of HSV infection for neonates is acquisition of the virus during delivery, and yet infected genital tract secretions in women are more common compared with neonatal infections. In addition, in numerous countries, neonatal infection is less common than in the United States despite the high prevalence of genital infections, suggesting other unknown means of protection to the neonate.

HSVs are a group of large double-stranded DNA viruses within an icosahedral nucleocapsid and a lipid envelope. There is considerable cross-reactivity between the two serotypes, HSV-1 and HSV-2. Glycoprotein G is responsible for the antigenic specificity between them, as shown by the antibody response. The seroprevalence of HSV in the United States has continued to increase for HSV-1 and HSV-2. HSV-1 is now responsible for 50% of neonatal infections, probably resulting from its increased seroprevalence and its increased maternal-to-neonatal transmission during reactivation of genital infection. Maternal HSV-2 infections recur more commonly than HSV-1, and there is more viral shedding in HSV-2 than in HSV-1 with recurrences, but the antibody to HSV-2 is more protective. The virus enters via breaks in the skin and mucous membranes, attaches to the epithelial cells, and begins to replicate. The virus is transported by retrograde axonal flow from the sensory nerve endings in the dermis to the sensory ganglia, where at least some portion of the viral DNA persists for the lifetime of the individual. HSV-1 usually persists in the trigeminal ganglion, whereas genital herpes persists in the sacral dorsal root ganglia or other local sensory ganglia.

Fever, ultraviolet light, stress, and many undetermined sources may cause the virus to reactivate, at which time the virus is transported antegrade down the sensory nerve axon to the skin or the mucous membrane, where it again results in either symptomatic or asymptomatic disease. Either way, the virus is infectious. Analyses of viral DNA from individuals with recurrent lesions indicate that the identical virus is virtually always responsible. Superinfection with a different viral strain is uncommon. Infection is not seasonal, and humans are the only known carriers of the infection.

HSV infections are labeled as first-episode, primary infections when the individual who has neither HSV-1 nor HSV-2 antibody (indicating prior infection) acquires either HSV-1 or HSV-2 in the genital tract. A first-episode, nonprimary infection occurs when an individual who already has HSV-1 antibody acquires HSV-2 genital infection, or vice versa. Recurrent infections occur with reactivation of latent infections.[123]

Epidemiology and Transmission

Labial and oropharyngeal infections are predominantly caused by HSV-1 and may be transmitted by respiratory droplet spread or direct contact with infected secretions or vesicular fluid. Most HSV-1 infections occur in childhood and are usually asymptomatic, sometimes causing gingivostomatitis or mononucleosis-like syndrome. Girls have a higher seroprevalence compared with boys. Black children have a 35% seroprevalence by age 5 years compared with 18% in white children, and the seroprevalence remains

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Abstract

Although many viruses are well known, many new viruses are being discovered which may have devastating effects on the fetus and newborn. Most therapeutic measures are of little efficacy so prevention is of prime importance. Congenital CMV remains the largest source of non-genetic hearing loss and developmental disorders in children, and yet therapy is of little efficacy and there is no vaccine. Mother-to-child transmission of HIV, the most common source of infection in infants and children, may be nearly eliminated with antenatal testing, Caesarian delivery, antiretroviral therapy during pregnancy and prohibition of breast feeding. Polio, measles, mumps, rubella, varicella and hepatitis B may largely be prevented. However, apart from palivizumab, there are few therapies or preventive measures for respiratory viruses. Acyclovir can be used to treat HSV but there remain no vaccines.

Keywords

HSV
HIV
CMV
adenovirus
RSV
Zika virus

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twice as high through the teen years but is equivalent by age 60 years.[123]

Because genital infections are usually transmitted by direct sexual contact with HSV-2, transmission most often occurs during or after adolescence. Most genital herpes infections are asymptomatic, but symptomatic and asymptomatic individuals may transmit infection. Primary genital infection may cause localized pain and burning of the labia and vaginal mucosa 2-14 days after contact. After a period of paresthesia, vesicles full of seropurulent fluid develop. These vesicles break down easily, forming shallow ulcers and releasing numerous infectious virus particles. There is often copious watery vaginal discharge, edema, dysuria, and bilateral pelvic and inguinal lymphadenopathy, accompanied by systemic symptoms of fever, malaise, and headache. Healing may occur several weeks later. Many primary genital infections, however, are asymptomatic. Children may infect themselves genitally by autoinoculation from an oral HSV-1 infection, but sexual abuse should always be considered.

Seroprevalence rates among pregnant women have indicated that at least 30% of women have serologic evidence of infection with HSV-2, but most of these women lack a history or symptoms of infection. Not only was this seroprevalence largely unsuspected among these pregnant women, but asymptomatic viral shedding also occurred among them at a rate (roughly 1% viral shedding at any time in pregnancy) similar to that in women with symptomatic recurrences. Seroprevalence increases dramatically as the number of sexual partners increases. Recurrence is higher among women with genital HSV-2 infection than among women with HSV-1, probably because HSV-2 is more likely than HSV-1 to establish latency in the inguinal dorsal root ganglia. When viral replication is not medically suppressed, there are four HSV-2 recurrences, on average, in the first year after a primary infection. HSV-1 recurs about once a year. Finally, for 70% of all women whose infants develop HSV infection, there is no history of infection or symptoms or of intercourse with a partner who has had the infection.

About 10% of HSV-2 seronegative women have HSV-2 seropositive partners. These women may remain uninfected with HSV-2 over prolonged periods despite continued, unprotected contact with a partner who is HSV-2 seropositive. Because the seroconversion rate is 20% per year for these women and most genital HSV-2 infections are asymptomatic, these women are at high risk of an unsuspected, primary HSV-2 genital infection during pregnancy.[123] Seroconversion rates are similar among pregnant and nonpregnant women. It is estimated that about one third of women who asymptomatically shed HSV during labor have been recently infected and that their infants have a 10-fold or greater risk of being infected than the infants of mothers with recurrent disease.

Women who are seronegative for HSV-1 and HSV-2 and have HSV-1–seropositive partners may acquire HSV-1 genital infection through oral sex. Oral sex has become more popular among teens because they believe it is safer sex. Overall, a woman who is seronegative for HSV-1 and HSV-2 with a discordant partner has a 3.7% chance of acquiring infection with either virus during pregnancy, and a woman who is seropositive for HSV-1 and seronegative for HSV-2 with an HSV-2–seropositive partner acquires HSV-2 infection in 1.7% of pregnancies.[123]

Transmission from mother to infant may occur via many different routes, including transplacental, intrapartum, and postnatal transmission. Transplacental transmission (5%), which is responsible for in utero infection, is inferred by the documentation of HSV skin lesions and viremia at birth and by elevated specific cord immunoglobulin M (IgM) levels. Primary and recurrent maternal infections have been associated with congenital infection.

Intrapartum transmission is responsible for 85% of neonatal infections. The actual transmission is influenced by the type of maternal infection. A high titer of viral particles ($>10^6$/0.2 mL inoculum) is excreted for about 3 weeks with a primary maternal infection, which is more likely to involve cervical shedding than a recurrent maternal infection, in which 10^2 to 10^3 viral particles per 0.2 mL inoculum are shed for only 2-5 days. Maternal neutralizing antibodies may also be partially protective for a newborn in recurrent infections and may not yet be present (and available to cross the placenta) in a primary maternal infection. In a 20-year trial, 0.3% of women were found to be shedding either HSV-1 or HSV-2 asymptomatically at delivery. Neonatal disease resulted in 57% of first-episode primary maternal infections (defined as HSV-1 or HSV-2 isolated from genital secretions without having concurrent HSV antibodies), 25% of first episode nonprimary maternal infections (defined as HSV-2 isolated from genital secretions of a woman with only HSV-1 antibodies, or HSV-1 isolated from a woman with only HSV-2 antibodies), and 2% of recurrent maternal infections (present when the virus isolated from genital secretions was the same type as antibodies present in the serum at the time of labor).[34]

Because recurrent infections are so much more common, half of all neonatal HSV-2 infections occur secondary to recurrent maternal infection, even though transmission from mother to infant occurs in only 2% of the cases. The amount of neutralizing antibody also affects the severity of neonatal disease. Infants who do not receive much transplacental transfer of antibody are more likely to develop disseminated disease. Prolonged rupture of membranes (>4-6 hours) also increases the risk of viral transmission, presumably from ascending infection. Delivery via cesarean section, preferably before rupture of membranes, but at least before 4-6 hours of rupture, can reduce the risk sevenfold.[34]

Neonatal infection does still occur, however, even with cesarean delivery. Fetal scalp electrodes may accelerate transcervical infection and breach the infant's skin barrier, also increasing risk of infection. It was shown more recently that vacuum extraction may cause scalp lacerations resulting in HSV skin lesions at the site of application. The relative risk of vacuum extraction resulting in HSV infection was nearly 7.5 times that of spontaneous vaginal or cesarean delivery.

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Antenatal maternal viral culture screening for HSV shedding is of no predictive value in determining who will be shedding virus at delivery.

Finally, transmission may occur postnatally (10%). Restriction enzyme DNA analysis has been used to document postnatal acquisition of HSV and its spread within a nursery by identifying infection with the same herpes strain in infants of different mothers. The father and the mother, as well as maternal breast lesions, have been implicated in neonatal infections. There is also concern regarding symptomatic and asymptomatic shedding among hospital personnel, one third of whom may have a history of HSV-1 lesions and 1% of whom still have recurrent labial lesions. Individuals with a herpetic whitlow should be removed from the nursery. Removal of health care workers with other lesions would pose significant risk to neonates because it would cause significant disruption of care. Orolabial lesions should be covered with a mask, and skin lesions should be covered with clothing or a bandage. Workers should be counseled on good hand hygiene and to not touch a lesion.

Congenital Herpes Simplex Virus Infection

Congenital infection was found in 5% of the infants in the National Institute of Allergy and Infectious Disease (NIAID) Collaborative Antiviral Study Cohort.[283] These infants with growth restriction characteristically have skin lesions, vesicles and scarring, neurologic damage (intracranial calcifications, microcephaly, hypertonicity, and seizures), and eye involvement (microphthalmia, cataracts, chorioretinitis, blindness, and retinal dysplasia). Congenital infections are described throughout pregnancy and after primary and recurrent infections but are most likely with a primary infection or if the mother has disseminated infection and is in the first 20 weeks of pregnancy. Most cases are caused by HSV-2. The manifestations probably result from destruction of normally formed organs rather than from defects in organogenesis because the lesions are similar to lesions of neonatal herpes. A few children have isolated skin lesions, usually in association with prolonged rupture of membranes, and these lesions may be more amenable to antiviral therapy.

Neonatal Herpes Simplex Virus Infection

Although asymptomatic HSV infections are common in adults, they are exceedingly rare in neonates. Of all neonatal infections, 50% are caused by HSV-1 rather than HSV-2. Half of the infants are born prematurely, usually between 30 and 37 weeks of gestation, and many have complications of prematurity, particularly respiratory distress syndrome. Two thirds of term newborns have a normal neonatal course and are discharged before the onset of disease. They may also have simultaneous bacterial infections. One fourth of the infants have symptoms on the first day of life and two thirds by the end of the first week.

Clinically, neonatal infections are classified as (1) disseminated, involving multiple organs, with or without central nervous system (CNS) involvement; (2) encephalitis, with or without skin, eye, or mouth involvement; and (3) localized to the skin, eyes, or mouth. Approximately 25% of cases are disseminated; 30% have CNS involvement; and 45% are localized to the skin, eyes, or mouth.

Among the 202 infants with HSV infections followed up in the NIAID Collaborative Antiviral Study Group, mortality was significantly greater with disseminated infection (57%) than with encephalitis (15%) and did not occur with disease limited to the skin, eyes, or mouth.[283] The relative risk of death was 5.2 for infants in or near coma at onset of treatment, 3.8 for those with disseminated intravascular coagulopathy, and 3.7 for premature infants.[281] Among infants with disseminated disease, mortality was higher among those with pneumonitis. Sequelae among survivors were more common with encephalitis or disseminated infection, particularly with HSV-2 infection, or in the presence of seizures but also were more likely in infants with SEM infection who had three or more recurrences of vesicles within 6 months.[281] Sequelae were found in 75% of survivors with HSV-2 and in only 27% of survivors with HSV-1 infection, and this may be related to the in vitro susceptibility of HSV-1 to acyclovir.[282]

Disseminated Infection

Infants with disseminated infections have the worst prognosis. Disseminated infections may involve virtually every organ system, but predominantly involve the liver, adrenal glands, and lungs. Infants usually present by 10-12 days of life with signs of bacterial sepsis or shock but often have unrecognized symptoms several days earlier. Although the presence of cutaneous vesicles is helpful in diagnosis, 20% of infants never develop vesicles. Disseminated intravascular coagulation (DIC) with decreased platelets and with petechiae and purpura are common, and bleeding often occurs in the gastrointestinal tract. Pneumatosis intestinalis may also be present. Hepatomegaly or hepatitis, or both, is usually present, with or without jaundice. Respiratory distress, often with pneumonitis or pleural effusion seen on the chest radiograph, has a poorer prognosis.

Many infants die before manifesting symptoms of CNS involvement, which is common (60%-80%). These infants may present with irritability, apnea, a bulging fontanel, focal or generalized seizures, opisthotonos, posturing, or coma. Cerebrospinal fluid (CSF) may be normal or may show evidence of hemorrhage. Virus can be isolated from CSF of only one third of infants with CNS symptoms. The routine use of polymerase chain reaction (PCR) on CSF has aided considerably in recognition of the disease. Death usually occurs at about age 2 weeks, roughly 1 week from the onset of symptoms, and often involves respiratory failure, liver failure, and DIC with shock.

Encephalitis

Encephalitis may occur as a component of disseminated disease, via blood-borne seeding of the brain, resulting in multiple lesions of cortical hemorrhagic necrosis often in

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association with oral, eye, or skin lesions, at 16-19 days of life. Brain involvement results from neuronal transmission of the virus. Regardless of the source of neurologic infection, only about 60% of infants have skin vesicles, and less than half have virus isolated from CSF. Although CSF is occasionally normal, it usually shows mild pleocytosis, with predominance of mononuclear cells, elevated protein concentration, and normal glucose concentration. Infections that are discovered late may have significant numbers of erythrocytes in CSF. Lethargy, poor feeding, irritability, and localized or generalized seizures may be the presenting manifestations. Nearly all electroencephalograms show nonspecific abnormalities.

In 12 infants with HSV-2 encephalitis, diffusion-weighted magnetic resonance imaging (MRI) showed extensive, often bilateral changes that were not visible on computed tomography (CT) or conventional MRI in eight infants. Disease was found in the temporal lobes, cerebellum, brainstem, and deep gray nuclei. Hemorrhage and watershed distribution ischemic injury were also seen. These areas progressed to cystic changes on follow-up imaging.[271] Nearly half of untreated children die from neurologic deterioration 6 months after onset, and virtually all survivors have severe sequelae (microcephaly and blindness or cataracts).

Fever is a known symptom of HSV infection and is a common reason for an infant in the first month of life to be taken to the emergency department. The American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommends considering HSV infection in neonates with fever, irritability, and abnormal CSF findings, especially in the presence of seizures. In a study of nearly 6000 infants with laboratory-confirmed viral or serious bacterial infections admitted from the emergency department, only 30% of the infants with HSV infections were febrile; 50% were fever free, and 20% were hypothermic. Of the febrile infants with CSF pleocytosis, bacterial meningitis (1.3%) was more common than HSV infection (0.3%), but not statistically so. Similarly, febrile infants with mononuclear CSF pleocytosis were not statistically more likely to have HSV infections (1.6%) than bacterial meningitis (0.8%), and 1.1% of hypothermic infants presenting with a sepsis-like syndrome had HSV infection.[40] In all of these infants, HSV infection should be considered when they present in the first month of life, especially if they fail to improve on antibiotics and bacterial cultures remain negative for the first 24-48 hours.

Skin, Eye, and Mouth Infections

Infants with disease localized to the skin, eyes, or mouth usually present by 10-11 days of life. Greater than 90% of these infants have skin vesicles, usually over the presenting part at birth and appearing in clusters. Recurrences are common for at least 6 months. Infants at risk should be monitored for localized infections (vesicles) of the oropharynx. Either HSV-1 or HSV-2 can cause keratoconjunctivitis, chorioretinitis, microphthalmos, and retinal dysplasia, later possibly leading to cataracts. One third of these infants later develop neurologic sequelae indicative of undiagnosed neurologic involvement.

Diagnosis

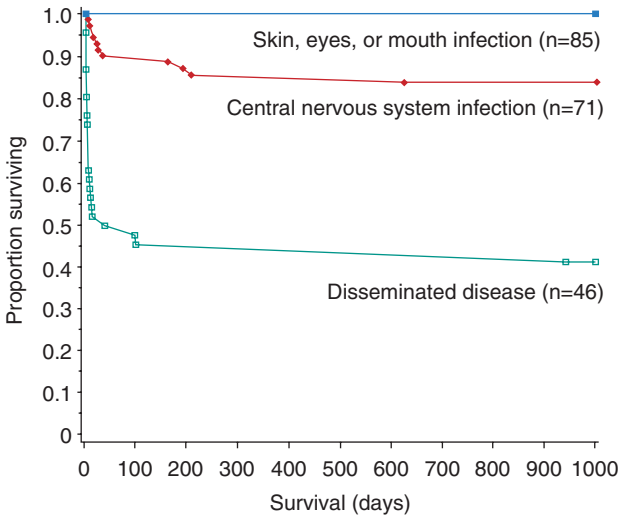
Isolation of virus is definitive diagnostically. Cultures of the newborn (scrapings of mucocutaneous lesions, CSF, stool, urine, nasopharynx, and conjunctivae) should be delayed to 24-48 hours after birth to differentiate viral replication in the newborn from transient colonization of the newborn at birth. The specimens for culture may be combined to save money because it is not important where the virus is located, but whether the virus is present, with the exception of CSF specimens, which are needed to determine CNS involvement.[123] If the culture shows cytopathic effects, typing should be done. Serologic testing is not useful in neonatal disease because transplacentally transferred maternal antibody confounds the interpretation, but finding low-avidity HSV-2 IgG in the maternal serum near term does indicate an elevated risk of neonatal disease. PCR testing has become invaluable, especially for CSF, which has a very low recovery rate for HSV cultures. PCR can also be used to test blood, scrapings of lesions, the conjunctiva, or the nasopharynx. However, PCR has detected HSV DNA in the amniotic fluid of women with symptomatic infection, and yet the infants were uninfected and healthy.[7] In addition, all three forms of neonatal disease (disseminated, CNS, and skin, eyes, and mouth [SEM] disease) may have viremia, so blood PCR should not solely be relied upon to determine extent of disease, and blood PCR should not be used to monitor response to therapy.

Therapy

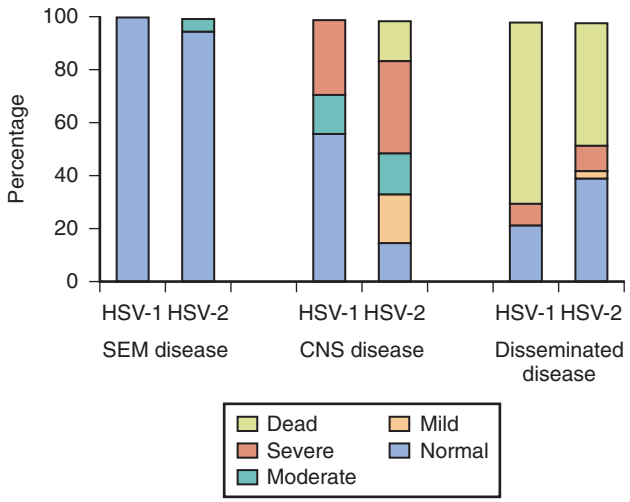
Vidarabine was the first antiviral agent used to treat HSV and was efficacious despite its toxicity. Acyclovir, a deoxyguanosine analogue, is preferentially taken up by virus-infected cells and phosphorylated by thymidine kinase, which is encoded in the virus. Host cell enzymes then effect di- and triphosphorylation. Acyclovir triphosphate prevents DNA polymerase and is a chain terminator, preventing viral DNA synthesis. Acyclovir is the only drug recommended for use in neonates. When a low-dose acyclovir (30 mg/kg/day in three divided doses) was compared with vidarabine, the morbidity and mortality were equivalent, but the ease of acyclovir administration and decreased toxicity resulted in it readily supplanting vidarabine in use. High-dose intravenous (IV) acyclovir (60 mg/kg/day in three divided doses) was then compared with low-dose acyclovir for a longer treatment duration (21 days for disseminated or CNS disease and 14 days for disease localized to the skin, eyes, or mouth). High-dose acyclovir resulted in a much improved survival rate: Infants with disseminated infection had an odds ratio of survival of 3.3, and infants with CNS disease had a similar survival. The likelihood of developmentally normal survival had an odds ratio of 6.6 compared with infants treated with the lower dose.[127,128]

Infants with an abnormal creatinine clearance need to have the acyclovir dose adjusted, and all infants need to be

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• **Fig. 50.1** Survival of infants with neonatal herpes simplex virus infection, according to the extent of disease. More recent data show improved survival. (From Whitley R, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *N Engl J Med*. 1991;324:450.)



• **Fig. 50.2** Morbidity and mortality among patients after 12 months of age by viral type, 1981-1997. CNS, Central nervous system; HSV, herpes simplex virus; SEM, skin, eyes, or mouth. (From Kimberlin DW, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001;108:223.)

monitored for neutropenia. All neonates should have ophthalmologic and MRI examinations. CT and ultrasonography may be used alternatively but are not as sensitive to abnormalities. Infants with CNS disease need to have a repeat lumbar puncture at the end of the course of treatment. Treatment should be continued until CSF is PCR negative. Infants who continue to have detectable HSV DNA in CSF by PCR at the end of therapy are more likely to die or have moderate to severe impairment. Poor prognostic indicators are lethargy and severe hepatitis in disseminated disease, and prematurity and seizures in CNS disease.[127,128]

Mortality has been tremendously decreased with high-dose acyclovir and is now 29% for disseminated disease; 4% for CNS disease; and 0% for SEM disease.[127,128] Although the percentage of survivors with normal development (31%) has not changed for CNS disease, normal development among survivors of disseminated disease is now 83%, and for SEM disease is greater than 98% (Figs. 50.1 and 50.2).[127,128] Neonates with SEM disease with neurodevelopmental abnormalities on follow-up may represent undetected CNS disease, adverse effects of inflammation secondary to disease, or seeding from recurrent skin lesions. In a study of 77 neonates with culture-proven HSV disease, CSF PCR detected HSV DNA in 7 of 29 infants who had been classified as having SEM disease, 13 of 14 classified as having disseminated disease, and 26 of 34 who had been classified as having CNS disease. HSV DNA remains in CSF for an average of 10 days after the onset of CNS disease.[126] It has also been shown that infants with fewer than 100 copies of HSV DNA per microliter of CSF after 4 days of treatment had improved survival and neurologic outcome.[68] To improve outcome, earlier recognition and treatment of infection are needed. Initiation of therapy in the high-dose acyclovir trial usually began 4-5 days after onset of symptoms, which is no better than that in the low-dose trial.[127] Topical ophthalmic antiviral drugs should be given to infants with ocular involvement in addition to parenteral therapy. This may include 1% trifluridine, 0.1% iododeoxyuridine, or 3% ganciclovir. All other therapy is supportive. Early data indicate that quantitative PCR for HSV DNA in blood may be useful in determining outcome and treatment, but there are not enough data to recommend this currently. Infants with disseminated disease have higher viral loads compared with infants with CNS disease and infants with SEM disease.[132] The viral load is also higher in those infants who die than in those who survive with neurologic disease or those who survive without neurologic disease.

Oral suppressive acyclovir therapy for 6 months after completion of treatment has been used to decrease recurrences in infants,[122] which occurred in 50% of infants within 1-2 weeks of stopping the initial acyclovir course. There is a significant reduction in the recurrence of skin lesions in infants with any of the three disease classifications and improved neurodevelopmental outcomes with CNS HSV disease.[27,130,235] Infants are treated with three doses per day at 300 mg/m^2/dose, and the neutrophil counts need to be checked at 2 and 4 weeks and then monthly during therapy.

Resistance to acyclovir is a concern and has been seen in mothers who have had multiple recurrences treated with suppressive acyclovir, mothers who have taken oral acyclovir for suppression in the later part of pregnancy, and even in a few infants on suppressive therapy for the 6 months after the end of treatment.

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Prevention

In 1999, the American College of Obstetrics and Gynecology recommended that cesarean delivery be performed if a mother has HSV genital lesions or prodromal symptoms at the time of delivery. Seventy percent of mothers of infants with neonatal disease do not have a history or symptoms of HSV infection, however, and their partners do not have a history of HSV infection, and neonatal infection may still occur even if a cesarean delivery is performed. Repetitive cervical cultures do not predict whether a mother will be shedding virus at delivery. Mothers should be counseled regarding the signs and symptoms of disease, and some may then recognize infection. If rupture of membranes has been present longer than 6 hours, some experts still recommend cesarean delivery in the face of genital lesions, but data are lacking, and controversy exists. Scalp electrodes should be avoided. There is also no consensus about treatment when a mother has genital lesions and ruptured membranes, except in the case of a very immature fetus.

If an infant is delivered vaginally to a mother with recurrent genital lesions (5% risk of infection), most experts do not recommend treating the infant. The infant does not need contact precautions. Cultures and PCR of the neonate should be obtained at 24 hours of life, and the infant should be observed carefully. Circumcision should be delayed until cultures are known to be negative. Hand washing should be emphasized. The infant should be managed with contact precautions. If the mother has an active herpes labialis or stomatitis, she should wear a disposable surgical mask while handling her infant until the lesions have crusted and dried. She should not kiss the infant. Breastfeeding may be allowed if there are no lesions on the breast. The mother needs to be taught the signs and symptoms of neonatal disease because culture does not always detect neonatal disease.

Whenever a mother has active genital lesions at the time of delivery, and she has no history of prior herpetic infection, both herpes culture and PCR need to be performed, regardless of whether the birth is via cesarean section or vaginal delivery (Figs. 50.3 and 50.4).[131] Type-specific serology can be used to determine if this is a recurrent infection or is a first episode infection (Table 50.1). Because the risk of infection to the newborn is greater than 50% in a primary, first-episode infection and 25% in a nonprimary, first-episode infection in the mother, these infants should have surface cultures and blood and surface PCR for HSV, serum alanine aminotransferase (ALT) and CSF cell count, chemistries, and PCR for HSV performed at 24 hours of life, and earlier if the baby is ill or premature or there was prolonged rupture of membranes. Acyclovir should be started after the evaluation. If it is a recurrent infection, the acyclovir may be discontinued after a negative evaluation. Empiric acyclovir treatment should be considered for 10 days for any first-episode infection, whether primary or nonprimary, even if the baby's evaluation is negative. If a CSF infection is suspected, treatment should be continued for 21 days, after which a repeat CSF PCR needs to be sent. Acyclovir should be given for another 7 days whenever the PCR is positive for HSV.

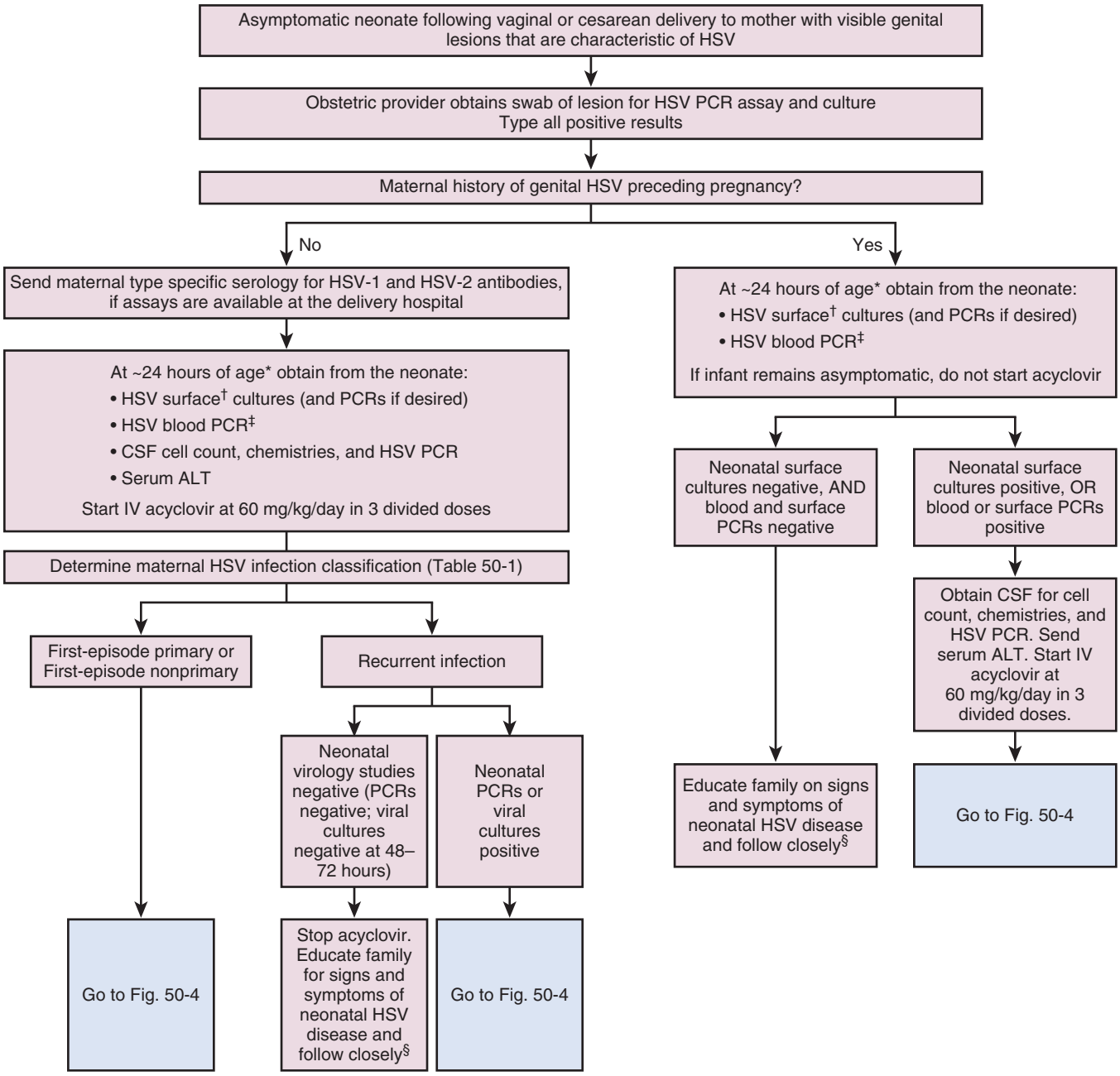
There is also considerable controversy concerning the prevention of a primary HSV genital infection in a seronegative pregnant woman. Some authorities advocate for type-specific serologic screening for HSV in all pregnant women, arguing that many mothers want the information; that they may be counseled against oral or unprotected sex; and that strategies may be devised from the data that are collected. However, others argue against testing, stating that it is not cost effective, that there is no recommended intervention, and that the unexpected positive test result can cause significant psychological and social distress. Targeting

TABLE 50.1 Maternal Infection Classification by Genital HSV Viral Type and Maternal Serology*

Classification of Maternal Infection	PCR/Culture From Genital Lesion	Maternal HSV-1 and HSV-2 IgG Antibody Status
Documented first-episode primary infection	Positive, either virus	Both negative
Documented first-episode nonprimary infection	Positive for HSV-1 Positive for HSV-2	Positive for HSV-2 AND negative for HSV-1 Positive for HSV-1 AND negative for HSV-2
Assume first-episode (primary or nonprimary) infection	Positive for HSV-1 OR HSV-2 Negative OR not available†	Not available Negative for HSV-1 and/or HSV-2 OR not available
Recurrent infection	Positive for HSV-1 Positive for HSV-2	Positive for HSV-1 Positive for HSV-2

*To be used for women without a clinical history of genital herpes.
†When a genital lesion is strongly suspicious for HSV, clinical judgment should supersede the virologic test results for the conservative purposes of this neonatal management algorithm. Conversely, if in retrospect, the genital lesion was not likely to be caused by HSV and the PCR assay result or culture is negative, departure from the evaluation and management in this conservative algorithm may be warranted.
From Kimberlin DW, et al. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics*. 2013;131:e635.

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¶ This algorithm should be applied only in facilities where access to PCR and type-specific serologic testing is readily available and turnaround time for test results is appropriately short. In situations where this is not possible, the approach detailed in the algorithm will have limited, and perhaps no, applicability.

** Evaluation and treatment is indicated prior to 24 hours of age if the infant develops signs and symptoms of neonatal HSV disease. In addition, immediate evaluation and treatment may be considered if:*

- *There is prolonged rupture of membranes (>4–6 hours)*
- *The infant is premature (≤37 weeks' gestation)*

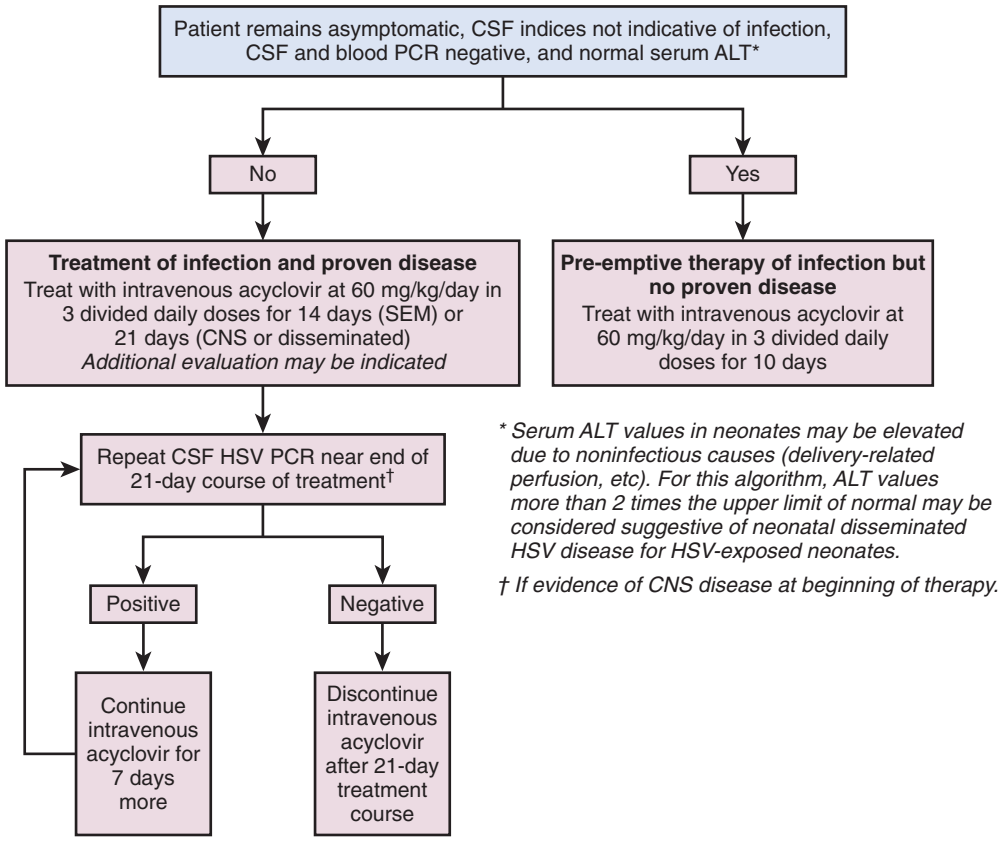
† Conjunctivae, mouth, nasopharynx, and rectum, and scalp electrode site, if present.

‡ HSV blood PCR is not utilized for assignment of disease classification.

§ Discharge after 48 hours of negative HSV cultures (and negative PCRs) is acceptable if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital until HSV cultures are finalized as negative or are negative for 96 hours after being set up in cell culture, whichever is shorter.

• **Fig. 50.3** Algorithm for the evaluation of asymptomatic neonates after vaginal or cesarean delivery to women with active genital herpes lesions. ALT, Alanine aminotransferase. (Modified from Kimberlin DW, et al. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics*. 2013;131:e635.)

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• **Fig. 50.4** Algorithm for the *treatment* of asymptomatic neonates after vaginal or cesarean delivery to women with active genital herpes lesions. ALT, Alanine aminotransferase; CNS, central nervous system; CSF, cerebral spinal fluid; SEM, skin, eyes, mouth. (Adapted from Kimberlin DW, et al. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics*. 2013;131:e635.)

for testing only women who are at high risk for infection misses too many seronegative women. Some treatment strategies do exist, however. It has been shown that the use of condoms in at least 70% of sexual intercourse between a woman seronegative for HSV and a man seropositive for HSV reduced transmission by greater than 60%.[123] Antiviral suppression with valacyclovir for 8 months in seropositive male partners reduced the transmission of HSV-2 infection to pregnant women by 48% and symptomatic infection by 75%.[54]

Obstetricians now recommend antiviral prophylaxis (usually valacyclovir or acyclovir) from 36 weeks of pregnancy onward to suppress viral recurrences. No major malformations have been associated to date with the use of acyclovir in pregnancy. In a Cochrane Database meta-analysis of third-trimester antiviral prophylaxis, women were less likely to have recurrence at delivery (relative risk 0.28), cesarean delivery for genital lesions (relative risk 0.30), and HSV detected at delivery (relative risk 0.14).[106] Although there were no cases of neonatal disease among the infants, there were too few patients to draw a conclusion about neonatal risk. Neonatal infection may occur because viral shedding still does occur. There has been some success in vaccine development for women who are seronegative for HSV-1 and HSV-2, but the trials still need to be performed.

Cytomegalovirus (Human Herpesvirus 5)

CMVs are the largest viruses in the Herpesvirus family and are noted for their worldwide distribution among humans and animals. The virus is highly species specific, and humans are the only known reservoir for disease. Infection occurs throughout the year. After primary infection, the virus enters a latent state, and reactivation may frequently occur. Reinfection may also result from any of the thousands of human strains, which are homologous, but not identical. The differing antigenic makeup of the various strains may make it possible to identify the source of the viral infection. It also allows re-infection to occur with other strains in an already seropositive individual.

The virus has a double-stranded DNA core surrounded by an icosahedral, or 20-sided, capsid. This capsid is surrounded by amorphous material, which, in turn, is surrounded by a lipid envelope, probably acquired during budding through the nuclear membrane. The virus is named for the intranuclear and paranuclear inclusions seen with symptomatic disease—cytomegalic inclusion disease. These inclusion bodies often yield an "owl's eye" appearance to the cells. The virus does not code its own thymidine kinase or DNA polymerase, which is important when considering treatment. The virus is cultured in the laboratory only in

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human fibroblasts, although it replicates in vivo primarily in epithelial cells.

Epidemiology and Transmission

CMV is currently the most common intrauterine infection. CMV is responsible for congenital infection in 0.15%-2% of newborns, and it is the leading cause of nongenetic deafness and learning disability. Infection is more prevalent in underdeveloped countries and among lower socioeconomic groups in developed countries, where crowding and poor hygiene are more common. Each year, 2% of middle- to high-socioeconomic-class women of childbearing age seroconvert compared with 6% of women from lower socioeconomic groups. Seropositivity also increases with age, breastfeeding for longer than 6 months, non-white race, number of sexual contacts, and parity. A study of US national death certificate and census data from 1990-2006 documented that African Americans and Mexican Americans were at increased risk for congenital CMV infection and that African Americans and Native Americans had a much greater rate of mortality among infants under age 1 year because of congenital CMV.[30] Of note, the highest rate of congenital CMV infections occurs in populations with the highest rates of maternal seroprevalence rather than in countries with only moderate seroprevalence among pregnant women, as in the United States. Primary and nonprimary maternal infections may contribute differently to the development of congenital CMV in different populations.

Transmission of CMV requires close contact with contaminated secretions because the virus is not very contagious. The virus can be cultured from urine, cervical secretions, saliva, semen, breast milk, blood, and transplanted organs, and all these sites intermittently excrete virus. Viral excretion is particularly prolonged after primary infection, but it also occurs with reactivation of infection or re-infection with a different strain. Congenitally infected infants may shed the virus for years and serve as a large reservoir for spreading infection to others. Toddlers also may shed the virus for prolonged periods compared with adults, in whom the humoral and cellular defense mechanisms lead to a latent state within a few months.

Transplacental transmission is responsible for congenital infection in 1% of newborns, and intrauterine fetal death is more likely. Primary maternal infection during pregnancy is more likely to result in maternal-to-fetal transmission, but fetal infection may also result in women with pre-existing antibody to CMV. This may occur via reactivation of a prior maternal infection, or infection with a newly acquired strain. Roughly two thirds of infants with congenital CMV worldwide are born to mothers with pre-existing antibody to CMV because of the high prevalence of CMV in the population.[273] Overall, only 5%-10% of congenital infections are symptomatic, and these are more likely after a primary maternal infection, although symptomatic infections have been reported in women with pre-existing antibody. Symptomatic infants have a mortality of 20%-30%, and two thirds of survivors may have sequelae. The 90% of infants with asymptomatic infection at birth, however, also have a 5%-15% risk of later sequelae.

Even with primary maternal CMV infection during pregnancy, transplacental infection occurs in only 30%-40% of the fetuses, and only 10%-15% of these infected fetuses develop symptomatic disease. With recurrent maternal CMV infection or re-infection with a new strain during gestation, only 1%-3% of fetuses are infected. Although the risk of transmission seems to be increased in the third trimester, the risk of malformations (which occur during the period of organogenesis) and developmental disabilities lessens. The fetus may be infected throughout gestation. The rate of intrauterine transmission was 9% preconceptually, and 31%, 34%, and 40% in the first, second, and third trimesters, respectively.[208] Maternal IgG crosses the placenta and provides passive immunity for the fetus but may also facilitate transport of CMV across the placenta, as IgG-virion complexes use the fetal F_C receptor on the syncytiotrophoblast for transcytosis. Villus core macrophages can neutralize complexes formed with high-avidity antibodies, but low-avidity antibody allows the virus to escape[48] and seems to be more significant in the first half of pregnancy when the virus has considerable teratogenic potential. Neurons migrate from the periventricular germinal matrix to the cortex between 12 and 24 weeks of gestation. This process may be interrupted by infection, resulting in CNS malformations. In the second half of pregnancy, during the period of myelination, white matter lesions may develop, as seen on MRI.[153]

Perinatal infection is responsible currently for an additional 3%-5% of infections among newborns, resulting from exposure to cervical secretions and blood during delivery or via breast milk.[182] Transmission in early childhood may occur from child to child and from child to other family members. There is also an implication that infection may occur via fomites because virus may survive in urine for hours on plastic surfaces and has been cultured from toys in daycare centers. Nearly half of mothers of premature infants infected in the nursery seroconvert within 1 year, and the same proportion of susceptible family members seroconvert when a single family member is infected.

Daycare compounds the problem. There is a 15% rate of infection among parents of children in daycare, particularly if the child is younger than 18 months. Mothers of children in daycare, particularly if they are of middle socioeconomic status and previously seronegative, are at significant risk of developing a primary CMV infection in a subsequent pregnancy; this may account for 25% of symptomatic congenital infections. Seronegative women who work at daycare centers have an 11% seroconversion rate per year, well above any predictable rate, and are at considerable occupational risk. Among children attending daycare, 30%-70% excrete the virus.

Similar concern has been expressed about female health care workers and their occupational risk. Early data did not support an increased risk of transmission of the virus, but current infection control measures and diagnostic

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methodologies did not exist at that time, so the risk is not really known.

After early childhood, viral transmission seems to be minimal until puberty, when sexual activity begins. Infection rates are highest among adults with multiple sexual partners. An additional risk of infection occurs with blood transfusions and organ transplantation, as the virus is present within the leukocytes and tissues. Transmission may be prevented by mandating that all blood products come from seronegative donors. Alternatively, the white blood cells carrying the virus may be removed by using frozen, deglycerolized red blood cell transfusions or by using filters to remove the leukocytes. However, neither the use of only seronegative blood nor the use of filters completely protects against transmission of virus. Thus, some recommend using both mechanisms.

CMV transmission via human breast milk feeding has been reported to result in infection in premature infants (<32 weeks' gestation), resulting in a sepsis-like infection. The virus is found in the whey portion of the milk, and mothers may excrete virus in their milk when they are not excreting the virus elsewhere, such as in urine or saliva. The long-term outcome has not yet been determined, but in a report of 40 preterm infants who developed viruria in the nursery, most likely from breast milk feedings, neonatal outcome was not different from that in control infants. The infants exhibited cholestasis, elevation of C-reactive protein, mild neutropenia, and thrombocytopenia, but these symptoms resolved.[183] There is still debate as to whether the virus contributes to bronchopulmonary dysplasia or whether the most immature infants will develop hearing, neurologic, or developmental abnormalities.

Maternal Clinical Manifestations

Most women are asymptomatic during primary infection and even more so with re-infection or recurrent infection, and pregnancy does not alter the clinical picture. A mononucleosis-like illness, which is heterophil negative, may develop in 5%-10% of women. Other manifestations are rare.

CMV frequently infects the decidua of the placenta, causing fibrosis and edema that result in intrauterine hypoxia and the release of cytokines further stimulating the placenta. This placental injury and hypoxia can cause fetal intrauterine growth restriction (IUGR), even without transmission of the virus to the fetus.

Asymptomatic Congenital Infection

Although 85%-90% of all infants with congenital CMV are asymptomatic at birth, 15% may be at risk for later sequelae. The results of follow-up of 330 infants with asymptomatic infection who were mostly of low socioeconomic status are shown in Table 50.2. The most important sequela seems to be sensorineural hearing loss, which is often bilateral and may be moderate to profound. The presence of periventricular radiolucencies or calcifications on CT is highly correlated with hearing loss. The hearing loss may be present at birth or may appear only after the first year of life and is frequently progressive as a result of continued growth of the virus in the inner ear. There is a very low risk of chorioretinitis, which may not be present at birth but may develop later secondary to continued growth of the virus. A further finding may be a defect of tooth enamel in the primary dentition, leading to increased caries. Neurologic handicap may occur but is uncommon. Premature infants are most at risk.

TABLE 50.2 Sequelae in Children After Congenital Cytomegalovirus Infection

Sequelae	Symptomatic Infection (%)	Asymptomatic Infection (%)
Sensorineural hearing loss	58	7.4
Bilateral hearing loss	37	2.7
Speech threshold, moderate to profound	27	1.7
Chorioretinitis	20.4	2.5
IQ ≤70	55	3.7
Microcephaly, seizures, or paresis/paralysis	51.9	2.7
Microcephaly	37.5	1.8
Seizures	23.1	0.9
Paresis/paralysis	12.5	0
Death	5.8	0.3

Data from Stagno S. Cytomegalovirus. In: Remington JS, et al., eds. *Infectious diseases of the fetus and newborn infant*. 5th ed. Philadelphia: Saunders; 2001:408.

Symptomatic Congenital Infection

Cytomegalic inclusion disease occurs in only 10%-15% of infected infants and results in multiorgan involvement, particularly of the reticuloendothelial system and the CNS. Death may occur at birth or months later, resulting in an overall mortality of 20%-30%, usually from DIC, bleeding, hepatic failure, or bacterial infection.

CNS involvement may be diffuse. Infants may be microcephalic, exhibit poor feeding and lethargy, and be hyper- or hypotonic. Intracranial calcifications of the basal ganglia and cortical and subcortical regions, ventricular enlargement, cortical atrophy, or periventricular leukomalacia may also be present. Most commonly, an infant who is small for gestational age or premature has hepatosplenomegaly and abnormal liver function tests. Hyperbilirubinemia, which occurs in more than half of the infants, may be transient but is more likely to be persistent, with a gradual increase in the direct component. Petechiae, purpura, and thrombocytopenia (direct suppression of megakaryocytes in bone

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marrow) usually develop after birth and may persist for weeks. Approximately one third of infants with congenital infection have thrombocytopenia, and one third of those have severe thrombocytopenia, with platelet counts less than 10,000/dL. There may also be a Coombs-negative hemolytic anemia. Diffuse interstitial or peribronchial pneumonitis is possible, but less common than with perinatally acquired disease. Table 50.3 lists the clinical findings in 24 newborns with symptomatic CMV infection. Persistent CMV may be responsible for a severe necrotizing pneumonitis in preterm infants and is hypothesized to result in a greater severity of bronchopulmonary dysplasia.

TABLE 50.3 Clinical Findings in the First Month of Life in 24 Newborns With Symptomatic Cytomegalovirus Infection After Primary Maternal Infection

Finding	No. (%)
Jaundice	15 (62)
Petechiae	14 (58)
Hepatosplenomegaly	12 (50)
Intrauterine growth restriction	8 (33)
Preterm birth	6 (25)
Microcephaly	5 (21)
Hydranencephaly	1 (4)
Death	1 (4)

Data from Fowler K, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med*. 1992; 326:663. Copyright 1992 Massachusetts Medical Society. All rights reserved.

Prognosis

Fowler et al.[85] showed that although maternal antibody may not prevent congenital CMV infection, it lessens the severity (Table 50.4). Sequelae were found in 25% of infants after primary infection, but in only 8% after recurrent infection. Likewise, mental impairment (intelligence quotient [IQ] <70), sensorineural hearing loss, and bilateral hearing loss were found in 13%, 15%, and 8% of infants, respectively, after primary maternal infection, but only 5% of infants born after recurrent maternal infection had sensorineural hearing loss, and none had mental impairment or bilateral hearing loss. These infants also showed the progressive nature of sequelae after primary and recurrent infection (Fig. 50.5).

Ramsay et al.[220] looked at the 4-year outcome of 65 neonates with symptomatic congenital CMV in the United Kingdom and found a better prognosis than previously reported from the United States (Table 50.5). Overall, the rate of neurologic abnormalities was 45%. Infants who presented with abnormal neurologic findings other than microcephaly had the worst prognosis, with a 73% rate of gross motor and psychomotor abnormalities compared with a 30% rate among children who did not present with neurologic findings. A Japanese study of 33 congenitally infected infants found that abnormal abdominal findings (ascites or hepatosplenomegaly) on fetal ultrasonography were associated with liver dysfunction and a 53-fold increase in mortality; infants who had no abdominal findings survived.[158] Evidence is also accumulating that neonatal viral blood load (>1000 copies per 10^5 polymorphonuclear leukocytes

TABLE 50.4 Sequelae in Children With Congenital Cytomegalovirus Infection According to Type of Maternal Infection

Sequelae	Primary Infection*	Recurrent Infection*	*P* Value
Sensorineural hearing loss	15 (18/120)	5 (3/56)	0.05
Bilateral hearing loss	8 (10/120)	0 (0/56)	0.02
Speech threshold ≥60 dB	8 (9/120)	0 (0/56)	0.03
IQ ≤70	13 (9/68)	0 (0/32)	0.03
Chorioretinitis	6 (7/112)	2 (1/54)	0.20
Other neurologic sequelae	6 (8/125)	2 (1/64)	0.13
Microcephaly	5 (6/125)	2 (1/64)	0.25
Seizures	5 (6/125)	0 (0/64)	0.08
Paresis or paralysis	1 (1/125)	0 (0/64)	0.66
Death	2 (3/125)	0 (0/64)	0.29
Any sequelae	25 (31/125)	8 (5/64)	0.003

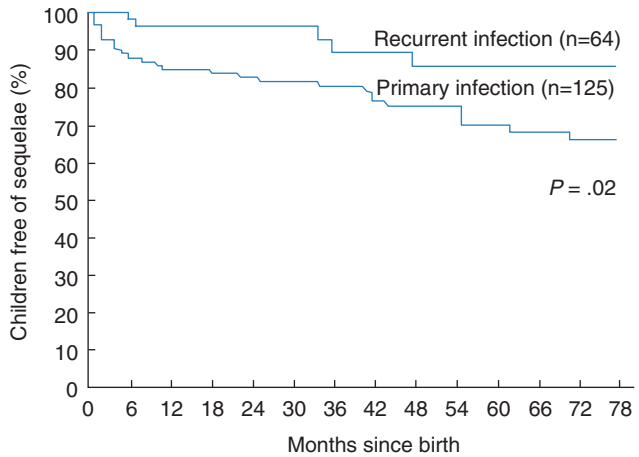
*Percentage (number with sequelae/total number evaluated).
Data from Fowler K, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med*. 1992;326:663. Copyright 1992 Massachusetts Medical Society. All rights reserved.

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TABLE 50.5 Outcome of Symptomatic Congenital Cytomegalovirus Infection

Neonatal Presentation	No. Infants	Normal *N* (%)	Disability	
			Motor or Psychomotor *N* (%)	Sensorineural Deafness *N* (%)
Group 1	22	6 (27)	14 (64)	2 (9)
Group 2	35	22 (63)	8 (23)	5 (14)
Group 3	8	8 (100)	0	0
All groups	65	36 (55)	22 (34)	7 (11)

Group 1: Abnormal neurologic findings at presentation.
Group 2: Hepatomegaly, splenomegaly, or purpura at presentation without neurologic abnormality.
Group 3: Microcephaly or respiratory problems at presentation without neurologic abnormality.
Data from Ramsay MEB, et al: Outcome of confirmed symptomatic congenital cytomegalovirus infection. *Arch Dis Child* 1991;66:1068.



• **Fig. 50.5** Percentages of children with congenital cytomegalovirus infection who remained free of sequelae, according to the type of maternal infection. *P* value was obtained by log-rank test. The advent of treatment may modify these data. (From Fowler K, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med*. 1992;326:663.)

[PMNLs] via quantitative PCR) may also predict infants who will develop sequelae, regardless of whether the infants were symptomatic or asymptomatic after birth.[138] Chorioretinitis, periventricular calcifications, and microcephaly remain standard predictors of poor cognitive outcome. In contrast, children who have normal development and no hearing loss at 1 year of age are unlikely to develop neurodevelopmental handicaps.

Perinatal Infection

Mothers with recurrent CMV infection or re-infection usually transfer significant antibody to the infant in utero. Even if this antibody transfer does not occur, a term infant who acquires infection after birth, denoting a perinatal infection, is usually asymptomatic. Transmission may occur in passage through the birth canal, via breast milk, or secondary to blood transfusion. Breastfeeding infants largely seroconvert. The incubation period is 4-12 weeks. Term infants may develop pneumonitis secondary to CMV and present with cough, tachypnea, congestion, wheezing, and apnea. Few infants require hospitalization, and there is spontaneous resolution in most term infants. In contrast, premature infants, often infected through blood transfusion, have a high rate of serious or fatal illness. They also may develop pneumonitis, but with a picture of overwhelming sepsis, hepatosplenomegaly, thrombocytopenia, and neutropenia. There may be an increased risk in these infants of neuromuscular handicaps, although there does not seem to be a higher rate of sensorineural hearing loss, microcephaly, or chorioretinitis. Transmission via blood transfusion can now be largely eliminated, indicating that most infants are infected postnatally by maternal breast milk.

Neurologic Impairment

Not all infants with symptomatic disease at birth have neurologic impairment. One third of these infants may have a normal neurologic outcome, and none of 45 infants with normal ultrasonography results had long-term sequelae (Table 50.6).[10] However, 5%-15% of asymptomatic infants may have sequelae.

Initially, CT was considered the gold standard to diagnose cerebral involvement in congenital CMV infection, and 90% of symptomatic infants with abnormal CT findings had neurodevelopmental or neurosensory sequelae. However, MRI is much more sensitive in diagnosing white matter and migrational abnormalities. Cranial ultrasonography is more sensitive in diagnosing lenticulostriate vasculopathy and germinolytic cysts, which are especially found in the anterior temporal region along with ventriculomegaly and ventricular septations. Infection in the first trimester may result in abnormal CNS development, which, in turn, may cause abnormal neuronal migration and cerebellar hypoplasia. Infection occurring between 16 and 18 weeks' gestation may result in lissencephaly, whereas infection occurring between 18 and 24 weeks' gestation is related to the development of polymicrogyria. Migrational disorders correlate with poor neurodevelopment and sensorineural hearing loss, and polymicrogyria correlates with cognitive

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TABLE 50.6 Value of Cranial Ultrasound Scanning in Predicting Outcome in 57 Patients With Congenital Cytomegalovirus Infection

	No. (%) Newborns With Poor Outcome					
	Normal US Results	Pathologic US Results*	Odds Ratio (95% CI)	*P* Value	PPV (%)	NPV (%)
DQ ≤85	0/45	8/11 (72.7%)	NE	<0.001	72.7	100
Motor delay	0/45	6/11 (54.5%)	NE	<0.001	54.5	100
SNHL	3/45 (6.7%)	6/11 (54.5%)	16.8 (3.2-89)	<0.001	54.5	93.3
Death or any sequela	3/45 (6.7%)	11/12 (91.7%)	154 (17.3-1219.6)	<0.001	91.7	93.3

CI, Confidence interval; DQ, developmental quotient; NPV, negative predictive value; NE, could not be estimated; PPV, positive predictive value; SNHL, sensorineural hearing loss; US, ultrasonography.
*One newborn with pathologic US results died during the neonatal period. Follow-up data were available for 11 of the 12 patients who lived.
Data from Ancora G, et al. Cranial ultrasound scanning and prediction of outcome in newborns with congenital cytomegalovirus infection. *J Pediatr* 2007;150:157.

and motor delay and epilepsy. Periventricular calcifications are also a poor prognostic indicator of developmental delay.

Abnormalities in balance and posture causing delays in walking, abnormalities in gross motor function, and cerebral palsy are now being seen in children with sensorineural hearing loss. These may reflect abnormal vestibular function in the ear and/or cerebellar lesions. A few reports have noted an increase in autism spectrum disorders, but this is not universal. In contrast, a normal fetal brain MRI result generally indicates a good clinical outcome, although there may still be some cases of mild hearing loss.

Hearing and Visual Impairment

Congenital CMV is the most significant cause of nongenetic sensorineural hearing loss in childhood: 10%-15% of all infants experience hearing loss, but it may also be detected in 30%-65% of symptomatic infants.[153] One fourth of hearing loss detected by 4 years of life is secondary to congenital CMV infection. The hearing loss tends to be more severe and to occur earlier in infants with symptomatic infection. These children also tend to have bilateral loss, whereas infants with asymptomatic infection are more likely to have unilateral loss of hearing. The loss can be progressive or fluctuate and may be delayed by years. Less than half of all sensorineural hearing loss secondary to CMV is detected by newborn screening. Increased blood and urine viral load with more prolonged urinary excretion at an earlier age is associated with a higher risk of sensorineural hearing loss in both symptomatic and asymptomatic infants. These children often shed virus for greater than 4 years. The cause of this continued and fluctuating hearing loss is not well understood. It has been variably attributed to a direct cytopathic effect of the virus, to the host's immune response, and to injury to the endolymphatic structures. Rehabilitation with hearing aids or cochlear implants can provide useful speech comprehension, even if language development is not as advanced as in uninfected children who do not have other neurologic handicaps.

Chorioretinitis may be found in 15%-30% of symptomatic newborns. Children often have impairment or strabismus secondary to chorioretinitis, optic atrophy, or central cortical lesions and to macular scarring. Chorioretinal scars, resulting in visual impairment, are frequent in children receiving cochlear implants.[76]

Antenatal Diagnosis

Because most women with CMV infection remain asymptomatic, screening for primary infection is necessary to determine risk. Detecting CMV IgG, which has high sensitivity and specificity, in a woman known previously to be seronegative reliably diagnoses primary infection. Few European or American countries routinely screen for seroconversion, however, because there is no consensus for treatment of either a newly infected pregnant woman or her infant. Detection of CMV IgM may indicate a recent infection, but IgM also increases with reactivation of latent infection or re-infection. CMV IgG avidity testing may be helpful: The binding capacity or avidity of IgG is low just after an infection and remains low for 18-20 weeks after infection and then increases with time. Also, the synthesis of IgG antibodies against glycoprotein B (gB) is delayed in a primary infection, so the absence of these antibodies in an immunoblot test is a marker for recent infection. Finally, CMV DNA may be detected during acute infection from the peripheral blood.

If a primary maternal infection is suspected, or ultrasonography shows abdominal or cerebral findings or IUGR, fetal diagnosis may be undertaken. Cordocentesis is unnecessary because the sensitivity is lower and the risks are greater than with amniocentesis. CMV may be detected in the amniotic fluid by viral culture or by PCR for CMV DNA. The amniotic fluid should only be sampled at least 6 weeks after the onset of maternal infection to allow for delayed passage of virus across the placenta and at 21-23 weeks' gestation to allow for fetal renal maturity to be able to excrete the virus.[141] A high viral load was initially

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correlated with the development of a symptomatic infection and neurodevelopmental sequelae, but this was not confirmed in subsequent studies.

Neonatal Diagnosis

CMV must be identified in an infant by 21 days of age to be certain it is a congenital infection rather than a perinatal infection. Urine culture for CMV, either by routine viral culture or by rapid shell vial culture, was the gold standard for the diagnosis of CMV infection for years. More recently, it has been replaced by PCR amplification testing of urine, saliva, or blood. PCR testing performs as well as or better than rapid culture.[230] PCR offers more rapid turn-around, is not as affected by storage and transport conditions, costs less, and is better for high throughput than culture.[230] It performs well in targeted testing and large volume screening testing. Both saliva and urine are acceptable in large-volume screening programs, but saliva is easier to collect and comparable in reliability.[230] In a study in the United Kingdom, 98% of salivary swabs collected by parents from newborns who failed the routine hearing screen were successfully tested before 21 days of life for CMV.[286] Cost benefit analyses of this program[285] and a similar program in the United States[19] compared well with other screening programs, suggesting a potential for targeted screening of at-risk infants who might benefit from treatment. Screening of pregnant women in general is not recommended in the United States or in many European countries because of the lack of a successful treatment modality. However, it has been suggested that screening of women undergoing assisted reproduction might identify those recently infected and should, therefore, delay their efforts. In addition, dried blood spots, as collected on the Guthrie cards in newborn screening programs, can be used to retrospectively diagnose a congenital infection in an older infant. The sensitivity of PCR testing of dried blood spots is slightly lower, making them less suitable for screening programs. Finally, the diagnosis may be made by determining a fourfold increase in specific IgG titers or presumptively by detecting anti-CMV IgM because IgM does not cross the placenta. However, there are false-positive and false-negative results with IgM, rendering it less useful.

Treatment

Ganciclovir (GCV) and its oral prodrug valganciclovir (VGCV) are used to treat the newborn with symptomatic congenital infection. GCV is an acyclic deoxyguanosine nucleoside analogue, which acts as a chain terminator during elongation of the CMV DNA.

Kimberlin et al.[129] randomly assigned neonates with symptomatic CNS disease to receive 6 weeks of therapy with ganciclovir, at 6 mg/kg/dose given every 12 hours versus no treatment and monitored hearing with brainstem auditory evoked response. When tested at 6 months, in 84% of treated infants, normal hearing was maintained or hearing was improved, in contrast to 59% of control infants. None of the treated infants had worsening of hearing at 6 months compared with 41% of untreated infants. When tested at 1 year, 21% of treated infants and 68% of control infants exhibited worsening of hearing. Neutropenia was three times more common (63%) in treated infants than in untreated infants. Maintenance of IV access was also an issue. Viral excretion in urine returned to pretreatment levels within 2 weeks after GCV was discontinued, as did the viral load.[189] In addition, the Denver Developmental Screening Test was also performed at 6 weeks, 6 months, and 1 year of age.[189] Infants who were treated with GCV had fewer developmental delays at 6 months and at 1 year of age.

Subsequently, it was determined that oral administration of VGCV given twice daily at 16 mg/kg/dose provided comparable systemic coverage.[124] A second randomized, placebo-controlled trial comparing 6 weeks of oral VGCV treatment to 6 months of oral VGCV in infants with symptomatic congenital infection was begun.[125] Although no difference in best ear hearing as determined by brainstem auditory evoked response was seen at 6 months' follow-up, there was a small, but significant improvement in hearing at 12 and 24 months among the infants treated for 6 months. The infants treated for 6 months also performed better on the Bayley Scales of Infant and Toddler Development (3rd edition) at 24 months. Of note, neutropenia was comparable between the two groups and lower than in the GCV trial. Therefore, it is recommended that infants with symptomatic congenital disease in their first month of life be treated with 6 months of oral VGCV after counseling the parents regarding the 20% risk of neutropenia. Carcinogenicity and gonadotoxicity have been seen in animal models, but not in humans. Infants with asymptomatic congenital disease should not be treated. Recently, a small study of 54 infants with symptomatic infection and hearing impairment at birth were treated with 12 months of GCV/VGCV.[22] Hearing improved in 65%, with return to normal hearing in most. There was no control group, and hearing was not reported beyond a year of life.

Prevention

Pasteurization can be used to inactivate CMV in human milk, and freezing of the milk decreases, but does not eliminate, the virus. If a mother is known to be CMV seronegative and her infant must receive donated, fresh human milk, the use of a seronegative donor would be beneficial.

The development of a vaccine against CMV is a public health priority. Several live-attenuated vaccines have been developed, but trials have not demonstrated sufficient protection, and none of the vaccines has been licensed for use. In addition, it is now understood that natural immunity does not prevent transmission of the virus to the fetus and that a significant proportion of congenital infections result from nonprimary infections during pregnancy. Clinical isolates of CMV strains show significant genetic variation and recombination into a tremendous number of strains, implying that multivalent vaccines may be needed. These vaccines

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may need to target both the cellular and humoral immune responses to the virus to be effective. There is some promise in recombinant live-attenuated vaccines, which delete the genes responsible for immune evasion.

However, prevention remains the most important available means to avoid infection. CMV may be transferred to human hands by contact with mucosal surfaces, saliva, urine, or stool from small children shedding the virus or from surfaces contaminated by those children. The human skin maintains an acidic microenvironment, so the virus does not survive on human hands as long as it does on other surfaces. Nevertheless, it can be transferred from the hands to mucosal membranes, potentially resulting in infection. Hand washing with soap, antibacterial soap, or even just water removes much of the virus, and hand sanitizers and, to a lesser extent, diaper wipes can inactivate the virus. Female childcare workers, especially when their children are younger than 2 years of age, need to be counseled about the risks of CMV in pregnancy and taught good hand washing procedures, as do women health care workers, particularly in nurseries. The US Centers for Disease Control and Prevention (CDC) has developed a set of hygiene practices to reduce the risk of CMV infection for women who are pregnant or planning to become pregnant. These include thoroughly washing hands with soap and warm water after changing diapers, feeding or bathing a child, wiping the nose or drool, or handling the child's toys. The pregnant woman should not share food, drinks, eating utensils, or toothbrushes with a young child or put a pacifier in her own mouth. She should avoid saliva when kissing a young child, and she should clean toys, countertops, and other surfaces in contact with either saliva or urine. There was an 84% reduction in seroconversion among seronegative pregnant women in high-risk occupations when they were educated about CMV and hygiene in comparison with those who did not receive counseling.[226]

Transmission of CMV via blood transfusions may be largely eliminated by using blood from antibody-negative donors, by using frozen, deglycerolized red blood cells, or by using leukocyte-depletion filters. Because both methods have a small failure rate, some recommend using both antibody-negative donors and leukocyte depletion filters.

When a pregnant woman has been infected with CMV and her fetus has been diagnosed with infection, few options are available other than abortion. The use of passive immunization with CMV-specific hyperimmune globulin (HIG), primarily given intravenously, initially suggested a lower rate of transmission of the virus to the fetus,[186] but a subsequent randomized double-blind trial of HIG in 124 women found a fetal transmission rate of 30% in treated women with a primary infection, and 44% in control women, which did not reach statistical significance.[225] There was also a higher rate of obstetric complications among treated women, so the use of HIG is not routinely advised. A large scale trial in the United States is currently in progress.

Varicella-Zoster Virus (or Human Herpesvirus 3)

Varicella (chickenpox) is one of the most highly communicable human diseases. It is the result of a primary infection with varicella-zoster virus (VZV), which is one of the human DNA herpesviruses. After infection, latent virus persists in the dorsal root ganglia. The localized rash of herpes zoster results from a reactivation of infection, in which the virus begins to multiply within the ganglia and propagate down the sensory nerves to its dermatomes.

Epidemiology and Transmission

Humans are the only known reservoir of VZV. Immunity is lifelong and widespread. Of young adults, 70%-80% have a history of chickenpox, and this has been found to be quite reliable. Conversely, only 10%-20% of individuals lacking a history of chickenpox have been found to be seronegative, even though asymptomatic infection is believed to be unusual. Chickenpox rarely occurs in immunocompetent, seropositive individuals, although it has been reported to occur among pregnant women. Most reinfections are mild. Because of the implementation of universal immunization in the United States in 1995, as well as the recommendation of a second vaccine dose in 2006, varicella infections have decreased by greater than 90%. Primary varicella infection in pregnancy now only amounts to roughly 2-3/1000 pregnancies/year.

The initial protection against VZV depends on IgG. Neonates become ill because they are exposed to high titers of the virus from the mother and yet antibody is absent. In contrast, limitation of the severity of the infection and recovery from infection largely depend on cellular immunity, or T cells. Pregnant women and others who are immunosuppressed have decreased T-cell immunity, so disease can be very severe. Severe disease may also develop when the individual is receiving high doses of steroids.

Chickenpox is seen year round, with some increase in winter months, and is worldwide in distribution. In household contacts, 90% of susceptible individuals are infected. Transmission of the virus occurs via air-borne droplet spread or via contact with the virus in the vesicular lesions of either varicella or, rarely, zoster. Although it is well documented that susceptible individuals may develop varicella after exposure to zoster lesions, varicella-zoster does not develop after exposure to chickenpox. Transmission may occur 1-2 days before the onset of the rash until all vesicular lesions are dried and crusted, at least 6 days after onset of the rash. The incubation period is 10-21 days after exposure, unless the individual has been given varicella-zoster immunoglobulin, which may delay the onset of the infection for 28 days. When the mother has varicella around the time of delivery, the onset of the rash in the newborn is usually 9-15 days after the onset of the rash in the mother.

After replication of the virus within the nasopharynx and invasion of the local lymph nodes, there is transient viremia,

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which seeds the viscera. Viral multiplication continues, causing a greater viremia and widespread cutaneous involvement. Subsequent viremias result in crops of vesicles, followed by the development of latency within the dorsal root ganglia.

Clinical Manifestations

After a short prodrome of fever, headache, and malaise, there is generalized exanthema, which begins on the face and trunk and proceeds centripetally. Recurrent crops of vesicles appear for 2-5 days and then crust and scab, usually healing without scarring. Secondary bacterial infection of the cutaneous lesions is the most common complication and may lead to sepsis, pneumonia, and meningitis. Most other complications are rare, including encephalitis, hepatitis, myocarditis, arthritis, and glomerulonephritis. Reye syndrome, which sometimes occurred after chicken pox, has almost disappeared now that it is recommended not to use salicylate-containing products with chicken pox.

Varicella pneumonia is the most common cause of mortality. The onset of fever and cough usually occurs within 2-4 days after the development of the rash but may occur later. Radiographic changes consist of diffuse, nodular lesions with perihilar prominence. Dyspnea, cyanosis, rales, and chest pain may be severe, and there may be hemoptysis. Although only 15% of adults develop pneumonia, 90% of all cases of chickenpox pneumonia occur among adults. Immunocompromised individuals are also at increased risk.

Shingles, or varicella zoster, is characterized by clusters of vesicles in 1-3 sensory dermatomes as a result of VZV reactivating from the latent state in the sensory ganglia where it had resided. These vesicles are pruritic and painful and, occasionally, result in postherpetic neuralgia, which can last a few days to months. Occasionally, there can be reactivation of VZV viscerally without any skin lesions.

Varicella in Pregnancy

There does not seem to be an increased risk of spontaneous abortion or prematurity as a result of maternal chickenpox, although prematurity and IUGR are common among infants with congenital varicella syndrome. Mortality of 40% with chickenpox pneumonia has been reported among pregnant women who did not receive antiviral therapy. Some experts recommend oral acyclovir or valacyclovir for pregnant women with varicella, especially during the second and third trimesters, when the risk of severe infection is greatest. IV acyclovir is recommended in the presence of varicella complications.

Because of the potential for increased mortality, varicella-zoster immunoglobulin (VZIG) may be useful for passive immunization of a susceptible pregnant woman after significant exposure to varicella. Controlled trials are, however, still unavailable. VZIG needs to be administered within 96 hours of exposure and, preferably, after susceptibility has been confirmed serologically. VZIG, or Varizig, is approved by the US Food and Drug Administration (FDA) for use in newborns, premature infants, children less than 1 year of age, and pregnant women. Uncertainty continues regarding its effect on the fetus. VZIG may not protect the fetus from infection. Likewise, the absence of signs of maternal chickenpox after the use of VZIG does not indicate that the fetus is protected, and there is at least one report of congenital varicella syndrome when the mother received VZIG 4 days after exposure.[233] Ultrasonography revealing a wasted limb may assist in the diagnosis of infection of the fetus, although this is, of necessity, a late diagnosis, which rules out the option of an abortion.

Congenital Varicella Syndrome

Intrauterine infection occurs as a result of hematogenous dissemination across the placenta and can occur even with mild maternal infection.[73,200] The lowest risk of congenital varicella syndrome (CVS) occurs with maternal infection before 12 weeks of pregnancy (0.55%) and rises to 1.4% between 13 and 20 weeks, giving an overall risk of 0.91% in the first 20 weeks of pregnancy[277] (Table 50.7). Only a couple of cases of CVS have been described between 20 and 28 weeks' gestation. A few infants (1.1%) may develop herpes zoster in the first 2 years of life when the mother had had varicella in the late second or third trimester of pregnancy. A later maternal infection is more likely to result in less severe fetal manifestations. Although portions of the congenital syndrome have been seen after maternal zoster, the full syndrome has not been seen, presumably because viremia is uncommon with zoster, and some pre-existing immunity is present. Theoretically, the fetal lesions result from the occurrence of zoster in utero.

Typical features of the congenital syndrome include cicatricial cutaneous lesions, often in a zigzag shape, with limb involvement, ocular abnormalities, and severe mental retardation. The condition may progress to an early death. Skin lesions usually occur over an involved limb, sometimes over the contralateral limb, and are often depressed

TABLE 50.7 Incidence of Congenital Varicella Syndrome in Large Cohort Studies (*N* >100)

Study	First Trimester	Second Trimester	Third Trimester
Enders et al.[73]	1/236*	7/351*	Not reported
Jones et al.[115]	1/110*	1/46*	0/13
Harger et al.[99]	0/140*	1/122*	0/100
Mean %	0.41	1.73	Not reported

*The number of infants born with congenital varicella syndrome out of the number of women infected.
Data from Weisz B, Book M, Lipitz S, et al. Fetal outcome and amniocentesis results in pregnancies complicated by varicella infection. *J Obstet Gynaecol Can*. 2011;33:720-724.

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and pigmented in a dermatomal distribution. Cataracts, microphthalmia, chorioretinitis, cerebral atrophy, seizures, and mental retardation may occur; sometimes bowel and bladder dysfunction also may occur. Hypoplasia of the bone and muscle of a limb is prominent.

Maternal counseling is difficult because the incidence of the syndrome is so low as to preclude routinely recommending abortion. Maternal infection may have a 25% incidence of fetal varicella, but this does not indicate that the fetus will develop congenital varicella syndrome. Similarly, chorionic villus sampling with PCR to show virus and cordocentesis to show fetal VZV IgM indicate only fetal infection, not the development of the congenital syndrome.

The most helpful prenatal test is fetal ultrasonography. Unfortunately, the abnormalities may occur late, thus precluding elective abortion. Limb abnormalities carry a 50% risk of mental retardation and early death. Hydrocephalus, liver calcifications, hydrops fetalis, and polyhydramnios may also be seen.

Perinatal Chickenpox

Chickenpox is considered congenital when it occurs within the first 10 days of life, and it results from transplacental transmission of the virus from mother to fetus. Maternal varicella, particularly occurring from 5 days before delivery until 2 days after delivery, results in a higher neonatal mortality (20%-30%) because there has not been enough time for maternal antibody to develop and transfer across the placenta to the fetus. The fetal attack rate is 24%-50%. The incubation period is shorter—9-15 days from the onset of the maternal rash to the development of fetal or neonatal disease. Infants may have a very mild infection with few lesions or may have severe disease, with widespread cutaneous and visceral involvement, including encephalitis and hepatitis. Death most often occurs secondary to pneumonia. Zoster may also occur and represents an intrauterine infection.

Dried blood spots from the Guthrie cards of greater than 400 children with cerebral palsy were compared with case controls for the presence of neurotrophic viruses as determined by PCR.[92] Although seroprevalence was high even in control infants (nearly 40%), the presence of VZV DNA nearly doubled the risk of cerebral palsy.

Postnatally acquired chickenpox occurs between 10 and 28 days of life. The infection is usually mild and is unlikely to result in death. An outbreak may occur within the neonatal intensive care unit (NICU) but is much less common than in pediatric units.

Laboratory Diagnosis

PCR of vesicular fluid or a scab, or even saliva during the acute infection, is now the preferred method for diagnosis. Culture and direct fluorescent antibody (DFA) testing are less reliable. Serologic testing for IgG can detect an increase in antibody titer and document infection retrospectively. The presence of specific IgM usually indicates recent infection but is an unreliable indicator.

Therapy and Prevention

The primary approach to varicella should be preventive. The vaccine seems to protect 85% of individuals vaccinated. Pregnancy should be avoided for at least 1 month after vaccination, but there have been no cases reported of fetal malformations in inadvertently immunized pregnant women. Nursing mothers may be immunized as the vaccine strain has not been detected in breast milk. Healthy children should be vaccinated promptly, according to the immunization schedule, at ages 12-15 months and 4-6 years. Parents should be counseled about the possibility of a febrile seizure resulting after vaccination. There should be at least 3 months between doses when catch-up vaccination is being given. There are separate recommendations for children with chronic disease or immunodeficiency or those who are receiving steroids. The vaccine should also be given to an otherwise healthy child at least 12 months of age within 3-5 days of exposure and repeated at the appropriate age.

VZIG should preferably be given within 96 hours after exposure. It modifies the course of infection but does not prevent it. Passive immunization should be administered to any infant born to a mother who develops varicella 5 days before delivery to 2 days after delivery. Because a high dose would be needed, it is not recommended that the mother be given VZIG before delivery for passive immunization of the infant.

Acyclovir is the antiviral drug of choice for any infant with severe or potentially severe chickenpox, whether congenital or postnatal in origin. No acute toxicity has been shown after acyclovir use for neonatal HSV infections, although the dosage for neonatal chickenpox is much higher, and long-term toxicity is unknown.

Although nosocomial cases of chickenpox are uncommon in the nursery, they may occur. Strict respiratory droplet isolation of any patients with active lesions or in the incubation period needs to be implemented, and only visitors and staff with prior immunity should be allowed in the room. Strict hand washing and contact precautions are a necessary. Postnatal exposure of a term infant 2-7 days of age should carry little additional risk. Infants with low birth weight or preterm infants may be at considerable risk, however, because they were born before the transfer of maternal antibody across the placenta. All hospitalized exposed preterm infants with birth weight 1000 g or less or gestational age less than 28 weeks should receive VZIG or IV acyclovir, regardless of the maternal immune status. Hospitalized, exposed preterm infants (≥28 weeks' gestation) should receive VZIG or IV acyclovir if the mother lacks a reliable history of chickenpox or serologic evidence of immunity. VZIG cannot be used to control the spread of varicella in a nursery because it only modifies, but does not prevent, the course of chickenpox. Infants with congenital varicella syndrome do not need to be isolated if all the skin lesions have healed.

Strict preventive measures are also necessary in the delivery and nursery services. If the mother has active lesions

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of chickenpox at the time of delivery, she must be isolated from other patients and the staff. If the maternal lesions appear within 5 days before delivery and 2 days after delivery, the infant should be protected further with VZIG. If the mother had chickenpox before delivery and her lesions have healed, she need not be isolated, but the infant should be, preferably in the mother's room, during the incubation period. An infant with congenital chickenpox also needs isolation and treatment but may remain with the mother. If the mother was exposed to chickenpox 6-20 days before delivery and she has no history of chickenpox, she and her infant need to be isolated while her susceptibility is being confirmed via serology, and VZIG should be given to the infant if the mother develops lesions within 48 hours of delivery. The mother and the infant may be discharged home together. If the mother develops the varicella rash postnatally, the infant has already been heavily exposed, and transplacental transfer of maternal anti-VZV IgG and breast milk antibodies may decrease the severity of the infant's infection.

Epstein-Barr Virus (Human Herpesvirus 4)

EBV, a B-lymphotropic herpesvirus, is among the most prevalent of human viruses. Greater than 95% of pregnant women are seropositive. When EBV infects adolescents, it may cause infectious mononucleosis, but most infections are asymptomatic. The development of a rash is more common when infection is treated with ampicillin or other penicillins. CNS and hematologic symptoms and, rarely, disseminated disease, which is usually fatal, may occur. Lymphoproliferative disorders may also result from infection. The virus has been associated with a few malignancies, most often in Africa and Asia. A case-control study of more than 400 children with acute lymphoblastic leukemia (ALL) showed an association of maternal infection with EBV at 12-14 weeks' gestation.[145] Further study indicated reactivation may also be associated with non-acute lymphoblastic childhood leukemia.[257] However, the Guthrie cards of 54 children with ALL failed to show any DNA of EBV via PCR testing.[96] Findings from this and other studies have left the matter open to question. Finally, using quantitative real-time PCR to detect viruses in the tissue of infants who died as a result of sudden infant death syndrome compared with controls, there was a statistical association with EBV and HHV-6[9] and sudden infant death syndrome.[9]

Humans are the only natural hosts for the virus; as is typical of herpesviruses, the virus is excreted intermittently during reactivations for the remainder of the individual's life. Transmission, via saliva, seems to require close, personal contact. Fomites are not believed to transmit infection, even though virus may be viable for hours in saliva outside the body. Infection is endemic year round. Blood transfusion has also been documented to transmit virus occasionally.

Primary infection is rare during pregnancy because nearly all pregnant women are immune. The virus can be detected in cervical secretions by DNA hybridization. IgG and IgM to the viral capsid antigen can be detected in the acute infection, whereas IgG to the EBV nuclear antigen is detectable during latent infection.

Several studies have associated the occurrence of a primary infection in the first trimester of pregnancy with an adverse outcome, including prematurity and pregnancy-induced hypertensive diseases, although these associations remain unproven. EBV can cross the placenta and has been shown to cause placental infection, but the pregnancy outcome seems to be normal. There do not appear to be any congenital anomalies.

There is a report associating the presence of CMV and EBV viral DNA (rarely found in the blood of the newborn screening cards) with the development of cerebral palsy. The viruses were not found in the blood of the case controls.[161]

Human Herpesvirus 6 and 7

The role of the T-lymphotropic viruses HHV-6 and HHV-7 in human infection is just being recognized because HHV-6 was identified only in 1986, and HHV-7 was identified even later. They are double-stranded DNA members of the herpesvirus family, and are closely related to CMV. Like all herpes viruses, they cause persistent and lifelong infection. They are present worldwide, and humans are the only known hosts. There is only one variant of HHV-7, but two variants of HHV-6—A and B. Reflecting the high seroprevalence in adults, most infants have maternally acquired HHV-6 and HHV-7 IgG antibody, which wanes over the first 6 months of life, at which time these infants become seronegative and more susceptible to infection. HHV-6B infection is common in infants 6-12 months of age, and most children are seropositive by age 2 years. HHV-7 is acquired later than HHV-6 but is usually acquired by age 5-6 years. After infection, the virus persists for life and is shed in saliva, which is recognized as the major source of transmission. The mean incubation period is 9-10 days for HHV-6 and not known for HHV-7.

Many infants with primary HHV-6 infection are afebrile, although infants infected at younger than 6 months of age were more likely to be febrile than infants infected after 6 months.[292] Symptoms were present, however, in greater than 90% of cases of primary infection. These may include high fever without rash and sometimes cervical or postoccipital lymphadenopathy, otitis media, and respiratory or gastrointestinal disease. There may rarely be hepatitis or a mononucleosis syndrome. One fourth of the infants were diagnosed with infantum subitum (roseola), which causes an erythematous maculopapular rash when the fever resolves. Persistent and reactivated infection has not been shown to cause illness but does persist in the brain, and HHV-6 has been implicated in some cases of meningitis and encephalitis in infants and children younger than 2 years of age. It is also associated with febrile seizures in 10% of these febrile infants, and some of these infants develop

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status epilepticus. HHV-7 infections are usually asymptomatic, but a few may cause roseola and may be responsible for recurrent cases of roseola, in which case it remains unclear whether they are the primary cause or simply able to reactivate HHV-6. HHV-7 is also responsible for febrile illness and cases of febrile seizures. Again, whether the seizures are caused by the HHV-7 infection or by reactivation of HHV-6 is still being debated.

HHV-6 is the only herpesvirus that can integrate its genome into the human chromosome, and many authors have hypothesized that HHV-6 congenital infection is inherited chromosomally and not transferred across the placenta.[256] There are no cases of congenital HHV-7, which cannot integrate into the chromosome.[98] About one third of congenital HHV-6 infections are caused by HHV-6A. The remaining two thirds are caused by HHV-6B. All cases seem to be asymptomatic.[98] This is in contrast to HHV-6 infections later in infancy, all of which are caused by HHV-6B. Although HHV-6 can be transmitted transplacentally from mother to fetus with maternal re-infection or reactivation of infection, congenital HHV-6 infections can be inherited from the chromosomes of either or both parents. Congenital infection was found in 1% of US infants, a rate similar to those in other western European countries,[98] and is not known to cause any clinical disease. However, there is one report of 57 newborns with HHV-6 congenital infection and 242 control newborns without infection showing significantly lower developmental scores on the Bayley-II Mental Index at 12 months of age compared with the scores in the controls. There were no effects on the visual or hearing screens.[39] HHV-7, but not HHV-6, has been found in human milk.

Diagnosis remains difficult. Few assays are commercially available. Indirect immunofluorescence can be used to distinguish HHV-6 from HHV-7 IgG antibody and can be followed for a fourfold rise in serial titers, but IgM antibodies cannot always be detected in young children with primary infections. Also, antigen detection can be used to determine active HHV-6 and HHV-7 infections, but the assays are not sensitive in young children. Of note, confirmation of infection does not change the management of the infant in the majority of cases.

Paramyxoviruses Family

Paramyxoviruses are being increasingly noted as significant causes of human disease. Their spectrum has been greatly expanded with the discovery of human metapneumovirus (hMPV). They are single-stranded, RNA viruses with a lipid envelope. Among the human pathogens, there are two subfamilies. The Paramyxoviridae subfamily includes the parainfluenza viruses (PIVs) and the mumps and measles viruses. hMPV, along with the related respiratory syncytial virus (RSV), belongs to the other subfamily, the Pneumovirinae.

Parainfluenza Virus

PIVs are enveloped, single-stranded, negative-sense RNA viruses in the Paramyxoviridae family. The four antigenic types (1-4) belong to the same subfamily as the mumps and measles (rubeola) viruses. Spread occurs through direct contact with infected respiratory secretions, via either respiratory droplets or contact with contaminated secretions on fomites. PIV-3 has been shown to survive for at least 10 hours on nonabsorptive surfaces (countertops) and 4 hours on absorptive surfaces, such as hospital coats, but die within minutes on finger pads.[12,26] Infection may occur year round, but seasonal or nosocomial outbreaks also occur. PIV-1 and PIV-2 outbreaks of croup or other respiratory illnesses tend to occur in the fall season, whereas PIV-3 outbreaks, which are associated with bronchiolitis and pneumonia in infants, are more likely to occur in spring and summer. Parainfluenza may also exacerbate symptoms of chronic lung disease.

Nearly everyone is infected with all PIV types by 5 years of age. PIV-3, the most common cause of respiratory illnesses of all the serotypes, is also the most common type in infants younger than 12 months of age, infecting about half of them in that first year.[279] PIV-3 seems to spare infants in the first 4 months of life because of the presence of transplacentally acquired neutralizing antibodies, but it is the usual source of nosocomial nursery outbreaks, spread via health care workers,[93,163,177] often in the presence of overcrowding. Older, convalescing preterm infants seem to be at increased risk of severe disease in nursery outbreaks, consistent with waning levels of maternally acquired antibody,[177] and this may result in a high mortality rate among chronically ill infants. The incubation period is 2-6 days, and virus may be shed for 3 weeks or longer by infected infants. Immunity is incomplete, so re-infections may occur with all of the serotypes, but they mostly cause only mild upper respiratory infections.

PIVs have been regarded as second in frequency to RSV as a cause of respiratory infections. Rhinovirus seems to be more common in respiratory infections, however, and the more recently discovered hMPV is also probably more common than PIV. As a group, PIVs are responsible for upper respiratory infections, laryngotracheitis (croup), bronchiolitis, and pneumonia. PIVs may also exacerbate asthma symptoms. PIV-1 and PIV-2 are more likely to cause croup, whereas PIV-3 is highly associated with bronchiolitis and pneumonia, particularly in infants and young children. Respiratory infections from PIVs may be difficult to differentiate clinically from infections caused by RSV. In young children and infants, these infections tend to be mild with a very low mortality rate. Infected children may require supplemental oxygen but rarely need ventilatory support. A few infants are asymptomatic. PIVs have been identified as a cause of 13% of community-acquired pneumonia in infants.[144] Co-infection with other respiratory viruses may occur in 20%-60% of infants and may increase the severity of the infection.[50] In newborns, the infection is more similar

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to a severe RSV infection. Infants may have apnea, bradycardia, and pneumonia, and there may be worsening of chronic lung disease.[93,163,177,279]

PIV infection may be diagnosed by isolating the virus from nasopharyngeal secretions or by rapid antigen detection techniques, such as immunofluorescence and by PCR antigen detection. Serologic detection is not helpful. Prevention of nosocomial infections requires strict adherence to contact and respiratory precautions and strict hand washing. Treatment is largely supportive. Severely ill infants must be monitored closely for need for oxygenation and ventilation. Severe laryngotracheobronchitis has been treated with racemic epinephrine and parenteral corticosteroids, which decrease symptom severity and duration of hospitalization. Antibiotics may be used if there is bacterial superinfection. The usefulness of ribavirin or IVIG remains unproven.

Mumps

The mumps virus is an RNA virus in the paramyxovirus family, and humans are the only natural hosts. The virus is transmitted via respiratory droplets, saliva, and fomites. The incubation period ranges from 7-23 days, but is generally 14-18 days. The virus is readily isolated from saliva, urine, and CSF but is usually identified by reverse transcriptase PCR (RT-PCR) of buccal swabs. Diagnosis can also be made by observing an increasing antibody titer. Treatment is supportive. Respiratory droplet precautions should be taken for any individual within the incubation period or with active mumps.

The mumps vaccine was licensed in 1967 and recommended for routine childhood vaccination in 1977. A two-dose routine was begun in 1989. Since then, the incidence has declined to 0.1/100,000. Because of the high immunization coverage in the United States, there have been a couple of outbreaks of mumps since 2006, primarily among college students who received two doses of the vaccine. Two doses of the vaccine are considered 88% effective in preventing infection. Symptoms in breakthrough disease are usually mild.

Clinically, the virus causes a prodrome of fever, malaise, and myalgia, usually followed by salivary gland swelling within 24 hours and then resolving within 1 week. The parotitis is usually bilateral and more often involves the parotid glands than the submaxillary glands; the sublingual glands are involved only rarely. Orchitis may rarely develop in infancy, but is usually found only in postpubertal boys, and rarely causes sterility. Likewise, aseptic meningitis and pancreatitis are uncommon complications usually found in older children. CSF pleocytosis is common, even without CNS symptoms. Finally, infection may be asymptomatic or limited to respiratory symptoms. Therapy is nonspecific and supportive.

There is no evidence that mumps is either more common or more severe among pregnant women compared with nonpregnant women. Deaths are exceedingly rare. Siegel and Fuerst[241] found no significant increase in risk of low birth weight among infants born to mothers with mumps when studied prospectively. In contrast, there is a considerable increase in the risk of a first-trimester (but not a second- or third-trimester) abortion; the risk can be 27% among women with first-trimester mumps compared with a risk of 13% for uninfected, controls.

Although there have been multiple reports of birth anomalies after mumps in pregnancy, there is lack of proof of association, and studies using controls have failed to find any increase in congenital malformations. There has been considerable discussion about a possible association between gestational mumps and endocardial fibroelastosis in infants. Statistical evidence is, however, lacking, and the issue remains debatable. Pregnancy should be avoided for 28 days after the live-virus mumps vaccine has been given, although there are no reports of malformations in the infants of pregnant women who were inadvertently vaccinated.

Congenital and postnatal cases of mumps are exceedingly rare and nearly always subclinical or very mild. Mumps as a cause of parotitis or aseptic meningitis is rare; even mothers with active mumps rarely infect their infants. There have been a few reports of mumps pneumonia causing severe respiratory distress and death in infants. There have been no reports of nosocomial epidemics of mumps in the nursery; transmission within the hospital is possible, but rare.

Rubeola (Measles)

The measles virus, which is also a paramyxovirus, has an RNA core and a lipid envelope. Humans are the only natural hosts. There is only one serotype.

Transmission

Rubeola is the most infectious of the childhood viral illnesses. It is most commonly found in late winter and in spring in temperate climates. The virus is usually transmitted via respiratory droplets but may be airborne. Individuals are infectious from the onset of the prodrome (3-5 days before onset of the rash) until 4 days after the onset of exanthema. The incubation period is usually 10-12 days with a range of 7-21 days, but it is difficult to recognize the time of exposure because patients are infectious during the prodrome. There is a 5% primary vaccine failure rate in individuals who receive only a single dose of the vaccine; therefore, a two-dose vaccine schedule is now routinely recommended. Most cases and outbreaks of measles in the United States continue to occur in nonvaccinated individuals from other countries, and the virus is no longer considered endemic in the United States. However, there continue to be cases among infants less than 12 months of age and in women with waning immunity. This is of concern as the age of childbearing has increased during recent years.

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There have also been calls for the development of a better vaccine.[212]

Transplacental, hematogenous transmission may also occur. In this instance, the fetus may have onset of disease virtually simultaneously with the mother, implying a large enough initial viral titer so as not to require further viral replication and viremia in the fetus.

Laboratory Diagnosis

Although the virus may be cultured from nasopharyngeal secretions, blood, urine, or other specimens, it is difficult to isolate, so most diagnoses are made through serology. A significant increase in IgG antibody concentration can be used if acute and convalescent sera are obtained, but most commonly, serum IgM titers are used. IgM may remain elevated for at least 1 month after the onset of the rash. RT-PCR can identify viral RNA in nasopharyngeal, blood, urine, and throat specimens. Measles is required to be reported to the CDC within 24 hours of suspicion of infection. Also, it is recommended that specimens be tested for rubella in any instances in which there is a suspicious rash with a negative IgM for measles.

Clinical Manifestations

Clinically, the prodrome of measles begins with fever, cough, coryza, and conjunctivitis (with photophobia) and ends with the development of myriad Koplik spots, tiny, red-ringed white spots on the buccal mucosa. The maculopapular exanthema then begins over the head and neck, spreading to the trunk and upper extremities, then to the lower extremities, and finally fading in the same order over 7-10 days.

Measles pneumonia, often complicated by bacterial superinfection, is the most serious complication and is the usual cause of death in children younger than 1 year of age. The mortality rate in the United States is, however, only 0.1%. Measles encephalitis, leading to drowsiness, seizures, and coma is uncommon but may occur in newborns and has a mortality rate of 11% and the potential for significant morbidity. Otitis, croup, purpura, myocarditis, pneumonia, diarrhea, and subacute sclerosing panencephalitis (SSPE) may also occur. SSPE is rarely seen now that there is widespread measles immunization. It is a degenerative CNS disease occurring 7-11 years after wild-type measles infection and leading to behavioral and intellectual deterioration and death.

Effects on the Pregnant Woman

The clinical course of rubeola in either a pregnant or postpartum woman is the same as in a nonpregnant woman. The earliest reports of overwhelming pneumonia (often associated with congestive heart failure) caused by infection during pregnancy were tempered by many others in which maternal morbidity and mortality rates were not increased. In the measles epidemic in the United States from 1988-1991, infection during pregnancy was again associated with more serious complications, such as pneumonia and hepatitis. The mortality rate was 3%-8%.

Effects on the Fetus

Measles during pregnancy does not seem to be teratogenic because few to no malformations have been reported among infants born to mothers infected during epidemics. There are reports of fetal losses with infection during pregnancy. Measles also seems to be responsible for premature delivery, and these deliveries occur during or shortly after the acute illness. Some infants have experienced growth restriction.

Perinatal Measles

Perinatal measles includes infections acquired transplacentally and infections acquired postnatally. Infection is assumed to be transplacental in origin if it occurs before 10 days of life. Most infants born to mothers with measles at or just before delivery remain uninfected, however, and become susceptible to disease later on. The disease itself may be mild but may also be fatal and is often associated with pneumonia, particularly among infants born prematurely. Postnatally acquired rubeola is usually mild with minimal mortality because the infants still have good levels of maternally derived antibody. Of great concern are reports of infants who were infected with measles before 2 years of age and went on to develop subacute sclerosing panencephalitis without the prolonged incubation period normally seen. They become ill with rapidly progressive disease before age 5 years.[60]

Therapy and Prevention

The therapy for measles is usually symptomatic. No specific antiviral therapy is available. Ribavirin is not licensed for use in the treatment of measles. Vitamin A is now recommended for all children with measles, regardless of where they live, because it is known that some infants and children in the United States have vitamin A deficiencies. Infected patients should be isolated, and the isolation should include precautions against air-borne transmission. Exposed, unimmunized individuals may be given measles vaccine within 72 hours of exposure because vaccination sometimes affords protection.

Nonimmunized pregnant women and newborns who have no history of rubeola and who are exposed should be given immunoglobulin, 0.25 mL/kg, preferably within 72 hours of exposure. The live attenuated measles vaccine should be administered to infants at 12-15 months of age, when maternally transferred antibodies are beginning to wane. The dose should be repeated at the time of school entry to ensure that individuals with waning immunity are protected. Vaccination given before a child reaches 12 months of age should not be counted toward the two doses. The dose should be repeated at age 12-15 months. The vaccine is contraindicated in pregnancy, and a vaccinated woman should be counseled not to become pregnant for 28 days. Susceptible women who deliver during the incubation period or with rubeola need to be isolated from their infants

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if the infant is not born with a rash. Only immune staff and visitors may be allowed in the room. Immunoglobulin should be given to the mother and infant, preferably within 72 hours of exposure or immediately after delivery if no rash is present. If siblings at home have measles when a susceptible mother and infant are discharged, the mother and infant should receive immunoglobulin.

True prevention of rubeola lies in maintaining high immunity in the population. This maintenance of immunity necessitates second vaccine doses to young adults, and this is particularly important now that women are becoming pregnant at an older age, at which time their immunity may be waning, especially if they had received only a single vaccine in their childhood. It has also been shown that preterm infants born before 32 weeks' gestation have very low levels of transplacentally transferred antibody and are susceptible to infection by 6 months postnatally. Extremely preterm infants vaccinated at age 15 months, however, show an antibody response that is similar to that of term infants. It is particularly important that pediatricians continue to emphasize to their patients' families that MMR (mumps-measles-rubella) vaccination has *never* been shown to have a causal relationship to autism in numerous very large studies.

Respiratory Syncytial Virus

RSV is now recognized to be the most common respiratory pathogen in infants and children, infecting nearly all children by age 2 years and re-infecting about 50% of children each year. In the United States, about 2%-3% of infants younger than 1 year of age are admitted to the hospital with bronchiolitis. Most of the hospitalizations for RSV actually occur in the first 3 months of life. The mortality rate is roughly 2 per 100,000 infants. In infants who acquire the virus nosocomially, the mortality rate appears to be high, possibly because of underlying, pre-existing pulmonary disease.[280] RSV usually causes a mild upper respiratory infection but may be responsible for severe pneumonia and bronchiolitis, especially in high-risk populations. RSV usually occurs in the winter to early spring months in temperate climates, with a few relatively isolated infections during the rest of the year. This season overlaps that of other respiratory viral pathogens, so co-infections are common (≈20%). It is unclear how this affects disease severity. hMPV has roughly the same season as RSV and is increasingly being found to cause co-infection with RSV, now that it can be identified, but rhinovirus and adenovirus are also commonly found with RSV; influenza, parainfluenza, and newer coronaviruses (CoVs) are found less commonly. Infection is predominant in tropical climates during the rainy season.

RSV is a single-stranded, enveloped RNA paramyxovirus that can be divided into A and B types and divided further into subtypes. Both types may be present during epidemics, although one type is usually predominant. Although viral load seems to correlate with severity of infection, the subtype may also correlate with severity, clinical course, and outcome. Because there is a 50% sequence divergence between type A and type B, infection with one type does not protect against infection with the other. Also, immunity is incomplete, and re-infection commonly occurs among infants, children, and adults. The viral genome encodes for 10 different proteins. Two surface proteins are particularly important. The fusion (F) protein is similar in all strains. It is responsible for the cell fusion, or syncytium, for which the virus is named. The G glycoprotein is an attachment protein, and it is responsible for the strain differences. There is no neuraminidase or hemagglutinin activity.

A few infants are infected with RSV during the first 3 weeks of life when levels of transferred maternal neutralizing antibody are at their highest. Infants with the highest antibody concentrations may have less severe infections. The effect of antibody in breast milk is inconsistent.

Transmission

Transmission of RSV most commonly occurs by direct contact with infected secretions from the hands to the nose or the eye. Humans are the only source of the virus. Hospital staff members play a major role in the nosocomial spread of RSV via this mechanism, but this can be addressed effectively with good hand washing. Transmission may also occur via large droplets for less than 3 feet or via fomites because live virus may be isolated for a half hour from skin, 2 hours from gowns and gloves, and 1 day from glass or plastic. Viral shedding usually occurs over 3-8 days, but may last for weeks in high-risk or immunocompromised children. Incubation may be 2-8 days. Nursery epidemics of RSV bronchiolitis and pneumonia have been described, and some have occurred simultaneously with parainfluenza and rhinovirus. In such epidemics, one third of the nursery staff may be infected, and this may be the cause of much of the spread within the nursery.

Clinical Manifestations

Children in high-risk groups, particularly children who have pulmonary hypertension, heart disease, and lung disease, have a greater likelihood of severe disease, hospitalization, and mortality. Premature infants are particularly likely to require hospitalization if they have bronchopulmonary dysplasia but are still 10 times more likely to be rehospitalized compared with term infants with RSV, even if the premature infants do not have chronic lung disease. They are also more likely to be rehospitalized with RSV disease if they are born just before or during the RSV season or are discharged between September and December. Children with cyanotic or complex congenital heart disease or those who have Down syndrome are noted to have a higher mortality, and children who are immunocompromised or have cystic fibrosis are more likely to have severe disease, higher rates of mortality, and pneumonia. Long-term corticosteroid therapy seems to prolong the duration of viral shedding, and has not been shown to decrease the severity of disease. Finally, healthy infants younger than 6 weeks of age

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are more likely to develop lower respiratory tract infection and require prolonged hospitalization and intensive care. More recently, it has been shown that infants with vitamin D deficiency at birth are more likely to be infected with RSV during infancy.[17]

There have been numerous studies to determine risk factors for infection, with a fair amount of variation in results. Because 3%-5% of all infected infants are born at 33-35 weeks' gestation, the cost of administering palivizumab to all is prohibitive, so treatment with palivizumab is usually limited to infants at higher risk. High-risk factors include preterm birth, chronic lung disease of prematurity, postnatal age less than 6-10 weeks at the onset of the RSV season, cyanotic and complex congenital heart disease, pulmonary hypertension, neurologic disease, and immunodeficiency. Most studies report increased risk from other children, but this is variously documented as having two or more siblings, having school-age siblings or preschool-age siblings, or attending daycare.

Some reports find disease associated with the adverse effects of maternal prenatal smoking on lung growth and development in the fetus, whereas others indicate a worse effect secondary to smoking within the home. In the United States, Hispanic infants and Native American and Alaskan infants are more likely to be hospitalized compared with infants in the general population. Other reported risk factors include small for gestational age (<10% birth weight), male gender, multiple birth, cystic fibrosis, and family history of eczema. Reports vary concerning a family history of asthma or the effects of breastfeeding.[25,81,217,231,232] Single-nucleotide polymorphisms, such as those in the promoter region of the gene for interleukin-8 (IL-8), have also been associated with chronic pulmonary morbidity after RSV infection in term infants.

Young infants with infection may be asymptomatic. When symptoms occur, they are often nonspecific or are mild upper respiratory symptoms, such as a clear nasal discharge, cough, and coryza. Some infants have presented with respiratory arrest secondary to apnea. Others have simply developed bradycardia. Dyspnea, cyanosis, pulmonary infiltrates on the chest radiograph, wheezing, respiratory decompensation, and fever all are well described. About two thirds of young children develop bronchiolitis, and one third develops pneumonia. Very premature infants may have minimal respiratory symptoms at first and may simply present with poor feeding, irritability or lethargy, and apnea. Fifty percent of infants may also have otitis media.

Although most febrile infants with bronchiolitis have a low risk of concurrent bacterial infection, the risk is significantly higher in preterm infants. Resch et al.[223] reported that 9.5% of infants born at less than 37 weeks' gestation had concurrent bacterial infections compared with 3.1% of term infants. Length of hospital stay was more than doubled. Infections tend to occur in the urinary tract and in the tracheal aspirate, and some occur in the bloodstream.

The diagnosis is usually made rapidly from anterior nasopharyngeal or nasal swabs by using immunofluorescence and enzyme immunoassay techniques, which have variable sensitivity, depending on the assay used and the amount of virus being shed. Culture of secretions is possible but results in delayed diagnosis and may miss co-infection with another virus. Infections with parainfluenza, rhinovirus, adenovirus, and hMPV may mimic RSV infection in an infant. Serologic testing is of limited value, particularly in young infants. PCR may also be used to detect antigen, but it detects RNA rather than DNA. The RNA may persist for weeks after the infection has subsided. Infections with parainfluenza, rhinovirus, adenovirus, and hMPV may mimic RSV infection in an infant.

Subsequent Respiratory Morbidity

Infection with RSV in term infants, particularly in the first year of life, is associated with chronic respiratory sequelae; this has been documented consistently in all clinical studies.[249,290] Term infants hospitalized for RSV bronchiolitis are three times as likely to have recurrent wheezing and 10 times more likely to need bronchodilators at age 10 years.[187] Likewise, the prevalence of asthma at 7½ years of age was 30% among infants hospitalized for RSV bronchiolitis, but only 3% in controls.[242] In contrast, the incidence of asthma was significantly less (50%) among 7-year-olds who had two or more uncomplicated upper respiratory infections, or "colds," before age 1 year.[109,134,249] RSV bronchiolitis in the first year of life increases the likelihood of recurrent wheezing but may or may not increase atopy.[102] The incidence of recurrent wheezing seemed to decrease in studies of longer duration, but there may be some abnormalities in pulmonary function even in adults. It is unclear why these infants are more predisposed to recurrent wheezing. Severe infection may be a marker for a genetic predisposition,[248] or RSV bronchiolitis may induce long-term changes in the lungs when infection occurs at a certain developmental stage.[134]

Preterm infants are more likely to be infected with RSV and develop more severe lower respiratory tract disease compared with term infants. Preterm infants, particularly if they develop chronic lung disease of prematurity, have smaller airways, which are more likely to become obstructed with mucus, necrotic tissue, and edema. They are also more likely to have immature immunity and lack significant maternal transfer of antibodies. Likewise, term infants with abnormal pulmonary function resulting in smaller-size airways are predisposed to developing severe lower respiratory tract infection with RSV. Similarly, Broughton et al.[32] showed that symptomatic RSV infections were more likely to develop in preterm infants with increased respiratory resistance at discharge from the NICU at 36 weeks' corrected gestational age. On follow-up at 1 year of age, preterm infants who had RSV infections have significantly higher airway resistance, but similar lung volume, as in controls.[33] Finally, preterm infants treated with palivizumab who were not hospitalized for RSV were less likely to develop recurrent wheezing (13%) compared with all preterm infants who did not receive palivizumab (26%) and compared with

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untreated preterm infants who were also not hospitalized for RSV (23%).[244]

Prophylaxis and Therapy

The primary treatment for RSV infection is supportive care and includes oxygen therapy to correct hypoxemia and hydration. Care must be taken to prevent hyponatremia because infants with bronchiolitis have elevated levels of antidiuretic hormone. Bronchodilators have frequently been used but are not recommended because they do not improve oxygenation or reduce the need for hospital admission, the time to disease resolution, or the length of hospital stay. Likewise, nebulized epinephrine has not been shown to be beneficial. Corticosteroids are not recommended for bronchiolitis in infants and may cause prolonged shedding of virus. Palivizumab is also not recommended for treatment of infection because it has not shown any efficacy. Nebulized hypertonic saline may be of benefit. Antimicrobial therapy is not indicated for bronchiolitis or pneumonia caused by RSV unless there is a concurrent bacterial infection. They may be considered for otitis media. Chest physiotherapy has not been shown to be of benefit either. Nasal continuous positive airway pressure (CPAP) may improve ventilation and oxygenation, as may high flow nasal cannula therapy with heated humidified air. Intubation may be needed for the most severe respiratory failure.

A Cochrane review of 12 trials lacked the power to provide firm conclusions regarding the use of ribavirin.[267] Ribavirin may cause a small improvement in oxygenation, but the evidence does not support a decrease in intensive care unit (ICU) admission or length of stay or the need for ventilation. Weighing against these findings are the cost of treatment and potential toxic risks to the patient and staff, particularly because it is given as an aerosol, so ribavirin use is extremely limited or not used at all. Inhaled nitric oxide and extracorporeal membrane oxygenation have been used for respiratory failure. Most infants do not need antibiotic coverage; possible exceptions are infants needing intensive care and preterm infants.

Infected infants should be isolated with contact precautions. Use of gowns and gloves in addition to masks and goggles has decreased hospital spread. Staff members should not care for infected and uninfected infants simultaneously. Education of staff and family must include hand washing before and after patient care. Staff and family should not be in the hospital when they have respiratory infections. During the RSV season, sibling visitation should be eliminated. In the event of an epidemic, there should be laboratory screening for RSV infection and segregation of infected and uninfected patients and staff. There are no data on the use of RSV immunoglobulin in an epidemic, although there are many anecdotal reports of its use in NICU epidemics. Antibiotics are not routinely needed, except in cases of bacterial co-infections or, sometimes, concomitant otitis.

The primary defense against RSV infection should be avoidance of high-risk settings. The families of all high-risk infants should be instructed in avoidance behavior and careful hand washing. Whenever possible, high-risk infants should not be placed in high-risk situations, such as daycare or other situations where infected children are likely to be present. Infants should never be exposed to tobacco smoke. This is in the control of the family and is much less costly than palivizumab.

RSV IVIG made from donors with high serum titers of neutralizing antibody to RSV was licensed in 1996 by the FDA for prophylaxis of severe lower respiratory tract disease in children younger than 2 years of age at high risk because of bronchopulmonary dysplasia or preterm birth at 35 weeks' gestation or less. It has been replaced by palivizumab and is no longer available.

Palivizumab, a humanized mouse monoclonal IgG_1 antibody, was licensed by the FDA in 1998. The product consists of 95% human amino acids and 5% mouse amino acids. The mouse sequence for antigen binding was grafted to gene segments coding for human IgG; this prevents an antimouse reaction on repeated use. It is active against the A and B viral strains. The antibody binds to the F protein of the virus, preventing its conformational change on the viral surface and, thus, preventing the fusion of the RSV viral envelope with the plasma membrane of the respiratory tract epithelial cell, rendering the virus incapable of entering the cell to replicate. It is given intramuscularly every 30 days for a total of five doses at a dose of 15 mg/kg. The first dose should be given at the onset of the RSV season. Five doses in a season provide adequate serum concentration to cover 6 months in a season. Efficacy is similar to that of RSV IVIG (a 55% reduction in hospitalizations because of RSV in high-risk infants),[110] but it does not prevent otitis media or hospitalizations for other respiratory viruses. It is much easier to administer.[95] Home-based programs for administration seem to improve compliance with regular, 30-day administration and decrease the risk of other exposures in the doctor's office or clinic. No increase in adverse effects has been observed in comparison with controls. Also, palivizumab does not interfere with other vaccinations. It may cause an allergic reaction. If so, no further doses should be given. It is not effective and not approved for the treatment of RSV infections. A follow-up study of preterm infants in their second year of life who had received palivizumab in their first year of life and had not been hospitalized with an RSV lower respiratory tract infection showed a low rate of airway morbidity, recurrent wheezing, and RSV hospitalization in their second season.[77] The AAP Committee on Infectious Diseases in 2014 analyzed the cost-benefit data and concluded that the small decrease in wheezing provided by palivizumab did not justify the costs of the program and severely curtailed the recommended indications for its use.[52] This issue remains extremely controversial.[290]

A trial of palivizumab for infants with acyanotic and cyanotic congenital heart disease showed a 45% reduction in RSV hospitalizations (9.7% versus 5.3%) with the larger decrease in infants with acyanotic lesions.[78] Adverse events and deaths were similar in treated infants and in infants who received a placebo. Also, a 58% reduction in palivizumab

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serum concentration was noted after cardiopulmonary bypass, so the antibody needs to be given when off bypass.

Among infants with less than 33 weeks' gestation, the rate of rehospitalization was at least 13.4% for lower respiratory disease because of RSV when the infants did not receive any RSV prophylaxis. In addition, 11% of the infants were rehospitalized twice in 1 year for RSV.

Current recommendations of the AAP Committee on Infectious Diseases for the use of palivizumab for prophylaxis[52] are as follows:

Eligibility Criteria for Prophylaxis With Palivizumab

A. *Infants with chronic lung disease (CLD) of prematurity*
   1. Preterm infants with a gestational age less than 32 weeks, 0 days, who need greater than 21% oxygen for at least the first 28 days of life during the RSV season in their first year of life.
   2. These preterm infants may continue to receive prophylaxis during their second year of life if they continue to require medical support (steroid therapy, diuretic therapy, or supplemental oxygen) during the 6 months prior to the onset of the RSV season.

B. *Infants with congenital heart disease (CHD)*
   1. Children with hemodynamically significant disease who are receiving medication to control congestive heart failure and will require cardiac surgery, and children with moderate to severe pulmonary hypertension who are in the first year of life and within 12 months of the onset of the RSV season.
   2. Infants with cyanotic heart disease in the first year of life have an unknown benefit from palivizumab, and the decision to administer prophylaxis needs to be made in consultation with the pediatric cardiologist.
   3. Infants younger than 2 years who undergo cardiac transplantation during the RSV season.
   4. Children receiving prophylaxis with palivizumab and who continue to receive prophylaxis after a surgical procedure involving cardiopulmonary bypass, or who are at the conclusion of extracorporeal membrane oxygenation (ECMO), should receive a postoperative dose of 15 mg/kg palivizumab because the procedure causes a mean decrease of serum concentration of 58%.
   5. Infants who do not qualify for palivizumab prophylaxis include:
      a. Infants and children with hemodynamically insignificant heart disease (secundum atrial septal defect [ASD], small ventricular septal defect [VSD], pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus [PDA]).
      b. Infants with lesions corrected by surgery, unless they continue to need medication for congestive heart failure.
      c. Infants with mild cardiomyopathy not receiving medical therapy for the condition.

C. *Preterm infants without CLD or CHD*
   1. Preterm infants born before 29 weeks, 0 days, who are less than 12 months of age at the onset of the RSV season.
   2. Preterm infants born before 29 weeks, 0 days, who are born during the RSV season need less than the full 5-monthly doses.
   3. Infants born after 29 weeks, 0 days, may qualify to receive prophylaxis on the basis of CHD or CLD or other condition.

D. *Children with anatomic pulmonary abnormalities or neuromuscular disorder*
   1. No prospective data for risk are available.
   2. Infants with neuromuscular disease or congenital anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough do have increased risk of prolonged hospitalization for lower respiratory tract infection and may be considered for prophylaxis in the first year of life.

E. *Immunocompromised children*
   1. No prospective data regarding efficacy of prophylaxis for RSV exist, but children receiving chemotherapy or who are immunocompromised may develop severe or fatal RSV disease.
   2. Prophylaxis may be considered for immunocompromised children during the first 24 months of life.

F. *Children with Down syndrome*
   1. There appears to be a slight increase in hospitalization rates in children with Down syndrome, but not enough to justify prophylaxis on the basis of Down syndrome alone.
   2. Prophylaxis may be given if there is qualifying CHD, CLD, airway clearance issues, or prematurity less than 29 weeks, 0 days.

G. *Children with cystic fibrosis*
   1. Children with cystic fibrosis with clinical evidence of CLD and/or nutritional compromise in the first year of life.
   2. Children with cystic fibrosis in the second year of life with manifestations of severe lung disease or weight for length less than the 10th percentile.

H. *Breakthrough RSV hospitalization*
   1. Palivizumab prophylaxis should be discontinued in a child who experiences a breakthrough RSV hospitalization because the likelihood of a second RSV hospitalization is less than 0.5%.

Efforts toward development of a vaccine for active prevention of disease have been hampered by the results of the trial of the formalin-inactivated RSV vaccine, in which vaccinated infants had more severe disease and were more likely to die compared with nonvaccinated infants, possibly because the vaccine interfered with the secretory and neutralizing antibody response to the virus, allowing more active replication. Currently, there is significant interest in developing a maternal vaccine that would lead to transfer of antibody to the fetus. However, preterm infants would

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miss the majority of antibody transfer and might not benefit.

Human Metapneumovirus

Discovered in Holland in 2001, hMPV is an enveloped, negative-sense RNA virus of the Paramyxoviridae family, in the same subfamily with and sharing many clinical characteristics of RSV. It is most closely related to RSV in that both viruses encode for three envelope glycoproteins—the F (fusion), G (attachment), and SH (short hydrophobic) proteins—and both viruses form a syncytium with infected cells. There are four major genotypes: A1, A2, B1, and B2. All four genotypes circulate simultaneously throughout the season, but in varying proportions. It is unclear what effect this simultaneous circulation has on immunity and whether certain genotypes are more virulent than others. hMPV is difficult to grow in the laboratory and has escaped detection but can now be identified through RT-PCR.

A large proportion of previously unidentifiable causes of respiratory tract disease in children and adults have been attributed to hMPV, and it is associated with upper and lower tract disease. Virtually all children are infected by age 5 years,[15] and infection may be recurrent throughout life. hMPV seems to be second only to RSV as a cause of bronchiolitis in children younger than 1-2 years of age.[37] Although RSV is most common in infants younger than 6 months of age, hMPV is more common in infants 6-12 months of age.[90,191] Protection against infection in the first 6 months may reflect the presence of maternal-specific antibody. hMPV occurs in epidemics, mostly in the winter and spring months, and overlaps seasonally with RSV. It may cause a co-infection with other respiratory viruses.[152] During epidemics, bronchiolitis may be caused by RSV or hMPV, alone or together, and infections by various other respiratory viral pathogens have been reported as co-infections. Under these circumstances, disease severity has variably been reported as more severe or unchanged. hMPV is also present in smaller numbers year round. The virus is worldwide in distribution. Humans are the only known source of infection. It is not clear whether the viral load correlates with severity of the disease.

In one study of nasal wash specimens obtained over a 25-year period from newborns to 5-year-olds, hMPV was responsible for 20% of previously virus-negative lower respiratory tract infections, suggesting that 12% of lower respiratory tract infections in these children (newborns to 5-year-olds) were caused by hMPV.[287] In this cohort, the mean age of infected children was 11.6 months. Three fourths of all infections occurred in the first year of life. Infection primarily occurred between December and April and resulted in a hospitalization rate of 2%.

Infection with hMPV seems to be slightly less severe than that with RSV. The disease spectrum has included upper respiratory tract infection (15%), bronchiolitis (59%), croup (18%), pneumonia (8%), and asthma exacerbation (14%). Asymptomatic infection may occur, particularly in healthy children or adults, and most healthy, symptomatic children have only mild or moderate infection. Others present with rhinitis, mild fever, a wet cough, or wheezing. Otitis has also been reported.[222] Increasingly, studies are indicating that severe prematurity (birth ≤32 weeks' gestational age) and chronic lung disease are significant risk factors for the need for hospitalization, ICU admission, and death among children under 5 years of age with lower respiratory tract infections. These children have higher clinical severity scores, need for supplemental oxygen, and a doubled duration of hospitalization.[72,173,194] Because formerly preterm infants often developed hypoxia and children with asthma did not have an increased length of hospitalization, it is hypothesized that this may have resulted from further alveolar damage rather than increased airway reactivity. Infection is believed to occur via contact with contaminated secretions, and the incubation period apparently is 3-5 days. The duration of viral shedding is unclear but may be prolonged in the face of immunodeficiency. Infection may be recurrent at all ages but is usually mild or asymptomatic. A few children may require hospitalization at a lower rate with hMPV infection compared with RSV infection, but similar to the hospitalization rates of influenza or parainfluenza.

Hospitalized patients should be isolated with contact precautions and an emphasis on careful hand washing. Covering the mouth and nose while coughing or sneezing is important. Treatment is supportive. Respiratory monitoring is important and may indicate a need for oxygen or mechanical ventilation. Bacterial superinfection seems to be unusual.

Human Immunodeficiency Virus

Epidemiology

Data from the CDC for the 2010-2014 period showed a decline in the rates of HIV in both male and female adolescents and adults in the United States. In 2015, 19% of all adults and adolescents diagnosed with HIV infection were women. Even though this represents a decline of 5% in this gender group, it is still a significant problem.[43] Most women newly diagnosed with HIV infection acquired it through heterosexual contact. Rates of HIV positivity are disproportionately high among women from minority populations. Despite a decline in the rates of newly diagnosed HIV infection in African American women (by 42% from 2005 to 2014), the rates are still high compared with those of other race groups. In 2015, the CDC reported that the incidence of new HIV infections in African American women was 26.2 per 100,000 compared with 5.3 and 1.6 per 100,000 in Hispanic and white women, respectively.[43] In 2015, according to CDC statistics, a total of 120 children younger than 13 years of age were diagnosed with HIV in the United States; of these cases, 86 had perinatally acquired infection.[43]

In contrast to most adult HIV infections in the United States, that in the developing world is contracted through

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heterosexual means. The incidence is highest in east and central sub-Saharan Africa, Southeast Asia, and parts of South America. In these areas, most HIV-positive patients are middle-aged adults, with the prevalence among childbearing women in some urban centers exceeding 30%. The debilitation and fatality resulting from AIDS have led to the depletion of the vital workforce in tenuous economies and the orphaning of numerous uninfected offspring.

Currently, virtually all HIV-infected infants are found to have acquired the virus from an infected mother. Consequently, most mothers of infected infants in the United States fall into a high-risk category—IV drug use or sexual activity with a man at high risk (bisexuality or IV drug use). Infected children demonstrate a socioeconomic pattern nearly identical to that seen in HIV-1–infected women, and greater than 85% are from minority populations. Reflecting a medical success story of remarkable proportions, the incidence of perinatal HIV in the United States decreased by nearly 80% in the latter half of the 1990s. In the first decade of the 2000s, only 100-200 cases of perinatally acquired HIV infection per year were reported to the CDC. Much of this decline was the result of increased voluntary HIV testing during pregnancy and the widespread application of intragestational prophylaxis with antiretroviral (ARV) drugs. This success has extended to developing countries as well. The World Health Organization (WHO) reported a decline in perinatal HIV from 28% in 2009 to 14% in 2014 in 21 countries where a global plan of transmission reduction had been introduced.[196,263] The goal for the developing world, however, has not been reached, which is to achieve a transmission rate of 5% or less in breastfeeding populations and less than 2% in non-breastfeeding populations.[74]

Pathogenesis

HIV is an RNA-containing retrovirus with an approximately 9.7-kb genome. The virus infects cells contain the surface molecule CD4+, most notably helper T lymphocytes and macrophages. An infected adult initially exhibits a robust immune response to the virus, with the appearance of HIV-specific antibodies and CD8+ cytotoxic T lymphocytes. After an initial mononucleosis-like syndrome, adults experience a prolonged period of clinical latency, characterized by the establishment of stable, low-level plasma viral titers (referred to as the *set point*) and near-normal CD4+ T-lymphocyte counts. During this period, the number of target cells destroyed by HIV is balanced by CD4+ cell repletion. This state may last for years.

Despite the healthy appearance of patients with latent infection, HIV actively replicates in lymph nodes and circulating CD4+ cells and ultimately overwhelms the host, leading to increasing concentration of virus in plasma and tissues, clinical deterioration, and CD4+ cell depletion. This last phenomenon results in profound disruption of the immune system because CD4+ T cells coordinate many aspects of immunity. Thereafter, the host is placed at risk for acquiring infections with organisms that normally possess low pathogenicity (opportunistic infections) and AIDS-related cancers. The strongest predictor of progression of disease in adults is the concentration of plasma-borne virus, commonly referred to as the *viral load*. The viral load is measured by a quantitative RT-PCR test, which is widely available commercially. The number of CD4+ T cells also is an additional independent predictor of disease progression in adults.

Generally, untreated children with perinatal HIV-1 infection experience more rapidly progressive disease compared with adults. Similar to other intracellular pathogens, it is likely that HIV infection of the fetus early in gestation, when natural killer (NK) and T cells are low in number and immature in function, results in particularly severe disease. Even in a full-term newborn, however, T cells possess multiple functional deficiencies that render the host particularly susceptible to pathogens, such as HIV. Early HIV-specific cytotoxic T-cell lymphocyte responses, which are crucial for the initial control of HIV infection in adults, frequently are sluggish or absent in infected newborns. There is evidence that the fetal and newborn immune cells may provide better substrates for HIV infection or replication compared with mature cells because neonatal macrophages and memory T cells support HIV replication better than cells derived from adults. Consequently, infected newborns typically show very high plasma viral loads early in life, frequently registering hundreds of thousands to millions of viral RNA copies per millimeter of plasma by 4 weeks of age. Infants usually are unable to establish a set point, reflecting poor early control of viral replication, and, as a result, show unmoderated high viral loads throughout early childhood.[238]

As in adults, the strongest predictor of disease progression in perinatally acquired HIV-1 is the plasma-borne viral titer. High viral loads in infancy presage major manifestations of HIV and death early in life. Several factors other than viral load also have been associated with disease progression in perinatally acquired HIV-1. Thymic dysfunction, manifested by the early depletion of CD4 and CD8 T-cell populations, occurs in a small percentage of HIV-1–infected infants and is strongly associated with early severe disease. Co-infections with other pathogens in early life may detrimentally affect disease progression further. CMV in particular, long suspected of enhancing HIV-1 replication in adults through transactivating transcription factors, results in higher mean titers of HIV-1 and the early appearance of HIV-1–associated signs and symptoms and death in infants infected with CMV and HIV-1.

Mother-to-child transmission occurs in approximately 25%-30% of infants born to mothers who have not taken antiviral medications during their pregnancy. Intrauterine transmission has been shown directly by detection of virus in aborted fetal tissue. Most infants are negative for HIV immediately after birth, however, and become positive within the first several weeks after delivery, supporting the contention that most perinatal transmission occurs near the time of delivery or as the infant traverses the birth canal. Cervical secretions harbor HIV in concentrations

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proportionate to concentrations in the bloodstream. Infection at or near the time of delivery, when the mucous membranes of the infant are exposed to infected maternal secretions and blood, is assumed to be the principal mode of perinatal acquisition of HIV.

The primary factor that places an infant at risk for perinatal HIV transmission seems to be the degree of maternal viremia during pregnancy and its correlates—severity of maternal clinical illness and CD4 cell depletion.[89] In several studies, the risk of transmission was proportionate to the maternal viral load. No level of maternal viremia is absolutely safe for the fetus, and transmission occasionally has been reported even when the maternal viral load has been undetectable. Nevertheless, vertical transmission rates approaching zero have been associated with viral loads smaller than 500-1000 HIV RNA copies per milliliter of plasma. Other risk factors for perinatal transmission are less well established. The presence of chorioamnionitis and the occurrence of premature rupture of membranes have been suggested as risks for perinatal HIV transmission. Instrumentation during delivery, with the associated exposure of the newborn to infected maternal blood and cervical secretions, also increases the risk of transmission. There also has been speculation that some viral genotypes may be more likely to cross from mother to child than others.

As transmission rates decline, a new population—the HIV-exposed but uninfected infant— has emerged. These infants have been found to have higher morbidity and mortality rates compared with the HIV-unexposed infants. Studies in developing countries have shown that lower respiratory tract infections and oral thrush are more common in this population group compared with their uninfected counterparts. Opportunistic infections, such as *Pneumocystis jiroveci* infection, which is rare in the non-immunocompromised populations, have also been more often described in these children.[74] Immunologically, these children have been found to differ from the rest of the population. CD4 and CD8 counts are lower, and cell-mediated immunity is altered, leading to hyper- or hypo-responses to specific antigens. Neutrophil counts are also decreased, and in the first few weeks of life, there is in innate cytokine production. However, vaccine responses are adequate and sustained in this population. It is hypothesized that exposure to the HIV virus in utero in addition to exposure to ARV drugs may lead to a "hyper-reactive" uterine environment that primes the immune system of these infants.[2]

HIV infection from mother to child also may occur though the ingestion of contaminated breast milk. Breast milk contains the virus in macrophages and in the cell free fraction, and the viral concentration in breast milk correlates with the concentration measured in the bloodstream. In the United States, where alternative infant nutrition is available, breastfeeding is contraindicated in HIV-infected mothers, even in those taking combination ARV therapy (ART). However, in the developing world, the high incidence of mother-to-child transmission of HIV attributable to breastfeeding is estimated to be 4%-22%. Although the risk of breast milk–related late postnatal transmission is highest in the first 6 months post partum, transmission occurs throughout the duration of breast milk exposure.

Breast milk–transmitted HIV is believed to enter the infant either through the gastrointestinal mucosa or possibly through tonsillar lymphoid tissue. Several factors that increase the risk of breast milk transmission, including the duration of breastfeeding, severity of infection in the mother, presence of breast lesions, and inflammation of the infant's gastrointestinal mucosa (particularly by *Candida* infection), have been identified. Several immunologic and chemical factors in breast milk have been found to inhibit HIV growth in vitro, and the relative concentrations of these factors in a particular specimen may influence the risk of transmission.

For resource-poor countries, where breastfeeding is the norm and formula feeding is not readily available, and possibly unsafe because of lack of clean water, the WHO has issued recommendations to prevent transmission to infants through breastfeeding.[288] It is a fact that children born to HIV-infected mothers have a higher risk of transmission through breastfeeding, but have a lower rate of hospitalizations for diarrheal illnesses and other infections in resource-poor areas.[133] Prospective studies have shown that the use of ART starting early in pregnancy is associated with lower transmission rates through breastfeeding as well as the use of ARV drugs (i.e., nevirapine) in the infant during the breastfeeding period in certain scenarios.[46,120,205] Mothers of uninfected infants in resource-poor countries who breastfeed are advised to not introduce any other form of feeding in the first 6 months so as to prevent gastrointestinal irritation from formula and possible transmission of the virus.[288]

Care of the Mother and Prevention of Vertical Transmission

Advanced HIV infection in the mother can adversely affect the outcome of the pregnancy, even if the infant is not infected. Studies performed in Africa have indicated that women with HIV infection bear infants who are smaller for gestational age and more premature compared with women without HIV infection. Perinatal mortality also is increased. Infants born to asymptomatically infected women have negligible effects. These data suggest that covariate factors in advanced HIV disease, particularly malnutrition, secondary and coexisting infections, and illicit drug and alcohol use, are the most important factors mediating the immediate health of the newborn and must be addressed appropriately during the obstetric care of the mother. All women should be placed on multivitamin supplements, which should be continued after gestation.

Care of the Mother and Infant in Developed Countries

Intragestational and postgestational administration of ARV drugs is extremely effective in preventing vertical transmission of HIV-1 and has become the standard of care in

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the developed world.[175] In a landmark prospective, multicenter, randomized trial conducted in the early 1990s (PACTG 076), zidovudine prophylaxis resulted in reduction of vertical transmission, from 25.5%-8.3%.[53] The regimen employed in this study included three phases: (1) a maternal oral dose of 100 mg five times a day beginning between 14 and 34 weeks of gestation; (2) intrapartum IV zidovudine at 2 mg/kg of body weight over the first hour, followed by 1 mg/kg hourly until delivery; and (3) oral dosing of zidovudine at 2 mg/kg every 6 hours for 6 weeks for the infant. In response to the success of this study, the CDC recommended wide application of the PACTG 076 protocol to limit vertical transmission of HIV in the United States. Subsequent experience has indicated that in some populations, intrapartum and postpartum use of zidovudine could result in a 5% or less transmission rate.

Even as public health recommendations for this regimen were being established, significant changes in ARV strategies in HIV-infected adults were evolving and produced dramatic reductions in plasma-borne viral loads and AIDS-related deaths. These changes included the administration of multidrug regimens (rather than monotherapy) and the early institution of ARV medication based primarily on viral load rather than CD4-T cell depletion or the presence of symptoms. As a result, by the late 1990s, many women with HIV infection entering pregnancy already were taking multidrug regimens (formerly known as *highly active antiretroviral therapy* [HAART]) comprising various combinations of nucleoside reverse transcriptase inhibitors (sometimes, but not always, including zidovudine), non-nucleoside reverse transcriptase inhibitors, and protease inhibitors to maintain their own health.

The basic evaluation of pregnant women with HIV-infection should include, among others, the following:

1. Current and previous CD4 lymphocyte counts and HIV RNA viral load in copies/mL.
2. Documentation of any previous HIV-related illness to determine if the patient needs prophylaxis against opportunistic organisms.
3. Screening for co-infections, such as hepatitis B and C virus infections and tuberculosis, and for sexually transmitted diseases, such as gonorrhea and chlamydia. Review of immunization status, including tetanus, diphtheria, acellular pertussis (Tdap) immunization.
4. History of prior and current ART, resistance studies, and side effects of the regimens.

In addition, care of the pregnant patient with HIV infection ideally should be multidisciplinary, with constant communication between the primary caregiver for HIV treatment, the obstetrician, social workers, and other services to ensure patient adherence to the ARV regimen. It is also advisable to involve the pediatrician who will care for the infant to plan for prophylaxis for the infant and to ensure follow-up testing and evaluations.

In 2012, the results of a randomized trial studying three different regimens—zidovudine monotherapy for 6 weeks, 6 weeks zidovudine plus 3 doses of nevirapine in the first 8 days of life, and 6 weeks of zidovudine plus nelfinavir and lamivudine (3TC) for 2 weeks—in the prevention of HIV transmission to neonates whose mothers did not receive ARV during pregnancy were published. The trial (NICHD-HPTN 040/PACTG 043) showed that combination therapy was superior to monotherapy in preventing intrapartum HIV transmission.[185] Following the publication of this trial, the Department of Health and Human Services updated its recommendations to reflect the results of this and other important recent trials.[197]

As data emerge from clinical trials, guidelines are being updated regularly. Therefore, it is recommended that these guidelines be consulted for the most up-to-date information. The full text of these guidelines and updated information are available at http://AIDSinfo.nih.gov.

Some key points from these recommendations (last updated November 14, 2017) can be summarized as follows:

Maternal Antepartum/Intrapartum Care

1. All pregnant, HIV-infected women should receive combination ARV drugs ante partum, starting as early as possible during pregnancy *regardless* of their HIV RNA levels and CD4 T lymphocyte counts. A French cohort study, which looked at factors associated with mother-to-child transmission of HIV despite low viral load at the time of delivery, showed that women who transmitted the virus to their offspring were less likely to have had viral loads less than 500 copies/mL and were also less likely to have received ART at the time of becoming pregnant and early in the pregnancy.[261] It is also known that mother-to-child transmission is possible even with low RNA levels and in mothers on ART. There have been reports of discordance between the viral loads in blood and those in the genital tract; women with undetectable levels in blood have been found to shed the virus in the genital tract.[197,275]
2. Resistance testing is indicated in women whose RNA levels are above the resistance testing threshold (>500-1000 copies/mL) before starting or modifying ARV drug regimens in patients with known HIV infection and those diagnosed early in pregnancy. However, if HIV infection is diagnosed late in pregnancy, therapy should be started even if the results of resistance testing are not available. In all pregnant patients on ARV, the importance of strict adherence to the ARV regimen should be strongly emphasized.
3. IV zidovudine continuous infusion (2 mg/kg IV over 1 hour followed by continuous infusion of 1 mg/kg until delivery) is *recommended* for HIV-infected mothers with **viral loads greater than 1000 copies/mL** near delivery, those in whom viral loads are unavailable near the time of delivery, or in women who did not receive any antepartum ART regardless of the antepartum regimen or mode of delivery.

   Women who are on ART and have well-controlled **viral loads less than 50 copies/mL** consistently during late pregnancy and near delivery and in whom compliance

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has not been a problem, *do not need* IV zidovudine and should continue their drug regimen orally on schedule as much as possible during labor and even before a scheduled cesarean section. This can be accomplished by taking the medication with small sips of water.

For women with **viral loads between 50-999 copies/mL**, the current available data are not sufficient to determine whether IV zidovudine offers additional protection to the infant. Some studies have shown lower maternal-to-fetal transmission in women with viral loads below 50 copies/mL as compared with those with 50-1000 copies/mL; 0.25 versus 2%.[181] Experts, therefore, recommend that IV zidovudine be *considered* in this group of patients, but this is left to the clinical judgment of the provider.

In women who are scheduled for a cesarean section and require IV zidovudine, it should be started 3 hours before the surgery (1-hour loading dose and 2-hour continuous infusion). For emergency cesarean section, the aim is to try to complete the 1-hour loading dose before proceeding with the cesarean section.

4. Expedited testing for HIV should be performed in all mothers without documentation of their HIV status unless they "opt out." Women who are considered to be at increased risk for acquiring HIV (partner with HIV infection, multiple sexual partners during pregnancy, illicit drug use, exchange of sex for money, or living in an area with high incidence of HIV infection in childbearing age) should also be tested at the time of labor, even if testing earlier in pregnancy yielded negative results. Testing should be done with HIV-1 and HIV-2 antigen/antibody combination immunoassay and an HIV RNA assay. These testing modalities should be available in institutions that offer maternity and neonatal intensive care and nursery services. For women who test positive, IV zidovudine should be started immediately.

Infant Management (Summarized in Table 50.8)

1. Depending on maternal risk, infants may receive prophylaxis, empiric HIV therapy, or HIV therapy:
   - *HIV prophylaxis:* This is defined as the administration of one or more ARV drugs to an infant without confirmed HIV to reduce the risk of maternal fetal transmission.
   - *HIV empirical therapy:* This refers to administration of three-drug combination ARV regimen to newborns with high risk of acquiring HIV. This serves as therapy

TABLE 50.8 Management of Neonates According to HIV Risk

Situation	• Mother received ART during pregnancy *and* • No compliance concerns *and* • Sustained viral suppression near delivery	• Mother did not receive antepartum or intrapartum ARV drugs • Mother received only intrapartum ARV drugs • Mothers with detectable viral loads near delivery despite receiving antepartum and intrapartum drugs (especially vaginal deliveries) • Mothers with acute HIV infection during pregnancy or breastfeeding	Presumed newborn HIV exposure: • Mother with unknown HIV status who tests positive at delivery or post-partum • Newborn with positive HIV antibody test	Newborn with confirmed HIV • Confirmed positive HIV virologic testing/NAT
Risk	Low risk of perinatal HIV transmission	Higher risk of perinatal transmission	Higher risk of perinatal transmission	Confirmed HIV
Newborn Management	Prophylaxis with 4 weeks of zidovudine	Combination prophylaxis with 6 weeks of ZDV plus 3 doses of NVP (at prophylactic dose) *Or* Empiric HIV therapy with ZDV, 3TC, and NVP (at treatment dose)	Combination prophylaxis with 6 weeks of ZDV plus 3 doses of NVP (at prophylactic dose) *Or* Empiric HIV therapy with ZDV, 3TC, and NVP (at treatment dose) Discontinue therapy if supplemental test confirm mother is not infected with HIV	3 drug combination ARV therapy: • Start therapy as soon as possible without delaying to wait for confirmatory NAT test result

ART, Antiretroviral therapy; ARV, antiretroviral; HIV, human immunodeficiency virus; NAT, nucleic acid test; NVP, nevirapine; ZDV, zidovudine.

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for those who are later confirmed to be HIV infected and as prophylaxis for those exposed to the virus in utero, during delivery, or via breastfeeding but who do not acquire the virus.

- *HIV therapy:* This refers to administration of three-drug combination ART to newborns with confirmed HIV infection.

2. *Prophylaxis with zidovudine alone:* A 4-week course (as opposed to 6 weeks) can be considered *if* the mother received and absolutely adhered to standard combination ART with consistent viral load suppression during pregnancy and delivery. Data for this recommendation come from a 10-year observational cohort study performed in Ireland, where, since 1999, there was a countrywide adoption of a 4-week neonatal prophylaxis regimen for prevention of mother-to-child HIV transmission. Their regimen included monotherapy with zidovudine if the mother had received more than 4 weeks of ART, had achieved viral suppression, had been adherent to her therapy, and had rupture of membranes less than 12 hours before delivery. Otherwise, they would receive combination therapy with zidovudine, nevirapine (two doses), and lamivudine 3TC. In addition, all mothers received intrapartum zidovudine. In 916 children with known outcome (HIV PCR results known at ≥6 weeks), the vertical transmission rate was 1.09%, and if the analysis was restricted to those whose mothers received at least 4 weeks of ART, the vertical transmission rate was 0.4%.[79] The prophylaxis should be started within 6-12 hours of delivery at doses appropriate for gestational age (Table 50.9).
3. *Combination ARV prophylaxis:* Combination of zidovudine for 6 weeks started within 6-12 hours of delivery plus three doses of nevirapine (nevirapine first dose given within 48 hours of birth, second dose 48 hours after first dose, and third dose at 96 hours after second dose) at

TABLE 50.9 Dosing of Antiretroviral for the HIV-Exposed Infant by Gestational Age*

Antiretroviral	Dose†	Dose Adjustment	Duration
Zidovudine	<30 weeks' gestation at birth 2 mg/kg/dose orally twice daily‡ ≥30 to <35 weeks' gestation at birth 2 mg/kg/dose orally twice daily‡ ≥35 weeks gestation at birth 4 mg/kg/dose orally twice daily‡	Increase to 3 mg/kg/dose at age 4 weeks of life Increase to 3 mg/kg/dose orally at 2 weeks of life Continue same dose through week 4-6 of life	Birth-4 weeks for prophylaxis of infants born to mothers with low risk for maternal-fetal HIV transmission of HIV§ Birth-6 weeks for combination ARV prophylaxis or empiric HIV therapy of infants born to mothers higher risk for maternal-fetal transmission of HIV§
Lamivudine 3TC	>32 weeks' gestation at birth 2 mg/kg/dose orally twice daily	Increase dose to 4 mg/kg/dose orally twice daily at 4 weeks of life	Birth-6 weeks for combination ARV prophylaxis or empiric HIV therapy of infants born to mothers higher risk for maternal-fetal transmission of HIV§
Nevirapine	Prophylactic dose Birth weight 1.5-2 kg 8 mg/dose orally once daily Birth weight >2 kg: 12 mg/dose orally once daily (note: dose is *actual dose* and *not* in mg/kg	Prophylactic dose: needs no adjustment	Birth-6 weeks for combination ARV prophylaxis of infants born to mothers higher risk for maternal-fetal transmission of HIV§
	Empiric treatment dose 34 to <37 weeks' gestation at birth Birth-1 week: 4 mg/kg/dose orally twice daily	Increase dose to 6 mg/kg/dose orally twice daily at 1 week of life	Birth-6 weeks for empiric HIV therapy of infants born to mothers higher risk for maternal-fetal transmission of HIV§
	Empiric Treatment Dose >37 weeks' gestation at birth 6 mg/kg/dose orally twice daily	Continue same dose through week 6 of life	

*Please refer to text for full explanation of recommendations. Please refer to aidsinfo.nih.gov for the most up-to-date recommendations and dosing information as they are updated regularly.
†First dose started within 6-12 hours of birth.
‡If unable to tolerate orally, use 75% of the oral intravenously.
§If the diagnosis of HIV is established, consult with a pediatric HIV specialist.
Adapted from AIDSinfo.nih.gov[196]
ARV, Antiretroviral; HIV, human immunodeficiency virus.

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weight-appropriate prophylactic dose (see Table 50.9) is recommended for infants at high risk of perinatal HIV acquisition. This includes:

- Infants born to mothers who did not receive antepartum or peripartum ARV drugs.
- Infants born to mothers who only received peripartum ARV drugs.
- Infants born to mothers who received antepartum and peripartum ARV drugs but did not attain virologic suppression near the time of delivery, especially if the delivery was vaginal.
- Infants born to mothers with acute or primary HIV infection during pregnancy.

The data from this recommendation come from a study of 1684 infants born to women with a diagnosis of peripartum HIV infection and who, therefore, had not received antepartum prophylaxis. The infants were randomized to three regimens: 6 weeks of zidovudine monotherapy, zidovudine for 6 weeks plus nevirapine × 3 doses, or zidovudine for 6 weeks plus nelfinavir and lamivudine (3TC) for 2 weeks.[185] Intrapartum transmission was higher in the zidovudine monotherapy group as compared to the 2- and 3-drug combination regimens (4.8% versus 2.2% and 2.4%, respectively). In the multivariate analysis, higher maternal viral loads, zidovudine monotherapy, and maternal use of illicit substances were associated with higher transmission rates.

4. *Empiric HIV therapy:* In the 2013 annual conference of retroviruses and opportunistic infections, a case of a baby who may have been cured of HIV infection by early initiation of ART was presented.[228] Also known as the "Mississippi baby," this child was born to an HIV-infected mother whose HIV status was unknown until after the delivery and hence did not receive ARVs antepartum or peripartum. The infant was born at 35 weeks' gestation, and two different tests confirmed the HIV infection (RNA and DNA PCR). At 30 hours of life, the infant was found to be HIV positive. The patient was started on AZT, 3TC, and nevirapine. The infant tested positive by DNA PCR at 6, 12, and 20 days, but the test done at 29 days was negative for HIV. The baby was treated with ART for 18 months, and at the 21-month follow-up, the child was still tested negative, but there was virologic rebound at age 4 years. In a similar case described shortly thereafter, very early administration of zidovudine, 3TC, and nevirapine at 30 hours of life resulted in a sustained period of "remission" with virologic rebound at age 4 years with discontinuation of ART.[36] Both cases illustrate that early treatment with a three-drug ARV regime may result in sustained periods of viral suppression. Several studies from Canada have also shown that early treatment within 30 hours of life with triple ARV regimens results in reduced levels of proviral HIV-1 DNA viral replication in CD4+ in newborns with perinatally acquired HIV.[36] These data have led the panel to recommend a three-drug regimen with zidovudine, 3TC, and nevirapine (at treatment dose) as an option for children at higher risk of HIV transmission. This approach is particularly favored by experts in the setting of acute HIV in pregnancy as the risk of in utero transmission is higher.
5. *HIV therapy:* Three-drug combination ART is recommended for infants with confirmed positive newborn HIV nucleic acid test (NAT). Most experts recommend starting therapy as soon as possible without waiting for a confirmatory NAT because false-positive HIV NAT tests are not common. The results of these tests are usually available during the first week of life. For term and preterm neonates, combination of zidovudine, 3TC, and nevirapine is recommended noting that this is the only regimen recommended for preterm infants at this time because safety and dosing data for other regimens are lacking. Combination of emcitarabine and raltegravir is another option that can be used starting at birth in term neonates. Lopinavir/ritonovir is recommended for term infants older than 2 weeks of age.
6. *Special situations:*
   - Newborns born to mothers with unknown HIV status at the time of delivery: In this situation, expedited testing should be performed on mothers and/or newborns as during labor or as soon after birth. Results should be available within 60 minutes. If testing positive, the infant should be started on combination ART or empiric HIV treatment without waiting for confirmatory tests. Mothers should be instructed to not breastfeed. If confirmatory tests are negative, then breastfeeding can be resumed and ART discontinued.
   - Newborns born to mothers with an ART-resistant HIV infection: Presently, there is no evidence that customized regimens for infants born to mothers with ARV drug–resistant HIV infection are superior to standard newborn prophylaxis. Consequently, in this scenario, it is advisable to consult with a pediatric HIV expert prior to delivery. For areas in which pediatric or adult HIV specialists are not available, the **National Perinatal HIV hotline (1-888-448-8765)** can provide guidance.
   - Mothers diagnosed with HIV infection while breastfeeding: In this circumstance, breastfeeding should be stopped until HIV infection is ruled out. Mothers can either pump and discard or pump and store the breast milk until the confirmatory results are available. Some experts recommend starting postexposure prophylaxis for 4-6 weeks after stopping breastfeeding. Consultation with a pediatric HIV expert is advised.

It is important to plan the discharge of babies on ARV carefully to maximize compliance. Because in many instances there is a delay in registering the infant for insurance and because liquid forms of ARV agents may be difficult to procure from community pharmacies, every effort should be made to supply the family with the infant's medications (not just a prescription) at discharge. In the United States and other resource-rich regions, mothers should be

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counseled against breastfeeding, whether or not they are continuing ART after pregnancy. In addition, the risks of HIV transmission through premastication of food should be emphasized. In 2008, three cases of pediatric HIV were reported. In these children, the feeding of premasticated food by caregivers who had HIV infection was thought to be the method of transmission.[91] Transmission was presumed to be caused by the presence of blood in the caregiver's mouth. Therefore, the CDC recommends that mothers or caregivers with HIV infection should not premasticate food for uninfected infants because this may serve as a potential route of transmission.

Safety

The effectiveness of ART in the mother and intrapartum and postpartum prophylaxis in the infant in decreasing the incidence of vertical HIV transmission is incontrovertible. By the early 2000s, transmission rates after applying this strategy were less than 2%. Despite a broad experience, concerns remain, however, regarding the safety of deliberate exposure of the pregnant woman, the fetus, and the young infant to ARV drugs. The adverse effects of zidovudine exposure, as defined by the PACTG 076 trial, have been investigated through follow-up studies of mothers and children enrolled in this and similar trials. Mild and reversible anemia in infants occurs during the 6-week period of postnatal administration, but no further untoward effects have been consistently documented after years of observation.[174] Anemia may be more severe in an infant born to a mother who was receiving multiple ARV drugs during pregnancy. The current guidelines recommend a baseline complete blood count with differential (CBC/diff) on all newborns who will be started on zidovudine.[197] Some experts recommend repeating the CBC/diff at 4 weeks of age when the second HIV DNA PCR is performed, whereas others advocate repeating the CBC/diff only if the patient is symptomatic. However, the mild anemia that is associated with this regimen is usually reversible by age 12 weeks.

European investigators have raised some concern that a small percentage of children exposed in utero to zidovudine may have persistent defects in mitochondrial function, a subcellular target of zidovudine in vitro. Older children and adults receiving long-term nucleoside reverse transcriptase inhibitors, such as zidovudine, occasionally develop a high anion gap acidosis because of mitochondrial dysfunction. Studies of a large cohort of European children exposed as fetuses and infants to ART suggest that mitochondriopathies may occur in 0.26%, an incidence that is 20-fold greater than that expected in the general population. A retrospective evaluation of greater than 16,000 uninfected, exposed American children failed to reveal any subject with symptoms consistent with a mitochondrial disorder.[174]

The safety of non-zidovudine drugs when administered during and immediately after pregnancy is less well studied. The non-nucleoside reverse transcriptase inhibitor efavirenz is teratogenic in primates at serum concentrations routinely achieved after conventional dosing in humans.[174] Conversely, a recent meta-analysis looking at the safety of efavirenz in the first trimester of pregnancy found that the relative risk of defects in women on efavirenz-based regimens compared with those on efavirenz-sparing regimens was 0.85 (95% CI 0.61-1.20). In the study, in 39 of 1437 live births, the infants had birth defects of many kinds but only one neural tube defect.[82] Because the incidence of neural tube defects in fetuses exposed to efavirenz is not as high and because changing the regimen of a pregnant woman who sustained virologic response before conception may lead to uncontrolled viral load and hence higher risk for the baby, efavirenz should be continued in the first trimester in those mothers who were already on it at the time the pregnancy was diagnosed. Initial studies from Europe suggested that multidrug ART during pregnancy, especially protease inhibitors (PIs), predisposed to preterm delivery. This finding was not supported by data collected in an American cohort of 369 women receiving combination therapy without PIs and 137 additional women receiving combination therapy with PIs.[262] However, more recently, the Pediatric HIV/AIDS Cohort Study network's Surveillance Monitoring for ARV Toxicity study showed that the odds of preterm birth and spontaneous preterm birth were higher in mothers who used a protease inhibitor regimen during the first trimester.[276] When started later in pregnancy, there were no associated risks. The authors speculated that changes in immunologic and inflammatory mechanisms caused by the initiation of ARV therapy could interfere with cytokines involved in the maintenance of pregnancy, such as IL-10.

Studies examining the effectiveness of zidovudine/3TC and short courses of the non-nucleoside reverse transcriptase inhibitor nevirapine in preventing vertical transmission of HIV in developing countries likewise have not shown toxicity from these drugs either to the mother or to the infant, although the combination of zidovudine/3TC has been associated with a higher incidence of hematologic abnormalities (anemia and neutropenia). Therefore, CBC/diff should be checked at 4 weeks in infants receiving this combination.[113,206]

The use of some agents should prompt careful monitoring of the mother. Prolonged courses of nevirapine occasionally have been associated with significant hepatotoxicity in pregnant women, especially when the CD4+ counts exceed 250/mm^6; such dosing requires frequent, serial liver function tests. Nucleoside reverse transcriptase inhibitors, especially the combination of stavudine and didanosine, rarely may be associated with the development of lactic acidosis in the mother during pregnancy.

Lopinovir/ritonovir is not recommended for use in newborns younger than 14 days of age and premature infants because of the multiple side effects, including the potential for heart block, adrenal insufficiency, and electrolyte imbalances, among others.

For premature infants only zidovudine, 3TC and nevirapine are recommended at this time because of lack of

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safety data. Consultation with a pediatric HIV specialist is strongly advised if other regimens are being considered.

Data regarding potential toxic effects of a wide range of other ARV drugs are being collected through long-term follow-up studies, and the clinician is encouraged to record all cases of ARV drug exposure with the Antiviral Pregnancy Registry.[263]

Prenatal Testing

The availability of effective prophylactic regimens against vertical transmission of HIV mandates routine prenatal HIV testing.[101] It currently is standard practice to add voluntary HIV testing to other prenatal screening tests. Most authorities recommend an "opt out" strategy for prenatal HIV testing; that is, the test is performed routinely unless the woman specifically requests that it be excluded, assuming such a strategy is consistent with state statute. For women with negative test results exhibiting high-risk behaviors or residing in high-incidence areas, the assay should be repeated during the third trimester. Problems still exist in reaching some populations of HIV-infected women, particularly women using illicit drugs, in a sufficiently timely fashion to prevent transmission to their offspring.

Cesarean Section Delivery

Multiple studies have documented the benefit of delivering infants born to HIV-infected mothers by cesarean section. A meta-analysis of 15 observational studies indicated consistent and significant reductions in vertical transmission when elective cesarean delivery is offered to these women. Nevertheless, the additional benefit gained by cesarean delivery is minimal in an adherent mother receiving ART with a very low or undetectable viral load late in pregnancy. Cesarean section may be most appropriate for the woman unable to administer ART to herself or to her newborn or in a mother who has a persistently high viral load (≥1000 copies/mL) despite receiving multidrug therapy. Operative delivery also should be considered in an infected woman when the viral load is unknown.

When elective cesarean section is indicated, it should be scheduled at 38 weeks of pregnancy and, if possible, should be performed while the membranes are intact. Premature rupture of the membranes decreases the benefit from cesarean delivery, but the duration of ruptured membranes beyond which operative delivery adds no benefit is unknown. IV zidovudine should be initiated at least 3 hours before surgery, and other ARV medications should be continued before and after delivery. Postpartum complication rates after elective cesarean section approximate the rates seen in noninfected women, although they are higher after emergent cesarean delivery and in women with advanced disease.

Clinical Manifestations

Virtually all infants born to an HIV-infected mother are asymptomatic at birth. Most HIV-infected offspring begin to show signs and symptoms within the first 1 or 2 years of life. A smaller proportion, termed *rapid progressors*, become symptomatic within 1 or 2 months after delivery. Infants with rapidly progressive disease have plasma viral loads early in life that are two or three times higher than the plasma viral loads in infants with more indolent infection.

With the exception of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, most opportunistic infections occur late in the course of the child's illness. *P. jiroveci* pneumonia commonly manifests in the first months of life. In contrast to *P. jiroveci* pneumonia in adults, virtually all of whom have pre-existing immunity to *Pneumocystis* before acquisition of HIV infection, *P. jiroveci* pneumonia in infants is caused by primary infection in the absence of pre-existing immunity and results in severe, frequently overwhelming, bilateral pneumonia. Other characteristics of untreated or poorly controlled perinatal HIV infection are nonspecific. Recurrent bacterial infections are frequent in infants with HIV infection. Most of these are minor (e.g., otitis media), but some are severe (bacteremia, pneumonia, or meningitis). Other commonly encountered early manifestations include persistent mucocutaneous candidiasis, abdominal organomegaly, diffuse lymphadenopathy, chronic diarrhea, failure to grow, and developmental delay. Children also acquire a diffuse, interstitial pneumonia of uncertain origin, termed *lymphocytic interstitial pneumonia*. HIV-specific cancers, such as B-cell lymphomas, Kaposi sarcoma, and leiomyosarcomas, are unusual in children and generally occur late in the course of the illness.

Diagnosis and Care of Infants Exposed to Human Immunodeficiency Virus

All infants born to a mother with known HIV infection or to a mother who falls into a high-risk category should be longitudinally evaluated for HIV infection. The routine diagnostic HIV tests employed in adults (fourth-generation HIV-1/HIV-2 antigen/antibody combination and differentiation immunoassays) cannot be used to confirm infection in children. The sensitivity of the antigen is much lower than the NAT in the first months of life.[162,255] The antibodies cannot distinguish infant-derived IgG from that transplacentally acquired from a seropositive mother and are virtually always are positive in the newborn period whether the offspring is infected or not and are of little usefulness under 18 months of age.

The definitive diagnosis of HIV infection in a newborn requires the detection of virus with HIV DNA/RNA PCR. Virtually all untreated newborns have HIV viral loads well above the level of detection, and this test is greater than 90% sensitive and virtually 100% specific by 4 weeks of age. Viral load assays further give an estimation of the severity of the infection and a baseline for judging the success of ART. Virologic testing should be performed at 14-21 days of life, at 1-2 months, and again at 4-6 months. In infants who are at high risk for transmission, a test should be

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obtained at birth, and because some studies have shown that the RNA PCR assay may be affected by combination ARV prophylaxis the test should be repeated 2-4 weeks after the ARV prophylaxis is discontinued.[35] To exclude HIV infection, two negative virologic test results are required, one obtained at 1 month of age or greater and another at 4 months of age or greater. Any positive result needs to be confirmed by a second specimen as soon as possible. Because maternal antibodies may persist for longer periods, some experts advocate a final HIV antibody test at 12-18 months in infants with prior negative results on virologic testing to document loss of maternal antibodies.

The CDC's updated guidelines recommend initiating ART for any infant diagnosed with HIV infection before age 12 months regardless of clinical status, CD4 percentages, or viral load.[195] Treatment of infants with multidrug regimens poses difficulties, and proper use of these complex and potentially toxic agents requires the advice of an expert with substantial experience in perinatal HIV infection.

Because *P. jiroveci* pneumonia is the major life-threatening complication during the first year of life of the HIV-infected infant's life, many experts recommend that prophylaxis for *P. jiroveci* pneumonia be administered beginning at 4-6 weeks and continuing for at least 1 year, or until HIV infection can be definitively excluded. The most effective prophylactic regimen is trimethoprim-sulfamethoxazole, 75 mg/m^2 per dose, twice a day, 3 days a week. The immunization schedule for the HIV-infected newborn includes recombinant hepatitis B vaccine at birth. The Bacillus-Calmette-Guerin (BCG) vaccine, which is administered to newborns in tuberculosis-endemic countries, is contraindicated in HIV-infected infants because of the risk of disseminated BCG vaccine. Preliminary data suggest that in the HIV-exposed child, the BCG vaccine may induce CD4 T-cell activation and may increase the risk of HIV infection through breastfeeding in these children.[103]

Prognosis

Before the introduction of ART, the median survival of children with HIV infection in the United States and Europe was 8-13 years. In the absence of ART, rapid progressors usually have multiple, life-threatening complications and die early in life. A few perinatally infected children have reached adolescence and remain symptom-free, with their immune systems intact, even without antiviral chemotherapy. The ultimate outcome of these unusual cases is unknown. As in adults, the survival of children in industrialized countries has markedly improved since the introduction of ART, reflecting the benefits of ARV regimens seen in adults. Longitudinal studies conducted in the late 1990s, the period during which HAART became standard in adults and children, documented a dramatic decline in yearly mortality rates among children with HIV infection. The reduction in mortality was experienced by all subgroups defined by age, gender, CD4 T-lymphocyte counts, and ethnicity.

Enteroviruses and Parechoviruses

Enteroviruses belong to the family Picornaviridae. The four traditional groups of enteroviruses are the polioviruses, echoviruses, coxsackie viruses, and enteroviruses. More than 100 types of non-polio enteroviruses have been described. Although these groupings are still widely employed, more recent molecular analyses have categorized enteroviruses into five genetically defined species and have indicated that some of the original members belong to non-enterovirus genera altogether. In particular, hepatitis A, initially designated an enterovirus, has been reclassified as a distinct and unique genus. Two additional former enteroviruses, echovirus 22 and 23, are sufficiently genetically and structurally different from the other enteroviruses to be assigned to a new genus name, *parechovirus*. Several new parechoviruses have been identified.

In fall 2014, the United States experienced an outbreak of a non-polio enterovirus that spread rapidly among children predominantly between ages 2 and 13 years—enterovirus D68 (EV-D68) (PMID 25552624). This virus shared the clinical features of other non-polio viruses, including upper and lower respiratory symptoms and neurologic manifestations, such as flaccid paralysis. During this outbreak, neonates and adults were, however, largely spared, suggesting that maternal immunity played a protective role in infants.[14,84,166,274]

Epidemiology and Transmission

Humans are the true hosts for the enteroviruses, but these viruses have been described in various animals, probably secondary to contamination by humans. These viruses are transmitted primarily by the fecal-oral route, but they have also been transmitted by the oral-oral route and have been isolated from swimming pools, from contaminated hands, and from flies. Typically, within a given geographically defined population, a narrow range of serotypes is responsible for most endemic disease. The community incidence of enteroviral disease peaks in temperate areas in summer and fall but occurs throughout the year in tropical areas. In addition to geographically confined organisms, occasional strains cause epidemics that can reach worldwide proportions. In all four enterovirus groups, there are far more subclinical, undiagnosed infections than recognized disease, but when disease occurs, it is particularly severe in the neonatal period.

Perinatal infection can occur before, during, or after parturition. Enteroviruses may be transmitted transplacentally, presumably during maternal viremia, and congenital infections have been most often described after a maternal infection in the third trimester; such infections can result in fetal death. Most infection in the neonatal period is, however, the result of exposure of the oral or respiratory tract mucosae to organisms harbored by the mother at the time of birth or from secretions from the mother or others shortly thereafter.

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Epidemics of enteroviral diseases in the nursery have been described. The virus may be introduced by health care personnel, but more commonly, the infant index case has acquired the virus from his or her mother at the time of delivery. Risk factors for infection in the nursery include low birth weight, administration of antibiotics or blood, proximity to the index patient, care of the index patient by the same nurse within a nursing shift, and nasogastric feeding or intubation.

Infection During Pregnancy

Enterovirus infection during pregnancy is common, especially during peak periods of enteroviral disease in the community, with some surveys documenting an intragestational incidence of 9% or greater. Few data indicate any risk from either the polioviruses or the echoviruses for the development of congenital anomalies, but the situation is less clear for coxsackie viruses. Early investigations found an association of coxsackie viruses A9 and B2 to B4 with a higher rate of anomalies, particularly urogenital and cardiovascular anomalies, but others have found no such association. Reports of prematurity and stillbirth exist for all the enteroviral groups after infection late in pregnancy, but these effects seem to be uncommon. In most pregnant women, the infection is either asymptomatic or associated with mild, nonspecific illness. By contrast, mothers infected with echoviruses or coxsackie B viruses, the enteroviral groups most commonly associated with significant illness in newborns, frequently complain of fever and abdominal pain near the time of delivery.

The first case of EV-D68 in an adult occurred in a 35-year-old pregnant woman with a twin gestation. She presented at 33 weeks' gestation with cough, headache, dyspnea, and hypoxemia, which warranted her admission to the ICU. CT of the chest showed bilateral patchy infiltrates, and she tested positive for the virus on PCR testing. Her symptoms improved after 48 hours, at which time labor was induced because of a history of severe preeclampsia. She delivered healthy twins, who remained asymptomatic and were discharged home without at-home oxygen requirements.[274] No other reports of neonates exposed to this virus strain have been reported to date in the medical literature.

Neonatal Infection

The non-polio enteroviruses cause a wide spectrum of illnesses, and substantial data have been collected regarding specific types and strains. The severity of disease in a newborn is a function of the infecting strain, the titer of passively transferred specific antibody in the infant, and the timing of infection. Maternal infection just before delivery, before the mother can mount an antibody response, with high-titer viral transmission immediately before or during birth is associated with the most severe symptoms in the newborn.

Most neonatal enteroviral disease manifests as a nonspecific mild febrile illness. These infections probably are acquired postnatally. Signs and symptoms occur between the first and second weeks of life, usually after the infant has been discharged from the nursery, and consist of fever of 38° C to 39° C, irritability, vomiting or diarrhea, and poor feeding. These infants frequently are admitted to the hospital for a bacterial sepsis evaluation and discharged 3 days later when the bacterial cultures show negative results and the infant's symptoms have spontaneously improved. Occasionally, infants exhibit respiratory distress, rash, or aseptic meningitis. The course is self-limiting, and recovery without residual is the rule.[149] A history of an intercurrent viral-like illness in a family member can usually be elicited. Nosocomial infection, acquired horizontally after birth, also frequently has this relatively mild course.

A more fulminant, life-threatening illness occurs as a consequence of vertical transmission at the time of birth and before the development of significant serotype-specific antibodies in the mother. The risk of mortality is highest for echovirus-11, but other serotypes, particularly some coxsackie B viruses (especially Coxsackie B1) and several parechoviruses, also have been implicated.[121,270,284] Approximately one third to one half of infants with severe enteroviral disease are born prematurely.[3] In fulminant cases, onset of illness typically occurs within the first 2-5 days of life. Severe neonatal disease shares many characteristics of overwhelming bacterial infection, with extreme lethargy and hypoperfusion. Infants also present with fever, which may be greater than 39° C, poor feeding, and rash. The rash is usually macular or maculopapular, sometimes with petechiae. The most fulminant cases are complicated by hepatitis, first manifesting as hepatomegaly and jaundice. Such cases can progress to necrosis of the liver and fulminant hepatic failure with intractable coagulopathy and hemorrhage, as well as profound hepatocellular dysfunction. Mortality from enteroviral hepatitis and coagulopathy ranges from 30%-80%.[3]

Despite the life-threatening nature of the acute hepatic failure, recovery of hepatic function among survivors is the rule. Coincident with hepatitis, or sometimes separate from it, there may be myocarditis, characterized by respiratory distress, tachycardia, and arrhythmias, with mortality approaching 50%. As with hepatitis, if the infant survives acutely, full recovery over a long course is usual. Both these severe manifestations may occur coincidentally with meningoencephalitis. In these infants, CSF examination often is typical for viral CNS disease, but some serotypes produce CSF changes typical of bacterial meningitis, including marked hypoglycorrhachia, and still others result in no CSF pleocytosis at all. Although there are a few reports of neurologic sequelae among survivors of aseptic meningitis, development is normal in nearly all children. In contrast, neonatal encephalitis resulting from parechovirus may be severe, causing white matter injury and long-term sequelae in a significant proportion of affected infants.[269]

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Enteroviral infection shortly after birth also has been implicated in a few cases of sudden infant death. Some infants have died within the first week of life. Mild prodromal symptoms usually precede the infant's death. Evidence of enterovirus has been found in the heart and respiratory tract at postmortem examination.

Laboratory Diagnosis

Traditionally, the diagnosis of enteroviral infection has been established by isolation of the virus in culture. Some serotypes of enterovirus are, however, very difficult to grow in vitro. More recently, PCR technology, using primers that flank a highly conserved region in the 5′ noncoding region of the genome present in nearly all serotypes, has become commercially available for the diagnosis of enterovirus. When applied to infection in newborns and young infants, PCR testing is more sensitive and much more rapid than viral culture. The widely used enteroviral PCR tests do not detect parechoviruses, however. Enterovirus can be identified by culture and PCR of serum, urine, CSF, nasopharynx, and stool. The usefulness of serology and antigen detection for diagnosis of enteroviral disease is precluded by the large number of non–cross-reacting serotypes.

Enterovirus D68, however, shares some biologic and molecular characteristics with human rhinovirus, particularly with human rhinovirus 87 and, therefore, PCR testing with real-time PCR will not distinguish between both viruses. Sequencing for this virus is available at the CDC.[160]

Therapy and Prevention

The most important measure in limiting the spread of enteroviral disease is strict hand washing. Access to the nursery should be limited to healthy personnel. Cohort nursing care during nursery epidemics may be effective in limiting spread. There is some evidence that passive immunization with immunoglobulin during a nursery outbreak may be beneficial in limiting new cases and decreasing the severity of illness in affected infants.

High-dose IVIG has been used in established neonatal disease, although there have been no controlled trials testing its effectiveness. It has also been used as prophylaxis for outbreaks in neonatology units.[88] Passive immunization has been shown to have a virologic effect in the infant only if the lot of immunoglobulin possesses very high titers against the offending serotype. The antiviral drug pleconaril, which is promising in the treatment of neonatal enteroviral infection, is still in development. This compound binds to sites on the enteroviral surface, prohibiting attachment to the target cell and subsequent uncoating. It has activity against numerous enteroviruses in vitro at concentrations that are readily achieved in the serum with human dosing. Preliminary experience, including data collected in neonates, indicates that the drug is highly bioavailable, has a large volume of distribution (including the CNS) and long half-life, and has few side effects. There have been numerous reports of pleconaril administration in infants with severe enteroviral disease, with recovery frequently occurring soon after drug initiation. The results of randomized controlled trials in neonatal infection have not been published, however, and in the absence of controlled studies, the effectiveness of pleconaril in severe newborn enteroviral disease remains uncertain. It is important to mention that pleconaril did not receive FDA approval and that the drug is no longer available for compassionate use. In 2015, the results of a randomized, double-blind, placebo-controlled trial of this drug for the treatment of neonates with severe enteroviral sepsis were published. Nineteen centers enrolled patients between the years 1999 and 2010, at which time the study was stopped because the drug was no longer available. Patients enrolled in both arms were allowed to receive other medications, including IVIG. The primary endpoint of the study was the reduction in the number of newborns with a positive viral culture from the oropharynx 5 days after initiating pleconaril, and some of the secondary endpoints were duration of positive cultures in all sites (oropharynx, rectum, urine, and serum), reduction in the duration of hospitalization, and lower mortality rates. Of the 61 patients enrolled, 43 tested positive for enterovirus (31 in the treatment arm and 12 in the placebo arm). The primary endpoint of the study was not met because a surprising number of newborns did not test positive on cultures from the oropharynx on day 1 (only 25% and 30% in the study and placebo group, respectively), and by day 5 no cultures tested positive in either group. However, time to negativity was shorter for samples from all culture sites in the pleconaril group compared with the placebo group, and the cumulative survival time over 2 months was greater in the treatment arm than in the placebo arm. In addition, the drug was safe and well tolerated. This study, therefore, highlights the need for further investigation of this drug and calls for the development of other treatments for this high mortality infection in newborns.[4,172]

Hepatitis Viruses

Hepatitis may result from various viral infections, including CMV, herpesvirus, rubella virus, EBV, VZV, and coxsackie virus. The disease usually occurs as part of a systemic infection. Primary infection of the liver, resulting in acute or chronic hepatitis, or both, may also be caused by specific hepatotropic viruses, as discussed in the following sections (see Chapter 91).

Hepatitis A Virus

Hepatitis A virus (HAV) is a spherical, single-stranded, positive-sense RNA particle in the picornavirus group. HAV is found worldwide. The infection is highly contagious and is spread most commonly by the fecal-oral route. Common-source outbreaks resulting from contaminated food, particularly raw shellfish culled from tainted waters, also occur. Rarely, HAV is transmitted via blood

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transfusion or from mother to child. Fecal excretion of HAV begins 2-3 weeks before onset of the disease and may continue for 4-6 weeks. The average incubation period is 25-30 days.

HAV is a common infection in children, and children in daycare are at particular risk. Most pediatric infections are asymptomatic and anicteric. Children who do exhibit symptoms usually have a gastroenteritis-like syndrome and experience only mild hepatitis with virtually complete resolution. Adults are more likely to develop the typical signs and symptoms of hepatitis, with jaundice, abdominal pain, malaise, fever, acholic stools, dark urine, and vomiting. Fulminant disease is uncommon, and the mortality rate is less than 1%. The carrier state does not occur. The diagnosis is made by detecting anti-HAV IgM antibodies in the serum, which appear with the onset of disease and persist for several months. Detection of anti-HAV IgG, which persists throughout life, may indicate either recent or distant infection.

Acute HAV in pregnancy does not seem to increase the risk of congenital malformations, stillbirths, IUGR, or spontaneous abortion. The risk of perinatal transmission is minimal, even when the mother develops acute disease within the last weeks of pregnancy.[259] Perinatal transmission can rarely occur, however, and spread in special care nurseries has been reported. In most instances, neonatal disease is asymptomatic or mild and is self-limiting. Occasional reports suggest that maternal disease with HAV during pregnancy can result in meconium peritonitis in the fetus.[47,61]

Although vertical transmission of HAV is unusual, some authorities recommend treating the infant with 0.02 mL/kg of serum immunoglobulin intramuscularly if maternal symptoms develop 2 weeks before to 1 week after delivery. Even though the virus can be detected in breast milk, maternal immunoglobulins likely play a protective role, and therefore, breastfeeding should not be discouraged.[47,61]

Any unusual nursery outbreak of HAV should be managed with the administration of prophylactic immunoglobulin to susceptible staff and infants and with emphasis on good hand washing. Two formalin-inactivated HAV vaccines are available in the United States and are highly protective but are not yet licensed for children younger than 12 months of age.

Hepatitis B Virus

Hepatitis B virus (HBV) is the prototype of the family of viruses known as *hepadna viruses* (hepatotropic DNA viruses). The complete infectious virion is a 42-nm sphere. Hepatitis B surface antigen (HBsAg) is found in the viral envelope and is produced in excess during infection, resulting in circulating, free spherical and tubular particles. It is detected (usually with radioimmunoassay [RIA] or enzyme-linked immunosorbent assay [ELISA]) in acute and chronic infection. Subdeterminants of the surface antigen define four major serotypes. All four share an epitope designated "a"; antibody to HBsAg (anti-HBsAg) is directed against this common epitope and confers some protection against all four serotypes.

The viral inner core nucleocapsid contains hepatitis B core antigen (HBcAg), DNA polymerase, and partially double-stranded DNA. Hepatitis B core antigen is expressed on the surface of the infected hepatocyte but does not circulate and cannot be detected by routine assays. Anti-HBcAg, total and IgM specific, can be detected with RIA or ELISA. HBeAg, a soluble polypeptide encoded within the same open reading frame as the core antigen, is detectable when HBV replication is rapid. Its appearance usually indicates a high concentration of HBV. HBeAg-negative individuals are infectious, but transmission of disease occurs at a lower rate. HBeAg and anti-HBe also can be detected with either RIA or ELISA. Several genotypes of HBV have been defined and designated types A through H. Hepatitis B virus DNA initially is transcribed into RNA intermediates, which serve as messages for viral proteins or as a template for progeny viral genomic DNA through reverse transcription by the viral polymerase.

Clinical Manifestations and Hepatitis B Virus Blood Tests

HBV infection is most often contracted via injection drug use but may be transmitted through intimate physical contact or vertically from mother to infant. Blood products are routinely screened for HBV, and transfusion, previously the most common source of HBV infection, is now only rarely implicated. The incubation period is 50-180 days. HBsAg usually is present 1-3 months after exposure and appears before the onset of symptoms. Elevation of hepatocellular enzymes in the serum may be found 2 weeks to 2 months after HBsAg is detected. This period in adults frequently is characterized by a prodrome of nausea, vomiting, headache, and malaise, which progresses to jaundice.

Within 1-2 weeks of the onset of jaundice, HBsAg usually is cleared from the serum. With self-limiting disease, there is often a window period between the disappearance of HBsAg and the development of anti-HBsAg, so both tests yield negative results. The appearance of anti-HBsAg is a marker of recovery and immunity against future reinfection. The IgM antibody response to HBcAg begins before the disappearance of HBsAg and persists through the window period. Testing for HBsAg and IgM anti-HBcAg is the most reliable strategy to document recent HBV infection. IgM anti-HBcAg disappears by 6 months, but the later-appearing IgG anti-HBcAg may persist for life. HBeAg is variably expressed in HBV disease and denotes actively replicating, high-titer infection. The development of anti-HBeAg signals improved control of viral replication, but not eradication. HBV vaccines are composed of recombinant HBsAg; recipients of vaccine test positive for anti-HBsAg. Vaccine recipients can be distinguished from hosts who have recovered from wild-type infection by the absence of antibody to other viral components, particularly anti-HBcAg.

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Most adults with HBV infection have a self-limiting disease and become noncontagious. Less than 1% develop fulminant hepatic failure, but many of these patients die. The virus is not cytopathic for the infected hepatocyte, and hepatic damage and subsequent viral clearance are the results of the host's immune response. Chronic active or persistent hepatitis, which may develop in 30% of chronic carriers, is characterized by persistent serum HBeAg in the absence of anti-HBsAg and is particularly common in patients superinfected with the hepatitis D virus.

Infants born to antigen-positive mothers or mothers with acute hepatitis have a 35% incidence of prematurity and are more likely to be of low birth weight. The risk of preterm birth seems to be related to degree of maternal illness. Fulminant fatal cases of neonatal hepatitis secondary to vertically transmitted HBV are uncommon, but do occur (1%-2% of all cases) and may be recurrent in successive pregnancies. More typically, infants infected with HBV develop a less robust immune response to the HBV-infected hepatocyte compared with adults and establish asymptomatic chronic infection ("chronic carriage"). The development of chronic carriage is strongly correlated with age: 95% of infants become chronic carriers compared with 30% of toddlers and 5% of adults.[108]

The consequences of chronic HBV carriage established in the newborn are not encountered until early adulthood, at which time the patient has a gradual onset of hepatic fibrosis and insufficiency. Carriers also may develop hepatocellular carcinoma after the initial infection. Hepatocellular carcinoma is most common in populations affected by a high incidence of vertically transmitted HBV and in populations with high cross-sectional prevalence of HBV surface and HBe antigenemia.[252] HBV itself is not oncogenic; the formation of tumor is probably the result of years of low-grade inflammation and repeated hepatocellular regeneration.

Perinatal Transmission

Multiple studies have shown that vertical transmission of HBV is strongly associated with high-grade maternal HBe antigenemia and that almost all infants born to HBeAg-positive mothers are infected in the first year of life, with 85%-90% developing chronic viral infection. The risk of vertical transmission of HBV from an asymptomatic carrier mother to her infant increases from 10%-85% when the mother is HBeAg positive. Mothers may transmit HBV vertically in sequential pregnancies. The risk of vertical transmission of HBsAg from mother to infant at birth is higher in Asia than in Western industrialized countries.

Transmission occurs significantly more often at birth or in the postpartum period than transplacentally. Cord blood samples frequently are HBsAg negative in infants who subsequently become infected. Peripartum transmission is implied further by observations made in mothers who acquire acute hepatitis B infection during pregnancy. The risk is very low with infection during the first two trimesters, but increases to 50%-75% with hepatitis late in pregnancy or in the early postpartum period. Entry of virus through the infant's gastrointestinal tract is suggested by the finding that 95% of the gastric contents of infants born to carrier mothers are HBsAg positive after birth.

Although HBsAg can be found in the breast milk of 70% of carrier mothers, studies have not shown an increased risk with breastfeeding, indicating that mothers who desire to breastfeed may do so with little risk. American studies indicate further that breastfeeding carries no detectable risk of vertical HBV transmission in an infant who has received appropriate immunoprophylaxis at birth.[104]

There is also risk of transmission of HBV to family contacts of HBsAg carriers as a result of close contact over long periods. The risk is higher from sibling carriers than from either parent and is increased when the family member has evidence of liver disease. In the developing world, a significant proportion of infant infection is the result of horizontal transmission from the mother or other family members during the child's early life, rather than infection at the time of birth.

Prevention

Approximately 0.8% of pregnant women in the United States are HBsAg positive. Active and passive immunization can prevent vertical transmission of HBV in 85%-95% of cases, even in high-risk situations. The institution of immunoprophylaxis has had a profound impact on the incidence of newborn-acquired acute and chronic HBV infection and the associated hepatocellular carcinoma, particularly among high-prevalence populations in the United States (e.g., Alaskan Natives) and in areas of high endemicity in the developing world.[45,143]

Less than 50% of HBV-infected women in the United States have risk factors for HBV infection. Consequently, present recommendations mandate routine, universal screening of all pregnant women for HBV and universal vaccination of all infants. Current guidelines recommend that all pregnant women be tested for the presence of HBsAg early in pregnancy. Women at high risk for acquiring HBV, such as IV drug users or women with clinical hepatitis, should be tested again shortly before parturition. Hospitals are advised to develop systems that ensure the results of HBV screening tests are available to the pediatrician at the time of delivery. In everyday practice, some women without identified risks may acquire infection after the initial screening test, and others fail to be rescreened, and it may be impossible to transmit every woman's HBV status to the pediatrician in a timely fashion. In large centers that can perform HBV testing daily, screening at the time of delivery may overcome both of these potential problems.

Treatment of the infant varies, depending on whether the mother is HBsAg positive, HBsAg negative, or of unknown status at delivery. Infants of HBsAg-negative mothers do not need treatment with hepatitis B immunoglobulin (HBIG). They should be vaccinated before leaving the hospital with either Recombivax HB (5 μg in 0.5 mL)

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or Engerix-B (10 μg in 0.5 mL). Both must be given intramuscularly. Subsequent doses should be given at 1-2 months (with a minimal interval of 4 weeks between dose 1 and dose 2) and 6 months of age (with a minimal interval of 8 weeks between dose 2 and dose 3), although the last dose may be given up to age 18 months. Combination vaccines that are currently available include HBV antigen and other childhood vaccines in the same vial. Only the monovalent preparation of hepatitis B vaccine should be used for the first dose, however, assuming it is administered at age less than 6 weeks.

Infants of HBsAg-positive mothers should be passively immunized with HBIG (0.5 mL given intramuscularly) and hepatitis B vaccine at a different anatomic site within 12 hours of birth, although some benefit can be obtained even if given 48 hours after birth. The vaccination schedule should be completed by 6 months to ensure rapid protection of the infant. In contrast with infants born to HBsAg-negative mothers, infants born to mothers with HBV infection should be tested for HBsAg and anti-HBsAg after the vaccine schedule has been completed (at age 9-15 months, to allow clearance of HBIG from the infant's bloodstream) to detect failure of seroconversion or vertical transmission despite vaccination.

If the mother's serologic status is unknown, maternal HBsAg should be tested at delivery, and the first dose of the vaccine should be given to the infant within 12 hours of birth. If the mother proves to be positive for HBsAg, HBIG should be administered to the infant as soon as possible, but certainly within the first 7 days of life.

Early studies examining hepatitis B vaccine response in preterm infants indicated a lower seroconversion rate among infants with very low birth weight born to HBsAg-negative mothers compared with infants weighing more than 2000 g. Subsequent studies have determined that medically stable preterm infants immunized at 30 days of age have an antibody response similar to full-term infants regardless of gestational age or birth weight. In a preterm infant born to a mother who is HBsAg negative, the first dose of HBV vaccine should be given at 30 days of life or when the infant's weight reaches 2000 g, before hospital discharge. In preterm infants born to HBsAg-positive mothers, HBV vaccine should be given within 12 hours of birth along with HBIG, but the full three-dose vaccine schedule should be initiated at 30 days of age (i.e., the infant should receive a total of four vaccine doses).

If a preterm infant is born to a mother with uncertain HBV status and her status cannot be determined within 12 hours after delivery, HBIG should be administered to the infant immediately because suboptimal immune response to vaccine alone precludes its use as a single intervention in the event that the mother proves to be HBV positive. If the mother's HBV tests ultimately show negative results, the vaccine schedule can proceed using the same schedule for mothers known to be HBsAg negative at delivery. Breastfeeding is not contraindicated and should be encouraged.

After nearly 20 years of widespread newborn vaccination, the hepatitis B vaccine seems to be exceedingly safe when given during infancy.[147] The original hepatitis B vaccine preparations contained the preservative thimerosal, a derivative of mercury. Concerns regarding the potential, albeit unproven, toxicity of thimerosal prompted a brief suspension of perinatal hepatitis B vaccination in the late 1990s and a mandate to develop vaccine formulations that did not contain this preservative. By 2001, all vaccines included in the childhood schedules were either thimerosal-free (including hepatitis B) or contained only trace amounts.

There are situations during pregnancy in which treatment of hepatitis B should be considered to prevent mother-to-child transmission of the virus. The American Association for the Study of Liver Diseases recommends that treatment should be considered, after carefully weighing risks and benefits, in mothers with HBV DNA viral loads greater than 200,000 IU/mL. Tenofovir, lamivudine, and telbivudine are the only drugs that have been studied during pregnancy, with tenofovir being preferred because of its safety profile (Category B). Treatment is started between 28 and 32 weeks' gestation and continued up to 3 months after delivery. Infants born to mothers who have received treatment should still receive the HBIG and hepatitis B vaccines, as described previously.

Even though these drugs are not secreted in largely through breast milk, the effects of these drugs in breastfeeding children have not been well studied. At present time, there is no contraindication to breastfeeding; however, risks and benefits should be discussed with the mother.[258]

All children born to mothers with hepatitis B infection should have post-vaccine serologies performed between 9 and 12 months, or 1-2 months after completion of the last hepatitis B vaccine series dose. The purpose of testing is mainly to identify those who may have been incubating the virus and whose transmission was not prevented through vaccination.[272]

Hepatitis C Virus

Hepatitis C virus (HCV) is a single-stranded RNA virus of the family Flaviviridae. HCV is composed of six genotypes and multiple subtypes. The severity of the infection corresponds to the HCV strain, with genotype 1 causing the most aggressive course. HCV is the most common chronic blood-borne infection in the United States and the most frequent condition requiring liver transplantation. The seroprevalence among volunteer blood donors in the United States is approximately 1%-2%. At present, IV drug use is the most prominent risk factor for acquisition of HCV. Health care workers experiencing a needle-stick injury or mucous membrane exposure to blood products also are at risk. Sexual transmission of HCV is uncommon, and household contact results in viral transmission only rarely, if at all.

Historically, transmission occurred most frequently after exposure to blood or blood products, including sporadic

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lots of intravenous immunoglobulin. The practice of administering multiple small-volume transfusions to ill neonates during the 1960s and 1970s resulted in inadvertent HCV infection in a substantial proportion of the recipients. The screening of potential blood donors with newer-generation antibody tests for HCV, however, has greatly reduced the incidence of transfusion-acquired infection in adults and children. Since the implementation of these screening programs, vertical transmission has become the most common mechanism of HCV infection in children.

HCV infection has a 30- to 60-day incubation period. In unusual circumstances, infection results in acute hepatitis with symptoms similar to those caused by other hepatotropic viruses—abdominal pain, jaundice, nausea, vomiting, fever, and malaise. Most acute infections in adults, however, are asymptomatic. More than half of all adults with HCV infection develop chronic hepatitis, which may resolve or may progress in one fourth of patients to cirrhosis and eventually to hepatic failure.[224] As with chronic HBV infection, chronic HCV infection is a significant risk factor for hepatocellular carcinoma. However, in 2011, the introduction of highly effective anti-HCV protease inhibitors changed the hepatitis landscape. The infection is now treatable with shorter courses, as short as 8-12 weeks and with high sustained virologic responses.[1] Notwithstanding, these newer agents are not recommended during pregnancy and antiviral therapy should be considered prior to pregnancy, if feasible. (AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.)

Although HCV infection is relatively prevalent among young adults, almost every expert recommends against screening for HCV during pregnancy, unless the woman possesses known risk factors for infection, such as transfusion or organ transplantation before 1992 or infusion of clotting factor concentrates before 1987; IV drug abuse; presence of a tattoo or body piercing that was placed unprofessionally; or HIV infection. Pregnancy does not seem to worsen the severity of HCV infection, and HCV infection does not seem to increase maternal or fetal morbidity and mortality beyond that conferred by concomitant maternal drug use. As in nonpregnant adults, most pregnant women infected by HCV are asymptomatic with only mildly abnormal liver function tests.

The incidence of mother-to-child transmission in women not co-infected with HIV is approximately 5%.[159] HIV co-infection in the mother increases the risk of vertical transmission of HCV twofold to fivefold. More recent data, however, suggest that effective multidrug therapies for HIV during pregnancy may reduce the risk of transmission of HCV as well. Maternal illicit drug use also increases the risk of vertical transmission of HCV to the newborn. Transmission seems to be a function of the degree of maternal viremia. If the mother's serum is HCV negative, as shown by PCR, the rate of transmission to the newborn approaches zero.[80] Conversely, studies have indicated that transmission rates are roughly proportional to maternal HCV plasma load.[111] However, no minimal level of viremia, below which the infant is safe, has been established.

Most infants probably are infected at or near delivery, and several investigators have documented that the risk of vertical transmission is increased by prolonged rupture of the membranes and invasive fetal monitoring, both of which heighten the exposure of the newborn to maternal blood.[159] Most series have been unable to document protection from HCV vertical transmission through cesarean section.[111] Some samples of colostrum and breast milk contain detectable HCV RNA, but studies indicate no increased risk of mother-to-child transmission attributable to breastfeeding as long as the nipples are not damaged or bleeding.[254] Administration of immunoglobulin to a newborn has no role in preventing vertical transmission because donors for commercial immunoglobulin preparations are screened and rejected for the presence of HCV antibodies.

Infants born to mothers infected by HCV are virtually all asymptomatic at birth and remain so for years.[260] There are few long-term longitudinal studies of these infants. Progression of disease seems to be slower in children than in adults, and most children experience only mild to moderate intermittent elevations of serum liver transaminase levels through at least the first two decades of life. Liver histologic changes tend to be mild as well. It is uncertain how many of these children progress to cirrhosis or hepatocellular carcinoma later in life. In a small proportion of children with vertically transmitted HCV, the infection clears spontaneously over the first few years of life. Maternal HCV antibodies may be detectable in the infant for 18 months and cannot be used for diagnosis unless they persist beyond this time. HCV-specific RNA can be detected in the serum with PCR. Most infants born to a mother infected with HCV have negative HCV PCR at birth, but with infection, PCR becomes positive after the first 1 or 2 months. Thereafter, the test is variably positive throughout life, reflecting intermittent episodes of viremia.

Hepatitis D Virus

Hepatitis D virus (HDV), formerly known as the δ agent, is a defective RNA virus that uses HBsAg as its surface coat and requires co-infection with HBV. Its epidemiology is the same as that of HBV. HDV is transmitted parenterally, and in the United States, it is most commonly found in drug addicts and those with hemophilia. HDV is worldwide in distribution. Perinatal transmission, which is rare, occurs only with HBV transmission and can be interrupted by interrupting HBV perinatal transmission.

Hepatitis E Virus

Hepatitis E virus (HEV) is a single-stranded, positive-sense, non-enveloped RNA virus unrelated to the other hepatitis agents. HEV disease has been identified in Asia, Africa, the Middle East, and Central America.[246] Occasionally, a case is diagnosed in an immigrant in the United States or

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Europe. In endemic areas, HEV occurs sporadically, but several instances of large outbreaks have been reported, typically affecting thousands of people. Infection is transmitted through contaminated water supplies sullied by sewage; person-to-person spread is uncommon. The diagnosis can be made through identification of viral particles in the stool, Western blot assays for anti-HEV IgM and IgG, and detection of circulating viral RNA by using PCR, but these tests are not routinely available in most hospitals in the United States. In nonpregnant women, infection with HEV is similar to that caused by HAV. Most cases are characterized by self-limiting icteric hepatitis and full recovery. Subclinical and anicteric infections also occur. Fulminant hepatitis results from a small fraction of infections. HEV infection does not lead to chronic hepatitis.

There is a striking association between pregnancy and the development of overwhelming HEV-related hepatitis, particularly in women from the Asian subcontinent. In some endemic areas, HEV is the most common identifiable cause of clinically apparent hepatitis in pregnant women, even when the prevalence of HEV in the general population is lower compared with other hepatotropic pathogens. Massive hepatic necrosis is particularly prominent during the third trimester of pregnancy, when the mortality rate can exceed 20%.[6] The reasons for this predilection are unknown, but some data suggest that hormonal elevations during pregnancy promote viral replication.[117]

Mild HEV disease during pregnancy can result in abortion, intrauterine death, stillbirth, or preterm delivery.[201] Reports studying a few subjects have documented vertical transmission of HEV in more than half of infants born to mothers who were viremic during pregnancy. Blood-borne virus can be detected soon after birth, suggesting intrauterine transmission. All the affected infants had abnormalities of liver function tests, and approximately 20%-25% died; one of these was found to have hepatic necrosis at autopsy. Liver function returned to normal in survivors after 2-3 months.

In 2011, a recombinant HEV vaccine was licensed in China for use in patients 16 years of age and older.[176,199] The vaccine has been shown in clinical trials to have an efficacy close to 87%, especially against HEV genotype 4. In addition, the protective effects of the vaccine last up to 5 years.[293] Unfortunately, this vaccine is not available in the rest of the world at this time.

Hepatitis G Virus and GB Virus Type C

Hepatitis G virus (HGV) and GB virus type C (GBV-C) were isolated independently, but subsequently, they proved to be nearly identical flaviviruses based on genetic sequence. HGV/GBV-C has a genomic organization similar to that of HCV. In adults, infection by HGV/GBV-C results in viremia that lasts for months to years, but the virus eventually is cleared by the appearance of antibody against the viral protein E2. Although initial studies suggested that HGV/GBV-C was a cause of hepatitis, subsequent surveys have failed to establish that HGV/GBV-C infection produces liver disease or any disease at all. This observation, along with data that suggest that HGV/GBV-C primarily infects lymphocytes rather than hepatocytes, has prompted some experts to recommend that the name "hepatitis G virus" be discontinued.

HGV/GBV-C is transmitted through the same routes as HIV and HCV—transfusion, injection drug use, sexual activity, and vertical transmission from mother to infant. Occasional patients with HGV/GBV-C infection have none of these risk factors, suggesting that other modes of acquisition occur as well. Prevalence studies have documented that active infection, defined by the detection of circulating HGV/GBV-C RNA, and past infection, defined by the presence of antibody to HGV/GBV-C, are extraordinarily common in healthy individuals and patients with underlying conditions. Approximately 2% of blood donors have evidence of active HGV/GBV-C infection, and an additional 15%-18% have evidence of past infection. Coinfection with HGV/GBV-C occurs in greater than 20% of subjects with HCV infection. Ongoing or past infection by HGV/GBV-C is detected in two thirds or more of IV drug users and patients with HIV. Although no clinically apparent disease has been identified in individuals infected with HGV/GBV-C, interest in this virus has been rejuvenated by studies suggesting that active HGV/GBV-C replication in HIV-infected patients may slow the progression of HIV disease. The mechanism of this putative protective effect in HIV-infected hosts is uncertain.

HGV/GBV-C is efficiently transmitted from mother to child. Studies that have included healthy women and mothers co-infected with HCV or HIV have documented HGV/GBV-C transmission to more than one half of their offspring. Typically, an infant becomes positive for HGV/GBV-C RNA by 3 months of age, and, similar to adults, active infection lasts for months. Most studies have failed to detect an independent association between HGV/GBV-C infection in vertically infected newborns and subclinical or clinically apparent liver disease. To date, no other clinical consequences have been identified in infected infants.[278]

Rotavirus

Rotavirus is the predominant cause of acute viral gastroenteritis in infants and young children. It is a double-stranded RNA virus containing 11 genomic segments. The virus is composed of three concentric capsid shells. Strains are characterized by the electrophoresis migration patterns of the RNA segments and by structural differences of the capsid proteins VP6, VP7, and VP4. VP6 serotype A accounts for most of the rotaviruses that are pathogenic in humans. The virus replicates primarily in enterocytes in the proximal small intestine, where infection leads to denuding of the villus tips and mononuclear cell infiltration of the underlying lamina propria. The virus seems to remain localized to the intestine. It has not been identified in breast milk.

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Epidemiology and Transmission

The distribution of rotavirus is widespread throughout the industrialized countries as well as the developing world. The virus causes an estimated 150 million diarrheal episodes in infants and young children each year, and approximately 0.5 million deaths. Rotavirus infections are usually prevalent in temperate climates during the winter months, whereas in tropical areas, infection is endemic year round. In some nurseries endemic infection rates reflect the incidence in the community, but in others, the incidence of disease is relatively constant. Rotavirus infection in neonatal units may also occur in the context of a clinically apparent outbreak. The distinction between endemic and epidemic rotavirus disease in the nursery, however, is blurred. Longitudinal prevalence surveys conducted in geographically diverse nurseries during periods without outbreaks indicate that 10%-70% of infants admitted in hospital for longer than 1 week excrete rotavirus at some time before discharge, often asymptomatically, and that typically only one or two strains account for all the infections over many months.

Epidemiologic aspects of rotavirus potentiate its spread in a confined environment, such as a nursery. The stool of infected individuals contains high titers of virus, and infection can be transmitted by very small inocula. Additionally, the virus survives on inanimate surfaces and is resistant to many commercial disinfectants. Rotavirus likely is introduced into the unit by a newborn who acquires infection during delivery after exposure to maternal stool, or by an infant or a staff member who imports the virus from the community. Thereafter, most infection is nosocomial, transmitted via the hands of personnel. Viral excretion in the stool begins 1-2 days before the onset of diarrhea, is highest after 3-4 days of diarrhea, and then wanes 1-2 weeks later. Outbreaks may spread rapidly through the nursery, where the most important factors determining spread seem to be the frequency of handling the infants and the closeness of the bed spaces.

Clinical Manifestations

Nearly all reports indicate that rotavirus infection frequently is asymptomatic or mildly symptomatic in newborns. Some data suggest that maternally derived serum and intestinal antibodies and possibly breast milk antibodies may be responsible for preventing or alleviating infection early in life. Additionally, a high proportion of nursery infections are caused by the VP4-serotype designated P[6].[150] This serotype is not usually isolated from older children with community-acquired symptomatic infection. The reasons underlying the predilection of newborns for P[6] strains are unknown, but this observation suggests that the relatively mild disease in infants may partially be the result of the intrinsic properties of the infecting virus.

Symptomatic infants develop irritability and poor feeding, followed by watery or mucous stools that are sometimes bloody and frequently contain increased reducing substances.[219] Occasionally, infants develop severe diarrhea and dehydration, but fatalities are rare. There has been speculation that rotaviral infection may predispose to necrotizing enterocolitis, but such an association has not been clearly established.

The diagnosis is usually made by detection of viral antigen in stools by using ELISA. The rate of false-positive results may be 1%-4%. Hand washing remains the most effective prophylactic measure. Hard surfaces should be washed with alcohol-containing disinfectants because quaternary ammonia–containing compounds are not active against the virus. Therapy consists of rehydration and maintenance of fluids and electrolytes. Some investigators have found that breastfeeding prevents infection or lessens the severity of the illness.

A tetravalent vaccine approved by the FDA in 1998 was removed from the market in 1999 because postmarketing surveillance indicated a rare association with intussusception. Two additional oral rotavirus vaccines were introduced in the mid-2000s: a pentavalent product composed of five re-assorted strains derived from human and bovine rotaviruses (RV5) and a monovalent vaccine composed of an attenuated human strain (RV1). Data for intussusceptions from the Vaccine Adverse Event Reporting System (VAERS) from 2006 through 2012 were recently published. The VAERS received 584 reports of confirmed intussusception cases after the administration of RV5 and 52 after RV1.[97] Most intussusceptions after RV5 occurred 3-6 days after the administration of the first dose. The overall risk after three doses of the vaccine was estimated at 0.79/100,000 cases, implying a slight increase in risk for intussusception. The CDC and the AAP continue to recommend the vaccine for infants in the United States because the benefits of the vaccine far outweigh the risks. So far, the vaccine has been shown to have prevented more than 382,000 hospitalizations from rotavirus-related illness, translating into approximately 1.2 billion dollars in savings in medical cost related to rotavirus morbidity.[146] The first dose of each vaccine is preferentially administered at 2 months, although both may be given at 6 weeks. Immunization of preterm neonates is recommended at the same postnatal age if the infant is otherwise stable and he or she has been discharged from the hospital. The vaccine should be avoided in infants suspected of having severe combined immunodeficiency syndrome (SCIDS) and in those with a history of allergy to any component of the vaccine and in those with a previous history of intussusception.[42] On the contrary, in the HIV exposed/infected infant the CDC supports the administration of the vaccine because the diagnosis of HIV may not be confirmed in infants at the time they receive the vaccine; and because the vaccine strain is attenuated, it is less risky for the infant to develop rotavirus from the vaccine strain than from the wild type. Studies of this vaccine in South Africa have shown that it is immunogenic and safe in this population.[247]

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Parvovirus B19

Parvoviruses are small (23-25 nm), single-stranded DNA viruses of the family Parvoviridae (genus *Erythrovirus*) that lack an envelope, but form capsids (*Parvum* is the Latin word meaning "small"). The viral genome consists of approximately 5600 nucleotides and encodes for only three proteins—a nonstructural protein, NS1, which functions in replication and is responsible for the destruction of the erythroid progenitors, and two structural proteins, viral protein 1 (VP1) and viral protein 2 (VP2).[291] Viral protein 1 differs from VP2 only in that it has 226 additional amino acids at its amino terminal. Although most of the capsid consists of VP2, which may assist in the entry of the virus into the cell, the additional 226 amino acids of VP1 form loops that are external to the capsid and contain the epitopes recognized by neutralizing antibodies. Immunity to parvovirus occurs primarily through the antibody response, and IgG confers lasting immunity.

Parvoviruses are animal viruses, which seem to be species specific. Parvovirus B19 replicates only in human erythroid precursors and is the only virus in the family definitely known to be pathogenic in humans. Parvovirus B19 was identified in 1975 in the sera of blood being screened for hepatitis B, and its name signifies the well in which it was identified. Parvovirus B19 is distributed worldwide, and infection occurs sporadically throughout the year, although there are seasonal increases in temperate zones, particularly in spring, and epidemics occur every 4 years.

Transmission of infection occurs mainly through contact with respiratory secretions or droplets but also occurs vertically from mother to fetus and via blood or blood products. IgG antibodies to parvovirus B19 are believed to confer lifelong immunity, and vertical transmission has not been documented in women with immunity before pregnancy. Secondary infection rates among nonimmune household contacts approach 50%, and child care personnel and teachers have an occupational risk of approximately 20%-30%. Although seroprevalence is found in only 5%-10% of young children, it increases to approximately 50% in young adults and is nearly 90% in older adults. The annual seroconversion rate of women of childbearing age is estimated to be 1.5%. The risk seems to be greatest in homes with multiple children, especially between ages 3 and 10 years. The incubation period usually is 4-14 days but can be 21 days. Rash and joint symptoms appear 2-3 weeks after infection. Individuals are most infectious before the onset of the rash, but are no longer so after the appearance of the rash, so school attendance with rash is not of concern. Hospitalized patients with aplastic crisis may remain contagious for a week after the onset of symptoms.

Clinical Manifestations

In most instances, infection with parvovirus B19 is asymptomatic and remains unrecognized. The most common illness is erythema infectiosum, or fifth disease. These individuals usually have a syndrome of malaise, headache, and low-grade fever, followed 7-10 days later by the development of an erythematous, "slapped cheek" rash, sparing the nasal bridge and circumoral region, followed by a blotchy, maculopapular rash of the trunk and then the extremities, particularly the thighs. These areas develop central clearing, resulting in a reticular or lacey pattern. This rash may recur over weeks to months later with heat or cold exposure. Individuals shed virus during the prodrome and are unlikely to be infectious by the time the rash aspect of the illness occurs. Another manifestation that is less common in children is a symmetric arthralgia or arthritis, particularly of the hands, wrists, and knees, which is usually self-limited. Both manifestations, rash and arthropathy, seem to be immune mediated. A few individuals develop a mild respiratory illness with no rash and, rarely, some develop a papular, purpuric "gloves and socks" syndrome, with painful, purpuric papules over the hands and feet.

Because the virus causes lysis of red blood cell precursors, it may cause a transient red blood cell aplasia, which is rarely significant in healthy individuals. Aplastic crises may result, however, in the presence of hematopoietic disease, such as sickle cell disease or thalassemia. Occasionally, parvovirus B19 will also cause thrombocytopenia, neutropenia, and lymphocytopenia. Chronic infection and anemia may result in patients with immunodeficiency disorders. Other reports suggest an association of the virus with myocarditis,[198] peripheral nerve abnormalities, or vasculitis.

Fetal Infection

Fifty percent of pregnant women are susceptible to parvovirus. When infection occurs, transplacental transmission of parvovirus is estimated to be 30%-50% and is less frequent with advancing gestational age. Spontaneous abortion has been seen in up to 30% of first-trimester infections, nonimmune fetal hydrops and/or fetal death in 12% of cases in the second-trimester, and fetal death in 7% of third-trimester cases.[31,216] Most pregnancies result in apparently normal newborns despite proven fetal infection,[135] although there may be an increase in the number of infants who are small for gestational age. Although there have been a few reports of congenital anomalies, most case series have not found an increased incidence of anomalies. In studies of viral causes of intrauterine fetal deaths, parvovirus was found in 13% of fetuses and was highly associated with chronic villitis and hydrops fetalis.[251] Parvovirus B19 attaches to the globoside glycolipid cellular receptor found on erythroid precursor cells (erythroblasts and megakaryocytes), erythrocytes, placental syncytiotrophoblasts, fetal myocardium, and endothelial cells, but replication occurs only in the erythroid progenitor cells.[291] The apoptosis of the red blood cells appears to be caspase mediated.

The most common adverse fetal outcome reported in infected fetuses is hydrops fetalis; parvovirus B19 may

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be responsible for 20%-30% of the cases of nonimmune hydrops, particularly during epidemics. Irrespective of when maternal infection occurs, fetal nonimmune hydrops most commonly occurs between 17 and 23 weeks' gestation, when hematopoiesis is occurring most rapidly and is located in the liver, and when the placental trophoblasts have the highest concentration of the P antigen, the B19 cell receptor.[24] The virus infects the erythroid progenitor, causing a maturation arrest at a time when the fetus is expanding its red blood cell volume and has a shortened red blood cell life span, resulting in severe fetal anemia in most, but not all, instances. Fetal anemia results in congestive heart failure, a known cause of hydropic changes, such as generalized edema, ascites, and pleural effusions. However, fetal hydrops has occurred in the third trimester and as late as 12 weeks after maternal infection, so follow-up with fetal ultrasonography must be continued with diligence.

The virus may also cause myocarditis, after attachment to the globoside receptors in the myocardial cell, which also results in hydrops. Some fetuses develop thrombocytopenia and hepatic damage. Meconium peritonitis has resulted from small bowel obstruction and perforation. Placental damage, resulting in leakage of α-fetoprotein, is often linked to poor outcome. The mother may also become ill with "mirror syndrome," which consists of a preeclampsia-like state, with anemia, hypertension, proteinuria, and edematous legs, mirroring the fetal infection.[56] The mirror syndrome is believed to be secondary to perfusion abnormalities of the placenta.

There are too few cases of hydrops secondary to parvovirus B19 to conduct a controlled trial, and most clinicians advocate intrauterine transfusion. Although untreated fetuses may also survive hydrops, survival in small case series appears to be lower (55%) than among the transfused fetuses. Measurement of the middle cerebral artery peak systolic velocity on fetal ultrasonography to determine severe anemia and high cardiac output can be used as an indicator of the need for fetal transfusion. When transfusion has been used, survival of the fetus has been 85%. Platelets should also be available for transfusion because the severely anemic fetus may also have thrombocytopenia. Most fetuses who survived intrauterine transfusion demonstrated a good neurodevelopmental outcome on follow-up.[63] However, a study of 28 infants indicated that 11% had neurodevelopmental impairment.[57] Digitalization has also been used for fetuses with myocarditis. Surviving fetuses do not seem to have heart disease. A few cases have also been reported of encephalitis, meningitis, perivascular calcifications, and intrauterine stroke. In these cases, virus seems to infect the immature endothelial cells.

Diagnosis

Because parvovirus B19 is too fastidious to grow in the laboratory, serology remains the best means of diagnosis, with the measurement of specific IgM or an increase in titer of specific IgG. IgM antibodies appear 7-14 days after infection and are often present for at least 2-3 months. IgG antibodies appear within days and persist for the life of the patient (Fig. 50.6).[67] Currently assays for parvovirus B19 IgM detect slightly greater than 90% of acute infections, and detection of viral DNA by PCR detects greater than 95% of infections. Acute maternal infection can best be diagnosed by using combination parvovirus B19 IgM serology and parvovirus B19 DNA detection by using PCR.[24] Not all fetuses make parvovirus B19 IgM, so viral DNA needs to be detected. Parvovirus B19 DNA may be detected in maternal serum, amniotic fluid, or fetal blood by using PCR, but the presence of the antigen does not always indicate recent infection because small levels of DNA may be detected for several months after acute infection. Placental infection has been documented at 14-16 weeks' gestation, but it is rare for the amniotic fluid to be infected before 21 weeks' gestation, and detection of amniotic fluid infection usually requires a delay of at least several weeks after the maternal infection. Placental infection does not invariably result in fetal infection.

Isolation

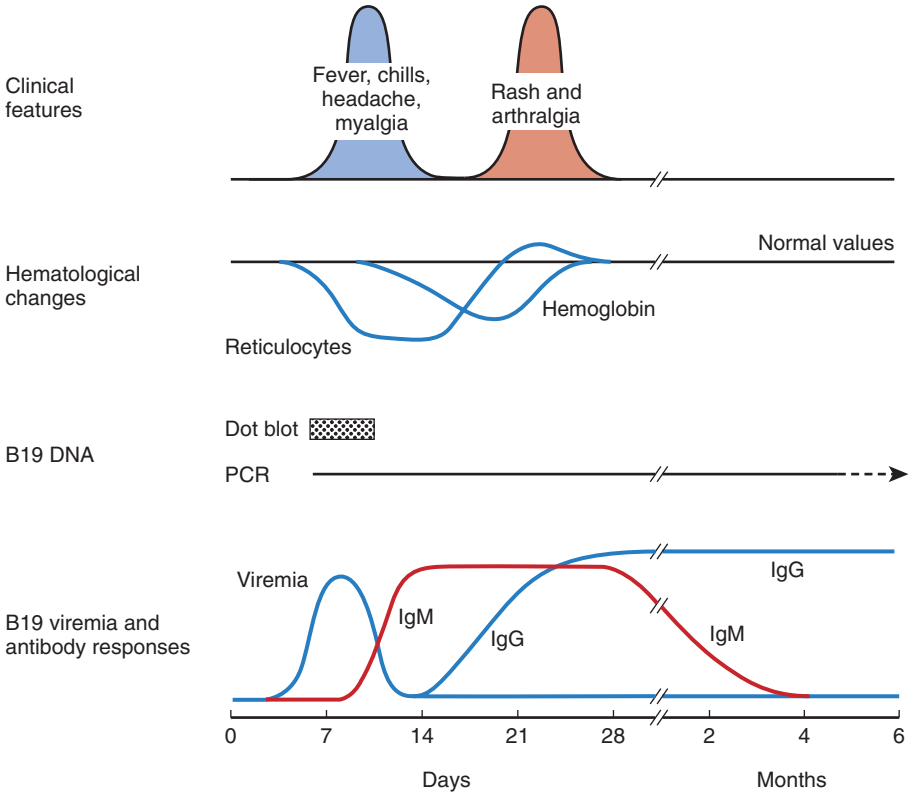
Contact isolation with use of gown, gloves, and mask is indicated for hospitalized patients with aplastic crisis. Pregnant health care personnel should be aware of their risks, although the magnitude of this risk is uncertain. Serologic testing and the option not to care for a patient with an aplastic crisis may be offered. Patients with only the rash of erythema infectiosum are not contagious.

Although pregnant childcare and health care workers are at increased risk of infection, they are also at risk of infection within the community and within their own homes, and the fetus, if infected, has a low risk of adverse outcome. Therefore, it is not recommended that these pregnant workers be kept away from their workplaces. They do, however, need counseling regarding hygiene.

Influenza A and B

The influenza viruses are RNA viruses of the family Orthomyxoviridae. Although there are three antigenic types (A-C), type C is only responsible for mild flulike symptoms, or coryza, in children. Its antigens are not included in the influenza vaccines. Types A and B are both responsible for epidemics, and their antigens are both included in the influenza vaccines. Type A virus is further classified by the presence of two distinct glycoprotein surface antigens, the hemagglutinin (H) and neuraminidase (N) antigens. Hemagglutinin is responsible for viral binding to cell receptors, and neuraminidase is responsible for the release of virus duplicated from the cell after replication. The H1, H2, and H3 hemagglutinin subtypes are particularly important in epidemics because immunity is largely caused by the production of antibodies to these antigens. "Drifts," or minor changes in the antigens, occur in both the influenza A

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• **Fig. 50.6** Course over time for clinical, serologic, and virologic characteristics of B19V infection in pregnancy. (Adapted from Dijkmans AC, et al. Parvovirus B19 in pregnancy: prenatal diagnosis and management of fetal complications. *Curr Opin Obstet Gynecol*. 2012;24:95.)

subtypes and in influenza B over time, requiring changes in the immune response to the virus.

An antigenic "shift," with the development of a new hemagglutinin or neuraminidase antigen, results in pandemic infection at infrequent intervals. When an antigenic shift occurs, the new antigenic viral strain almost completely replaces the prior seasonal strain. Therefore, the 2009 pandemic influenza A (H1N1) replaced the prior seasonal influenza A (H1N1). The virus type that predominates in a season alters the morbidity (hospitalizations) and mortality for that season.

Influenza A (H3N2) has nearly three times the average mortality, whereas influenza A (H1N1), which predominated in the 2009 pandemic, had four times the average mortality in children, because of a prior lack of exposure and immunity and because of its particular virulence in children. In one 10-year study of 209 infants in the first year of life, influenza A (H3N2) occurred most commonly, followed by influenza B and influenza A (H1N1), with infections in 178, 96, and 26 infants, respectively.[94]

Both swine influenza and avian influenza can occasionally cause infection with the typical influenza symptoms in humans. Swine influenza is usually associated with attendance at agricultural fairs and does not result in significant human-to-human transmission. Avian influenza is associated with contact with domestic or wild birds. Two avian influenza viruses have been responsible for severe disease and mortality in humans: influenza A (H5N1) has been reported in Asia, Africa, the Middle East, and Europe in 1997, and influenza A (H7N9) has occurred endemically in China since 2013.

The onset of influenza is characterized by the sudden onset of fever and chills, with associated malaise and headache, myalgia, sore throat, conjunctivitis and rhinitis, and sometimes vomiting and diarrhea, often resulting in otitis media. Full recovery occurs in most otherwise healthy children by 3-5 days. Occasionally, a previously healthy child may develop myocarditis, a lower respiratory tract infection (pneumonia or bronchiolitis), or CNS disease, ranging from febrile seizures to encephalitis. Secondary bacterial infections may be significant and may result in death. Aspirin or aspirin-containing products should never be given to any child suspected of having influenza infection to prevent the now-rare Reye syndrome.[100]

Most influenza infections in neonates are asymptomatic. Infection is less common in the first 6 months of life and usually less symptomatic, probably reflecting the transplacental transference of maternal antibody during pregnancy, which may protect the infant for the first 6 months, and antibody transferred via breast milk. Infants may, however, present with high fever and an upper respiratory tract infection, and the infection may be indistinguishable from bacterial sepsis. The highest mortality has been reported in infants younger than 6 months of age. In the 2003-2004

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influenza season, the mortality rate among infants younger than 6 months of age was 0.88 per 100,000 children. One third of the infants died at home, and one fourth had co-infections with bacteria, particularly pneumococcal or staphylococcal pneumonia. Chronic neurologic and neuromuscular conditions not previously recognized as at-risk conditions were present in one third of the children.[20] However, almost half of all deaths resulting from influenza occur in children with no underlying chronic conditions, such as pulmonary or cardiovascular disease or immunosuppression putting the child at risk.

Bronchiolitis, pneumonia or croup, fever, rhinorrhea, apnea, irritability, and feeding difficulties all may be primary symptoms. In a prospective study of the first year of life, one third of the infants were infected, but only 40% of the infants were infected in the first 6 months of life, and most lower respiratory tract disease and otitis media occurred in the latter 6 months, when the transferred maternal antibody would be expected to have waned.[94] There was also a very significant increase in risk of infection with increasing numbers of siblings, ranging from a 20% infection rate with no siblings to a 59% rate with three or more siblings. Lower respiratory tract disease was, however, far less common than with RSV or PIVs. One third of infants presenting to the emergency department during influenza epidemics had influenza infection, although they frequently had no respiratory symptoms. In contrast, one third of the infants presenting with a community-acquired pneumonia were also infected with influenza.[139,211]

Several influenza A and a few influenza B epidemics have been reported in NICUs. Low rates of immunization among staff members played a significant role in these epidemics. Prematurity and pulmonary disease, particularly bronchopulmonary dysplasia, seem to be risk factors.

Pregnant women infected with H1N1 influenza virus in 2009 had higher rates of hospitalization and death, accounting for 6% of such deaths in the United States. Risk factors for severe disease include obesity, asthma, multiparity, and multiple births. Pregnant women should be vaccinated during prenatal visits and may receive both seasonal flu vaccine and H1N1 flu vaccine at the same time in different body sites (one in each arm), when both viruses are in season. Vaccination of the pregnant woman may offer some protection to her newborn infant, which is particularly important, as the vaccine is not licensed for infants less than 6 months of age. Certainly, all caregivers of infants less than 6 months of age should also be vaccinated in an effort to prevent them from bringing influenza to the infant. Pregnant women should receive the injectable, inactivated vaccine. Breastfeeding is likewise compatible with vaccination and may offer some antibody protection to the infant.

To date, the virus has not been shown to cross the placenta, but the newborn may be exposed to contaminated secretions at birth. Thus, the newborn should be considered exposed, rather than infected, and should be carefully observed. The baby may be separated from the mother and kept in an incubator in the same room, or the baby may be put in a separate room until the mother has been treated with antivirals for at least 48 hours, has been free of fever while off antipyretics for at least 24 hours, and can control her cough and respiratory secretions. Breastfeeding should be supported, and expressed breast milk should be used to feed the newborn. In the 2009 pandemic, more than 50% of nurseries restricted breastfeeding by the mother while she was ill. When able to see her infant, the mother should wear a face mask, wash her hands with soap and water, and follow respiratory hygiene and cough etiquette guidelines for at least 7 days after symptom onset or 24 hours after resolution of symptoms, whichever is longer.

In past pandemics, secondary bacterial infections, particularly caused by *Streptococcus pneumoniae* (*Pneumococcus*), have also been the cause of increased morbidity and mortality. Continued pneumococcal vaccination is important.

Influenza is rapidly and easily spread person to person by aerosol droplet or by contact with contaminated secretions. The particles only travel a short distance (<6 feet) because of their size. Viral shedding and infectiousness are greatest in the 24 hours before onset of symptoms and at the peak of symptoms. Individuals should cover their noses when coughing or sneezing and should avoid touching their mouths, noses, or eyes with their hands. The virus may survive in the environment for 2-8 hours, although the role of fomites in transmitting infection is unclear. The virus can be destroyed by heat (75-100° C) or by numerous chemical germicides or household disinfectants. The incubation period is 1-3 days. Individuals are contagious the day prior to developing symptoms. Winter outbreaks are more common in temperate climates. School-age children have the highest attack rate and serve as a source of spread to adults and younger children. Hand washing with soap and water or alcohol-based hand cleansers and cohorting are the most effective means to interrupt epidemics within the NICU. Cohorting requires rapid diagnosis. PCR detection of influenza RNA is the most rapid and sensitive means of diagnosis. In addition, staff members should not work when ill, and family members should be carefully screened, particularly during the influenza season, for viral illness before admission to the NICU. The infection is *not* spread by eating any particular food, such as pork or pork products.

Infants who are born to pregnant women with influenza have an increased risk of preterm birth, low birth weight, and small size for gestational age, especially when the mother is severely ill. The decreased tidal volume and increased cardiac output, as well as the immunologic changes of pregnancy, put the pregnant woman at higher risk of severe illness requiring hospitalization. All women who may be pregnant during an influenza season should receive inactivated vaccine. The vaccine is safe throughout pregnancy and breastfeeding. Administration of the vaccine to the mother during the pregnancy is not associated with fetal death, preterm birth, or congenital malformations. Additionally, the neonatal antibody level is much higher and the infant is much less likely to develop influenza in the first 6 months of life. The vaccine may be given in any

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trimester. Staff members in the NICU should also be encouraged to be vaccinated; compliance has traditionally been low, although now most hospital programs require staff to either receive the vaccine or wear a clean mask before each patient contact throughout the influenza season. Also, inactivated vaccine should be given to family members of high-risk infants. Little is known about the safety and efficacy of antiviral prophylaxis in staff members and parents during epidemics in the NICU, although it has been used.[100]

Treatment should not be withheld while awaiting laboratory test results in a high-risk individual. The tests of choice include RT-PCR, viral culture, and rapid molecular assays, which are widely available and have high sensitivity and specificity.

Oseltamivir, a neuraminidase inhibitor, has been used in several nurseries during outbreaks, particularly during the 2009-2010 pandemic. The most commonly reported side effects include vomiting and diarrhea. The FDA licensed oseltamivir for use in children as young as 2 weeks of age. However, it is being used to treat both preterm and term infants at birth because the benefits appear to outweigh the risks. Fever needs to be controlled, most often using acetaminophen, but aspirin-containing products should never be given to individuals suspected of having influenza infection.

Recommendations for prophylaxis and/or treatment of influenza may be found online (www.cdc.gov/flu/professionals/antivirals/index.htm). Treatment is most effective if begun within 48 hours of onset of disease but can still be effective even if started later. Children should be evaluated for bacterial co-infections and, if infection is suspected, treated with antimicrobials. Siblings of infected children, particularly if they are less than 6 months of age or have other high risk, chronic conditions, may need prophylaxis or treatment. The inactivated vaccine should be given to children 6 months of age and older. Prior to 6 months of age, antibody response is inadequate. The vaccine contains no live virus. Both the trivalent and quadrivalent inactivated vaccines may be used. Live attenuated vaccine is *not* recommended. A dosing algorithm may be found in the annual AAP influenza policy statement published each year in the September issue of *Pediatrics*, or online (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Documents/Special-Considerations-to-Treat-and-Prevent-Flu-in-Newborns_FINAL.pdf). Children 6 months to 8 years of age who have not previously been vaccinated require two doses of vaccine given at least 4 weeks apart for protective titers to develop. All people should be vaccinated annually. The vaccine may be given with other live or inactivated viruses. Egg allergy does not preclude the use of the vaccine. Vaccination should be the mainstay of prevention of influenza.

Rubella Virus

Rubella virus is an RNA virus in the Togaviridae family. It is surrounded by a lipid-containing envelope, which is responsible for its infectivity. Only one immunologic strain has been identified; the epidemics that have occurred seem to be secondary to changes in the susceptibility of the population, rather than changes in the virulence of a strain.

Rubella produces a very mild but extremely contagious disease, sometimes referred to as *German measles*. The incubation period is 14-23 days. It primarily manifests in adults with a maculopapular rash that can last 3 days and spreads from the face to the trunk and extremities, and with postauricular, suboccipital, and posterior cervical lymph node enlargement. There may be conjunctivitis, headache, sore throat, and cough. Although arthralgia may occur, recovery is nearly always rapid and complete. Fever is slight. Thrombocytopenia and encephalitis are rare. Half of all infections may be asymptomatic.

Epidemiology and Transmission

Rubella virus exclusively infects humans and is spread via respiratory droplet contact. Infections are worldwide in distribution but tend to peak in late winter and early spring. Presumably, the viral reservoir is maintained by mild or asymptomatic infections that occur constantly throughout the year and by prolonged viral shedding (possibly ≥1 year) from congenitally infected infants. Most individuals shed virus from 7 days before the onset of the rash until 14 days afterward. In the pre-vaccine era (before 1969), epidemics occurred every 6-9 years. The last major epidemic in the United States was in 1965. The goal of routine rubella vaccination in the United States, which was initiated in 1969, was to eliminate congenital rubella syndrome. From 2001-2006, there were only four cases of congenital rubella syndrome in the United States. Three of the mothers were born outside of the United States.[164] In 2004, the CDC declared that rubella was no longer endemic in the United States. Rubella continues to occur among immigrants, however, and it is important that pediatricians continue to administer the vaccine. The current goal is global elimination.

Most cases of congenital rubella syndrome occur after a primary maternal infection that causes viremia and intrauterine transmission. A few cases have occurred after maternal re-infection with rubella, but these are very rare. Accidental vaccination with RA27/3 vaccine in pregnancy may result in fetal infection (2%), but congenital defects or congenital rubella syndromes have not been seen.

After a primary maternal infection in the first trimester, there may be fetal loss, stillbirth, placental infection, or congenital rubella syndrome, or the fetus may remain totally uninfected. Not all infected fetuses develop congenital rubella syndrome. The virus may cause persistent placental infection with or without persistent fetal infection. The placenta is a relatively effective barrier to fetal infection from 12-28 weeks' gestation, but it is not so effective in the first and third trimesters, particularly in the last month of pregnancy.

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Gestational age at the time of maternal infection is the most important determinant of fetal infection and of the development of congenital defects, although fetal infection may occur at any point in gestation. Among 273 infants delivered after maternal rubella infection, Miller et al.[168] reported that fetal infection occurred in 90% of infants after maternal infection before 11 weeks' gestation, in 67% of infants at 13-14 weeks' gestation, and in 25% of infants at 23-26 weeks' gestation. Infection increased to 53% of infants after maternal infection in the third trimester, however, and reached 100% in the last month of pregnancy.

In addition, the risk of fetal damage with fetal infection decreases with increasing gestational age. Peckham[204] followed up 218 congenitally infected infants for 2 years and found that fetal damage occurred in 52% of infants infected before 8 weeks' gestation, in 36% of infants infected at 9-12 weeks' gestation, and in 10% of infants infected at 13-20 weeks' gestation. No fetal damage was shown after infection beyond 20 weeks' gestation. Rubella results in chronic infection of the fetal tissues, however, causing an inhibition of fetal cell multiplication. Many infants who show no apparent involvement at birth experience consequences years later. In concordance with the chronicity of the disease, Peckham[204] later noted that at 6-8 years of age, these same infants had an 82% risk of sequelae after infection in the first trimester. The risk of fetal damage reported by Miller et al.[168] was even higher, with sequelae shown in 90% of infants infected before 11 weeks' gestation, 33% infected at 11-12 weeks' gestation, 11% infected at 13-14 weeks' gestation, and 24% infected at 15-16 weeks' gestation.

Congenital Rubella Syndrome

Congenital rubella is not a static disease. Nearly three fourths of infected infants show no apparent involvement at birth, but develop consequences years later. Greater than 50% of infants with expanded congenital rubella syndrome have IUGR (birth weight is often <1500 g) and fail to thrive postnatally. These infants often have myriad transient symptoms, including thrombocytopenia, petechiae and purpura, hemolytic anemia, hepatitis, jaundice, and hepatosplenomegaly. Nearly half the infants show "blueberry muffin" spots on the head, neck, and trunk, which represent dermal extramedullary hematopoiesis. Infants may also show myocarditis, cloudy cornea, long bone radiolucencies, interstitial pneumonia, and meningoencephalitis, manifesting as an elevated CSF protein level and pleocytosis. Although most of these symptoms are transient, they may also indicate severity of infection. Fulminant hepatitis or pneumonia, myocarditis with congestive heart failure, meningoencephalitis, thrombocytopenia, and bony lesions all are associated with a higher mortality.

Congenital rubella is best known for causing deafness and defects of the eye, CNS, and heart. Three fourths of infants develop sensorineural deafness, usually bilateral. Deafness may be the only sequela of congenital infection and may occur with maternal infection up to 20 weeks' gestation.

Congenital heart disease occurs only when the fetus is infected during the first 8 weeks of gestation, the period during which organogenesis occurs but is quite common with infection during that period. PDA, the most common lesion, may occur alone or in conjunction with pulmonary artery or valvular stenosis, or there may be stenoses of other vessels.

Microcephaly and neuropsychiatric problems are also common. Studies of long-term outcome show that 26% of children with congenital rubella syndrome had severe mental retardation, 12% had neurologic problems, 18% had behavioral abnormalities, and 6% had autism. Most rubella survivors without mental retardation had learning disorders, behavioral problems, difficulties with balance, and muscle weakness.

Ophthalmologic abnormalities may include cataracts in one third of children, often bilateral and occasionally accompanied by glaucoma. Other children may have microphthalmos or characteristic "salt and pepper" chorioretinitis. Rubella RNA can be detected and quantified in the lens of affected infants.

Attention has focused more recently on the effects of HLA haplotypes, immune complexes, and autoantibodies in predisposing congenital rubella survivors to autoimmune conditions. In a 60-year follow-up of congenital rubella survivors, Forrest et al.[83] reported that 20% had died (mostly of cardiovascular disease and malignancy); 68% had mild aortic valve stenosis, 22% had diabetes mellitus, 19% had thyroid disease, 73% had early menopause, and 13% had osteoporosis. HLA-A1 and HLA-B8 antigens were increased in frequency.

Diagnosis

Diagnosis of maternal rubella on the basis of clinical findings is unreliable, and serologic testing must be performed. If the maternal immune status is unknown at the time of rash illness, acute-phase titers should be obtained within 7 days of the illness; seropositivity usually indicates prior immunity with very little risk of current infection. Women with very low titers may be re-infected, which can result in a small risk of fetal infection. Latex agglutination, enzyme immunoassay tests, and immunofluorescence are now more commonly used than passive hemagglutination techniques.

Rubella-specific IgM may be determined 7-14 days after the illness. A high or moderate IgM titer is very helpful, but false-positive results may occur, and low IgM titers may be found in patients with subclinical reinfection. Rubella-specific IgM may be high with re-infection or post-vaccination, or it can be high as a false positive. Testing IgG avidity can help differentiate acute infection from these situations.

Traditionally, an increase in serum antibody titers obtained initially in the acute phase, preferably within 7 days of illness and repeated in the convalescent phase 10-14

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days later, is used to diagnose acute infection. The titers need to be run simultaneously in the same laboratory. If antibody is still not present 4 weeks after exposure, another serum sample should be tested at 6 weeks for certainty. Acute-phase titers may be obtained, with less accuracy, 28 days after illness, but are not interpretable thereafter.

The antenatal diagnosis of fetal rubella infection has been made with rubella cultures or detection of rubella-specific IgM or rubella-specific antigen or RNA by RT-PCR from amniotic fluid or percutaneous umbilical blood sampling. Chorionic villus sampling has also been used, but less is known of its reliability.

Any infant born to a mother suspected of having had a rubella infection during pregnancy or any infant born with clinical signs and symptoms consistent with congenital rubella syndrome should have a complete evaluation and diagnostic workup. Isolation of rubella virus from a newborn provides an absolute diagnosis. The virus is most often isolated from the nasopharynx but has been grown in blood, CSF, and urine or even from the lens of the eye or CSF years later. The diagnosis may also be made by detecting rubella-specific IgM in cord or infant blood or by detecting stable or increasing concentrations of rubella-specific IgG in the infant's serum over several months, although infants with hypogammaglobulinemia may fail to produce antibody. More recently, oral fluid testing for rubella-specific IgM or RT-PCR for rubella antigen has been very helpful.

Prevention and Therapy

All children with postnatally acquired rubella should be isolated for 7 days after the rash appears. In contrast, children with congenitally acquired rubella should be considered contagious for at least 1 year, unless repeated urine and blood cultures are negative. In addition, the families of these infants should be counseled regarding the risks to pregnant women.

Susceptible pregnant women exposed to rash illnesses should have a laboratory workup performed for diagnosis, as should the individual who is the origin of the illness. Immunoglobulin is not recommended for prophylaxis in an exposed pregnant woman because congenital rubella has occurred despite the lack of symptoms in women given immunoglobulin. Also, vaccination after exposure does not prevent infection from the current exposure but might prevent exposure and infection in the future.

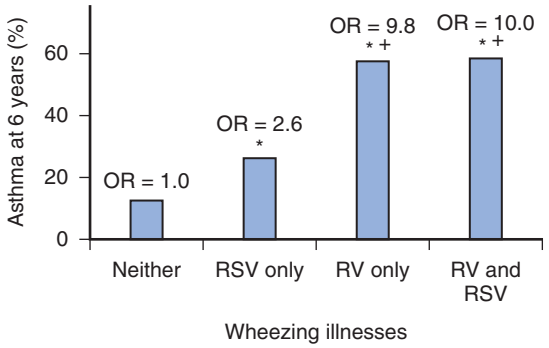
The goal in the United States is to eliminate rubella with vaccination. The RA 27/3 rubella virus vaccine is exclusively used in the United States and is highly effective. Infants should be vaccinated at 12-15 months of age and again at school entry. Preterm infants seem to lose maternal antibody to rubella at a much earlier age compared with term infants because the antibody is transferred primarily during the third trimester. The antibody response to vaccination is, however, similar to that of term infants. Postpartum and postpubertal women should be vaccinated unless contraindication exists. Breastfeeding is not contraindicated. Women should not be vaccinated during pregnancy because 3% of fetuses may be subclinically infected, but birth defects have not been reported after vaccination of pregnant women, even if the fetus is infected. The theoretical risk to the fetus is not greater than 1.3%. It is acceptable to vaccinate children of pregnant women because there is no evidence of transmission of virus after vaccination. Some parents continue to believe that the MMR vaccine may cause autism, even though numerous data and studies have shown that there is no association. The Immunization Safety Review Committee of the Institute of Medicine rejects any causal association.

Rhinovirus

Rhinoviruses are the most prevalent of human pathogens and are well known to cause the "common cold." Infection, which may persist for up to 2 weeks, usually begins with a sore throat and clear, watery rhinorrhea, which gradually becomes mucopurulent. Symptoms may include malaise and myalgia, fever, cough, sneezing, and headache. Rhinoviruses are small, non-enveloped, simple, positive-stranded RNA viruses classified as picornaviruses. There are three large groups of human pathogens among the Picornaviridae family: enteroviruses (enteroviruses, polioviruses, coxsackie viruses, and echoviruses), hepatoviruses (hepatovirus A), and rhinoviruses. There are more than 100 rhinovirus serotypes, and even more serotypes are being described with improved methodology. Immunity to one serotype offers little immunity to another, and immunity is of variable and brief duration and specific to a serotype. The rhinoviruses are usually spread from person to person via contaminated hands and self-inoculation of the nasopharynx but may also be spread via aerosol droplets. Infection may occur year round but may be epidemic in fall and spring in temperate climates; the incubation period lasts 2-7 days. Shedding has been documented for up to 6 weeks. Many strains will not grow in cell culture of the nasopharynx, and serology is confounded by the many strains. PCR is used to identify the virus and shows the prevalence and importance of this virus, particularly in infancy and early childhood.

A series of reports on 285 infants who were at high risk of developing asthma and were followed up to age 6 years emphasized the important role that rhinovirus infections play in the first year of life.[112] Human rhinovirus was found to be the most common etiology of upper respiratory tract infection (48%) and occurred early and repetitively in these high-risk infants. Co-infection with other viruses generally resulted in more severe upper respiratory tract infections.[114] Higher rates of infection were found in children enrolled in daycare or who had siblings in the home. A wheezing illness caused by rhinovirus at any point in the first 3 years of life in these high-risk infants resulted in a 10-fold increase in risk of asthma at 6 years of age—much more of a risk than found with RSV wheezing illness in early childhood (Fig. 50.7).[112] Yet it still remains unclear whether bronchiolitis or respiratory viral infections in the early years of life cause

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• **Fig. 50.7** Risk of asthma at age 6 years in children who wheezed during the first 3 years of life with rhinovirus (RV), respiratory syncytial virus (RSV), or both (*P = 0.05 versus neither; ^{+}P = 0.05 versus RSV only). OR, Odds ratio. (From Jackson DJ, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Resp Crit Care Med*. 2008;178:667.)

chronic respiratory disease—in particular, asthma—or are simply markers for children who have a genetic predisposition to asthma.

Rhinovirus is responsible for five hospitalizations per 1000 children younger than 5 years of age each year, which is far more significant than has been found for RSV.[137,169] Because rhinovirus is now known to cause lower respiratory tract disease, it has been argued that it may enhance susceptibility to asthma.[167] Infants with decreased pulmonary function, in particular higher airway resistance, are more likely to develop severe infection and to require hospitalization.[69,266] The virus is also responsible for many of the exacerbations of asthma.

Rhinoviruses have also been shown to be the etiology of sporadic, individual infections, or outbreaks, in the NICU. Infants may present with apnea, feeding difficulties, cough or rhinitis, and fever. They may also require increased oxygen or increased ventilatory support. Signs and symptoms may be indistinguishable from RSV. Infants who are not breastfed may also have a higher risk of severe infection owing to rhinovirus.[170] Preterm infants, particularly those with bronchopulmonary dysplasia, seem to be particularly susceptible to rhinovirus. In them, rhinovirus may be more common than RSV and is responsible for bronchiolitis and lower respiratory tract disease. The virus may cause significant worsening of the pulmonary status, necessitating prolonged increases in care in infants with bronchopulmonary dysplasia. In addition to rhinovirus, RSV, hMPV, and PIV are significant causes of lower respiratory tract infections requiring re-admission to the hospital and/or ICU in extremely preterm infants (≤32 weeks' gestational age). The role of human bocavirus remains controversial.

There is no effective treatment, and the only prophylaxis is use of infection control measures, such as contact precautions and hand washing, as well as respiratory droplet precautions. It is strongly urged by the FDA that cold medications available over the counter not be used in children less than 4 years of age, because of both safety and efficacy issues. Antibiotics are not of benefit and do not prevent bacterial superinfection. Rather, they may encourage antimicrobial resistance.

Coronavirus: Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome

Most human CoVs cause the "common cold", a limited upper respiratory infection resulting in malaise, fever, sore throat, sneezing, and cough. Occasionally, the virus is responsible for bronchiolitis, pneumonia, and croup. These lower respiratory tract infections are usually seen in infants or the immunocompromised. The CoV is a non-enveloped, single stranded, positive-sense RNA virus with crown-like projections seen on their surface on electron microscopy. CoVs are host specific. They can infect humans and other animals.

In 2002-2003, an epidemic of severe acute respiratory syndrome (SARS) occurred in China, Hong Kong, Vietnam, and Canada and was eventually reported in 16 countries, including the United States. A novel CoV, unrelated to other known human and animal CoVs, has been shown to be the cause of the outbreak. The horseshoe bats of southern China were found to be the natural reservoir of this enveloped RNA virus, which probably spread to the civet cat and then to humans in the marketplace. There have been no worldwide epidemics since 2004.[23] Severe disease caused by SARS-CoV primarily occurred in adults, although even among adults, infection ranged from asymptomatic to mild to severe. Patients developed the usual symptoms of the "common cold," but then worsened to a nonproductive cough and dyspnea 5-7 days later. Twenty percent required mechanical ventilation. Mortality occurred in 10% but rose to 50% in those older than 60 years of age. One fourth also had significant diarrhea.

A second CoV which can also cause severe disease has emerged—the MERS-CoV—which is responsible for the Middle East respiratory syndrome. As with SARS, disease can be asymptomatic, mild, or severe and fever, dyspnea, cough, and some vomiting and diarrhea can occur, with rapid worsening, chest infiltrates, need for mechanical ventilation, and a 50% mortality rate. As yet, infections have been limited to adults, usually male, who have other chronic diseases.

Virtually all cases of SARS in children have occurred via contact with infected adults, either in the home or in a health care setting. Co-infection may occur with other viral pathogens. Less than 10% of infections have occurred in children. The virus causes a mild, nonspecific respiratory illness in younger children, in contrast with the very serious, life-threatening infection in adults and teenagers older than 12 years. Most children present with fever but may have rhinorrhea, cough, coryza, myalgia, malaise, chills, or diarrhea.[148]

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In young children, the physical examination is normal, and the course is shorter and milder. As a group, young children apparently do not develop significant respiratory distress or require oxygen, and they make a complete recovery. Chest auscultation is unimpressive. Chest radiography shows mild focal alveolar infiltrates. (In some cases, high-resolution CT showed airspace disease, even though the chest radiography result was negative.) Less than 1% of children require mechanical ventilation.[148] Similar to adults, children have multiple laboratory findings, including lymphopenia from destruction of the CD4+ and CD8+ lymphocytes, thrombocytopenia, and mild DIC. Lactic dehydrogenase is also elevated in most cases. No deaths have occurred in young children, who become asymptomatic within 6 months. Most reports of infections in children begin with infants a few months old. One premature infant presented at 56 days of life, at a corrected age of 38 weeks. His illness was comparable with that of adults and required oxygen, CPAP, and NICU admission, although he made a complete recovery.[245]

No infants born to mothers infected with SARS-CoV have shown any evidence of transplacental or congenital infection. Pregnant women may be more severely affected, with a mortality rate of 25%. Only one infant survived of seven pregnancies in women infected in the first trimester in Hong Kong, but two less severely affected women in the United States had infants with normal outcomes. Infants born to mothers infected in the second or third trimester seem to survive, whether born via cesarean section prematurely because of the mother's deteriorating condition or vaginally at term to a convalescent mother. None of the infants had evidence of infection. Infants born soon after the mother was infected tend to be appropriately grown, whereas infants born later have IUGR and oligohydramnios[148]; this could be secondary to ribavirin or steroids used to treat the mother's illness or because of the mother's illness itself. Infants born prematurely had a high incidence of necrotizing enterocolitis and jejunal perforation. Extensive fetal thrombotic vasculopathy with zones of avascular villi was noted in the placentae of two infants who survived maternal SARS infection.[183]

Diagnosis may cautiously be made using RT-PCR, but false-positive results occur often. Serology is helpful, but not widely available. The Public Health Department should be consulted prior to making the diagnosis.

Diagnosis of disease in children may be based on the WHO definition of probable SARS (radiographic evidence and epidemiologic linkage) or the CDC definition of suspected SARS (radiographic evidence is unnecessary). Children seem more likely to have negative RT-PCR and viral culture results, possibly because of a lower viral titer in the upper airway.

Infected individuals should be quarantined, and there should be strict adherence to infection control principles to prevent spread via aerosol, droplet, or fomites. There is only one documented case of transmission of infection from children to adults, but there have been cases of not yet symptomatic parents infecting health care workers.[250] This situation may represent the lower viral titers in children.

Treatment is primarily supportive. Many agents have been used in a noncontrolled fashion to treat severe disease without evidence of efficacy.

West Nile Virus

West Nile virus (WNV) is an enveloped single-stranded, positive-sense RNA flavivirus that is part of the Japanese encephalitis virus complex, and is transmitted to humans by the bites of infected mosquitoes. This arbovirus (arthropod-borne) survives in nature in a cycle that goes from mosquito to bird to mosquito, and primarily involves the *Culex* species of mosquitoes. Birds, especially crows, serve as amplifying hosts because of their high-titer viremia and are responsible for the spread of the virus over distances, whereas mosquitoes serve as vectors of the virus to humans who are accidentally infected when bitten. Infected humans are generally regarded as a dead end, but infected donors may transmit disease via blood transfusion or organ transplantation. Indigenous to Africa, Asia, Europe, and Australia, WNV was first reported in the Western Hemisphere in 1999 in an epizootic in New York City. Since then, it has rapidly spread throughout eastern and midwestern parts of the United States, northward to Canada, and southward to the Central and South Americas. Human infection may be asymptomatic (80%) or result in simple West Nile fever (20%). It may also result in neuroinvasive disease causing encephalitis, meningitis, or a flaccid paralysis resembling polio. Children, who develop symptomatic disease less frequently compared with adults, have milder symptoms and usually experience complete recovery, although there are rare cases of death. Children represent only 2% to 5% of all cases of neuroinvasive disease.[16] The incubation period ranges from 2-14 days, but disease usually occurs in 2-6 days. Most infections occur in summer or early fall after expansion of the viral and mosquito populations in spring and early summer. Diagnosis is made by testing serum and CSF for WNV-specific IgM. Positive tests need to be confirmed by a neutralization assay or the detection of WNV RNA in plasma, CSF, or urine. There is no specific treatment for infection or vaccine to prevent infection. Treatment is supportive. A controlled trial of WNV hyperimmunoglobulin failed to show benefit. Preventive measures are the only defense and involve mosquito control and education of the public, including pregnant women, to wear protective clothing, use insect repellent on the skin and clothing when outdoors, and avoid the outdoors during peak mosquito hours (dusk to dawn).

There have been few reports of WNV infections in children younger than 1 year of age. Breastfeeding was implicated in a report from Michigan in 2002, when an infant was found to have WNV-specific serum IgM after breastfeeding for 17 days. The mother developed WNV meningoencephalitis

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9 days after receiving an infected transfusion, which had been given after the birth of the infant. WNV genetic material was detected transiently in the breast milk. The infant remained well.[105] However, although WNV-specific IgM and WNV RNA have been detected in the breast milk of infected mothers, transmission to the infant appears to be rare.[16] The CDC reported that five of six infants who were being breastfed during maternal disease presentation remained healthy; viral RNA and WNV-specific antibody were not detected in their sera.[16] The sixth infant developed a rash but was not tested. WNV-specific IgA was detected for a short time in the milk of one mother, but all other samples were negative for WNV RNA, IgA, IgM, and IgG. The breast milk was also tested in nine other seropositive mothers in Colorado. Two samples tested positive for WNV-specific IgM and neutralizing antibodies.[16] The CDC continues to recommend breastfeeding because the established benefits outweigh the risks.

Intrauterine infection was probably documented in 2002 in the fetus of a mother who developed paraplegia secondary to WNV during the second trimester of her pregnancy.[8] The infant appeared well at term and had normal physical examination results, including head circumference. Ophthalmologic examination revealed marked chorioretinal scarring, however, and MRI of the brain showed generalized lissencephaly and marked white matter loss. In a survey in Colorado during an epidemic, 549 cord blood samples were screened for WNV-specific IgG and IgM. Of the cord samples, 4% were positive for IgG, indicating maternal infection, but none was positive for IgM, and all infants had normal growth and outcome.[192] Likewise, the CDC followed the outcome of 77 pregnancies where the mothers had been infected with WNV. There were four miscarriages and two elective abortions. Of the 72 liveborn infants, none had conclusive evidence of congenital infection, although three infants developed infections that might have been congenitally acquired. Seven infants had major malformations, but only three of these could have been related to infection, and none of these infants had evidence of infection.[190]

Eighty-three pregnant women with WNV infection were registered with the CDC in 2003 and 2004; 77 were followed up.[213] There were equal proportions of infection in all three trimesters. The spontaneous abortion rate was similar to that of the general population, but there were more malformations (5.5%) than expected. The malformations, however, appeared to be unlikely to be caused by WNV infection. There were three possible intrauterine infections. One breastfed infant developed WNV meningitis at 10 days of life. The mother had had WNV neuroinvasive disease 6 days prior to delivery. A second breastfed infant had a rash and coarctation of the aorta at birth. The mother had had WNV fever at delivery. A third formula-fed infant died as a result of WNV encephalitis and lissencephaly. The mother had had WNV fever 3 weeks prior to delivery. The first two infants survived and had normal development at age 1 year on the Bayley-III Scales of Infant and Toddler Development. Eleven of the original 77 infants were followed up at age 3 years.[236] The ophthalmologic examinations were normal, and there were no global delays on the Bayley-III Scales of Infant and Toddler Development.

The CDC has developed guidelines for the evaluation of infants born to mothers infected by WNV during pregnancy and a registry for pregnancy outcome.[264] Screening for WNV in asymptomatic, pregnant women is not recommended because there is no therapeutic intervention, and the outcome is currently unknown. A detailed ultrasound examination of the fetus should be obtained no earlier than 2-4 weeks after the onset of symptoms in an infected pregnant woman. Amniotic fluid, chorionic villi, and fetal serum may be tested for infection; in the event of a miscarriage or abortion, all products of conception should also be tested. Infants born to women known to be infected during the pregnancy should have a thorough physical examination, including measurements of head circumference, length, and weight; a neurologic examination; and evaluation for dysmorphic features, any dermatologic lesions, or hepatosplenomegaly. The infant's serum should be tested for IgG and IgM specific for WNV, and the infant should undergo evoked otoacoustic emission testing or auditory brainstem response testing. The placenta should also be examined by a pathologist.

An infant suspected to have WNV infection should undergo an extensive workup, including ultrasonography of the head and an ophthalmologic examination. The infant should also undergo CBC and liver function tests. Examination of the CSF should be considered and should include an IgM for WNV. The IgM may persist for more than 1 year, and it may cross-react with other flaviviruses. Acute and convalescent sera showing at least a fourfold rise in virus-specific neutralizing antibodies can differentiate the WNV infection. The infant should be examined by a dysmorphologist, and developmental milestones and growth measurements should be monitored for the first year of life. At age 6 months, the infant should undergo additional hearing screening and determination of WNV IgG and IgM.

Adenovirus

Adenoviruses are double-stranded, non-enveloped DNA viruses that do not show the seasonal distribution of most respiratory viruses but are present through the entire year. Disease may be endemic, epidemic, or sporadic. The seven species (A-G) have multiple (at least 55) distinct serotypes, and the different serotypes cause different kinds of illness. The virus is most commonly found in the upper respiratory tract, and infection usually spreads via respiratory tract secretions. The virus is viable in the secretions for long periods, so fomites contaminated with secretions may transmit infection, in addition to aerosolized droplets and person-to-person contact. Viral shedding may occur intermittently for months after infection. Individuals may be re-infected and have asymptomatic infection. Health care workers and equipment, particularly ophthalmologic

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equipment, have been implicated as sources of infection, so control requires careful hand washing and contact and droplet precautions. Health care workers with conjunctivitis should not participate in direct patient care for 2 weeks after onset and should use gloves in addition to strict hand washing. Ophthalmologic medications should be single-dose in nature, and equipment needs careful sterilization. The CDC recommends frequent hand washing with soap and water; not touching the eyes, nose, or mouth; covering the nose and mouth while sneezing or coughing; and avoiding sick contacts. Daycare centers for young infants and children is another frequent source of infection, and there are few effective control measures other than careful hygiene because the virus is also shed in the stool.

Greater than 80% of adenoviral infections occur in children younger than 4 years of age. Immunocompetent older children and adults usually develop acute, self-limiting infections, resulting in respiratory and gastrointestinal disease.

Adenovirus is most often associated with the "common cold," pharyngitis, otitis media, or pharyngoconjunctival fever. Adenovirus may also cause pneumonia, bronchiolitis, croup, and a pertussis-like infection. Respiratory infections are most common in late winter to early summer. Enteric strains cause gastroenteritis, more often in young infants and children, and occur year round. Epidemic keratoconjunctivitis can be spread from contaminated water in inadequately chlorinated swimming pools in summer or from ophthalmologic equipment.

Infants and young children, similar to immunocompromised individuals, may develop disseminated infections, pneumonia, bronchiolitis, or meningoencephalitis. Infection may be confused with invasive bacterial disease and treated with antibiotics. Prolonged fever of 1-7 days' duration may be seen. The degree of inflammation is indicated by the considerable elevation of C-reactive protein, which, in turn, may be related to viral load and disease severity. These infants are usually infected with subgroup B viruses (serotypes 3, 7, 21, and 35) and, less commonly, with subgroup D viruses (serotypes 2 and 32), but recent reports have also noted outbreaks of subgroup C. These infants may develop pancytopenia, DIC, pleural effusion, wheezing, and hepatitis. Pneumonia may be fatal and, if the infant survives, may result in significant lung damage, necessitating increased respiratory support for months.

In Dallas, 26 neonates were hospitalized with adenoviral infections over 17 years (1995-2012): 88% had respiratory signs, and 65% temperature instability.[229] The infants presented at a mean age of 16 days. Fifty-eight percent had had ill contacts. Four neonates developed disseminated infections, and the mortality rate was 80%. None of the infants with localized infection died. Disease ranged from upper respiratory tract infection to fulminant disease, including hypotension, apnea, hepatitis, and pneumonia.[229] In contrast to other reports in the literature, all but one of these infants were full term. These authors found reports of 72 additional neonates with adenovirus infection. Forty-seven percent of these infants were born prematurely. The mortality was similar (67%) among the 30 infants with disseminated disease, but 31% among the 42 infants with localized infections. Combining both groups, respiratory signs (76%) were the most common presentations. With pneumonia, seen in 50%, the mortality rate was 71%. Two thirds of the infants received mechanical ventilation, and eight received ECMO. Of note, 30% of all the reported neonates presented within the first 3 days of life, and 41% of those infants presented at birth. Presentation within the first 3 days of life was associated with disseminated disease (66%), prolonged rupture of membranes for 18 hours or longer, and maternal flulike illness during pregnancy or at delivery. The authors noted that with an incubation period as short as 2-3 days, presentation under 3 days of life suggested in utero transmission.

Evidence for congenital infection is accumulating.[49] Virus has been identified by using PCR in the amniotic fluid and in stillborn infants and those with hydrops. There are other reports of intrauterine or postnatal myocarditis caused by adenovirus. These infants tend to be small for gestational age and die as a result of disseminated disease. The serotypes found in young children are not as commonly found in infants younger than 6 months of age, suggesting that transplacental maternal antibody may be protective.[209]

Several reports have documented outbreaks of epidemic keratoconjunctivitis secondary to serotype 8 in NICUs.[44,210] Affected infants have lid edema, erythema, fever, and, less commonly, conjunctivitis. They also develop acute and chronic respiratory manifestations.

Adenovirus type 30 has been identified as the source of an outbreak in the NICU affecting 21 infants.[75,209] Type 30 is a group D adenovirus not previously identified in NICU outbreaks, although group D adenoviruses have been known to cause gastrointestinal infections and keratoconjunctivitis. Eight infants developed pneumonia (of whom seven died), and eight infants developed conjunctivitis. In five asymptomatic infants, infection was detected only through surveillance cultures. Several items of importance were noted in this report. The ophthalmologists, who had upper respiratory infections but continued to work and did not completely follow the American Academy of Ophthalmology infection control best practices, seemed to have played a major role in this outbreak. Infection control measures were successful but were discontinued too soon, before all of the infants had stopped shedding the virus, and the outbreak began again. Steroid use in the infants with pneumonia was recognized to have a high association with mortality.[75,209]

Although diagnosis of adenoviral infection can be made via tissue culture, shell vial technique, or antigen detection via immunofluorescence in the pharynx, eye, body fluids, or stool, PCR is the most sensitive and specific test and is the diagnostic method of choice.

Treatment is supportive. Children with pneumonia or disseminated disease, particularly neonates, often require mechanical ventilation. Support has also expanded to include ECMO. In a review of the ECMO Life Support Organization (ELSO) Registry from 1988 through 1994,

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children with adenoviral infections represented one third of the children being supported by ECMO for viral infections and had the poorest survival (25%).[165] In a more recent review of the ELSO Registry (1998-2009), children requiring ECMO support for adenovirus infection had a 38% survival at hospital discharge, but survival was only 11% among the neonates younger than 31 days of age.[215] Mortality was associated with neonatal presentation, degree of acidosis, sepsis and increased peak inspiratory pressure on the ventilator. ECMO complications of pneumothorax and intracranial hemorrhage also increased the risk of mortality.

Human Papillomavirus

Human papillomavirus (HPV) is a double-stranded, nonenveloped DNA virus. The organism cannot be propagated in cell culture, and its presence is detected by the identification of viral DNA from tissue samples. Infection by HPV usually is asymptomatic. A few infected adults develop mucocutaneous lesions, most commonly cutaneous and genital warts and neoplasms of epithelial surfaces, especially the uterine cervix. HPV can be typed according to DNA sequence, and greater than 100 genotypes have been identified. The different types can be distinguished by their propensity to cause low-grade warts (particularly types 6 and 11) versus high-grade, carcinomatous lesions (particularly types 16 and 18). Genital HPV infection in adults is usually transmitted via sexual contact. Nonsexual modes of acquisition, such as autoinoculation and heteroinoculation, are, however, suspected.

HPV transmission to the newborn presumably can occur in three periods; around the time of conception, during gestation (prenatal), or during or immediately after birth (perinatal). The virus has been detected in sperm cells, oocytes, amniotic fluid, placenta, and umbilical cord serving as evidence that vertical transmission occurs. Although some studies suggest vertical transmission occurs in more than half the pregnancies involving women with known HPV-related genital lesions, the results of studies have been variable and, therefore, rates not well defined.[87] HPV isolated from the pharynx or genital tract of the infant soon after birth frequently is discordant from HPV found in the mother, suggesting at least some neonatal acquisition by horizontal routes. HPV detected soon after delivery usually causes no clinically detectable disease, and evidence of infection disappears within a few months[154]; seroconversion to the initially detected virus is unusual.

The childhood disease most strongly associated with vertically transmitted HPV is juvenile-onset recurrent respiratory papillomatosis (JORRP). This illness, which usually becomes clinically apparent by age 2-3 years, is characterized by the development of multiple benign laryngeal papillomas. These lesions require repeated surgical excision to avoid airway obstruction. Occasionally, papillomas spread to the lower respiratory tract. JORRP is most strongly associated with HPV types 6 and 11, and often there is a history of condylomatous lesions in the mother caused by HPV of the same type.[243] The prevalence of JORRP is approximately 2 per 100,000 persons younger than 18 years of age, far lower than the prevalence of genital warts in pregnant women, suggesting that most infants exposed to HPV types 6 and 11 during birth remain unaffected.

Some, but not all, studies suggest a lower risk of JORRP if the infant is delivered by cesarean section, but operative delivery is not always protective, and it is not routinely recommended in a pregnant woman with genital warts. It is suspected that vertically transmitted HPV also can result in the development of anogenital warts in the child within the first several years of his or her life, presenting a dilemma to the child's caregivers because identical lesions can be associated with sexual abuse.

Three FDA-licensed HPV vaccines are available in the United States. The bivalent vaccine (2vHPV) contains the major capsid proteins of HPV types 6 and 18; the quadrivalent (4vHPV), in addition to 16 and 18, also protects against types 6 and 11; the 9-valent (9vHPV), licensed in 2014, protects against types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Since 2016, only 9vHPV is being administered in the United States and is recommended for males and females starting at age 9 years through age 26 years.[207]

Because laryngeal and anogenital disease in newborns are caused primarily by HPV types 6 and 11, the broad application of 9vHPV has the potential to reduce significantly mother-to-child transmission of HPV infection.[237] Transmission dynamics models suggest that the herd immunity effect of vaccinating only girls is robust, even when coverage rates are low and that the potential for elimination of HPV types 6, 11, 16, and 18 exists if coverage of 80% were to be achieved in girls and boys and maintained overtime.[29] Data already attest to the efficacy of the HPV vaccines in general, showing that after 4 years on the immunization schedule, the incidence of HPV in women 14-19 years of age has decreased by 56% despite low vaccination rates, implying that vaccine effectiveness, in addition to herd immunity, may also play a role in the decline in incidence rates.[155] Another benefit of the vaccine may be the reduction of premature births. A recent study from New Zealand showed that having received the quadrivalent HPV vaccine was associated with a reduction of preterm births by 13%.[140] The HPV vaccine is recommended for women of childbearing age; therefore, some patients may receive a dose of the vaccine inadvertently while pregnant. In this situation, the CDC recommends postponing the series until the pregnancy is complete.[41] So far, no adverse events to the developing fetus have been reported. In a retrospective cohort study looking at outcomes of pregnancies of mothers who received the quadrivalent HPV vaccine during the periconceptual period or during pregnancy, there was no association between vaccination and adverse pregnancy or birth outcomes.[151] However, the vaccine is not recommended for pregnant women at this time. The vaccine, conversely, can be administered to lactating women.

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Emerging Viruses

Zika Virus

Epidemiology

Zika virus belongs to the Flaviviridae family along with other viruses, such as Dengue virus, yellow fever virus, WNV, and Japanese encephalitis virus.[70,136] They are single-stranded, positive-sense, enveloped RNA viruses transmitted by arthropods (predominately mosquitoes and ticks). Zika virus was first described in 1947 when it was isolated from a Rhesus monkey in the Zika forest of Uganda.[65,66] Sporadic human cases were described until 2007 when an outbreak occurred in the Yap Island of Micronesia.[70] More than 900 residents of the island were infected and experienced a mild self-limiting illness with rash, conjunctivitis, and arthralgia. In October of 2015, the Brazilian Ministry of Health issued a health warning after the state of Pernambuco, Brazil, experienced an increase in the number of cases of microcephaly from an average of 10 cases per year to 144 cases in 11 months. At the time, Zika virus had been reported to be circulating in the country, and the association was presumed.[180,193] Thereafter, the virus became widespread in the Latin American countries. In the United States, the first local transmissions were detected by July 2016 when 14 cases in Florida were confirmed by the Florida Department of Health.[240] As of November of 2017, the CDC reported 2311 pregnancies with laboratory evidence of possible Zika virus infection in the United States and in the District of Columbia. However, the number of cases since the peak of 2016 has sharply declined in Latin America and the Caribbean islands, reflecting widespread population immunity. It is unclear when the virus will resurge, but it is likely that cases at a lower scale will continue to occur.[51]

The vector for Zika virus is the *Aedes* mosquito. In Latin America, *Aedes aegypti* is the most commonly implicated. *Aedes albopictus*, which predominates in the United States, is a less common transmitter of the virus because this species feeds more frequently on animals than on humans. Nonetheless, mosquitoes from this species have also tested positive for the virus.[119] The incubation period ranges from 3-10 days. However, the virus can persists in body fluids for a prolonged period and, therefore, can be transmitted in other ways, such as through organ donation, blood transfusions, needle-stick injuries, sexual contact, and vertical transmission.[64,221,239] A study by Paz-Bailey et al. evaluated the persistence of the Zika virus RNA in different body fluids, namely, semen, vaginal secretions, urine, saliva, and serum and found that the virus remained detectable in urine, serum, and semen for 39, 54, and 81 days, respectively.[203]

The clinical manifestations of Zika in the general population overlap with those of other arboviral infections and range from being completely asymptomatic in 80% of the population to a clinical syndrome characterized by fever, maculopapular rash, arthralgia, and conjunctivitis. Conversely, in those acquiring the infections in utero, microcephaly is the hallmark.[55,239]

Through sequencing studies, two main Zika strains have been identified—the African lineage and the Asian lineage. The Zika virus strains that have been isolated in patients in Brazil are closely related to the Asian lineage, which has been associated with brain developmental defects.[64]

Congenital Zika Syndrome

There is now sufficient data to more definitively establish the teratogenic potential of Zika virus in humans, especially the tropism for the CNS of the developing fetal brain. One of the first reports suggesting such association was published in the *New England Journal of Medicine* in March of 2016.[171] A 25-year-old Slovenian woman, who had worked as a volunteer in a northern state in Brazil, returned to her native country where she terminated her 32-week pregnancy after multiple fetal structural abnormalities were identified, mainly confined to the CNS. These included IUGR, accompanied by microcephaly, ventriculomegaly, and numerous calcifications in various parts of the brain. Real-time RT-PCR was used to detect Zika viral RNA in several tissues, including brain tissue. The virus was only detected in the fetal brain tissue, and complete sequencing of the virus showed a high similarity with the Asian lineage strains, including strains that had been isolated in Brazil the previous year. More recently, a prospective, multicenter, case-control study from Brazil confirmed the association between Zika virus infection in utero and microcephaly. In this study, de Araujo et al. matched 91 infants born with microcephaly to 173 controls during an 11-month period in 2016.[55] In the microcephaly group, 35% tested positive for Zika virus by quantitative RT-PCR (qRT-PCR) in CSF or serum, whereas none of the controls tested positive. No child in the study tested positive for CMV infection, toxoplasmosis, or rubella. The overall matched odds ratio for microcephaly and Zika infection was 73.1 (95% confidence interval [CI] 13.0-∞). CT results as well as Zika virus test results were available in 79 children in the microcephaly group. Abnormalities (calcifications, ventriculomegaly, and cortical development malformations) were more common among infants who tested positive for Zika virus compared with those who tested negative (43% versus 10%; $P = 0.029$).

The mechanisms of neurologic injury caused by Zika virus are still not fully understood. In the 1970s, Bell et al. conducted experiments on mice and found that Zika virus infected neurons and astroglial cells.[18,202] When these cells were infected, the virus appropriated their mechanism of defense against viruses by producing inclusion bodies in the endoplasmic reticulum and mitochondria. These inclusion bodies served as viral replication factories. Autophagy (a mechanism of cell protection that involves lysosomal degradation) and cell division stability in the dividing cells were affected, resulting in delayed mitosis, earlier neural differentiation, and increased rates of apoptosis, all playing a role in the development of microcephaly in mice.[18,202]

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Studies in murine and rhesus monkeys suggest that the mechanisms of congenital Zika syndrome (CZS) is through vertical transmission via placental infection and subsequent fetal brain tissue injury.[21,116,184,202,203] Several mouse models have shown that mice infected early in pregnancy develop placental and brain infections, resulting in IUGR and fetal demise in many. In a study performed on eight infants who had clinical and epidemiologic evidence of Zika virus–related microcephaly and had died and on 44 women who were suspected to have contracted the virus during pregnancy, replicative Zika virus RNA in situ hybridization was found in the brain tissue of seven infants and in the placenta of the mothers who had suffered fetal losses in the first and second trimesters. This study demonstrated that the virus replicated and persisted in the placenta and brains of infected patients.[21] Placental macrophages (also known as *Hofbauer cells*) are the primary sites for the replication of Zika virus. These cells can reach fetal blood cells and are the likely mode of dissemination of the virus into fetal tissues.[21,116] During the first trimester, when placental macrophages are proliferating, the virus may target them, increasing infection in the placental basal decidua and chorionic villi and allowing transplacental transmission.[253] Epidemiologic studies have shown that infections in the first and second trimesters more commonly result in microcephaly compared with those occurring later in pregnancy, although CNS abnormalities have been described as occurring during all trimesters.[28,107,188,239]

The distinctive features of CZS are the result of direct damage caused by the virus in the developing fetal brain, resulting in volume loss. Severe microcephaly with features reminiscent of fetal brain disruption sequence may be observed in some infants. These include overlapping sutures, prominent occipital bone, redundant scalp skin, craniofacial disproportion, and severe neurologic impairment.[55,86,156,171,234,240] Radiologic features include subcortical calcifications, ventriculomegaly, thinning cortex, corpus callosum agenesis, and cisterna magna enlargement, among others. Nonetheless, radiologic features of CZS have been identified in normocephalic infants, and in some infants microcephaly develops after birth.[13,178,265] From a functional standpoint, hypertonia, hyper-reflexia, arthrogryposis, seizures, irritability, and dysphagia have been described.[55,86,118,156,171,234,239,240]

Similar to other congenital viral syndromes, ocular manifestations and sensory neural hearing loss may occur.[38,58,59,142,289] The presumed pathogenesis of eye involvement relates to the capacity of the virus to cross barriers. After infecting stromal placenta cell macrophages, Zika virus is thought to subsequently invade the blood-brain barrier infecting neuronal progenitor cells, including bypassing the retinal barrier.[38] From there, the virus provokes angiogenesis and inflammatory cytokine–related responses that lead to damage. This is supported by the findings of the viral RNA in endothelial cells and pericytes of the inner blood-retinal barrier and in retinal pigment epithelial cells. Infections occurring in the first trimester are more likely to result in eye alterations compared with those occurring later in pregnancy. In a study from Brazil of 29 infant with Zika virus–presumed microcephaly, 34% had ocular manifestations.[58] In another study, ocular findings were more common in infants born to mothers who had symptoms of Zika virus infection in the first trimester compared with infants of those who had symptoms later in pregnancy. Ocular findings were also more prevalent in infants with severe microcephaly.[268] Most commonly described funduscopic findings are chorioretinal abnormalities, including macular atrophy, focal pigmentary changes in the macular region, and optic nerve abnormalities, such as optic disc hypoplasia. These manifestations are usually bilateral.

Hearing loss, a common finding in other congenital infections, has also been described in infants infected with Zika virus in utero. Leal et al. studied 70 children from the State of Pernambuco in Brazil with microcephaly and confirmed Zika virus infection and evaluated them for hearing loss. Auditory evaluations were performed with auditory brainstem response testing. These authors found that 7.1% of the infants had sensorineural hearing loss, which varied in laterality and severity among the affected infants.[142] At this time, it is unknown if sensorineural hearing loss progresses over time, and hence the importance of follow-up testing in these children.

According to data gathered by the CDC through the US Zika Pregnancy Registry established in 2016, of 972 completed pregnancies of mothers with possible recent Zika virus infection during pregnancy, 5% of the infants developed birth defects. The percentage was higher in cases of confirmed Zika virus infection, with rates of 10%.[227] Other studies have shown similar rates.[28,107] Most recent US population health surveillance data on birth defects from the CDC revealed a rate of birth defects potentially related to Zika virus infection of 3 per 1000 live births (95% CI 2.9-3.2).[62]

Diagnosis

Zika virus detection can be accomplished by molecular (RT-PCR) or serologic methods (IgG and IgM). When a patient is infected by the virus, the RNA becomes detectable in serum at onset of symptoms and then declines as IgM antibodies rise in peripheral blood. Detection of viremia via Zika virus NAT is most useful in the first 6 weeks of infection, with the yield increasing when both urine and serum are tested. NAT can also be performed in other bodily fluids, with varying durations.[5,179,218,240]

Zika virus IgM antibodies are detected by using ELISA in the first 12 weeks, starting at approximately 1 week after onset of symptoms, which may persist for longer periods. Because the majority of infections are asymptomatic, determining if an infection occurred during pregnancy or earlier is challenging.[5,218] In addition, the close genetic relatedness between Zika virus and Dengue virus leads to immunologic cross-reactivity[214] and the possibility of false-positive test results. Positive and equivocal tests should be confirmed with plaque reduction neutralizing tests (PRNT). This assay

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measures neutralizing antibodies (which are mainly IgG) that form shortly after the IgM and remain positive lifelong. This assay also may encounter problems with cross-reactivity because patients who have experienced a previous flavivirus infection or those who have been vaccinated with the yellow fever vaccine will develop high titers of neutralizing antibodies, making it difficult to distinguish the virus responsible for the current infection. In addition, PRNT is labor intensive and only offered at specialized centers (CDC).[218] It is important to point out that as the number of cases decline, the rate of false-positive results will increase; therefore, the CDC has issued new recommendations for testing in the setting of low prevalence. CDC recommendations for testing pregnant women are summarized in Table 50.10.[11] These guidelines are updated on a regular basis and should be consulted for the most up-to-date and complete information.

Placenta, umbilical cord, fetal organs, and other products of conception can be sent for testing in cases of fetal loss, stillbirth, or infant death. The samples are processed at the CDC and require local health department notification and preapproval by the CDC. For preapprovals, the CDC can be contacted through email at pathology@cdc.gov. The role of amniocentesis in the evaluation of CZS is unknown, but if obtained, NAT testing should be considered.

Results should be interpreted with caution, taking into consideration the timing of pregnancy, the expected outcomes, and the patient's values, among others, and therefore, consultation with an infectious disease specialist is recommended. The CDC also offers assistance to health

TABLE 50.10 Summary of Zika Virus Testing Guidance According to Centers for Disease Control and Prevention Recommendations

	Pregnant *With* Symptoms of Zika Virus Disease *and* Possible Zika Virus Exposure		Pregnant *Without* Symptoms of Zika Virus Disease *and* Possible Zika Virus Exposure	
Whom to test	• Pregnant women who report possibly being exposed to ZV during the current pregnancy and have symptoms • Pregnant women who report possibly being exposed to ZV during the current pregnancy and have a fetus with US findings concerning for congenital Zika syndrome		• Asymptomatic pregnant women with *ongoing* (live or frequently travel to an area with documented risk of Zika transmission) possible ZV exposure • Not indicated but should consider in asymptomatic pregnant women without ongoing exposure*	
Timing	As soon as possible through 12 weeks after onset of symptoms		First test with onset of prenatal care in women without a diagnosis of ZV If initial test is negative, repeat testing two additional times during pregnancy	
Type of test	ZV NAT in serum *and* urine *and* ZV IgM serology in serum. Test concomitantly for Dengue with Dengue virus IgM		ZV NAT in serum *and* urine	
	Results	**Interpretation**	**Results†**	**Interpretation**
	ZV NAT positive and ZV IgM positive	Acute Zika virus infection	Positive NAT in serum ***and*** urine	Acute Zika virus infection
	ZV NAT negative and ZV IgM negative	No evidence of Zika virus infection		
	ZV NAT negative and **non**-negative ZV IgM (non-negative: positive or equivocal, possibly or presumably positive)	Send sample for plaque reduction neutralization test (PRNT)‡	Negative NAT in serum and urine	No Zika RNA detected, However, Zika virus infection cannot be ruled out§

ZV, Zika virus; NAT, nucleic acid test.
*If testing is considered, a discussion between the patient and the physician should weigh risks and benefits of testing taking into consideration the patient's values, clinical judgment, and expected outcome, among other issues.
†If NAT is only positive on serum or urine, the test should be repeated on the original NAT positive test. If results are still positive, the patient should be considered as having acute Zika infection. If the repeat NAT result is negative, consultation with an infectious disease specialist is recommended (author's recommendation), and the IgM test should be repeated 2 weeks after the original sample was tested.
‡Consultation with an infectious diseases specialist is recommended (author's recommendation).
§Because Zika virus RNA declines over time, the presence of the virus in urine and serum will differ among patients. Therefore, testing at only one point in time does not completely exclude infection. Consultation with an infectious diseases specialist is recommended to discuss IgM testing with patient (author's recommendation).
Adapted from CDC testing algorithms. For the most up to date guidance and complete information, refer to https://www.cdc.gov/zika/laboratories/lab-guidance.html. Accessed January 27, 2018.

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care providers with regard to sample submission and clinical questions through email at ZikaMCH@cdc.gov.

Infants born to mothers with possible or confirmed Zika virus infection and those with clinical features consistent with CZS should undergo testing as soon as possible after birth. Testing consists of NAT in serum and urine and possibly CSF and serum IgM. A positive NAT result from either sample (infant urine, serum, or CSF) regardless of the IgM result, confirms the diagnosis of CZS. However, testing beyond the immediate neonatal period may not allow for distinction between congenital infection and that acquired postnatally in areas with ongoing transmission. Conversely, negative results of NAT and IgM performed soon after pregnancy should be interpreted as congenital infection being unlikely. A negative NAT result in combination with a non-negative IgM result, defined as any test result other than a negative result, such as a positive, equivocal, presumptive positive, or possible positive result, should be confirmed with PRNT, as a false-positive IgM result is possible.[5] Cord blood may be contaminated with maternal blood and, therefore, should not be used for neonatal assessment.[294] In addition to testing for Zika virus NAT in serum and urine and IgM testing in serum shortly after birth, infants should undergo standard evaluations which includes:

- Thorough physical examination, including growth parameters.
- Vision screening as recommended by the AAP.
- Hearing screen at birth—automated auditory brainstem responses are the preferred method.
- Monitoring and screening of child development by utilizing AAP validated tools.

Additionally, head ultrasonography and a comprehensive ophthalmologic examination should be performed. The CDC recommendations are summarized in Table 50.11. If findings suggestive of CZS are identified at any time, referral to specialist to evaluate for congenital Zika virus infection is indicated.[5,13,227]

Infant Follow-Up

Infants diagnosed with congenital Zika virus infection require a multidisciplinary approach.[5,227] Special needs should be anticipated and early interventions instituted. Social services may be very useful providing families with coordination of care and supportive services. An infectious disease specialist should be consulted because other congenital infections may need to be excluded, and the specialists will assist with the interpretation of tests, especially when the results are non-negative. A geneticist may need to evaluate for other causes of microcephaly and congenital abnormalities. A neurologist and an ophthalmologist should evaluate these patients by 1 month of age and follow up closely thereafter because these infants may require electroencephalography (EEG) or advanced imaging. Infants identified with hearing loss need to be monitored frequently because, unlike in CMV infection, the progression of hearing loss with Zika virus infection is unknown at this time. An endocrinologist, an orthopedic specialist, a pulmonologist, and an occupational therapist may also need to be involved. Most importantly, compliance with routine general pediatric follow-up visits should be emphasized. Knowledge about CZS is still being accumulated, and it is likely that as these children grow older, previously undescribed conditions will emerge and, therefore, regular follow-up is pivotal.[5,227]

Prevention

Vector control, avoidance of exposure to mosquito bites, and epidemiologic surveillance are the current prevention strategies to prevent Zika virus infection in pregnant women. At the height of the epidemic in 2016, travel warnings for pregnant women or for those trying to become pregnant were issued, as well as recommendations for avoidance of unprotected sexual intercourse during pregnancy with anyone who may have been exposed to the virus and even postponement of pregnancy plans in areas of widespread transmission.[203,221,239,294] The Zika virus infection landscape, however, has changed, and very few to no cases have been reported in the past several months, so recommendations will likely change.[51] Therefore, epidemiologic surveillance and keeping up to date with the information provided by such agencies as the CDC and the WHO are important.

More than 40 vaccine candidates against Zika virus are being studied at this time. However, none is currently available.[71] Moreover, several factors that can delay the development of these vaccines have emerged. One is the decline in the number of worldwide cases, and the other is the safety concerns that have emerged following the results of the Dengue virus vaccine trials, in which the vaccine has been observed to provoke antibody-dependent enhancement (ADE).[157] Studies have now shown that in Dengue-endemic areas, pre-existing immunity to Dengue virus may affect an individual's immunologic response to Zika virus[214] and concerns regarding the risk of ADE with a Zika vaccine have been raised.[71,214] The epidemiology of the virus in the years to come will likely determine the availability of such vaccines.

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TABLE 50.11 Summary of Evaluation for Infants With Possible Congenital Zika Virus Infection According to Centers for Disease Control and Prevention Recommendations

Scenario	Possible Zika Exposure *and* Clinical Findings Consistent With CZS	Possible Zika Exposure *and* Infant *Without* Findings Consistent With CZS *and* Maternal Laboratory Evidence of Zika During Pregnancy	Possible Zika Exposure *and* Infant *Without* Findings Consistent With CZS *and* No Maternal Laboratory Evidence of Zika During Pregnancy
Initial Evaluation	• Standard evaluation* • ZV NAT (serum and urine) within a few days after birth • ZV IgM (serum) within a few days after birth • Consider ZV NAT and IgM on CSF • Head US by 1 month age • ABR by 1 month of age • Eye exam by ophthalmology by 1 month of age • Test for other diseases associated with congenital abnormalities • Referral to specialists and early intervention (See Table 50.3.)	• Standard evaluation* • ZV NAT (serum and urine) within a few days after birth • ZV IgM (serum) within a few days after birth • Head US by 1 month age • ABR by 1 month of age • Eye examination by ophthalmology by 1 month of age	• No further testing required • If findings of CZS are identified at any time refer to specialist and follow recommendations for clinical findings consistent with CZS
		Initial Evaluation	
		Normal	**Abnormal**
		• Infant with laboratory evidence of CZS†: follow recommendations for clinical findings consistent with CZS • Infant with no laboratory evidence of CZS: congenital infection unlikely.	Follow recommendations for clinical findings consistent with CZS syndrome
		Routine follow up	

ABR, Automated auditory brainstem response; CSF, cerebral spinal fluid; CZS, congenital Zika syndrome; NAT, nucleic acid test; US, ultrasonography; ZV, Zika virus.

*__Standard Evaluation:__ Thorough physical examination including growth parameters; vision screening as recommended by the American Academy of Pediatrics (AAP); hearing screen at birth (automated auditory brainstem response is preferred method).

Developmental monitoring and screening utilizing AAP validated tools.

†__Confirmed Congenital Zika Infection__: NAT positive *and* IgM positive/negative or non-negative (or equivocal, possibly or presumably positive).

__Probable Congenital Zika Infection__: NAT negative *and* IgM non-negative (positive or equivocal, possibly or presumably positive) Need to confirm with plaque reduction neutralization assay and consultation with expert recommended.

__Congenital Zika Infection unlikely:__ NAT negative and IgM negative.

Adapted from CDC testing algorithms. For the most up-to-date guidance and complete information, refer to https://www.cdc.gov/pregnancy/zika/testing-follow-up/follow-up-care.html. Accessed January 27, 2018.

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Key Points

- Many viruses are well known, and many new viruses that have devastating effects on the fetus and newborn are continually being discovered. Known therapeutic measures are frequently of little efficacy, leaving prevention as the primary means of protection for the fetus and the newborn.
- Mother-to-child transmission of HIV is now the most common source of HIV infection among infants and children. In high-economy countries, including the United States, this source of transmission is nearly completely eliminated with the universal use of antenatal HIV testing, combination ART during pregnancy, elective cesarean section, and prohibition of breastfeeding by infected mothers.
- Most women of childbearing years in high-economy countries are immune to measles, mumps, and rubella, as a result of MMR vaccination, limiting risk to the fetus and the newborn with the risk of maternal infection virtually eliminated. Similarly, the use of the varicella vaccine, coupled with acyclovir and VZIG treatment, has greatly decreased the incidence of varicella infection in pregnant women.
- The implementation of the hepatitis B vaccine and HBIG for prevention of mother-to-infant transmission is quite effective, and yet compliance remains an issue.
- Poliomyelitis has been virtually eliminated with universal vaccination, but there are, as yet, no vaccines and no specific therapies available for other enteroviruses that can cause severe, devastating infections in the neonate.
- Congenital CMV infection remains the largest source of nongenetic hearing loss and developmental disorders in children, and yet no vaccine has been approved for use as yet; therapy with ganciclovir/valganciclovir has limited efficacy.
- Neonatal HSV infection remains life-threatening and may have devastating consequences for the fetus and the newborn. There is no available vaccine, and therapy with acyclovir, particularly if infection is not promptly recognized and therapy is delayed, may still result in death or severe handicap in the infant.
- There are no effective therapies for viruses causing respiratory infections in the newborn. Prevention remains key. The use of palivizumab for prevention of RSV continues to be controversial.

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51

Normal and Abnormal Brain Development

PIERRE GRESSENS, SANDRINE PASSEMARD, AND PETRA S. HÜPPI

Normal development of the human central nervous system (CNS) encompasses several steps, including neuroectoderm induction, neurulation, cell proliferation and migration, programmed cell death, neurogenesis and elimination of excess neurons, synaptogenesis, stabilization and elimination of synapses, gliogenesis, and myelination (Table 51.1).

These different steps of brain development and maturation are controlled by the interaction between genes and the environment. Numerous genes involved in brain development have been identified: genes controlling neurulation, neuronal proliferation, neuronal size and shape, programmed cell death, neuronal–glial interactions, and synaptic stabilization.[104] However, it seems unlikely that the 30,000 genes in humans can totally control the organization of 100 billion neurons and trillions of synapses. A normal pattern of expression of these genes requires an adequate environment. Interactions with the intrauterine milieu (factors coming from the mother, placenta, or amniotic fluid) and with the postnatal environment critically modulate gene expression through reciprocal action with neurotransmitters, trophic factors, and hormones and their machinery. Accordingly, brain malformations can be due to environmental factors, genetic factors, or an interaction of both (Boxes 51.1 through 51.4).

This part of the chapter focuses primarily on the development of the neocortex. Detailed descriptions of the development of other CNS structures, such as the cerebellum, can be found in texts by ten Donkelaar et al.[110] and Wang and Zoghbi.[120]

Neural Induction and Neurulation

During the early stages of gastrulation, organizing centers produce inductive molecules that initiate genetic programs leading to the differentiation of the neural tissues from surrounding tissues.[107] Grafting experiments in amphibians have shown that the appearance of neural tissue depends on signals coming from mesodermic cells of the dorsal marginal zone (the Speeman organizing center) and that other signals deriving from this zone also allow regionalization of the neuroectoderm along the rostrocaudal axis. Studies have identified some of the factors implicated in neural induction, including follistatin, noggin, Notch, dorsalin1, Wnt1, and Hedgehog.

Neurulation is the process by which neuroectodermal cells transform into a neural tube, which will differentiate into the brain and the spinal cord. Neurulation can be divided into four steps that overlap both in time and space: (1) neural plate formation, (2) neural plate modeling, (3) neural groove formation, and (4) closure of the neural groove to form the neural tube. In humans, the neural plate appears at the beginning of the third gestational week in the mediodorsal zone of the embryo, just ahead (in the rostrocaudal axis) of the Hensen node. The neural groove appears during the third gestational week. Neural tube closure starts at the beginning of the fourth gestational week, with the formation of the neural crests (which will give rise to dorsal root ganglia, Schwann cells, and cells of the pia and arachnoid). Neural tube closure begins in the region of the lower medulla and proceeds both rostrally and caudally.

The anterior neuropore closes at approximately 24 gestational days and the posterior neuropore closes at approximately 26 gestational days. This posterior site of closure is located around the lumbosacral level, and more caudal spinal cord is formed secondarily by a separate process involving canalization (4 to 7 gestational weeks) and retrogressive differentiation (seventh gestational week to after birth; giving rise to the ventriculus terminalis and the filum terminale). The neural tube is initially a straight structure. Before the closure of the posterior neuropore, the anterior part of the neural tube is shaped into three primary vesicles: the prosencephalon, the mesencephalon, and the rhombencephalon. The prosencephalic phase and the formation of the hemisphere take place between 5 and 10 gestational weeks in humans.

CNS regionalization results from the combination of two mechanisms. Rostrocaudal regionalization creates

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Abstract

Normal development of the human central nervous system (CNS) is a dynamic process with several steps. These different steps of brain development and maturation are controlled by genes. However, it seems unlikely that the 30,000 genes in humans can totally control the organization of 100 billion neurons and trillions of synapses. A normal pattern of expression of these genes requires an adequate environment. Interactions with the intrauterine milieu (factors coming from the mother, placenta, or amniotic fluid) and with the postnatal environment critically modulate gene expression but also endogenous activity and environmental stimuli can modify brain development. Accordingly, brain malformations can be due to environmental factors, genetic factors, or an interaction of both. This part of the chapter focuses primarily on the development of the neocortex.

Keywords

brain development
genetic control
cortical malformation
experience dependent plasticity

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• BOX 51.1 Environmental Factors and Maternal Conditions With Potential Impact on the Developing Brain

Therapeutic Drugs

- Retinoic acid
- Antithyroid drugs
- Estroprogestative hormones, testosterone, and derivatives
- Antimitotic drugs
- Lithium and psychotropic drugs
- Benzodiazepines and antiepileptic drugs

Addiction Drugs

- Tobacco
- Caffeine
- Ethanol
- Cocaine
- Opiates
- Cannabis

Physical and Chemical Agents

- Dioxins and heavy metals
- Organic solvents
- Ionizing radiation
- Head trauma
- Repeated shaking

Maternal Factors and Status

- Sex hormones
- Catecholamines
- Thyroid hormones
- Diabetes mellitus
- Peptides (vasoactive intestinal peptide)
- Placenta and decidual hormones
- Oxygen and hypoxia–ischemia
- Hyperthermia

Infectious Agents

- Herpes simplex virus I and II
- Herpes zoster virus
- Cytomegalovirus
- Rubella virus
- Parvovirus B19
- Coxsackie virus, B group
- Human immunodeficiency virus
- Influenza virus
- Benign lymphocytic meningitis virus
- *Toxoplasma gondii*
- *Listeria monocytogenes*
- *Treponema pallidum*

• BOX 51.2 Major Etiologies of Human Holoprosencephaly

Chromosomal Holoprosencephaly

- Chromosome 13: trisomy, deletion or duplication of 13q, ring
- Deletion 2p, duplication 3p, deletion 7q, deletion 21q
- Triploidy

Syndromal Holoprosencephaly

- Meckel syndrome
- Varadi-Papp syndrome
- Pallister-Hall syndrome
- Smith-Lemli-Opitz syndrome
- Velo-cardio-facial syndrome

Nonsyndromal Genetic Holoprosencephaly (Sporadic or Mendelian Inheritance)

- SIX3: HPE2 locus on chromosome 2p21
- SHH: HPE3 locus on chromosome 7q36
- TGIF: HPE4 locus on chromosome 18p11.3
- ZIC2: HPE5 locus on chromosome 13q32

Environmental Holoprosencephaly

- Hypocholesterolemia
- Retinoic acid exposure
- Ethanol exposure

TABLE 51.1 Schematic Chronology of the Major Events During Human Neocortical Development

Neuroectoderm induction	3rd GW
Neurulation	3rd to end of 4th GW
Prosencephalic and hemispheric formation	5th to 10th GW
Neuronal proliferation	10th to 20th GW (?10th to end of gestation for interneurons)
Neuronal migration	12th to 24th GW (?10th to 41st GW for interneurons)
Programmed neuronal cell death	28th to 41st GW
Synaptogenesis	20th GW to puberty
Gliogenesis	20th to 24th GW to ?postnatal years
Myelination	36th to 38th GW to 2 to 3 postnatal years
Angiogenesis	5th to 10th GW to ?postnatal years

GW, Gestational week.

transverse domains with distinct competences in the neural plate and tube,[54,105,122] whereas dorsoventral regionalization creates longitudinally aligned domains.[102] The combination of these two axes yields a grid-shaped pattern or regionalization.[100] Different genes involved in this regionalization have been identified. These include the *BMP* (bone morphogenetic proteins), *PAX* (paired box genes), and *SHH* (sonic hedgehog) genes for the dorsoventral axis, and the *HOX* (clustered homeobox-containing genes), *KROX20*, *FGF8* (fibroblast growth factor-8), *EN* (engrailed genes), *WNT*, *OTX* (homeobox genes homologous of the *Drosophila* orthodenticle gene), *EMX* (related to the "empty spiracles" gene expressed in the developing *Drosophila* head), and *DLX* (homeobox genes homologous to the distal-less genes of *Drosophila*) genes for the rostrocaudal axis (Fig. 51.1).

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• BOX 51.3 Classification of Human Congenital Microcephaly

Primary Genetic Microcephaly

Microcephaly Primary Hereditary (MCPH): Autosomal Recessive Inheritance, Except for MCPH18

- *MCPH1* (Microcephaly), *WDR62* (MCPH2), *CDK5RAP2* (MCPH3), *CASC5* (MCPH4), *ASPM* (MCPH5), *CENPJ* (MCPH6), *STIL* (MCPH7), *CEP135* (MCPH8), *CEP152* (MCPH9), *ZNF335* (MCPH10), PHC1 (MCPH11), *CDK6* (MCPH12), *CENPE* (MCPH13), *SASS6* (MCPH14), *MFSD2A* (MCPH15), *ANKLE2* (MCPH16), *CIT* (MCPH17), *WDFY3* (MCPH18).

Primary Microcephaly With Dwarfism (Autosomal Recessive)

- Seckel syndrome: *ATR* (SCKL1), *RBBP8* (SCKL2), *CENPJ* (SCKL4), *CEP152* (SCKL5), *CEP63* (SCKL6), *NIN* (SCKL7), *DNA2* (SCKL8), *TRAIP* (SCKL9), *NSMCE2* (SCKL10),
- Microcephalic osteodysplastic primordial dwarfism: *PCNT*
- Meier Gorlin syndrome: *ORC1* (MGORS1), *ORC4* (MGORS2), *ORC6* (MGORS3), *CDT1* (MGORS4), *CDC6* (MGORS5), *GMNN* (MGORS6), *CDC45L* (MGORS7), *MCM5* (MGORS8).

Microcephaly With Simplified Gyral Pattern (Autosomal Recessive)

- Normal or thin corpus callosum
- Agenesis of the corpus callosum

Microlissencephaly, MLIS (Autosomal Recessive)

- With thin cortex: *RELN* (MILIS1 or Norman Roberts syndrome)
- With thin cortex, brainstem and cerebellar hypoplasia (MLIS2 or Barth syndrome)
- With intermediate cortex (MLIS3)
- With mildly to moderately thin cortex (MLIS4)

Microcephaly Associated With Other Brain Malformations

Microcephaly as Part of a Syndrome

- Neu-Laxova syndrome (autosomal recessive)
- *PHGDH* (NLS1), *PSAT1* (NLS2)
- Rubinstein-Taybi syndrome (autosomal dominant)
- *CREBBP* (RSTS1), *EP300* (RSTS2)
- Cornelia de Lange syndrome (autosomal dominant except for CDLS X-linked)
- *NIPBL* (CDLS1), *SMC1A* (CDLS2), *SMC3* (CDLS3), *RAD21* (CDLS4), *HDAC8* (CDLS5).

Microcephaly Associated With Biochemical Disorders

Microcephaly Secondary to Environmental Factors

- Hypoxia–ischemia
- Severe malnutrition
- Maternal hyperphenylalaninemia and phenylketonuria
- Ionizing radiation
- Ethanol exposure
- Infections (cytomegalovirus, benign lymphocytic meningitis virus, *Toxoplasma gondii*, Rubella virus, Zika virus)

• BOX 51.4 Genes and Environmental Factors Identified in Human Neuronal Migration Disorders

Periventricular Heterotopia

- *FLNA* (X-linked)
- With microcephaly: *ARFGEF2* (autosomal recessive)

Classic Lissencephalies

- *LIS1* (autosomal dominant)
- *DCX* (X-linked)
- *TUBA3* (autosomal dominant)
- *ARX* (X-linked)

Cobblestone Lissencephalies (Autosomal Recessive)

- *POMT1*
- *POMT2*
- *FCMD (FKTN)*
- *FKRP*
- *POMGNT1*
- *POMGNT2*
- *DAG1*
- *ISPD*
- *LAMB1*
- *POMK*
- *RXYLT1*

Lissencephaly With Cerebellar Hypoplasia

- *RELN* (autosomal recessive)

Peroxysome Biogenesis Disorders

- Zellweger syndrome, autosomal recessive: *PEX1* (PBD1), *PEX12* (PBD3), *PEX6* (PBD4), *PEX10* (PBD6),

Environmental Factors

- Ethanol exposure
- Cocaine exposure
- Cytomegalovirus
- *Toxoplasma gondii*
- Ionizing radiation

Neuronal Proliferation

There are no precise data concerning the number of neurons present in the brains of different mammalian species. In the human adult brain, estimates range from 3 billion to 100 billion neurons. Similarly, the precise proportion of glial cells is unknown, with a neuron-to-glia ratio estimated at between 1:1 and 1:10.

In some regions of the CNS, neuron production continues for the entire life span. This late neurogenesis is apparent in the olfactory bulb and the dentate gyrus. Its importance at the level of the neocortex, especially in physiologic conditions, remains to be demonstrated. In this context, production of neurons for the human neocortex is generally considered to be a phenomenon occurring during the first half of gestation.

The neocortex is composed of vertical units (neuronal columns): the number of neurons in a given unit seems stable throughout studied mammals and is constant throughout the different cortical areas (with the exception of the visual cortex). In contrast, the time necessary to produce the neocortical neurons of a given column progressively increases with increasing mammalian evolutionary

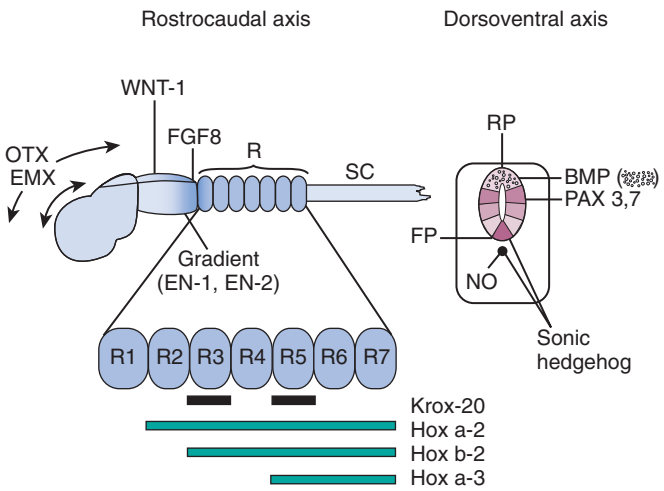
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complexity. Indeed, the period of neurogenesis neurons takes 6 days in mice, whereas it takes approximately 10 weeks in humans. Glutamatergic neurons of the neocortex are generated in the ventricular zone (VZ) and the subventricular zone (SVZ) of the lateral ventricles, whereas a large proportion of GABAergic neurons of the neocortex are generated in the ganglionic eminence (which also produces thalamic neurons).

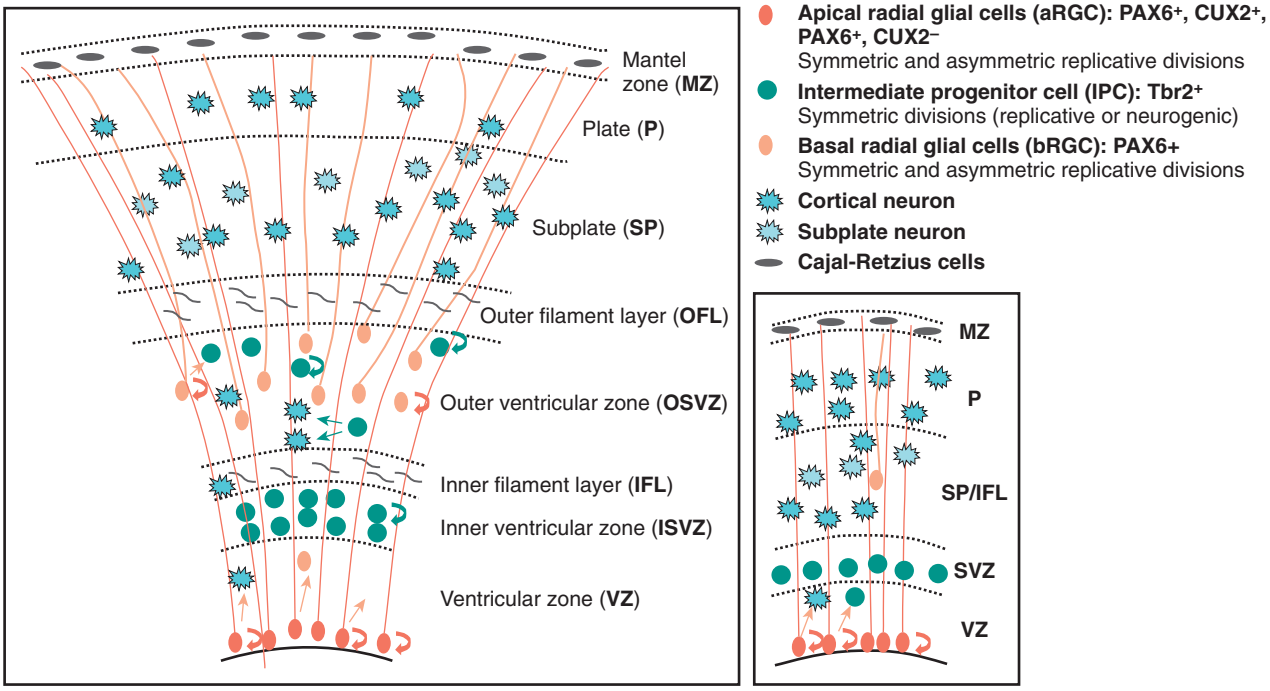
The cerebral cortex has evolved in size by expansion of the surface area, without a comparable increase in its thickness, thus imposing folding constraints and convolutions. Recent comparative studies performed during the development of the neocortex in lissencephalic and gyrencephalic models support that the increased capacity of the progenitors to proliferate, with subsequent amplification of cortical neuron populations, is largely involved in this evolution.

In mice, two main types of progenitors, radial glial cells (RGCs) and intermediate progenitor cells (IPCs), also called *basal progenitors*, have been described (Fig. 51.2).[71,74] RGCs occupy the VZ and are characterized by the expression of Pax6. They are highly polarized cells, with their apical pole connected to the ventricle luminal border and their basal pole to the pial surface. They thus extend their cellular process through the entire cortical wall and play a major role in guiding young neurons' migration into a specific layer. RGCs have the ability to self-renew either by autoreplicative symmetric divisions or by asymmetric division, which generates a further RGC and either an IPC or a neuron (neurogenic division).

Autoreplicative symmetric divisions are prominent in the mouse VZ until embryonic day 13, when the production of neurons becomes amplified through asymmetric neurogenic



• **Fig. 51.1** Schematic representation of some genes involved in the patterning of the rostrocaudal and dorsoventral axis of the central nervous system. FP, floor plate; NO, notochord; R, rhombomeres; RF, roof plate; SC, spinal cord. (From Lagercrantz H, Ringstedt T. Organization of the neuronal circuits in the central nervous system during development. *Acta Paediatr.* 2001;90:707, with permission.)



• **Fig. 51.2** Comparison of cortical development in mice and humans. In mice, cortical neurons arise mainly from two subsets of progenitors: radial glial cells (RGCs) in the ventricular zone (VZ), which generate intermediate basal progenitors (IPCs) migrating into the subventricular zone (SVZ). In humans, the lineage of RGCs is more complex. The SVZ is split into an inner (ISVZ) and outer (OSVZ) domain. IPCs occupy both areas, whereas another type of progenitors, basal RGCs (bRGC), is largely represented in the OSVZ.

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divisions. Notch activity is required to maintain the basal process and the RGC identity, but the pathways promoting asymmetric versus symmetric divisions remain to be determined. All RGCs give rise to IPCs, which settle in the SVZ. IPCs express Tbr2, divide symmetrically to self-renew or to give birth to two neurons, and are not polarized. They are limited to one or two further rounds of division in rodents.

In humans, the situation is much more complex (see Fig. 51.2).[71,74] Whereas RGCs remain the major cell type in the VZ, the SVZ is drastically enlarged and subdivided into the inner (ISVZ) and outer (OSVZ) parts (see Fig. 51.2). The ISVZ is mainly composed of IPCs, whereas OSVZ includes IPCs and another type of RGCs, which are not attached at their apical side to the ventricle but maintain the basal process connected to the pial neocortical surface. These SVZ basal RGCs (bRGCs) express Pax6, similarly to ventricular apical RGCs (aRGCs). Like their apical counterparts, bRGCs can undergo symmetric division to self-renew, and asymmetric divisions to self-renew and generate either IPCs or neurons. Remarkably, both IPCs and bRGCs are endowed with a high ability to proliferate. Their pools are thus largely amplified in humans, between the 11th and 17th gestational weeks, as well as in other gyrencephalic species. Amplification of IPCs and bRGCs is obviously an important process that strongly impacts the extent of neurogenesis and appears to be a major process for cortical expansion.

Neuronal Migration and Cortical Lamination

Neocortical neurons derive from the primitive neuroepithelium and migrate to their appropriate position in the cerebral mantle. In humans, migration of neocortical neurons occurs mostly between the 12th and the 24th weeks of gestation.[103] The first postmitotic neurons produced in the VZ migrate to form a subpial preplate or primitive plexiform zone (Fig. 51.3). Subsequently produced neurons, which will form the cortical plate, migrate into the preplate and split it into the superficial molecular layer (layer I or marginal zone containing Cajal-Retzius neurons) and the deep subplate. Schematically, the successive waves of migratory neurons pass the subplate neurons and end their migratory pathway below layer I, forming successively (but with substantial overlap) cortical layers VI, V, IV, III, and II (an inside-out pattern).

Neocortical migrating neurons can adopt different types of trajectories (Fig. 51.4)[39,97]:

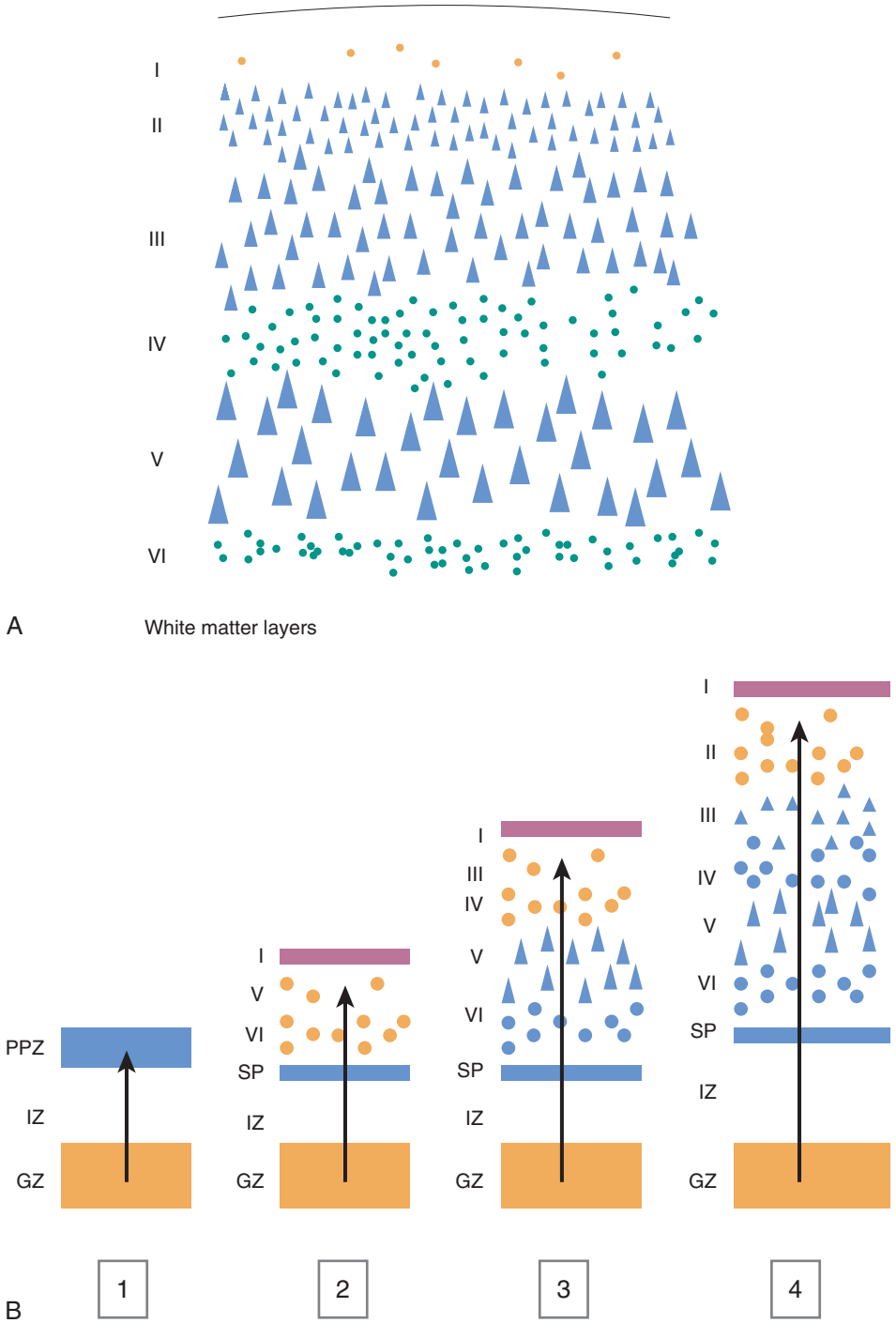
1. A large proportion of neurons migrate radially, along radial glial guides, from the germinative zone to the cortical plate. Radial glia are specialized glial cells present in the neocortex during neuronal migration; these cells display a radial shape with a nucleus located in the germinative zone, a basal process attached on the ventricular surface, and a radial apical process reaching the pial surface (Fig. 51.5). Rakic[96] postulated that these radially arranged glial guides keep a topographic correspondence between a hypothesized protomap present in the germinative zone (ventricular and SVZs) and the cortical areas.
2. An important group of neuronal precursors initially adopt a tangential trajectory at the level of the ventricular or subventricular germinative zones before adopting a classic radial migrating pathway along radial glia. This tangential migration could permit some dispersion at the level of the cortical plate of neurons originating from a single clone in the germinative neuroepithelium, increasing the clonal heterogeneity within a given cortical area.
3. Tangentially migrating neurons have also been described at the level of the intermediate zone (prospective white matter). Most of these neuronal cells displaying a migrating pathway orthogonal to radial glia originate in the ganglia eminence. Most gamma-aminobutyric acid (GABA)–expressing interneurons seem to be produced by this mechanism.

Studies over the last decade have identified several molecules involved in the control of neuronal migration and in targeting neurons to specific brain regions.[59,81,87]

These molecules can be divided into four categories (Fig. 51.6):

1. Molecules of the cytoskeleton that play an important role in the initiation and progression (extension of the leading process and nucleokinesis) of neuronal movement. Initiation controlling molecules include Filamin-A (an actin-binding protein involved in periventricular nodular heterotopia) and Arfgef2 (adenosine diphosphate [ADP]-ribosylation factor GEF2, which plays a role in vesicle trafficking and is involved in periventricular heterotopia combined with microcephaly). Progression controlling molecules include doublecortin (Dcx, a microtubule-associated protein [MAP] involved in double cortex and lissencephaly), Lis1 (a MAP and dynein regulator involved in isolated type 1 lissencephaly and Miller-Dieker syndrome), alpha-tubulin (involved in the formation of tubulin heterodimers), and other molecules that are associated with migration defects in transgenic mice but that have not yet been associated with human disorders (phosphatase inhibitor 14-3-3epsilon, MAP1B, MAP2, and tau).
2. Signaling molecules, which play a role in lamination. These molecules include the glycoprotein Reelin (involved in lissencephaly and cerebellar hypoplasia in humans and in the Reeler mouse mutant characterized by an inverted cortex) and other proteins generally associated with inverted cortex in transgenic or mutant mice but which have not yet been associated with human disorders, such as adaptor protein Disabled-1 (Dab1), ApoE receptor 2 (Apoer2), very low density lipoprotein receptor (Vldlr), two Reelin receptors, serine-threonine kinase Cdk5 (cyclin-dependent kinase 5), activator of Cdk5 p35, Brn1/Brn2, and transcriptional activators of Cdk5 and Dab-1.
3. Molecules modulating glycosylation that seem to provide stop signals for migrating neurons. These molecules

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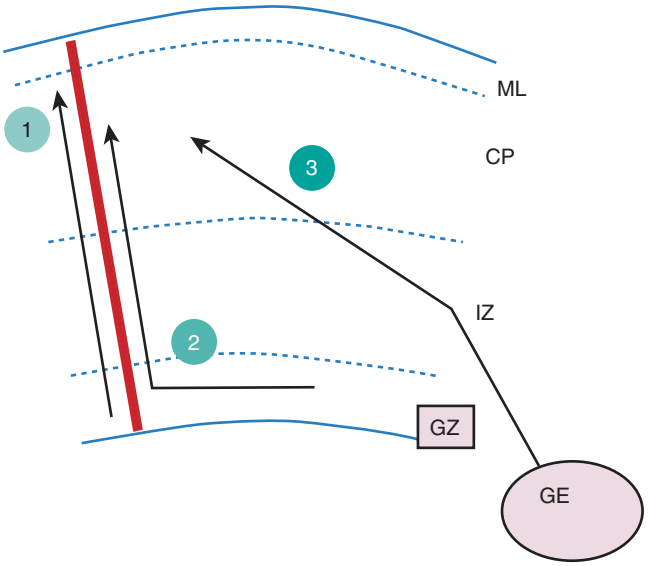


• **Fig. 51.3** **A,** Schematic representation of the six layers of the mature mammalian neocortex. **B,** Schematic illustration of mammalian neocortical formation and neuronal migration. GZ, germinative zone; I, cortical layer I or molecular layer; II to VI, cortical layers II to VI; IZ, intermediate zone (prospective white matter); PPZ, primitive plexiform zone; SP, subplate. *Arrows* and *orange circles* indicate migrating neurons; *blue circles and triangles* represent postmigratory neurons.

include POMT1 (protein *O*-mannosyltransferase associated with Walker-Warburg syndrome), POMGnT1 (protein *O*-mannose beta-1,2-N-acetylglucosaminyltransferase involved in muscle-eye-brain disease), Fukutin (a putative glycosyltransferase involved in Fukuyama muscular dystrophy), and focal-adhesion kinase (Fak involved in migration disorder in transgenic mice). These three human diseases comprise type 2 lissencephaly (cobblestone lissencephaly).

4. In addition to these three major groups of molecules, other factors have been shown to modulate neuronal migration, including neurotransmitters (glutamate and GABA),[8,9,76] trophic factors (brain-derived neurotrophic factor BDNF and thyroid hormones),[12] molecules

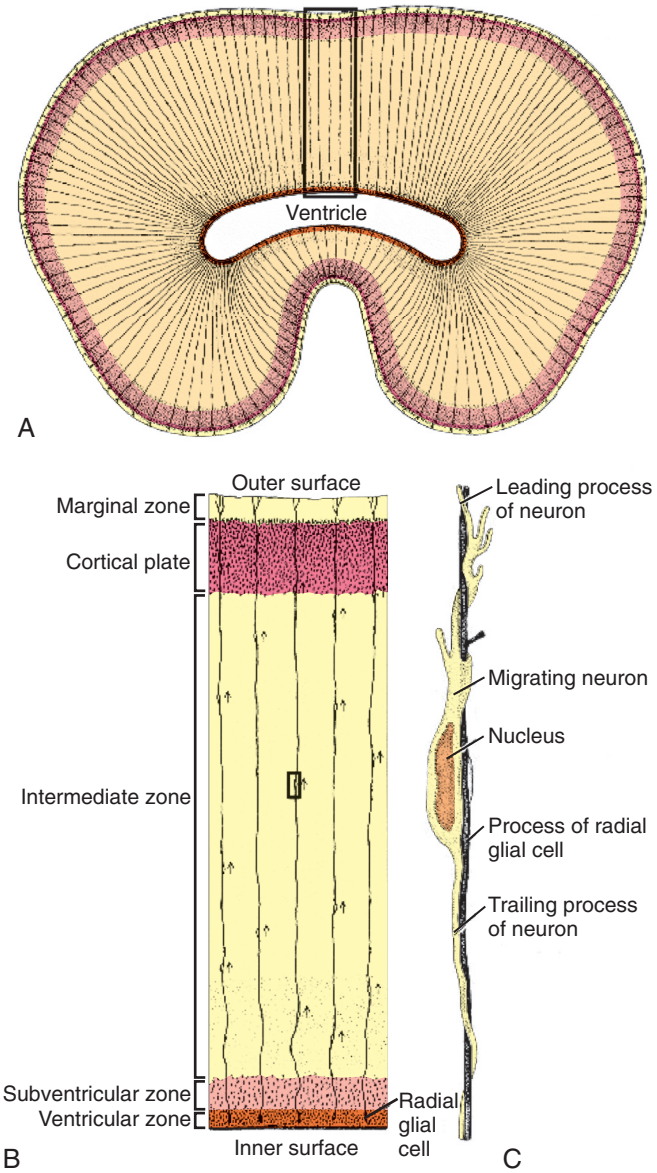
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• **Fig. 51.4** Schematic representation of the different migratory pathways adopted by neurons. (*1*) Radial migration along radial glial cells of neurons originating from the periventricular germinative zone (GZ). (*2*) Tangential migration in the GZ followed by a radial migration along glial guides. (*3*) Tangential migration in the intermediate zone (IZ) of neurons originating from the ganglionic eminence (GE). CP, cortical plate; IZ, intermediate zone (prospective white matter); ML, molecular layer.

deriving from peroxisomal metabolism, and environmental factors (ethanol and cocaine).

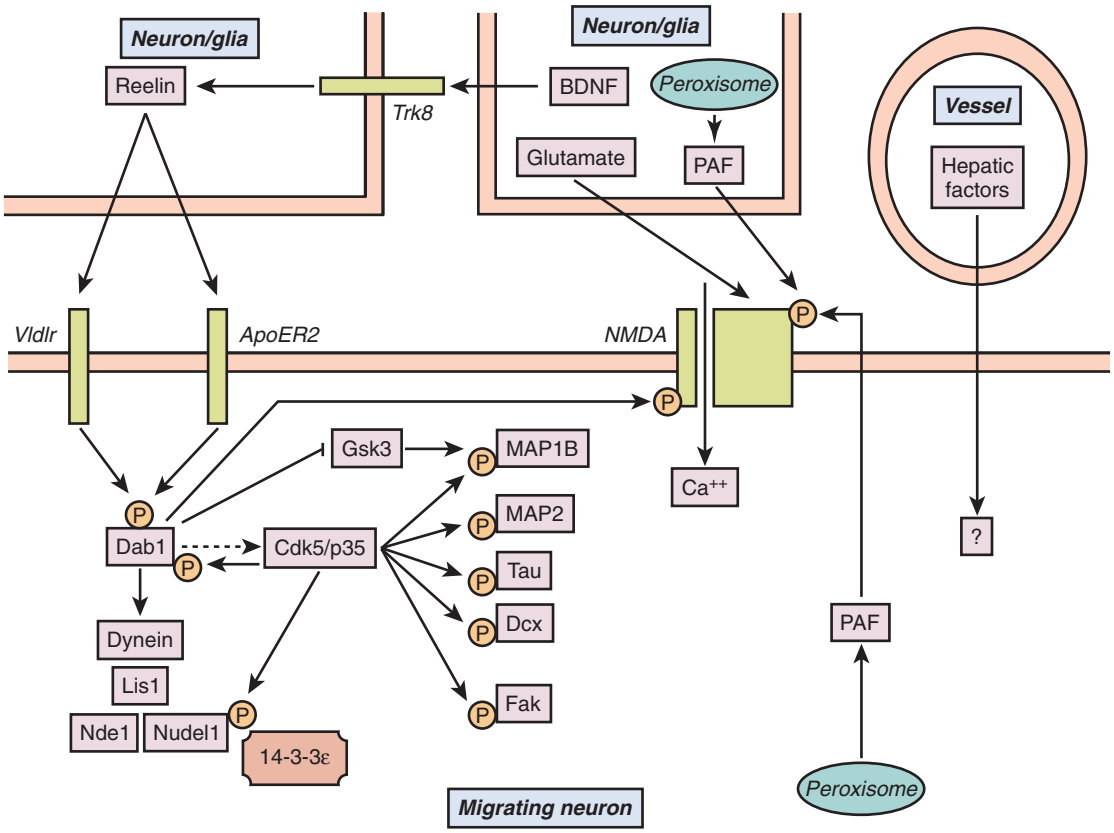
The application of diffusion-weighted magnetic resonance imaging (MRI) or diffusion tensor MRI to the evaluation of developing brain has opened up the possibility to study some of these developmental events in vivo. Quantitative indices derived from the diffusion tensor allow measurement of apparent diffusion and diffusion anisotropy, ultimately depending on microstructural tissue development. Several different diffusion tensor imaging (DTI) parameters are available in this assessment. These include the three diffusion tensor eigenvalues (l1, l2, l3, which represent diffusion along the three tensor principal axes), the mean diffusivity (D_{av}) or apparent diffusion constant (ADC), and a mathematical measure of anisotropy, and this describes the degree to which water diffusion is restricted in one direction relative to all others. Diffusion tensor MRI was used to study cortical development in human infants ranging from 26-41 weeks' gestational age; apparent diffusion of water in cortex was maximally anisotropic at 26 weeks' gestational age and declined to zero by 36 weeks' gestational age.[77] During this period, the major eigenvector of the diffusion tensor in cerebral cortex is oriented radially across the cortical plate. Vector maps illustrate diffusion anisotropy and direction of the major diffusion eigenvector. In the case of cortical gray matter, the vectors are oriented radially, consistent with the orientation of the radial glial fibers (Fig. 51.7).[77] Anisotropy changes are different in early intracortical maturation, where changes in fraction anisotropy (FA) are mainly due to changes in l1[20] confirmed also by studies in the developing rat brain.[48,106] One study on



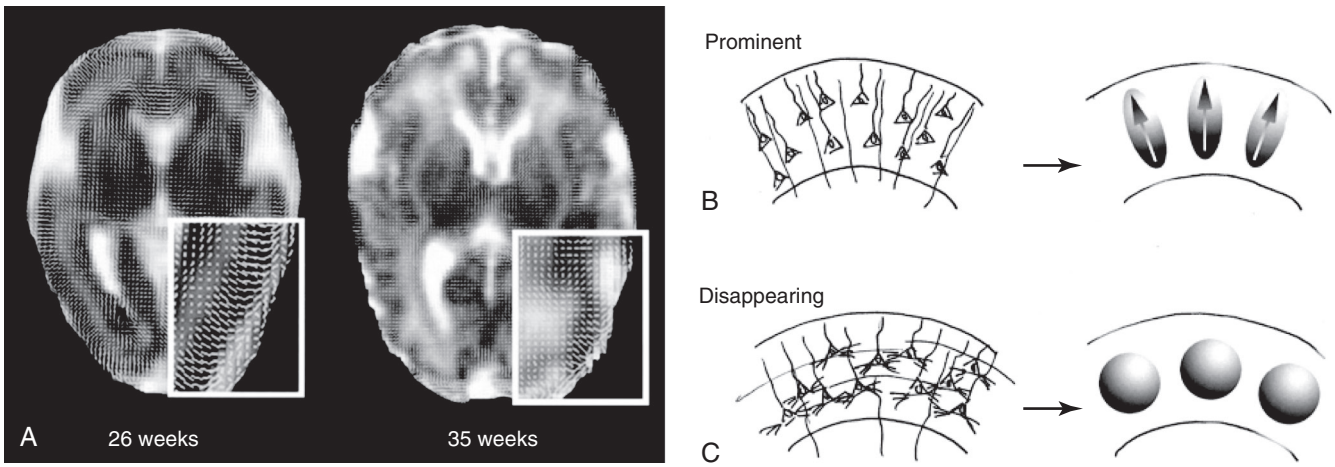
• **Fig. 51.5** **A,** Schematic representation of the immature primate brain. **B,** Illustration of section (box in **A**) through the primate brain with the laminar organization of the immature brain, with ventricular, subventricular, intermediate zone, cortical plate, and marginal zone, and the arrangement of radial glial fibers illustrated in magnification. **C,** Three-dimensional reconstruction of a migrating neuron (magnified box in **B**) with radial fiber from radial glial cell having their origin in the ventricular zone and their relations to the migrating neuron. (Modified from Rakic P. Mode of cell migration to the superficial layers of fetal monkey neocortex. *J Comp Neurol.* 1972;145:66.)

human fetal brain has shown that cortical anisotropy increases from 15 weeks' gestation to approximately 26 weeks' gestation and then shows a gradual decline to 32 weeks' gestation.[43] The increase of anisotropy in this period coincides with active neuronal migration along the radial glial scaffolding, whereas the decrease coincides with the phase of neocortical maturation with transformation of the radial glia into the more complex astrocytic neuropil. Neurite orientation dispersion diffusion imaging (NODDI) has been used to characterize both white matter and gray

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• **Fig. 51.6** Schematic representation of some critical molecular modulators of neuronal migration. This scheme illustrates the cross-talk between different groups of molecules, including cytoskeletal proteins, signaling molecules of the Reelin pathway, N-methyl-D-aspartate (NMDA) receptor–mediated pathway, and peroxisome-derived factors.



• **Fig. 51.7** **A,** Diffusion tensor images of preterm infants at 26 weeks' and 35 weeks' gestation illustrating the direction of major eigenvectors in the immature cortex. **B,** Predominantly radially oriented diffusion in immature cortex at 26 weeks (high anisotropy) represented schematically by the diffusion ellipsoid with the *arrow* pointing in the direction of maximal diffusion. **C,** Absence of radial organization and isotropic diffusion after 35 weeks' gestational age with diffusion equal in all direction represented schematically by a sphere. (From McKinstry RC, Mathur A, Miller JH, et al. Radial organization of developing preterm human cerebral cortex revealed by non-invasive water diffusion anisotropy MRI. *Cereb Cortex.* 2002;12:1237, with permission.)

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matter development in studies characterizing further the ongoing microstructural development in the newborn period.[28,69]

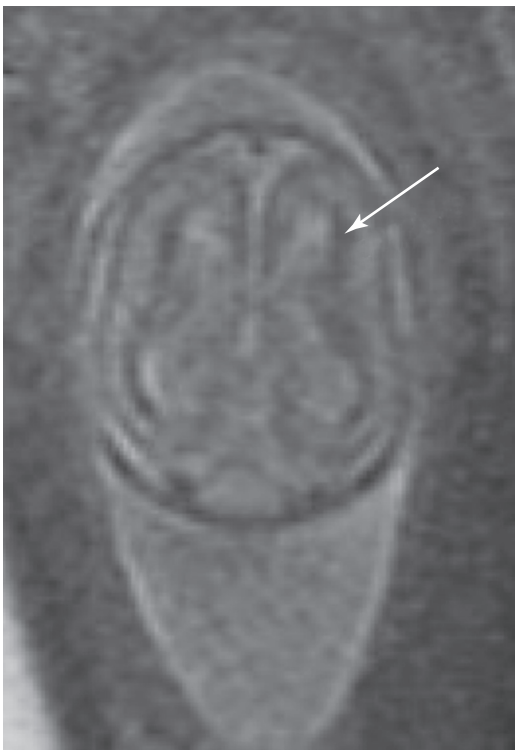
The use of new, ultrafast MRI sequences, such as multiplanar, single-shot, fast spin-echo T2-weighted images, helps obtain high-resolution images of the fetus in utero with imaging times of less than 1 minute.[2] The normal MRI pattern of fetal brain maturation from 13 weeks' gestation has been described, with documentation of the presence of the primary sulci and the insula by 15 weeks' gestation. Operculization of the insula begins by 20 weeks' gestation and all the main sulci, except the occipital sulci, are present by 28 weeks' gestation.[2] From 28 weeks' gestation, there is mainly an increase in secondary and tertiary sulcal formation. From 23-28 weeks in vivo[37] and from 15 weeks in vitro,[11,18] the typical multilayer pattern of the cerebral parenchyma can be observed with the innermost hyperintense signal (T1-weighted MRI) of the germinal matrix (Fig. 51.8). The five-layer pattern of the fetal forebrain, including the layers of neuroblast formation and migration, could be identified at 16-18 weeks' gestation in postmortem fetal brains.[18] During the last trimester, the gyri and sulci already formed become more prominent and more deeply infolded, with subsequent development of secondary and tertiary gyri at gestational age 40-44 weeks (Fig. 51.9).

Central Nervous System Organization

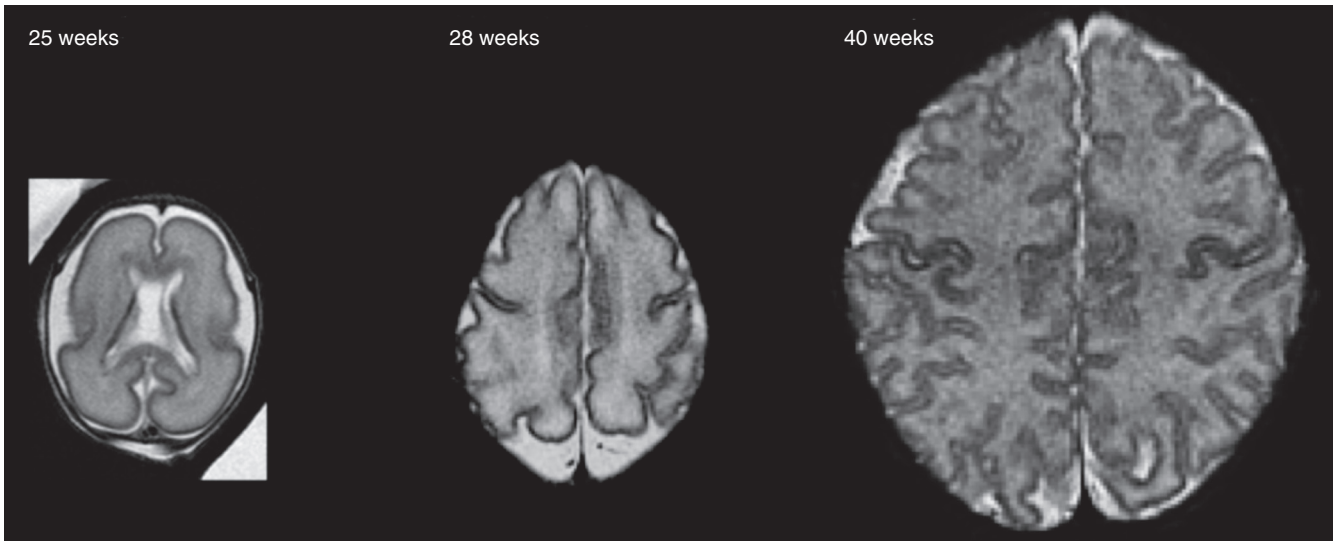
Subplate Neurons

As mentioned previously, subplate neurons constitute a distinct structure during neocortical development.[64] Neurons of the subplate are generated at approximately the seventh week of gestation, and the subplate is generated from the preplate at approximately 10 gestational weeks. This structure localized beneath the neocortical plate reaches its maximal thickness between 22 and 36 gestational weeks. The subplate is present in preterm neonates but has disappeared in full-term neonates. Some authors have suggested that these neurons disappear by apoptosis, whereas others have suggested that they are incorporated into layer VI of the mature neocortex.

Subplate neurons express different neurotransmitters, neuropeptides, and growth factors; receive synapses; and



• **Fig. 51.8** Germinal matrix illustrated by in vivo fetal T2-weighted magnetic resonance imaging (MRI) at 20 weeks' gestation. *Arrow* points to low signal intensity periventricular germinal matrix.



• **Fig. 51.9** Cortical folding illustrated from 25 weeks' to 40 weeks' gestation by in vivo magnetic resonance imaging (MRI). T2-weighted images at 25, 28, and 40 weeks' gestational age.

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make connections with cortical and subcortical structures. These neurons play several important roles during brain development: (1) They produce axons for the internal capsule that will serve as guiding axons for axons originating from neurons in layers V and VI; (2) between 25 and 32 gestational weeks, they produce axons for the corpus callosum; and (3) they act as a waiting zone for thalamocortical axons (with which they establish synapses) before they invade the cortical plate and reach layer IV. This waiting zone is necessary for appropriate target selection by thalamocortical afferents.

The subplate neurons can be lesioned or destroyed in preterm neonates with periventricular white matter lesions.[101] These data have been substantiated in animal models of periventricular white matter damage (see Chapter 52).[78]

MRI has been used to visualize the developmental evolution of the subplate zone and other laminar compartments of the fetal cerebral wall between 15 and 36 weeks' gestation. The combination of MRI and histochemical staining of the extracellular matrix enabled selective visualization of the subplate zone in the developing human brain.[63,116] The tissue elements of the subplate zone are embedded in an abundant, highly hydrophilic, and transient extracellular matrix that is most likely responsible for the low signal intensity on T1-weighted MRI in Fig. 51.10 and the slightly higher signal intensity on T2-weighted MRI as seen in vivo at 26 weeks (Fig. 51.11).

Axonal and Dendritic Growth

When neurons near their final destination, they start to produce axons and dendrites, allowing connection with distant cerebral structures. This ontogenic step occurs largely, but not exclusively, during the second half of gestation and extends into the postnatal period. For example, evoked visual potentials can be produced as early as 24-27 gestational weeks in human neonates, confirming the existence of an established wiring at this early developmental stage.

Growing axons have to find their path through developing structures to reach their target. In this process, growing axons and, in particular, their distal tip, called the *growth cone*, are helped by several mechanisms:

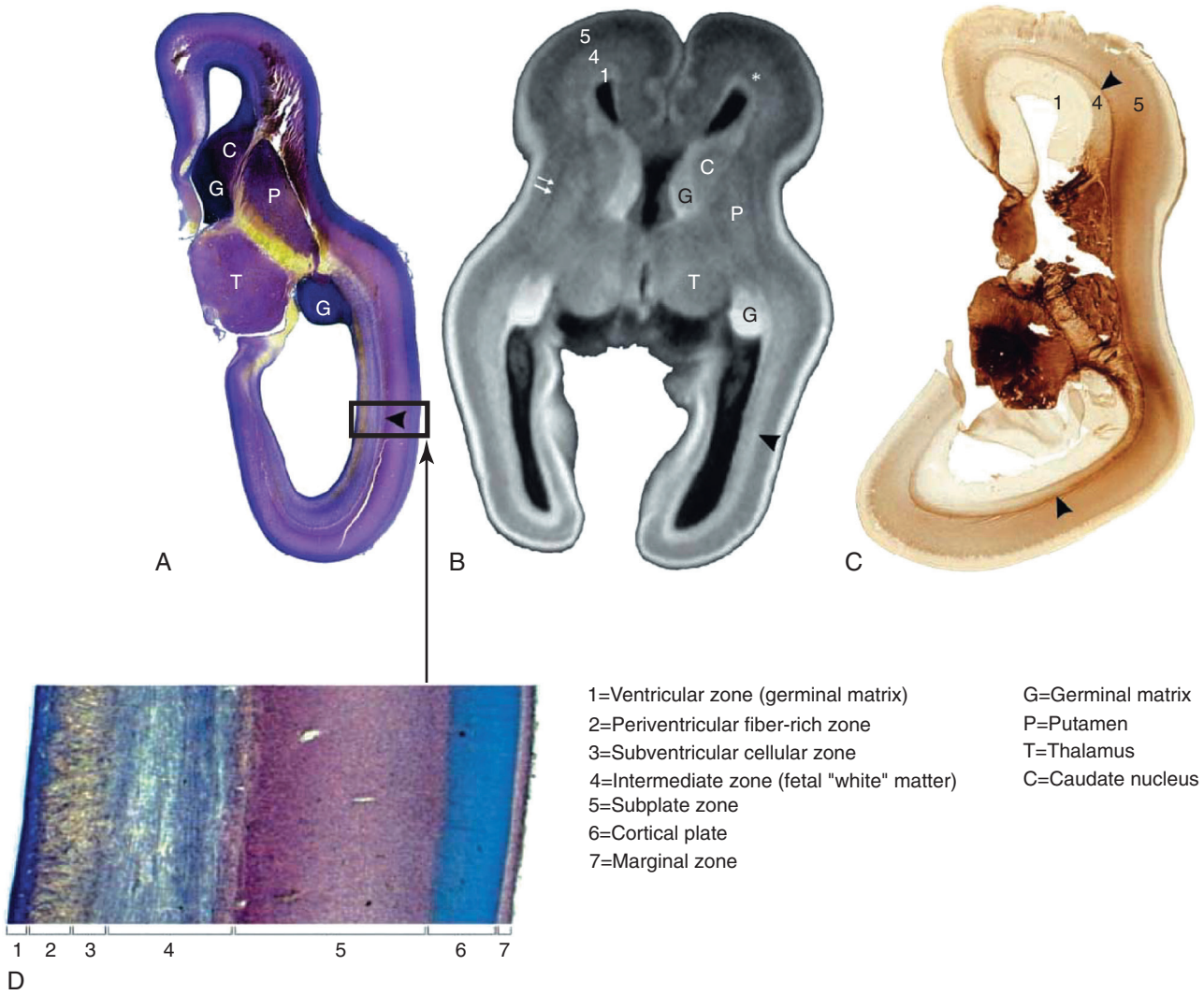
1. The transcriptome of each neuron contains information determining the types of connections that this neuron can establish.
2. Target neurons or neurons on the pathway of growing axons secrete or express on their membranes chemoattraction or chemorepulsion factors that interact with receptors present on growth cones, resulting in attraction or repulsion of these axonal growth cones. Several ligand-receptor families have been described, including netrin, slit, comm, robo, semaphorin, cadherin, and ephrin receptors.[70] The interaction between these different ligands and receptors leads to changes in calcium levels in the growth cones, which seem to play a key role in the resulting behavior of the growth cone.
3. Neurotransmitters and trophic factors are liberated that will favor or inhibit the extension of the growing axons expressing the corresponding receptor.
4. Growth cones can interact with various glycoproteins of the extracellular matrix that act as guiding cues.
5. At early stages of brain development, distances separating structures are rather small, facilitating the navigation of growth cones. These first-produced axons, called *pioneer axons*, serve as guides for later-produced axons, when distances between structures are significantly larger.

As for neuronal production, some axonal projections are produced in excess, connecting too many structures or neurons. This initial phase is followed by a regressive phase where redundant or misconnected axons are eliminated or retracted, allowing the emergence of adequate and functional connections. This balance between the maintenance and the elimination of axons is regulated by different mechanisms. Obviously, the survival of the neuron is determinant in this decision. Furthermore, competition for available trophic factors interacts with the genome to modulate this balance.[13] Also, electrical activity is a key determinant for the maintenance of axons. Accordingly, in utero and especially postnatal stimuli and experiences significantly shape the developing brain by modulating the maintenance or elimination of some axons.[15]

Some callosal connections, some "feedback" intracortical connections, and some corticofugal projections (e.g., the motor pathway) seem to be examples of connections largely under the control of this "overproduction–elimination" principle and, therefore, are highly dependent on the environment.[53] In contrast, some "feedforward" intracortical connections seem to be more genetically predetermined and, therefore, less susceptible to environmental cues.[94]

Studying white matter development with in vivo imaging was largely impossible before the advent of advanced MRI techniques, with diffusion imaging being of particular interest in the assessment of the white matter microstructure. Diffusion characteristics differ between pediatric and adult human brains in two primary ways. First, ADC values are higher for the pediatric brain than for the adult brain. Second, ADC maps of the pediatric brain show contrast between white and gray matter, with the ADC values for white matter being higher than those for gray matter. The precise cause of the decrease in ADC with increasing age is not known, although it has been postulated that the rapid decrease observed between early gestation and term is due to the concomitant decrease in overall water content. Brain water content decreases dramatically with increasing gestational age. As it does, structures that hinder water motion (e.g., cell and axonal membranes) become more densely packed, which further restricts the motion of the remaining water. The use of diffusion tensor MRI has allowed visualization of early white matter connectivity (Fig. 51.12) with demonstration of interhemispheric callosal fibers in the nonmyelinated stage at 28 weeks of gestation. During white matter development, decreases in diffusion are observed principally in l2 and l3 (and much less in l1), which reflect

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• **Fig. 51.10** The cerebral wall displays five laminar compartments of varying magnetic resonance imaging (MRI) signal intensity **(B)**, which partly correspond to laminar compartments delineated on Nissl-stained **(A)** and histochemical **(C)** sections. Starting from the ventricular surface, these laminar compartments are as follows: The ventricular zone (germinal matrix) of high MRI signal intensity, which corresponds to the highly cellular ventricular zone in Nissl-stained sections and, therefore, is marked with number 1 (1 in **D**). The periventricular zone of low MRI signal intensity, which largely corresponds to the periventricular fiber-rich zone (2 in **D**). The intermediate zone of moderate MRI signal intensity, which encompasses both the subventricular cellular zone and the fetal white matter (3 and 4 in **D**). The subplate zone of low MRI signal intensity, which closely corresponds to the compartment marked with 5 in Nissl-stained section (5 in **D**) and acetylcholinesterase-stained section (5 in **C**); therefore, it is marked with 5 on MR images (5 in **B**). The cortical plate of high MRI signal intensity, which closely corresponds to the compartment marked with 6 on Nissl-stained sections (6 in **D**) but on MR images cannot be separated from the marginal zone (7 in **D**); therefore it is always described on MR images as a band of high signal intensity situated above the subplate zone. (From Kostovic I, et al. Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. *Cereb Cortex.* 2002;12:536, with permission.)

changes in water diffusion perpendicular to white matter fibers and may indicate changes due to premyelination (change of axonal width) and myelination.[36,83,88]

Relative anisotropy values for white matter areas are relatively low in newborns and increase steadily with increasing age.[82] They are particularly low for preterm infants.[51] This increase has been attributed to changes in white matter microstructure that accompany the "premyelinating state."[121] This state is characterized by a number of histologic changes, including an increase in the number of microtubule-associated proteins in axons, an axon caliber change, and a significant increase in the number of oligodendrocytes. It is also associated with changes in the axonal membrane, such as an increase in conduction velocity and changes in Na^+/K^+–adenosine triphosphatase (ATP) activity. Myelination then further increases relative anisotropy values. Although myelin accounts for much of the change in relative anisotropy, diffusion anisotropy is present under

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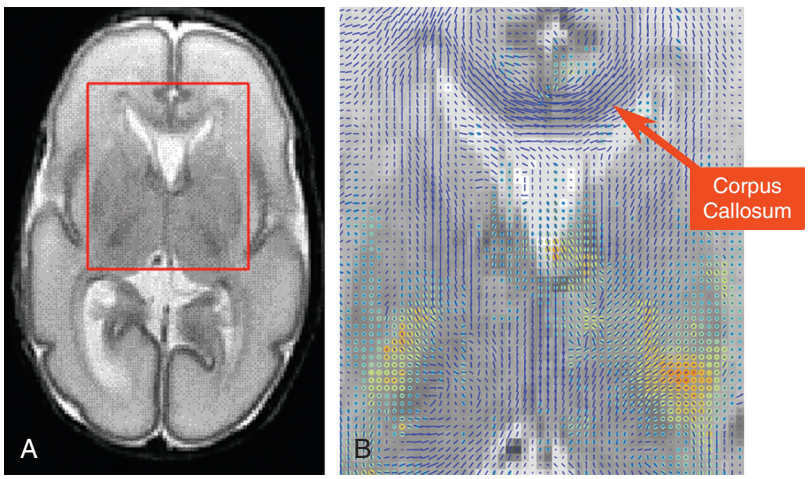
any circumstance in which the cytoarchitecture of the tissue is arranged in such a way as to lead to greater hindrance of water motion in one direction compared with others.

Making proper connections through white matter structures is probably one of the determining factors for further cortical organization. One major hypothesis for the morphogenetic mechanism of cortical folding is based on mechanical tension along axons in white matter.[114] A striking increase in cerebral cortical volume accompanies the axonal and dendritic growth described above. That this growth is particularly rapid between approximately 28 and 40 weeks' gestational age has been shown by quantitative three-dimensional MRI techniques with use of postacquisition image analysis. Volumetric analysis of MRI data sets is achieved by segmentation of the imaged volume into tissue types, depending on differences in signal intensity, followed by three-dimensional renderings.[42] Overall brain volume more than doubles between 28 and 40 weeks' gestation, and cortical gray matter volume increases fourfold in the same period.[52] This increase is thought to relate primarily to neuronal differentiation rather than to an increase in the total number of neurons. Cortical surface, changing from smooth and lissencephalic to highly convoluted, increases fivefold between 28 and 40 weeks' gestation (Fig. 51.13).[25]

So far, several hypotheses have been put forward on the mechanisms that underlie the folding process during development, but the potential influence of genetic, epigenetic, and environmental factors is still poorly understood. According to postmortem observations of fetal brains,[31] the primary folds would form in a relatively stable spatiotemporal way during intrauterine life, depending on physical constraints and mechanical factors.[98] An attractive theory suggests that the specific location and shape of sulci are determined by the global minimization over the brain of the viscoelastic tensions from white matter fibers connecting cortical areas.[45,46] This may explain why specific abnormalities in the sulcal pattern are observed in certain brain developmental disorders that are the result of subtle impairments in the neuronal migration and the setup of corticocortical

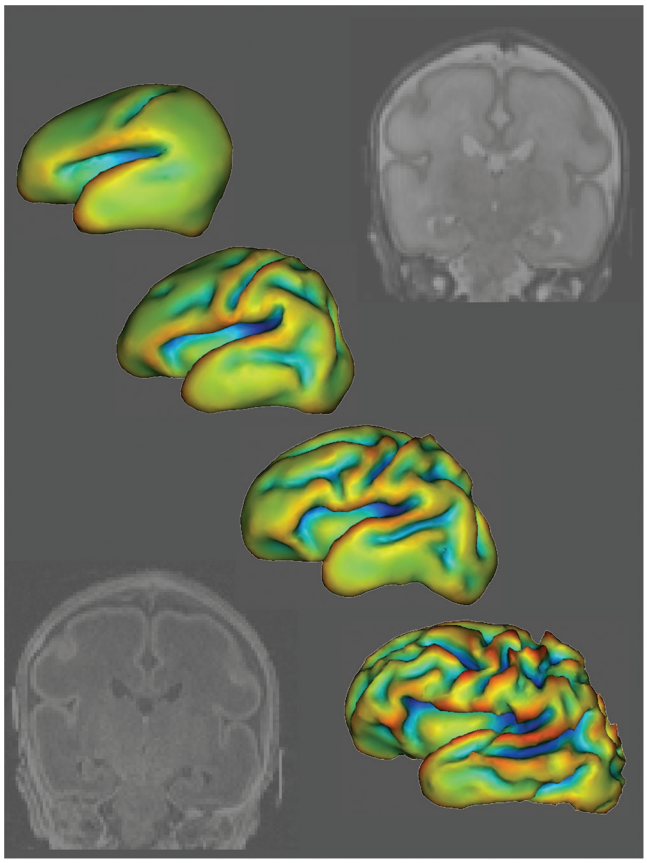


• **Fig. 51.11** T2-weighted magnetic resonance imaging (MRI) (axial plane) of a preterm infant at 26 weeks' gestation, with *arrows* indicating subcortical zone of higher signal intensity corresponding to the autopsy description of highly hydrophilic extracellular matrix in the subplate zone.



• **Fig. 51.12** **A,** Anatomic axial T2-weighted magnetic resonance imaging (MRI). **B,** Diffusion tensor vector maps for the regions indicated by the box in **A,** showing nonmyelinated interhemispheric fiber connections in the corpus callosum at 28 weeks' gestational age. The blue lines represent in-plane fibers; out-of-plane fibers are shown in colored dots ranging from green to red. (Hüppi PS, et al. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatr Res.* 1998;44:584, with permission.)

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• **Fig. 51.13** External and internal brain surface at from 26-36 weeks' gestation illustrated by three-dimensional models generated from magnetic resonance imaging, which illustrates timing of regional cortical folding and permits quantitative measures of surface and sulcation index. (Images reconstructed by specialized image analysis software, courtesy of Dubois J, Benders M, Cachia A, et al. Mapping the early cortical folding process in the preterm newborn brain. *Cereb Cortex*. 2008;18:1444.)

connections.[95,115] The emergence of the cortical foldings in the preterm newborn brain was studied by applying dedicated postprocessing tools to high-quality MRI scans acquired shortly after birth over a developmental period critical for the human cortex development.[25,44] Through the three-dimensional reconstruction of the developing inner cortical surface, a sulcation index was derived and allowed for measurement of variations with age, gender, and presence of brain lesions and mapped the individual sulci appearance, highlighting early interhemispheric structural asymmetries that may be related to the cortical functional specialization of the brain. Females have lower cortical surface and smaller volumes of cortex and white matter compared with males, but equivalent sulcation. The highest sulcal index is found in the central region, followed by the temporo-parieto-occipital region, with the lowest sulcation index in the frontal region, which confirms that the medial surface folds before the lateral surface and that the morphologic differentiation of sulci begins in the central region and progresses in an occipitorostral direction. Such spatiotemporal differences in brain maturation have been described in detail in older children through analyses of cortical volume and thickness changes.[34] In particular, occipital regions grow much faster than prefrontal regions in newborns born at term,[35] and higher-order association cortices mature only after lower-order somatosensory and heterotopia visual cortices.[108]

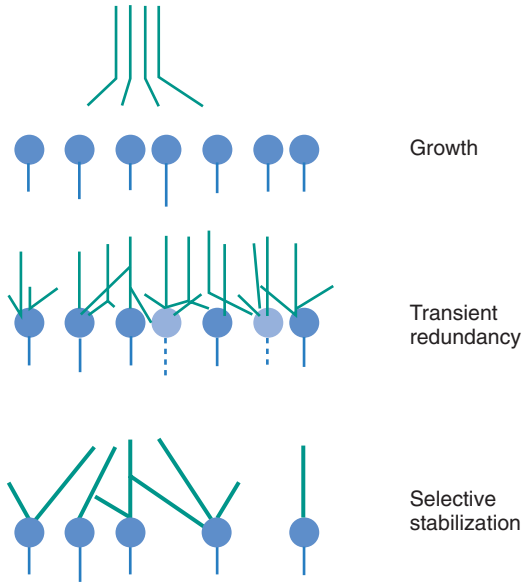
The right hemisphere presents gyral complexity earlier compared with the left hemisphere, and this is particularly evident at the level of the superior temporal sulcus, which parallels early functional competence in response to auditory stimuli in newborns.[26] Preterm birth may be responsible for the delay that was observed in the appearance of sulci in comparison with that in postmortem and fetal studies, in that both cortical volume[55] and surface area[1] of extremely preterm infants imaged at term equivalent age are decreased and less complex than in normal infants; this impairment seems to increase with decreasing gestational age at birth.[58] Furthermore, preterm infants with intrauterine growth restriction had more pronounced reduction of volume in relation to surface area and increased sulcation with resultant changes in cortical thickness, which correlated with impaired behavioral functions.[24] In more recent studies, three distinct waves of cortical folding patterns could be described, representing primary secondary and tertiary cortical folding, and preterm infants at term equivalent age had altered sulcal pattern compared with full-term newborns, again indicating the disruption of normal cortical development by prematurity.[27,72]

Synaptogenesis

The concept of synaptic stabilization (with the elimination of nonstabilized synapses) has been proposed.[16,29] During brain development, there are successive waves of overproduction of labile synapses, inducing redundant connections produced in a relatively random manner (Fig. 51.14). This step is under tight genetic control. Each wave of overproduction is followed by a period of stabilization of synapses that have a functional meaning and elimination of redundant or meaningless synapses. This period of stabilization and elimination is highly influenced by environmental stimuli and experience. In this model, a moderate increase in the number of genes would induce a richer substrate on which the environment could produce a more complex network. Neuronal activity–mediated glutamate release induces a postsynaptic calcium influx at the level of N-methyl-D-aspartate (NMDA) receptors. Calcium changes lead to production of trophic factors, such as brain-derived neurotrophic factor, which stabilize labile synapses, protecting them against elimination. Nitric oxide, which is rapidly produced after glutamate binding to its NMDA receptor, is another key player in synaptic stabilization and plasticity. This model of synaptic stabilization and elimination does not exclude the existence of an instructive process where synaptic connections are adequately established right away.

Studies have demonstrated a key role of quiescent microglia in synaptic elimination. In the normal developing brain, quiescent microglia continuously extend and retract motile

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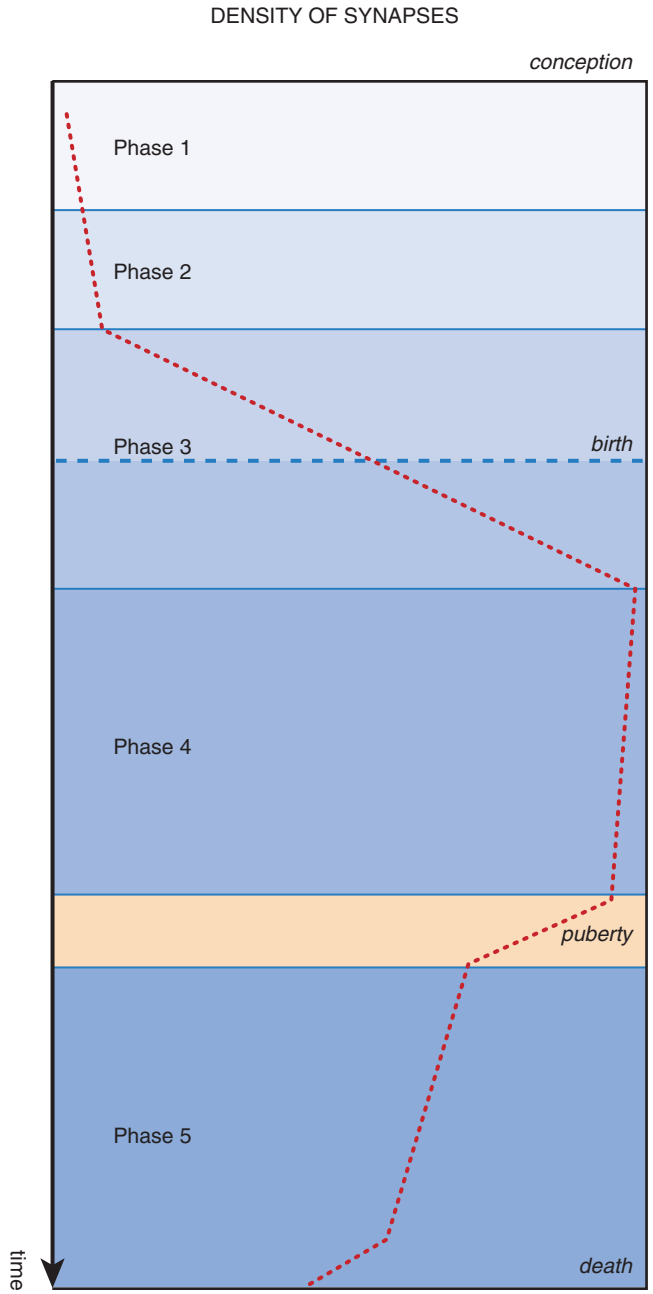
• **Fig. 51.14** Schematic representation of the epigenetic hypothesis based on selective stabilization of synapses. Spontaneous or evoked activity of developing neuronal networks controls the selective elimination of redundant synapses formed during the transient phase of synaptic redundancy. (Adapted from Changeux JP, Danchin A. Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. *Nature.* 1976;264:705.)

processes. These processes interact with synapses, leading to the elimination of synapses by mechanisms that include the phagocytosis of axon terminals and dendritic spines.[112]

In monkey occipital neocortex, five successive waves of synaptogenesis have been described.[10] Based on data obtained in human occipital cortex,[70] the following timetable for humans is proposed (Fig. 51.15): (1) the first phase starting approximately 6-8 weeks of gestation and limited to lower structures like the subplate; (2) the second phase starting after 12-17 weeks with relatively few synapses produced in the cortex (contacts on the dendritic shafts); (3) the third phase starting around midgestation and ending approximately 8 months after birth; this phase is characterized by an estimated rate of 40,000 new synapses per second in the monkey; (4) the fourth phase lasting until puberty and also characterized by a high rate of synapse production; and (5) the last phase extending until late adulthood but somewhat hidden by the intense loss of synapses characterizing these ages. Experimentally, the first two phases are not affected by lack of sensory stimuli. The third phase partially depends on this sensory input, whereas the fourth phase is highly dependent on sensory input and experience (Fig. 51.16).

Current understanding of the mechanisms of synaptogenesis and of synaptic stabilization raises numerous questions in neonatal medicine and pediatric neurology. Very preterm infants are a typical example of such an issue:

- What are the effects of environmental modifications of preterm birth on synaptic stabilization?
- What are the influences (positive or negative) of too early sensory stimuli for synaptogenesis?



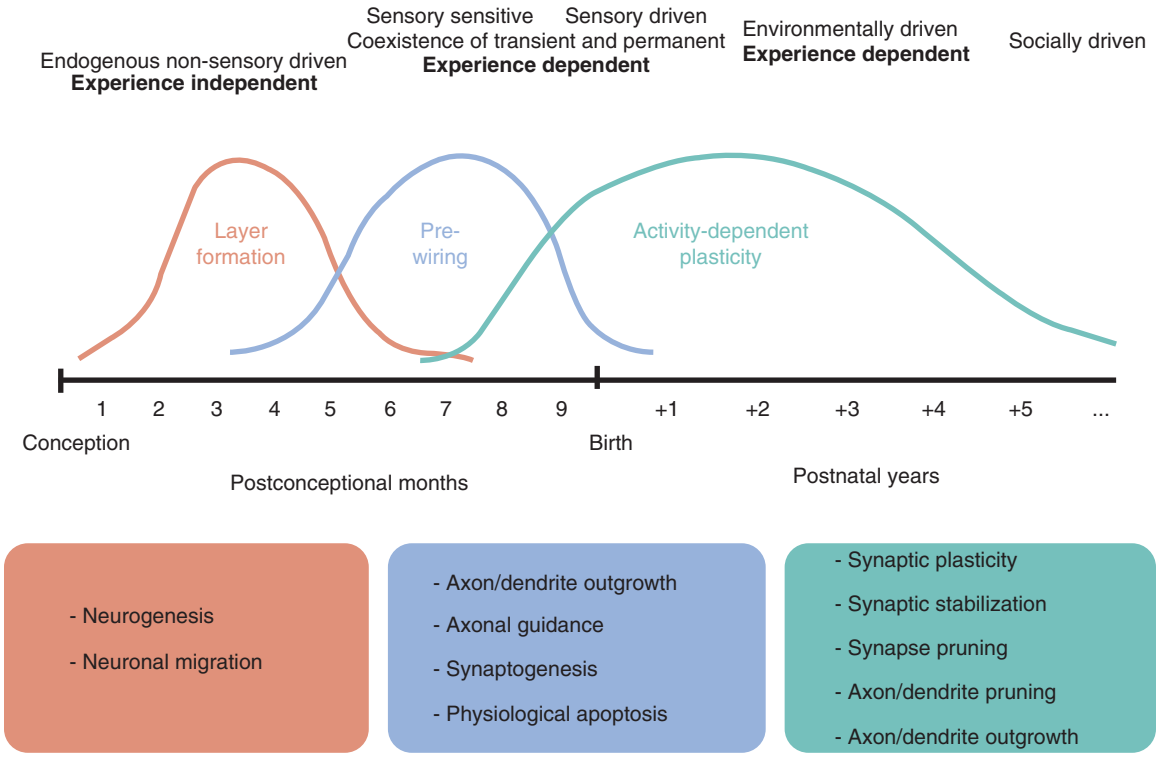
• **Fig. 51.15** Schematic representation of the synaptic density in the visual cortex of the macaque monkey. (From Bourgeois JP. Synaptogenesis, heterochrony and epigenesis in the mammalian neocortex. *Acta Paediatr Suppl.* 1997;422:27.)

- What are the effects on the synaptic equipment of drugs that interfere with the glutamatergic or the nitric oxide system?

Programmed Cell Death

Depending on brain area, between 15% and 50% of the initially formed neurons will be eliminated by a physiologic process called *programmed cell death*, or *apoptosis*. Approximately 70% of these neurons that are destined to disappear seem to die between 28 and 41 gestational weeks.

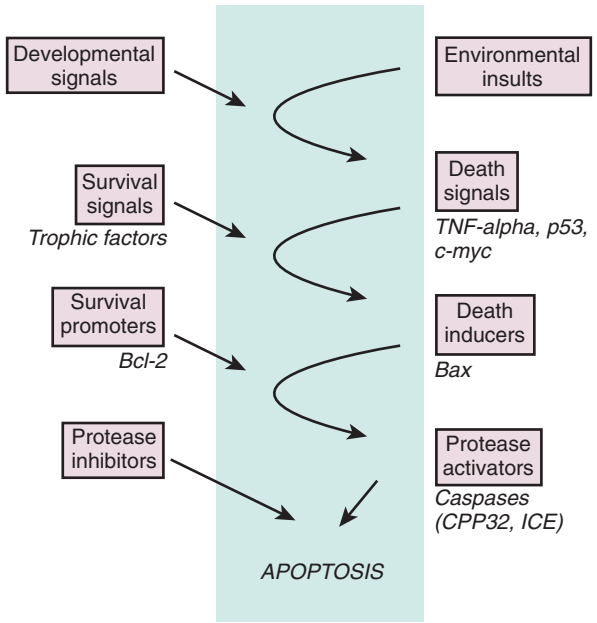
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• **Fig. 51.16** Schematic time dependent representation of major brain developmental events in the fetal, neonatal, and infant periods. Of note, the gradual switch from activity and experience independent to activity and experience dependent, environmentally driven plasticity. (Adapted from Kiss JZ, Vasung L, Petrenko V. Process of cortical network formation and impact of early brain damage. *Curr Opin Neurol.* 2014;27:133-141.)

Programmed cell death is a complex mechanism that involves a balance between death and trophic signals, death and survival genetic programs, and effectors and inhibitors of cell death (Fig. 51.17).[79,117] Under the influence of a combination of exogenous and endogenous factors, genetic programs are activated (hence the name, "programmed cell death") that are able to overcome the natural defenses of the neuron. The cell eventually dies and is rapidly removed by phagocytosis performed by neighboring glial cells. In this process, activation of the cascade of caspases (proteolytic enzymes) is a key step leading to DNA fragmentation and neuronal cell death. The caspase pathway can be activated by intrinsic and extrinsic mechanisms. The intrinsic mechanism or mitochondrial-dependent pathway is triggered by cytochrome C release by mitochondria and is controlled by members of the Bcl-2 family, whereas the extrinsic pathway is triggered by activation of death receptors, a subgroup of the tumor necrosis factor receptor superfamily. Neuronal apoptosis can be also triggered by a caspase-independent pathway involving apoptosis-inducing factor (AIF) release from mitochondria.

Electrical activity seems to be a critical factor for neuronal survival. During the period of brain growth spurt in rodents, administration of drugs that block electrical activity leads to a dramatic exacerbation of neuronal cell death in different brain areas. These drugs include NMDA receptor



• **Fig. 51.17** Schematic representation of the molecular cascade leading to neuronal apoptosis and showing the balance between pro-survival (*left side*) and prodeath (*right side*) factors.

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blockers (MK-801 or ketamine), GABA-A receptor agonists, such as classic antiepileptic drugs (phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, or valproic acid) and anesthetics (combination of midazolam, nitrous oxide, and isoflurane).[86] These effects on neuronal cell death are mimicked by acute administration of ethanol, which blocks NMDA receptors and activates GABA-A receptors. Although the mechanism is unknown, the systemic injection of a combination of sulfites (which are present in the excipient of some commercially available preparations of injectable glucocorticoids and vasoactive amines) and dexamethasone to newborn mouse pups led to an exacerbation of programmed neural cell death both in the neocortex and basal ganglia.[7,102]

Postnatal systemic steroid therapy had been widely used for chronic lung disease in the preterm infant until follow-up studies indicated higher rates of cerebral palsy and of subnormal (<70) cognitive function in steroid-treated infants. Quantitative MRI studies have indicated a possible origin of these functional deficits by showing marked reduction of cortical gray matter volume after repetitive antenatal and postnatal steroid treatments.[80,84] Different roles have been attributed to programmed cell death, although final proofs are still lacking. These comprise elimination of "sick" neurons; increase of neuronal diversity by eliminating redundant neurons; and competition for trophic factors with elimination of neurons that have lower access to these trophic factors. Consequences of cortical neuronal apoptosis may be widespread and include effects on cortical layering as well as distant effects on brain connectivity.[90]

Glial Proliferation, Glial Differentiation, and Myelination

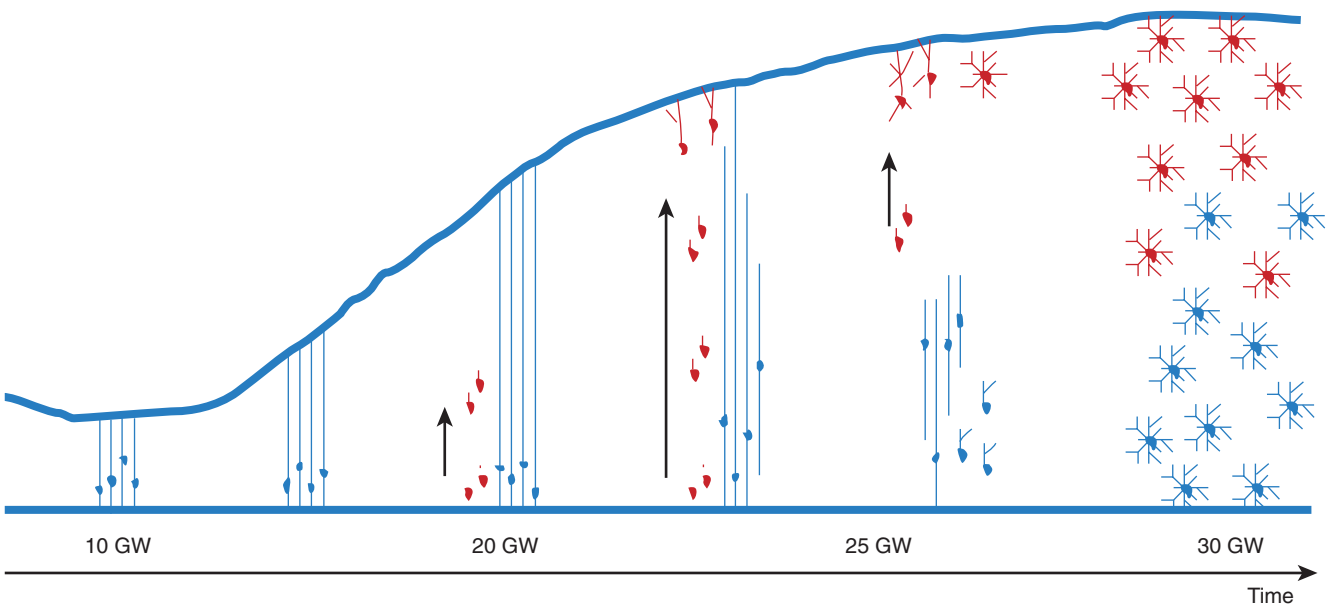
Glia comprise three types of cells: astrocytes, oligodendrocytes, and microglia (brain macrophages).

Astrocytes

Neocortical astrocytes have a dual origin (Fig. 51.18).[41] After the end of neuronal migration, radial glial cells (which are glial cells specialized in the guidance of migrating neurons) transform into astrocytes, which are found mainly in the deep cortical layers and underlying white matter. In addition, the periventricular germinative zone produces, after the end of neuronal production, astrocytic precursors that will migrate mostly into the superficial neocortical layers.

The presence of low-intensity periventricular bands in white matter on T2-weighted MRI has been recorded in studies of premature infants, predominantly less than 30 weeks' gestational age. These bands are thought to represent populations of migrating radial glial cells based on their position and on correlative neuropathologic data.[6,17] The presence of these bands on T2-weighted MRI is, therefore, thought to be a marker of normal brain development.

Transformation of radial glia into astrocytes involves an autophagic digestion of apical processes and a nuclear translocation from the germinative neuroepithelium toward white matter. Molecular mechanisms controlling this transformation remain unknown. In vitro, it was shown that neurons are necessary to maintain the radial phenotype of these glial cells.



• **Fig. 51.18** Schematic representation of the dual origin of neocortical astrocytes in human fetuses. Astrocytes destined to white matter and deep cortical layers derive from the progressive transformation of radial glial cells (*blue cells*), whereas most astrocytes destined to the more superficial cortical layers derive from precursors that migrate from the germinative neuroepithelium (*red cells*). GW, gestational weeks. *Arrows* indicate migrating astrocytes.

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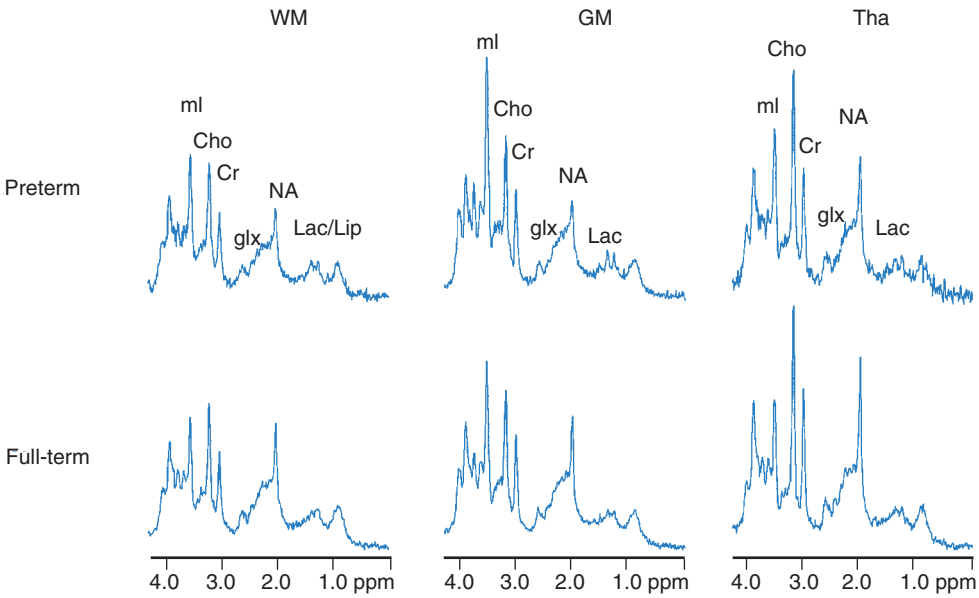
In the human neocortex, this astrocytic proliferation probably starts at approximately 24 weeks of gestation, with a peak at approximately 26-28 weeks. The final stage of astrocyte production is not known, but one might assume that the bulk of astrocyte production is completed by the end of normal gestation. However, it is important to remember that astrocytes retain the capability to divide throughout their life span. This peak of astrocyte production at approximately 26-28 weeks might be particularly important for preterm neonates. Indeed, astrocytes play several important roles during brain development, including axonal guidance, stimulation of neuron growth, synaptic formation, transfer of metabolites between blood vessels and neurons (magnetic resonance spectroscopy [MRS] results), establishment of scaffolding structures, production of extracellular matrix components, production of trophic factors, neuronal survival, myelination, and participation in the blood-brain barrier. For example, experimental transient blockade of astrocyte production in the rodent neocortex leads to increased neuronal programmed cell death and long-term changes in neocortical synaptic equipment.[124]

One of the essential contributors to progress in the noninvasive detection of tissue metabolism and in vivo biochemistry has been proton MRS (^{1}H-MRS), which gives specific chemical information on the biochemistry of numerous intracellular metabolites (Fig. 51.19). Neurochemistry has particularly benefited from this technique in that there is the possibility of detecting cerebral metabolites in vivo in otherwise inaccessible tissues. Astrocytes play a variety of complex nutritive and supportive roles in relation to neuronal metabolic homeostasis. For example, astrocytes take up glutamate and convert it to glutamine; removal of glutamate from the extracellular space protects surrounding cells from glutamate-induced excitotoxicity. Glutamate and glutamine are amino acids that are measured in ^{1}H-MRS when using short echo times. Alternatively, glutamate in the astrocyte can stimulate glycolysis with lactate production. Lactate is then released into the extracellular space and can also be taken up by neurons and used for energy generation.[89] In the immature brain, especially in the immature white matter, lactate is present in higher concentrations.[14,50]

Osmoregulation is another major metabolic task fulfilled by astroglia. Osmolytes synthesized by astrocytes or present in astroglia include taurine, hypotaurine, and myoinositol. Developmental changes in myoinositol have been described by Kreis et al.,[65,88] who found a decrease of myoinositol during the first year of life and a marked reduction of myoinositol in the first weeks after birth regardless of the gestational age at birth. Studies indicate that astroglial cells are also able to synthesize creatine from glycine, which will need to be considered in interpreting creatine concentrations in the brain[8,23] and the role of creatine as a neuroprotective agent.

Oligodendrocytes and Myelination

Oligodendrocytes, which produce myelin, can be divided into four cell types according to their stage of maturation: oligodendrocyte progenitor (NG2+), preoligodendrocyte (O4+, O1−), immature oligodendrocyte (O4+, O1+), and mature myelinating oligodendrocyte (O4+, O1+, MBP+, PLP+).



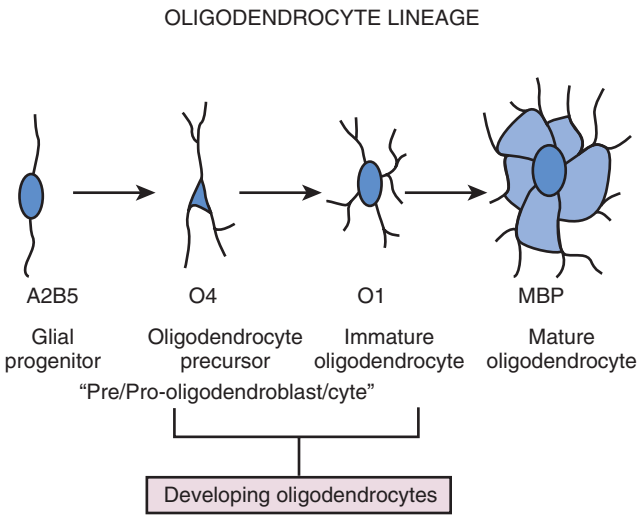
• **Fig. 51.19** Averaged in vivo proton magnetic resonance spectroscopy (^{1}H-MRS) spectra during human development in function of different regions of the brain: WM, white matter; GM, gray matter; Tha, thalamus. Metabolites identified are Lac, lactate; NA, N-acetyl-aspartate; glx, glutamine and glutamate; Cr, creatine and phosphocreatine; Cho, choline; ml, myoinositol. Spectra are scaled identically. Developmental changes in metabolite concentrations are illustrated by different peak heights comparing spectra from preterm and full-term newborns. (Spectra analyzed by Roland Kreis, MR Center, Inselspital, University of Berne, Switzerland.)

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The progenitors originate from the proliferative SVZ and are bipolar and mitotically active. They are produced during the last months of gestation and in the early postnatal period. During migration in white matter, differentiation into preoligodendrocytes occurs, which are multipolar cells retaining a proliferative capacity. This second cell type is the dominant one in the second half of gestation in periventricular white matter. The immature oligodendrocyte is a multipolar cell that starts in the third trimester to ensheath the axons in preparation for myelination. The last stage is differentiation into the mature, myelinating, highly multipolar cell. Each stage of differentiation can be marked by specific monoclonal antibodies (Fig. 51.20).[3]

Growth factors, hormones, and cytokines (basic fibroblast growth factor, neurotrophin-3, platelet-derived growth factor, insulin-like growth factor type 1, interleukin-6, thyroid hormone) are implicated in oligodendrocyte maturation, but up to 50% of oligodendrocytes undergo programmed cell death (apoptosis) during development.[118] Preoligodendrocyte progenitors are highly vulnerable to oxidative stress, excitotoxic cascade (through a-3-amino-hydrox y-5-methyl-4-isoxazole propionic acid [AMPA]-kainate and NMDA receptors), and hypoxic-ischemic insults.[118]

^{1}H-MRS as an in vivo technique to assess metabolic composition of brain tissue can help in characterizing integrity of developing white matter. N-acetylaspartate (NAA), an amino acid specific to the CNS, has been shown to be uniquely localized in neuronal tissue of the adult brain, whereas during development it is also found in oligodendrocyte type 2 astrocyte progenitor cells and immature oligodendrocytes.[113] NAA has been shown to be an acetyl group source in the nervous system.[79] The major requirement for acetyl groups is lipid synthesis, which takes place immediately before myelin deposition in the developing brain. A marked increase of NAA shown in several studies[49] in the period from 32-40 weeks of gestation, just before the initiation of myelination, supports the importance of NAA in lipid synthesis (see Fig. 51.19). Regional differences in age-dependent changes of NAA concentrations during early brain development show stable concentrations in perithalamic voxels,[14] where myelination is already initiated at 32 weeks, and a marked increase in central cerebral white matter[66] between 32 and 40 weeks of gestation (see Fig. 51.19).



• **Fig. 51.20** Schematic representation of the oligodendrocyte development showing their morphology and some major immunohistochemical markers (A2B5, 04, O1, and MBP [myelin basic protein]). (Adapted from Back SA, et al. Immunocytochemical characterization of oligodendrocyte development in human cerebral white matter. *Soc Neurosci Abst.* 1996;20:1722.)

Myelination occurs over a protracted period, ending long after birth (Table 51.2). The chronology and rate of myelination vary with the brain structure. Structures that function first tend to be myelinated first. However, although myelination leads to a marked acceleration in nerve conduction, human and experimental studies have reported several examples of dissociation between the degree of myelination and the maturation of a given function. Myelination starts in the cerebral hemispheres around birth and is largely complete by age 2-3 years. There is no detectable myelination in the forebrain before the seventh gestational month, and this process continues in some parts until the years of maturity. Myelination is most intense in the telencephalon during the third trimester and postnatally. Pathways of the olfactory, optic, acoustic, and sensorimotor cortex are the first to be myelinated, whereas projection and association pathways are the last. Projection fibers begin myelination before association fibers. The myelination of association fibers lasts until adulthood. Recent experimental studies further support the idea that myelination is directly linked to neuronal activity, and this underlines the role of environmental stimuli in the maturation of the developing brain.[33]

Imaging Characteristics of Myelination

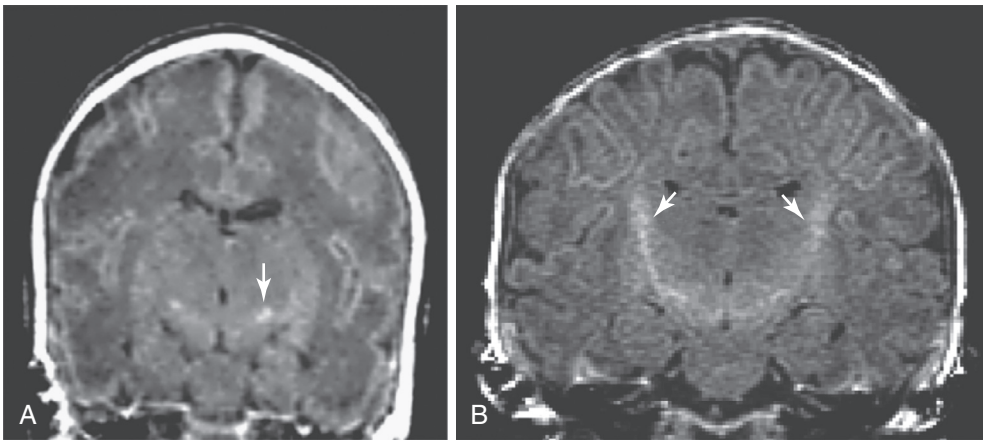
On histologic examination, mature myelin is present at 37-40 postconceptional weeks in the posterior limb of the internal capsule and in the lateral cerebellar white matter (see Table 51.2). Myelination advances at differing rates in different regions of the brain. Myelination occurs in an orderly and predictable fashion, proceeding cephalad from the brainstem at 29 weeks to reach the centrum semiovale by 42 weeks. Myelination advances at differing rates in different regions of the brain and is visible at different times on T1-weighted (lipid: high signal) and T2-weighted (water: high signal) MRI, the classic imaging sequences on conventional MRI.[5,6] The exact reasons for these differences are not clear. However, it is known that the T1 shortening correlates temporally with the increase in cholesterol and glycolipids that accompany the formation of myelin from oligodendrocytes.[92] Furthermore, the T2 shortening correlates temporally with the tightening of the spiral of myelin around the axon, the conformational changes in the myelin proteins, and saturation of polyunsaturated fatty acids in the myelin membranes. Portions of the proteins, cholesterol, and glycolipids that compose myelin are hydrophilic and form

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TABLE 51.2 Sequence of Myelination Based on Histologic Analysis and Magnetic Resonance Imaging (MRI)

Anatomic Region	Median Age for Detection of Myelin: Histology[123]	Age for Detection of Myelin: MRI[37]	
		T1-Weighted Images	T2-Weighted Images
Ventrolateral thalamus		28–30 wk	3234 wk
Posterior limb of internal capsule	38/44 wk*	38–40 wk	Posterior portion: 40–48 wk Anterior portion: 56–70 wk
Anterior limb of internal capsule	50/87 wk	48–53 wk	70–90 wk
Central corona radiata	37/52 wk	38–56 wk	52–65 wk
Genu corpus callosum	50/53 wk	56–64 wk	64–72 wk
Splenium corpus callosum	54/65 wk	52–56 wk	56–64 wk
Occipital white matter			
Central	47/87 wk	52–60 wk	76–96 wk
Peripheral	56/122 wk	56–70 wk	90–102 wk
Frontal white matter			
Central	50/119 wk	52–64 wk	90–106 wk
Peripheral	72/119 wk	70–90 wk	96–114 wk

*The first number corresponds to earliest identification of some myelin tubules by microscopic examination of hematoxylin and eosin (H&E) stained sections. The second number corresponds to mature myelin stained with blue dye by eye observation.
wk, Week.



• **Fig. 51.21** T1-weighted magnetic resonance (MR) images illustrating progress of myelination. **A,** At 28 weeks' gestation, distinct T1 shortening (high signal) is seen only in a small perithalamic region (*arrow*). **B,** At 40 weeks, distinct T1 shortening (high signal) is seen throughout the internal capsule reaching the central cortex (*arrows*).

hydrogen bonds more strongly with water molecules. With an increase in bound water to the myelin building blocks, there is a consequent decrease in free water and an increase in T1 shortening times. This reduction in free water accompanying the preparation for myelination may explain the pattern of T1-weighted MRI changes preceding anatomic myelination by histologic analysis (see Table 51.2). Sensory pathways are the first to myelinate: Vestibular, acoustic, tactile, and proprioceptive senses are myelinated at term birth. A shortened T2 relaxation time and, therefore, a T2 hypointense signal is observed in the ventro-postero-lateral nuclei of the thalamus as early as 28 weeks' gestation, in the posterior limb of the internal capsule as early as 36 weeks' gestation, and in the corona radiata and the sensorimotor cortex at term. The signal alteration in the sensory motor cortex might also be due to a more advanced organization of cortical neurons, oligo-dendro-glial cells, synaptic density, and dendrite formation, which would cause decreased interstitial water and a shortening of the T2 relaxation time (Fig. 51.21).[62] Phylogenetically older structures, such as the inferior and superior cerebellar pedunculi and vermis, are myelinated before term, whereas the cerebellar hemispheres

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are myelinated much later.[109] Similarly, the amygdala and hippocampus are partly myelinated at term.

Changes in the volume of myelinated white matter have also been determined by volumetric MRI studies, with myelin comprising less than 5% of total brain volume at 34 weeks' gestation and showing a rapid increase thereafter.[52] The dramatic fivefold increase in myelinated white matter after 34 weeks is of major interest for the understanding of brain injury during this period. This increase in myelin is presumed to be the result of the maturation of oligodendrocytes that have been actively differentiating during the immediately preceding period.

New methods based on "multicomponent relaxation" (MCR) analyses have introduced models that aim to distinguish different pools of water molecules from measured MRI signals, on the basis of the characterization of different T1 and/or T2 properties and of relationships through exchange processes. This approach applied to the developing white matter has recently provided quantitative reports of the spatiotemporal pattern of the myelination progression from the newborn period to childhood.[21]

Microglia and Brain Macrophages

Microglia constitute 5%-15% of the total cerebral cellular population. The prevailing view is that microglial cells are derived from circulating precursor in the blood that originates from bone marrow.[73] During the first trimester of human gestation, penetrating cells have ameboid morphology, with large ovoid cell bodies and no or few short processes, and express macrophage antigenic characteristics, depending on their location and activation state. This macrophage-like morphology evolves into an intermediate and a mature phenotype with a smaller cell body and longer processes. At midgestation, macrophage–microglia populations are mostly detected in white matter pathways, such as the external and internal capsules and corpus callosum. As suggested by rodent studies, these cells could contribute to physiologic developmental remodeling through phagocytosis of cellular fragments produced by neurodevelopmental apoptosis and elimination of exuberant axons and dendrites, as well as synaptic elimination.[75]

In the case of a cerebral lesion, experimental data support a neurotoxic role for the cerebral macrophage through the production of free radicals and nitric oxide. Under pathologic conditions, microglial cells can be transformed into functional brain macrophages with the reappearance of specific cell surface markers.

After development, mature microglia constitute a quiescent cellular population with small cell bodies, numerous long, thin processes, and a possible role in the regulation of the extracellular environment and immune protection of the brain.

Brain Vascular Development

Despite its major role in brain development and functioning, the ontogeny of the brain vasculature has not been the focus of numerous studies. Precise description of the successive steps of brain vessel development and its chronology is still lacking, and little information is available on the molecular mechanisms controlling the development and patterning of brain vessels. Accordingly, the exact timing of the switch from a neuronal anaerobic metabolism to an aerobic one is unknown, although this information might be critically important in understanding the potential consequences of hypoxia or ischemia at successive stages of brain development.

As soon as the neural tube is formed, blood vessels penetrate the primitive neuroepithelium. During migration of neocortical neurons, the density of blood vessels is rather low, with significant distances separating migrating cells from blood vessels. Penetration of vessels in the cerebral mantle is radial and ventriculopetal, starting from the leptomeningeal plexus and directed toward the ventricle.[68,85] No transventricular, paraventricular, or recurrent arteries ending in deep white matter have been identified. Horizontal collaterals progressively appear with a ventriculofugal gradient that reaches white matter at approximately 20 gestational weeks in the human fetus. The chronology of the horizontal ramification of vessels starts at approximately 20 weeks of gestation in the subplate and deep cortical layers, reaches layer III approximately at birth, and is completed (layers II and I) in the postnatal period.

Most neopallial vessels remain devoid of apparent muscularis until the final weeks of gestation.[67] Muscularis development follows a ventriculopetal gradient. The lack of muscular layers around neopallial arteries and the gradient of muscularization of these vessels could explain the high susceptibility of immature arteries to deep white matter and germinal matrix hemorrhages and the lack of vasomotor autoregulation in periventricular areas during a large part of the second half of gestation or the corresponding period in the preterm infant.

Abnormal Brain Development and Disorders

Generally, the different categories of congenital malformations of the CNS reflect the time at which a noxious event disrupted the normal sequence of CNS development rather than the nature of the noxious event itself. Therefore, in this section, the congenital CNS disorders are arranged according to time of onset of the morphologic alteration.

Disorders of Neural Tube Formation and Prosencephalic Development

Craniorachischisis Totalis, Anencephaly, Myeloschisis, Encephalocele, Myelomeningocele, and Occult Dysraphic States

Craniorachischisis totalis is secondary to total failure of neurulation with the formation of a neural platelike structure without overlying tissue. The onset of this malformation is

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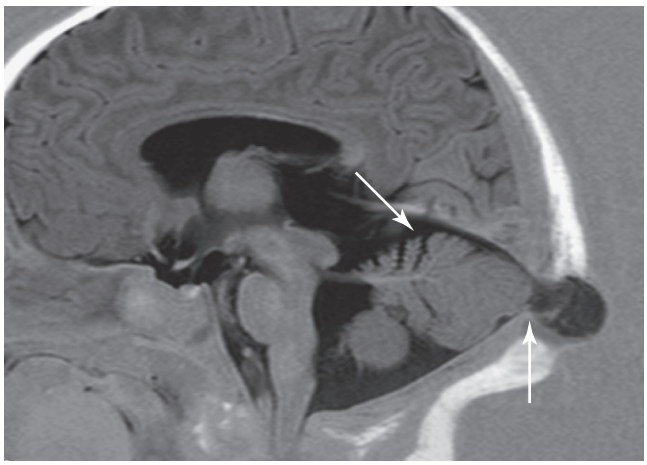
no later than 20-22 days of gestation and most cases are aborted spontaneously during embryonic life.

Anencephaly results from failure of anterior neural tube closure and occurs before 24 days of gestation. It is often associated with polyhydramnios. Approximately three fourths of these infants are stillborn, and the rest die in the neonatal period.

Myeloschisis results from failure of posterior neural tube closure and occurs before 24 days of gestation. A neural platelike structure without overlying tissue replaces large parts of the spinal cord. Most of these infants are stillborn.

Encephalocele is usually considered to be a restricted disorder of anterior neural tube closure, although its precise mechanisms remain unknown. It occurs before 26 days of gestation. Encephalocele is occipital in three fourths of cases, sometimes frontal (where it may protrude into the nasal cavities), and rarely temporal or parietal. Neural tissue (most often from the occipital lobe) in the encephalocele usually displays a normal gyration and underlying white matter and is connected to the brain through a narrow neck (Fig. 51.22). Hydrocephalus is present in approximately half the cases. In cases in which the encephalocele is located in the lower occipital region or upper cervical area, the cerebellum is usually present in the encephalocele, occipital tissue is present in approximately half the cases, and Chiari II malformation is associated (producing Chiari III malformation). Corpus callosum agenesis and anomalies of venous drainage are frequently associated. Encephaloceles are observed in a variety of chromosomal disorders (e.g., trisomies 13 and 18) and syndromes (e.g., Walker-Warburg, Meckel-Gruber, Dandy-Walker, Joubert, Goldenhar-Gorlin, Knobloch, and Robert syndromes).

Myelomeningocele is a restricted disorder of posterior neural tube closure that occurs before 26 days of gestation. (See also Chapter 13 for in utero diagnosis and treatment.) It involves all layers, including the spinal cord, nerve roots, meninges, vertebral bodies, and skin. Approximately three fourths of myelomeningoceles have a lumbar localization (thoracolumbar, lumbar, or lumbosacral). Hydrocephalus is present in 70% of cases, especially when the lumbar region is involved. Chiari II malformation is almost always present in lumbar myelomeningoceles (Fig. 51.23). Location and extent of the lesion determine the clinical symptoms. Thoracic myelomeningoceles have a generally poor prognosis. Varying degrees of paresis (often severe) of the legs and sphincter dysfunction are the major clinical signs. Although myelomeningocele can be observed in chromosomal abnormalities and in single-gene disorders, the vast majority of isolated nonsyndromal cases are thought to be caused by interaction of genetic susceptibility (e.g., specific mutations in the methylenetetrahydrofolate reductase gene) with environmental factors (e.g., valproate exposure or maternal type 1 diabetes mellitus).



• **Fig. 51.22** Occipital encephalocele (*right arrow*) with moderate displacement of the cerebellum (*left arrow*) and dilation of ventricular system, particularly the fourth ventricle. (Image courtesy of J. Delavelle, Department of Radiology, University Hospitals of Geneva, Geneva, Switzerland.)

In the case of a newborn with a myelomeningocele, the clinician is faced with difficult decisions about what to tell the parents and whether to close the spinal defect surgically. Surgery should be undertaken within the first 24 hours after birth to prevent further deterioration of the spinal cord and nerve roots and to prevent infection (meningitis). Fetal and neonatal therapies of myelomeningocele are discussed in Chapters 13 and 58.

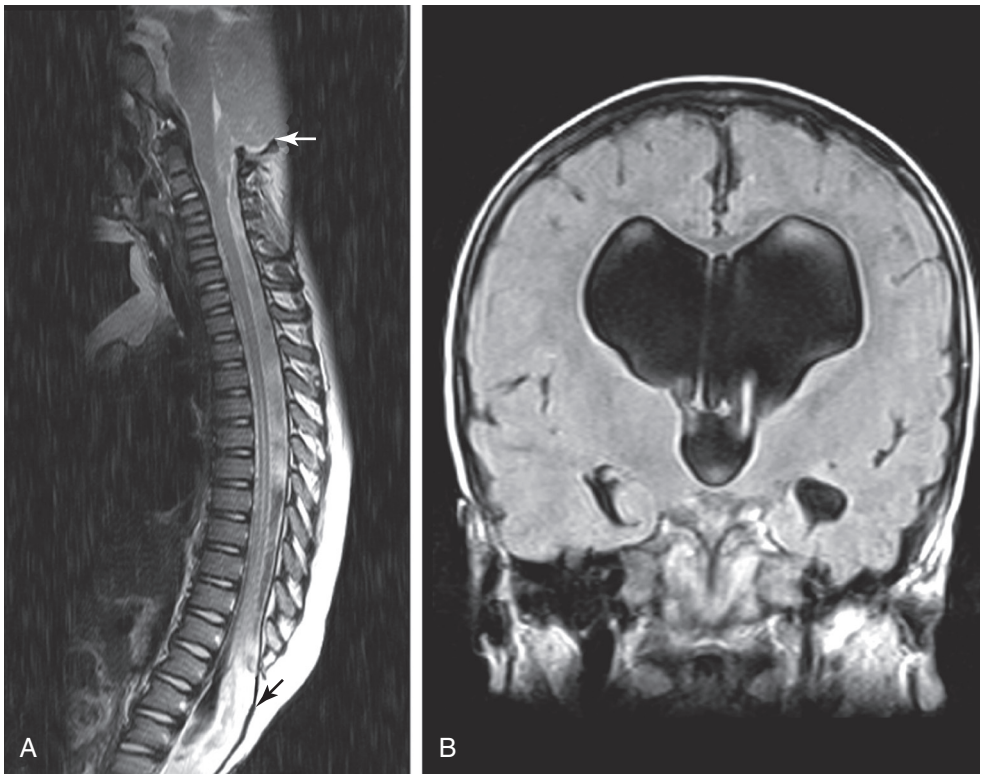
Factors that influence the decision for surgical closure include size and location of the lesion, the technical feasibility of closure, the prognosis for ambulation, the presence or absence of associated abnormalities (hydrocephalus, kyphosis, or other major structural abnormalities), the availability of personnel and a facility to provide adequate care for the infant, and the structure of the infant's family and the attitudes of family members toward the defect and its consequences. The usual decision is to proceed with early surgical closure of the spinal defect, followed by placement of a ventriculoperitoneal shunt if hydrocephalus is present (see Chapter 58). Thereafter, the infant requires long-term neurosurgical, orthopedic, and urologic follow-up to maintain shunt stability; promote ambulation, if possible; and minimize the untoward effects of multiple urinary tract infections.

Occult spinal dysraphisms are considered to be disorders of caudal neural tube formation (secondary neurulation) and include distortion of the spinal cord or roots by fibrous bands and adhesions, intraspinal lipomas, epidermoid cysts, fibrolipomas, subcutaneous lipomas, tethered cord (the most common condition), and diastematomyelia. Clinical symptoms are variable (absent, minimal, moderate, or severe), depending on the degree of neural tissue involvement. Clinical signs include motor and sensory deficits in the lower and sometimes upper (when posterior fossa or cervical cord malformations are associated) limbs, bowel and bladder dysfunction, and ophthalmologic complications (when hydrocephalus is present).

Holoprosencephaly and Agenesis of the Corpus Callosum

(See also Chapter 57.)

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• **Fig. 51.23** **A,** Lumbar myelomeningocele (*black arrow*) with distal displacement of medulla and cerebellum (*white arrow*) (Chiari malformation) with associated hydrocephalus **(B)**. (Image courtesy of J. Delavelle, Department of Radiology, University Hospitals of Geneva, Geneva, Switzerland.)

Holoprosencephaly refers to a large spectrum of brain malformations sharing a common embryologic origin. The frequency of holoprosencephaly is approximately 1 per 10,000 births, including miscarriages and terminations beyond 20 weeks of gestation, although it reaches approximately 40 per 10,000 if embryos are included, suggesting that holoprosencephaly is often accompanied by early embryonic loss.

Holoprosencephaly results from a defect in the cleavage of the prosencephalon in the rostrocaudal axis (between the diencephalon and the telencephalon) and in the transversal axis (division into two hemispheres). Holoprosencephaly can be divided into alobar variants (absence of interhemispheric fissure, corpus callosum, and third ventricle; unique ventricle; fusion of thalami), semilobar variants (presence of the interhemispheric fissure in the caudal part), and lobar variants (presence of a third ventricle; frontal horns partially formed; presence of the corpus callosum; hypoplastic frontal lobes) according to the severity of the malformation (Fig. 51.24). There seems to be a continuum between lobar holoprosencephaly and septo-optic dysplasia (Fig. 51.25). In all forms of holoprosencephaly, the septum pellucidum and the trigone are missing, whereas the olfactory bulbs and tracts are usually hypoplastic or absent (arhinencephaly).

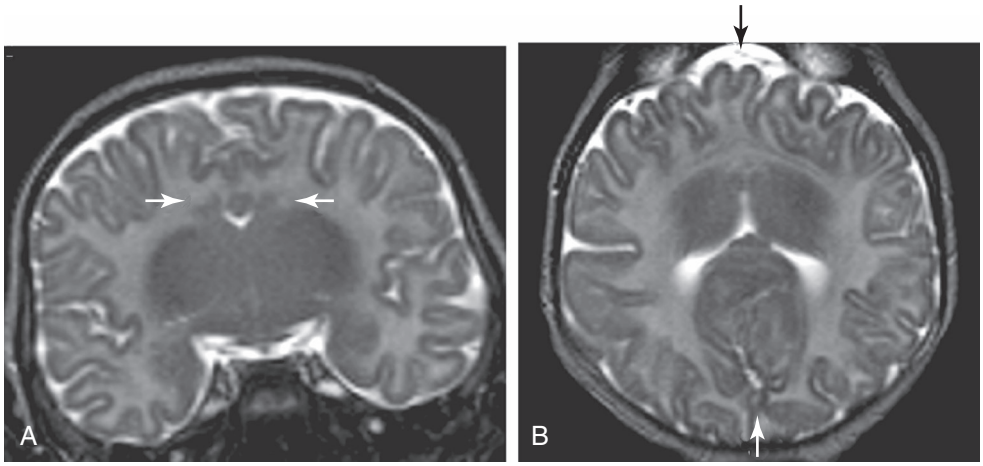
The most severe forms of dysmorphic facies are usually found in alobar holoprosencephalies; however, this is not a general rule, and facial anomalies do not always reflect the severity of the brain malformations. Malformations affecting mainly the cardiac, skeletal, genitourinary, and gastrointestinal organs are frequent. In the most severe cases, neurologic signs are already present in the neonatal period and include apneas, seizures, tonic spasms, lack of neurologic development, and death.

Causes of holoprosencephaly are variable, with genetic, chromosomal, syndromic, and environmental etiologies (see Box 51.2). Most cases are sporadic, although some familial cases have been reported. Several maternal factors, such as maternal diabetes or ethanol consumption, have been associated with holoprosencephaly. Holoprosencephaly is also observed in several syndromes, including the Smith-Lemli-Opitz syndrome, which is characterized by abnormalities in cholesterol metabolism.

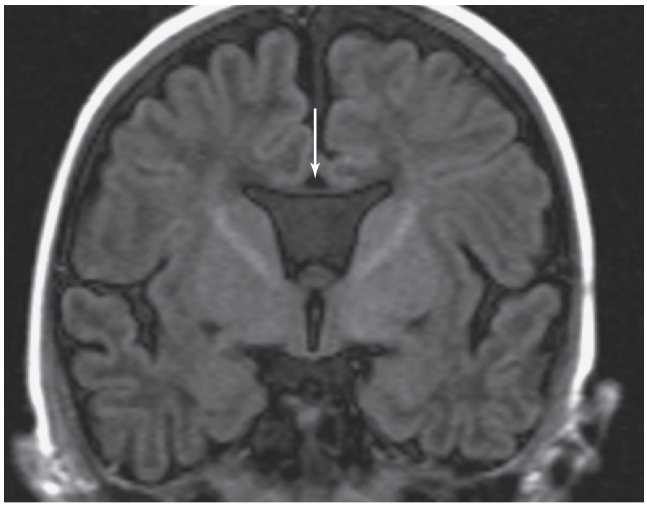
Approximately 12 loci, located on 11 chromosomes, have been identified for holoprosencephaly (HPE1 through HPE12). The genes *SIX3* (coding for a homeoprotein), *SHH* (transduction factor; see earlier), *ZIC2* (zinc finger transcription factor), and *TGIF* (TG-interacting factor, interacting with Smad2) have been identified as corresponding to loci HPE2, HPE3, HPE5, and HPE4, respectively. Among these genes, *SHH* is considered the most important one. Interestingly, abnormalities affecting genes located downstream to *SHH* in the *SHH* pathway also induce holoprosencephaly.

Agenesis of the corpus callosum is a relatively frequent malformation. Its prevalence in the general population is unknown because it might occur in a totally asymptomatic manner. Its prevalence in a population with mental

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• **Fig. 51.24** Semilobar holoprosencephaly **(A)** with absence of corpus callosum, anterior interhemispheric fissure (*black arrow* in **B**), and frontal horns of lateral ventricle (*white arrows*), but with presence of interhemispheric fissure (*white arrow*) in the posterior caudal part **(B)**. (Image courtesy of J. Delavelle, Department of Radiology, University Hospitals of Geneva, Geneva, Switzerland.)



• **Fig. 51.25** Septo-optic dysplasia with agenesis of the corpus callosum and septum pellucidum (*arrow*). (Image courtesy of J. Delavelle, Department of Radiology, University Hospitals of Geneva, Geneva, Switzerland.)

retardation reaches 2%-3%. Agenesis of the corpus callosum represents approximately 50% of the malformations of the midline.

Agenesis of the corpus callosum can be partial (affecting in most cases the posterior portion, except when it is associated with holoprosencephaly) or complete. The lateral ventricles are deformed by the fibers of the cerebral hemispheres that were destined to form the corpus callosum and that form the Probst bundles running longitudinally along the lateral ventricles. The Probst bundles are inconsistently present, and their presence has been considered a sign of better prognosis.

Corpus callosum agenesis can be associated with other brain malformations (e.g., neuronal migration disorders) or with extracerebral malformations. In the presence of associated malformations, the prognosis in agenesis of the corpus callosum is considered poor in most cases. In contrast, the prognosis in isolated agenesis of the corpus callosum (partial or complete) is much more variable, with some cases having a totally normal or near-normal neurologic outcome, some cases with moderate or severe neurologic handicap, and some cases evolving toward death within the first days or months after birth. Because of the relatively low number of reported cases and the relatively short follow-up in many of these cases, providing reliable figures for the neurologic outcome of the isolated malformation remains difficult.

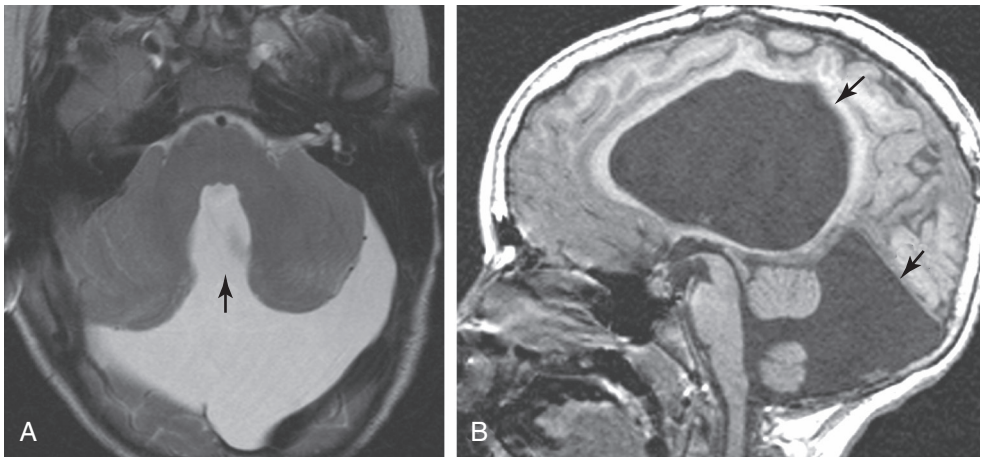
Dandy-Walker Malformation

Although it does not primarily affect the cerebral hemispheres, Dandy-Walker malformation is included in this chapter because it is frequently associated with malformations of the cerebral hemispheres (important for differential diagnosis and for determination of the outcome), it often has neonatal signs, and it is the prototype of cerebellar malformations observed in the neonatal period.

Dandy-Walker malformation results from abnormal development of the rhombencephalon, probably occurring between the 7th and the 10th gestational weeks. Dandy-Walker malformation is observed in approximately 1 per 25,000-30,000 births. This malformation is usually sporadic, with a few reported familial cases. Its etiology is unknown, and environmental factors (e.g., ethanol, warfarin sodium, viral infection) have been reported in a few cases.

Dandy-Walker malformation classically consists of three major abnormalities: (1) enlargement of the posterior fossa and elevation of the tentorium; (2) cystic dilation of the fourth ventricle; and (3) partial or complete agenesis of the corpus callosum. Hydrocephalus is often present but may appear late during pregnancy or even after birth. Other brain malformations (in particular, abnormalities of the midline and neuronal migration disorders) are observed in up to 70% of cases (Fig. 51.26). Extraneurologic malformations involving the heart, kidneys, limbs, and face also occur

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• **Fig. 51.26** Dandy-Walker malformation with enlargement of posterior fossa. **A,** Axial T2-weighted magnetic resonance imaging (MRI) with absence of cerebellar vermis (*arrow*). **B,** Sagittal T1-weighted MRI with elevation of the tentorium (*bottom arrow*) and hydrocephalus (*top arrow*). (Image courtesy of J. Delavelle, Department of Radiology, University Hospitals of Geneva, Geneva, Switzerland.)

frequently. The associated neurologic and extraneurologic abnormalities have a major impact on the prognosis of Dandy-Walker malformation, with better prognosis often (but not always) associated with cases of isolated Dandy-Walker malformation.

As reviewed by Volpe,[119] a prominent posterior fossa cerebrospinal fluid collection can be divided into three categories: (1) enlargement of the fourth ventricle (including Dandy-Walker malformation, other disorders with agenesis of the cerebellar vermis, such as Joubert syndrome and other familial vermian ageneses, and trapped fourth ventricle); (2) enlarged cisterna magna; and (3) arachnoid cyst.

Abnormalities of Neuronal Proliferation

Microcephaly

(See also Chapter 57.)

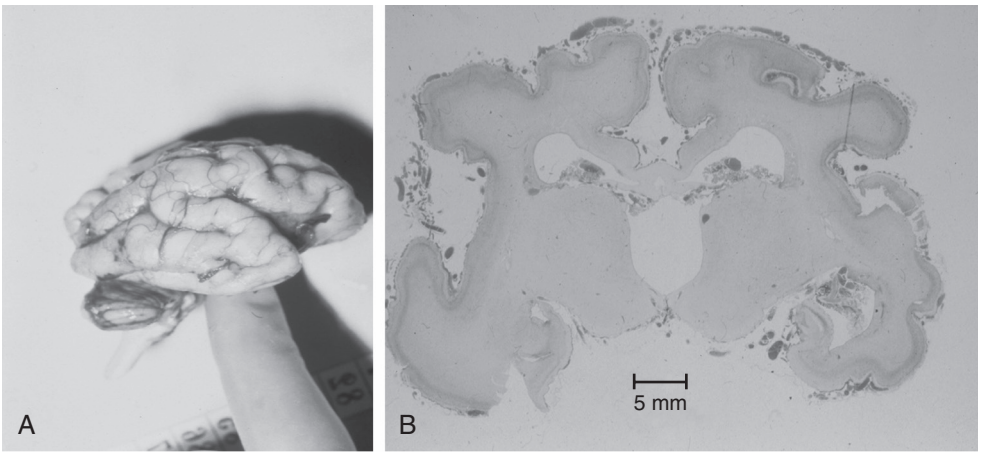
Microcephaly is defined by an occipitofrontal circumference below −2 standard deviations (SD) for age and gender. Severe microcephaly refers to a circumference below −3 SD. Skull growth is determined by brain expansion, which takes place during the normal growth of the brain during pregnancy and infancy. Microcephaly most often occurs because of failure of the brain to grow at a normal rate. Any condition that affects brain growth can cause microcephaly. Primary microcephaly is distinguished from secondarily acquired microcephaly, in which the brain attains the expected size during pregnancy but subsequently fails to grow normally. Microcephaly can be divided into acquired etiologies (e.g., anoxic/ischemic brain damage, severe malnutrition, fetal alcohol syndrome, intrauterine infection, maternal hyperphenylalaninemia and phenylketonuria, anticonvulsant drugs, irradiation) and primary developmental microcephaly (see Box 51.3). The latter can be divided into (1) isolated primary microcephaly; (2) primary microcephaly associated with dwarfism; (3) microcephaly associated with other brain malformations; (4) microcephaly associated with chromosome disorders; (5) microcephaly as part of a syndrome with multiple congenital anomalies (e.g., Neu-Laxova, Rubinstein-Taybi, and Cornelia de Lange syndromes); and (6) microcephaly associated with biochemical disorders.

Primary Microcephalies

Primary microcephalies are a rare (<1/10,000), genetically and clinically heterogeneous group of autosomal recessive disorders that result from insufficient production of mature neurons during neurogenesis (Fig. 51.27). Known causal genes are involved in cell-cycle control (verification of DNA integrity, DNA replication, centrosome duplication, and spindle pole organization). The common pathophysiologic endpoint of these processes is an alteration in the cell-cycle timing and fate determination of neuronal progenitors. This may result in premature neuronal differentiation and a reduced number of neurons, although the exact mechanisms remain unclear for most primary microcephalies studied so far. Alterations to these processes may lead to isolated primary microcephaly (MCPH) or primary microcephaly with dwarfism (Seckel syndrome [SCKL], microcephalic osteodysplastic primordial dwarfism type 2 [MOPD2], and Meier-Gorlin syndrome [MGS]). Causal genes are currently known in about 30% to 50% of patients.

Primary microcephalies are characterized by an occipitofrontal circumference at birth of greater than 2 SD below the mean for gender, age, and ethnicity, and at least 3 SD below the mean at age 6 months. Patients usually exhibit no neurologic anomalies except seizures, mild pyramidal syndrome, and behavioral disturbances. Cognitive impairment ranges from borderline to severe. The reduced brain volume of these patients is usually associated with a simplified gyral pattern, but not with cortical dysgenesis or infratentorial abnormalities. However, some patients exhibit migration or cortical organization defects. The recent discovery of several new genes with mutations causing primary microcephaly has changed the diagnostic approach and highlighted new ways to understand the mechanisms involved in brain growth[57,111]:

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• **Fig. 51.27** Primary microcephaly. **A,** Gross specimen. **B,** Microscopic section. (From Barkovich AJ, et al. Formation, maturation, and disorders of brain neocortex. *AJNR Am J Neuroradiol.* 1992;13:423, with permission.)

1) MCPH can result from mutations in at least nine genes—*MCPH1* (locus MCPH1), *WDR62* (MCPH2), *CDK5RAP2* (MCPH3), *CASC5* (MCPH4), *ASPM* (MCPH5), *CENPJ* (MCPH6/SCKL4), *STIL* (MCPH7), *CEP135* (MCPH8) and *CEP152* (MCPH9/SCKL5).

2) SCKS is caused by mutations in seven genes—*ATR* (SCKL1), *RBBP8* (SCKL2), *CENPJ* (SCKL4/ MCPH6), *CEP152* (SCKL5/ MCPH9), *CEP63* (SCKL6), *NIN* (SCKL7) and *ATRIP* (SCKL8).

3) *PCNT* is the only known *MOPD2* gene.

4) MGS is caused by *ORC1* (MGS1), *ORC4* (MGS2), *ORC6* (MGS3), *CDT1* (MGS4), and *CDC6* (MGS5) mutations. Although MGS has been defined as a syndromal form of primary microcephaly (because of ear and patellar anomalies), some patients have a phenotype that cannot be differentiated from MCPH or SCKS.

Microcephaly With Simplified Gyral Pattern

Microcephaly with simplified gyral pattern are disorders characterized by congenital severe microcephaly, reduced number and shallow appearance of gyri, and normal to thin cortex. Two clinical variants are delineated, one with a normal or thin corpus callosum and one with agenesis of the corpus callosum. Inheritance is autosomal recessive. Primary microcephaly and microcephaly with simplified gyral pattern are likely part of a continuous phenotype, with mild microcephaly with simplified gyral pattern being seen in some patients from families with typical primary microcephaly.[99]

Beyond the three genes described previously, several other loci have been mapped for microcephaly vera or microcephaly with simplified gyral pattern. Approximately 20% of families are still unlinked.

Microlissencephaly

Microlissencephaly disorders have simplified gyri but are distinguished from microcephaly with simplified gyral pattern by a cortex that is thicker than in normal brains. At least four different types have been identified on imaging and clinical grounds: (1) microlissencephaly with thick cortex (MLIS1, or Norman-Roberts syndrome); (2) microlissencephaly with thick cortex, severe brainstem, and cerebellar hypoplasia (MLIS2, or Barth syndrome); (3) microlissencephaly with intermediate cortex and abrupt anteroposterior gradient; and (4) microlissencephaly with mildly to moderately thick (6–8 mm) cortex. Inheritance is autosomal recessive. No gene has been mapped.

Megalencephaly

(See also Chapter 57.)

Megalencephaly (or macrocephaly) corresponds to an excess increase of the brain volume. It can affect one (hemimegalencephaly) or both hemispheres (symmetric megalencephaly).

Symmetric megalencephaly can be associated with other brain malformations, including hydrocephaly, tumors, or gyration abnormalities (e.g., pachygyria). Some cases of symmetric megalencephaly have a familial transmission with different modes of inheritance. Some of these transmissible forms are accompanied by familial mental retardation. Megalencephaly can also be part of a syndrome, such as Weaver and Proteus syndromes. In the absence of associated malformation or familial history, the prognosis of isolated symmetric megalencephaly is difficult to determine because some cases have a normal evolution, whereas mental retardation can be observed in other cases. Symmetric megalencephaly must be differentiated from congenital macrocrania with normal brain volume but increased pericerebral spaces. This entity, sometimes called *external hydrocephaly*, can have a familial transmission (usually autosomal dominant) and often has an excellent neurologic prognosis.

Hemimegalencephaly is characterized by increased growth of one hemisphere or a part of it. This hemisphere is abnormal, with foci of pachygyria, polymicrogyria, heterotopias, and white matter gliosis. The brainstem and the cerebellum can also be affected. Hemimegalencephaly can

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be isolated or associated with hemihypertrophy (as part of a syndrome, such as Protée syndrome, Klippel-Trenaunay-Weber syndrome, or Ito hypomelanosis) or, in some cases, with other malformations as part of Bourneville sclerosis. Hemimegalencephaly is usually sporadic. Its pathophysiologic process remains unclear but could involve genes implicated in brain symmetry, such as *LEFTY1*, *LEFTY2*, or *ZIC3*. Patients with hemimegalencephaly usually display a macrocrania, hemiplegia, severe or intractable epilepsy, and developmental delay that can be severe and exacerbated by the epilepsy.

Disorders of Neuronal Migration

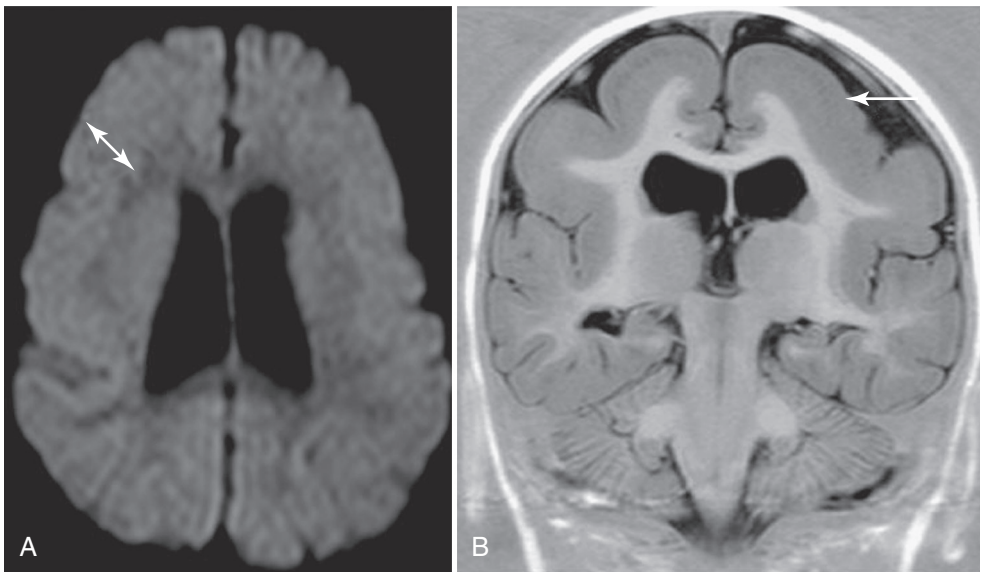
Abnormalities of neuronal migration have been described in a large variety of syndromic, genetic, and environmental conditions (see Box 51.4).

Classic Lissencephalies (Type I Lissencephalies)

Classic lissencephalies form a genetically heterogeneous group with highly variable neuroradiologic signs. Complete agyria (lack of gyration) has to be distinguished from pachygyria (incomplete gyration with a reduced number of flat and broad gyri separated by shallow sulci).[4] The shallow sylvian fissures result in a figure-of-eight appearance of the axial brain sections. Aspect and severity can vary according to the cortical area and generally follow a rostrocaudal gradient. Hippocampus and temporal cortex are often less affected. Dobyns and Truwit have proposed a radiologic score of severity based on the presence and location of agyria, pachygyria, and subcortical band heterotopias.[22] On MRI, the cortex appears more thickened (5–20 mm) in comparison with the normal thickness (2.5–4 mm). The microscopic cytoarchitecture is abnormal (reduction of the number of cortical layers and abnormal neuronal densities), yielding a neuropathologic pattern that is specific for each molecular abnormality described thus far. Lateral ventricles can be enlarged in their posterior portion (colpocephaly). Lissencephaly variants are characterized by major abnormalities of the corpus callosum and of the cerebellum. By definition, head circumference is greater than −3 SD in classic lissencephalies and is less than −3 SD in microlissencephalies (see earlier). The incidence of classic lissencephaly is estimated to be 1.2 cases per 100,000 live births.

LIS1 Mutations (Isolated Lissencephaly and Miller-Dieker Syndrome)

Abnormalities of the *LIS1* gene (platelet-activating factor acetylhydrolase isoform 1B alpha subunit gene, *PAFAH1B1*), which encodes the LIS1 (PAFAH1B1) protein, account for the pathology seen in 40% of patients with lissencephaly. Deletions and nonsense mutations of *LIS1* induce an agyri–pachygyric phenotype with a posteroanterior gradient (posterior being more severe; grade 2–3, according to Dobyns[22]). Missense mutations can induce less severe phenotypes (grade 4, according to Dobyns[22]). The cortex is thickened (10–20 mm), disorganized, and generally composed of four layers: a large molecular layer, a layer of superficial neurons, a paucicellular layer containing myelinated fibers, and a deep layer containing neurons that failed to reach their final target. The 17p13 deletion, which contains the *LIS1* gene, is responsible for Miller-Dieker syndrome, which combines a grade 1 lissencephaly and dysmorphic features (prominent forehead, bitemporal hollowing, micrognathia, malpositioned and/or malformed ears, short nose with upturned nares and low nasal bridge, long and thin upper lip, and late tooth eruption) (Fig. 51.28). Septum calcifications are sometimes observed.



• **Fig. 51.28** Type 1 lissencephaly, or Miller-Dieker syndrome, with **(A)** pachygyric "four-layered" thickened cortex (*arrow*). **B,** Axial diffusion weighted image also characterizes thickened cortex compared with underlying white matter (*arrow*). (Image courtesy of J. Delavelle, Department of Radiology, University Hospitals of Geneva, Geneva, Switzerland.)

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DCX Mutations

The *DCX*, or *XLIS*, gene, encoding doublecortin or DCX and located on the X chromosome, is responsible for the disease in about 40% of patients with lissencephaly and in 85% of patients with subcortical laminar heterotopia.[19,38,91] In boys, mutations induce a classic lissencephaly (grade 1 to grade 4) with a thickened cortex (10–20 mm) and a rostrocaudal gradient (i.e., a gradient reverse to that observed in patients with *LIS1* mutations). Heterozygous girls display a subcortical laminar heterotopia, which consists of a gray matter layer of variable thickness and located between the normally located superficial cortical gray matter and the lateral ventricle ("double cortex"). This double cortex can be limited to the anterior part of the hemispheres. The clinical phenotype in females is variable and ranges from a complete lack of neurologic signs to mental retardation and epilepsy. Female carriers do not have a preferential X chromosome inactivation, and therefore a normal MRI finding does not exclude the presence of a carrier status. Results of neuropathologic studies have shown that brains from patients with *LIS1* mutations exhibited the classic inverted four-layer lissencephalic architecture and unique cytoarchitectural findings, including a roughly ordered six-layer lamination in male patients with *DCX* mutations and lissencephaly.

Tubulin Mutations

Mutations of the alpha 3 tubulin gene *TUBA3* have been described[60] in one male patient and in one female patient. The first patient presented with a classic lissencephaly with a thick disorganized cortex and, clinically, with severe epilepsy, mental retardation, and motor deficits. The second patient exhibited less severe cortical abnormalities with temporal and rolandic pachygyria and abnormal organization of the hippocampus. Both patients had corpus callosum agenesis, inferior vermis abnormalities, and brainstem hypoplasia. The *TUBA3* gene is the human homologue of the murine *Tuba1*, which is expressed during early embryonic development. *Tuba1* mutations impair the ability of the protein to bind guanosine triphosphate (GTP) and to form native heterodimers with b-tubulin, which is very important for microtubule function. Mutations in murine *Tuba1* induce abnormal neuronal migration with disturbances in layers II/III and IV of the visual, auditory, and somatosensory cortices. Mutations in *TUBB2B* and *TUBA1A* genes have been described in patients with lissencephalies.

ARX Mutations

Mutations in the *ARX* (Aristales-related homeobox) gene cause a particular classic X-linked lissencephaly with or without corpus callosum agenesis. The cortex in three layers of *ARX* lissencephalies is less thick (5–10 mm) than in the other classic lissencephalies and the cortical abnormality displays a rostrocaudal gradient (frontal regions being more affected). Female carriers can have isolated or combined corpus callosum agenesis, epilepsy, and/or mental retardation.

X-linked lissencephaly with ambiguous genitalia (XLAG) syndrome is also associated with mutations of the *ARX* gene. Affected boys have lissencephaly, corpus callosum agenesis, facial dysmorphic features, ambiguous genitalia, thermoregulation troubles, and severe epilepsy, which can begin prenatally. *ARX* gene mutations are implicated in a wide spectrum of X-linked disorders, ranging from mild forms of X-linked mental retardation without apparent brain abnormalities to severe lissencephaly. Phenotypes include corpus callosum agenesis with mental retardation, X-linked West syndrome, and Partington syndrome (hand dystony). A phenotype–genotype correlation has not been established.

The *ARX* gene is expressed mainly in telencephalic structures. In adults, *ARX* gene expression becomes restricted to a population of GABAergic neurons.[93] *ARX* seems to be implicated in interneuron migration from the ganglionic eminence (future thalamus); however, its role in cell differentiation and neuronal migration needs to be further clarified.

Lissencephaly With Cerebellar Hypoplasia

Lissencephaly with cerebellar hypoplasia (LCH) is a heterogeneous group of lissencephalies associated with a cerebellar hypoplasia, preferentially of the vermis and hemispheres that display sulci. A temporary classification comprising eight subtypes has been proposed. Although the phenotype of type A LCH is caused by *LIS1* or *DCX* gene mutations, patients with type B LCH have or display *RELN* gene mutations.[47] The latter lissencephaly is more severe than type A LCH but has a rostrocaudal gradient similar to that seen in patients with *DCX* gene mutations. The cortex is quite thick (5–10 mm), and the cerebellum is hypoplastic and smooth.

Other genes responsible for other forms of LCH are unknown. Type C LCH patients usually have a cleft palate. Patients with type D LCH (patients with Barth syndrome) display a neuropathology that includes massive brain and cerebellum and corticospinal tract hypoplasia; their cortex is thick (10–20 mm). Type E LCH is closely similar to type A LCH, but has a marked gradient from frontal agyria to occipital pachygyria. Type F LCH includes a corpus callosum agenesis. Moreover, two new types of LHC have been reported: (1) LCH with corpus callosum agenesis and cerebellar dysplasia and (2) a subtype with cerebellar hypoplasia, Dandy-Walker malformation, and myoclonic epilepsy.

Syndromic Lissencephaly

Two types of lissencephalies are included in the group of syndromic lissencephalies: (1) lissencephalies associated with other neurologic abnormalities (e.g., lissencephaly/pachygyria associated with peripheral demyelinating axonopathy) and (2) lissencephalies observed in syndromes of multiple malformations (in which lissencephaly is generally inconstant and not necessary for diagnosis). Among these syndromes, craniotelencephalic dysplasia (extensive craniosynostosis, microphthalmy, encephalocele), Warburg microsyndrome (corpus callosum agenesis, microphthalmy, microcephaly, cataract, dysmorphic features), Goldenhar

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syndrome (hemifacial microsomia, branchial arch development abnormalities, hemifacial microsomia, microtia), and Baraitser-Winter syndrome (hyperthelorism, ptosis, coloboma, pachygyria/lissencephaly with a frontal predominance) have been reported.

Cobblestone Lissencephalies (Type II Lissencephalies)

Cobblestone lissencephalies are characterized by a pachygyric or granular brain appearance with shallow sulci and hypomyelination with subcortical cystic cavitations. Lateral and third ventricle dilation, which can be severe; vermis hypoplasia; or general cerebellar and brainstem hypoplasia with small pyramids can be observed. Additional brain anomalies, such as hypoplasia/agenesis of corpus callosum, occipital encephalocele, and Dandy-Walker malformation, have been described. Hemispheres can be merged on the median line by gliosis. The cortex is thickened (7–10 mm), disorganized, and invaded by gliovascular fascicles. White matter contains many heterotopic neurons. Typically, the brain is surrounded by a neurofibroglial envelope, which is not observed in classic lissencephalies and which induces a bumpy aspect (hence "cobblestone") rather than smooth aspect to the cortical surface. The cortical development defect occurs most likely between 6 and 24 weeks of gestation. Many neurons migrate too far through a defective glial-limiting membrane into the subpial space, that is, beyond the cortical plate. Cobblestone lissencephalies are linked to abnormal O-glycosylation of alpha dextroglycan. The *POMT1* (9q34 locus) and *POMT2* genes encode the two O-mannosyltransferases proteins 1 and 2 (POMT1, POMT2). POMGnT1 encodes an O-mannosyl-beta-1,2-N-acetylglucosaminyltransferase. The *FCMD* gene on chromosome 9q31 (FKTN) encodes the fukutin protein.

Clinically, cobblestone lissencephalies are observed in three autosomal recessive syndromes that have been shown to display a significant overlap, as indicated by molecular genetic discoveries. The incidence of cobblestone lissencephalies is not known but is most likely around 1 case in 100,000 live births.

Walker-Warburg syndrome is the most common and the most severe form of cobblestone lissencephaly. It is characterized by the combination of brain malformations, such as hydrocephalus, agyria, retinal dysplasia, and sometimes occipital encephalocele (HARD+/−E syndrome) with structural eye abnormalities and muscular dystrophy. Newborns die within the first postnatal months. Eye abnormalities include cataracts, microcornea, and microphthalmia, retinal dysplasia, hypoplasia or atrophy of the optic nerve, and glaucoma. In 30% of the patients, this phenotype is linked to *POMT1* or *POMT2* mutations.

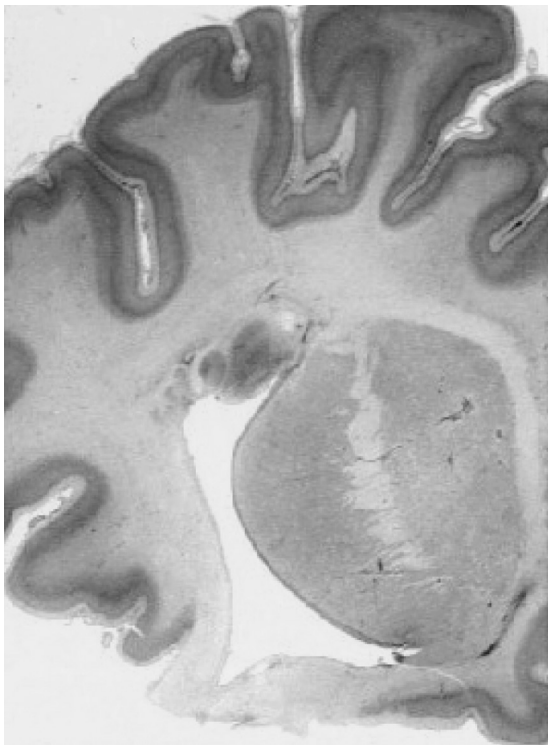
The severity of the brain involvement in Fukuyama syndrome is milder than that in Walker-Warburg syndrome and muscle-eye-brain (MEB) syndrome, and the eyes are only occasionally affected severely. MEB syndrome is characterized by eye involvement (congenital myopia and glaucoma and retinal hypoplasia), mental retardation, and structural brain involvement (pachygyria, flat brainstem, and cerebellar hypoplasia). Fukuyama disease is linked to mutations of the *FCDM* gene. MEB syndrome is linked to *POMGnT1* gene mutations.

Type III Lissencephaly

Type III lissencephaly is characterized by severe microcephaly, agyria, corpus callosum agenesis, cerebellar, basal ganglia hypoplasia, a thin six-layered cortex, and blurred white matter borders. This lissencephaly has been reported in three autosomal recessive syndromes: Neu-Laxova syndrome, Enchara-Razavi-Larroche lissencephaly (microcephaly, corpus callosum agenesis, cystic cerebellum, brain stem hypoplasia, fetal akinesia),[30] and a syndrome reported with lissencephaly, severe microcephaly, corpus callosum agenesia, cerebellar hypoplasia, dysmorphic features, and punctuate epiphysis. Neuropathologic findings are similar in these three entities and thereby suggest that they are either allelic diseases or linked to genes implicated in the same function or pathway.

X-Linked Periventricular Heterotopia

Human X-linked dominant periventricular heterotopia is characterized by neuronal nodules lining the ventricular surface (Fig. 51.29). Hemizygously affected males die within the embryonic period, and affected females have epilepsy, which can be accompanied by other manifestations, such as patent ductus arteriosus and coagulopathy. The gene responsible for this disease, Filamin A gene *FLNA*,[32] encodes an actin-cross-linking phosphoprotein, which transduces



• **Fig. 51.29** Periventricular nodular heterotopias. (From Barkovich AJ, et al. Formation, maturation, and disorders of brain neocortex. *AJNR Am J Neuroradiol.* 1992;13:423, with permission.)

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ligand-receptor binding into actin reorganization. Filamin A is necessary for locomotion of several cell types and is present at high levels in the developing neocortex.

Null mutations in the *FLNA* gene induce, through a loss-of-function mechanism, X-linked periventricular heterotopias and extraneural abnormalities (cardiac valvular anomalies, propensity to premature stroke, small joint hyperextensibility, gut dysmotility, and persistent ductus arteriosus).

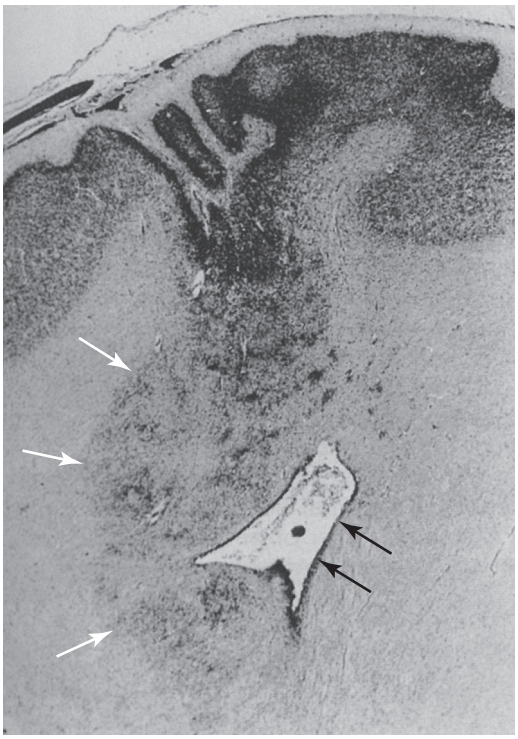
Zellweger Syndrome

Zellweger cerebro-hepato-renal syndrome is a fatal autosomal recessive disease caused by an absence of functional peroxisomes. One hallmark of this human disease is the presence of heterotopic neurons in the neocortex, the cerebellum, and the inferior olivary complex. Patients display severely retarded and/or rapid regression of psychomotor development, facial dysmorphisms, and severe muscular hypotonia; they usually die within the first postnatal months.

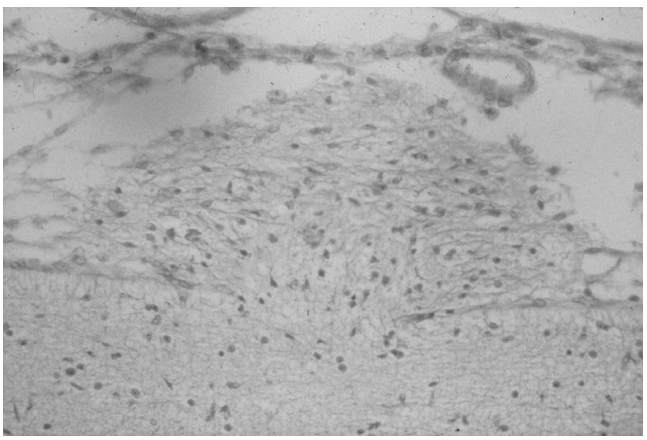
Animal models of this human disease have been produced by inactivation of a gene critically involved in peroxisomal assembly.[40] The analysis of these models showed that (1) the migration defect was partially caused by altered NMDA glutamate receptor-mediated calcium mobilization; (2) this NMDA receptor dysfunction was linked to a deficit in platelet-activating factor (PAF) synthesis; and (3) normal neocortex development requires normal peroxisomal metabolism in the brain and in the liver.

Effects of Environmental Factors on Neuronal Migration

Neuronal migration disorders have been described in humans or in animal models after in utero exposure to several environmental factors, including cytomegalovirus infection or toxoplasmosis (Fig. 51.30) and exposure to ethanol (Fig. 51.31), cocaine, or ionizing radiation.[39] In most cases, the mechanisms by which these factors disturb neuronal migration remain unclear. Cocaine exposure during gestation has been shown to disturb neuronal migration and cortical addressing both in mice and monkeys. Cocaine exposure in mice was also shown to specifically decrease GABA neuron migration from the ganglionic eminence to the cerebral cortex but not to the olfactory bulbs, suggesting a degree of specificity in the effects of cocaine on neuronal migration. In human fetal alcohol syndrome, neuronal molecular ectopias have been described in several cases, although this sign is not restricted to this syndrome (see also Chapter 14). Animal studies have identified abnormalities of radial glia and disturbances of transformation of radial glia into astrocytes.



• **Fig. 51.30** Combined polymicrogyria, white matter cystic lesion (*black arrows*) and white matter heterotopic neurons (*white arrows*) in a case of congenital toxoplasmosis. (From Barkovich AJ, et al. Formation, maturation, and disorders of brain neocortex. *AJNR Am J Neuroradiol.* 1992;13:423, with permission.)



• **Fig. 51.31** Neuronal ectopia in a case of fetal alcohol syndrome. (From Barkovich AJ, et al. Formation, maturation, and disorders of brain neocortex. *AJNR Am J Neuroradiol.* 1992;13:423, with permission.)

Disorders of Central Nervous System Organization and Maturation

Disorders involving subplate neurons, axonal and dendritic growth, synaptogenesis and synaptic stabilization, programmed cell death, and glial proliferation and differentiation are likely to have a major impact on brain functions. Unfortunately, little is known about these disorders, largely because the tools for adequate investigation of these steps are usually not available, even with postmortem tissues. The clinical consequences are rarely obvious in the neonatal period and usually occur later in life. These disorders can be schematically classified into primary (e.g., idiopathic mental retardation, Down syndrome, fragile X syndrome,

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Angelman syndrome, Rett syndrome, neurofibromatosis type I, tuberous sclerosis (Bourneville disease), Coffin-Lowry syndrome, Rubinstein-Taybi syndrome, Duchenne muscular dystrophy, thyroid deficiency, and autism) or potentially acquired (e.g., malnutrition deficiencies or effects of prematurity and related environmental factors, including therapeutic drugs and illicit drugs [e.g., cocaine], acting on the CNS and inducing organizational disorders).[56,119] In most of these disorders, several steps of brain development, such as cortical lamination, dendritic branching and arborization, synaptic contacts, axonal development, and myelination, are affected. For example, in tuberous sclerosis, neuronal proliferation and later glial differentiation and proliferation are disturbed.

Key Points

- Neurulation in which neuroectodermal cells transform into a neural tube begins in gestation week 3, with migration of neocortical neurons occurring between weeks 12 and 24.
- Advanced MRI techniques are able to define cortical folding and the increase in cortical volume accompanying axonal and dendritic growth between approximately 28 and 40 weeks' gestation.
- Following neural migration, astrocyte proliferation supports multiple nutritive and structural functions, whereas oligocyte precursor maturation results in myelination.
- Brain malformations can be caused by environmental factors, genetic factors, or their interaction.
- Brain malformations may result from failed neural tube closure, defects in neural development, or proliferation and disorders of neural migration.

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52

White Matter Damage and Encephalopathy of Prematurity

PETRA S. HÜPPI AND PIERRE GRESSENS

Brain injury in the premature infant is composed of multiple lesions, traditionally described as germinal matrix intraventricular hemorrhage (IVH) with or without parenchymal involvement, posthemorrhagic hydrocephalus (PHH), and periventricular leukomalacia (PVL). These mostly focal lesions mainly affecting white matter have, in recent years, been recognized to be associated with various other brain alterations, such as cortical and subcortical neuronal loss and distant alteration of white matter integrity.

Periventricular leukomalacia has classically been described as a disorder characterized by multifocal areas of necrosis, with formation of cysts in the deep periventricular cerebral white matter, which are often symmetrical and occur adjacent to the lateral ventricles. These focal necrotic lesions correlate well with the development of spastic cerebral palsy in very low birth weight (VLBW) infants. With the advances in neonatal care and the survival at increasingly low gestational ages, a large number of VLBW infants are now seen with mild motor impairment and often considerable cognitive and behavioral deficits,[91,147] which may relate to a more diffuse injury to the developing brain.

This chapter presents the current concepts of injury to the immature brain, which has been termed *encephalopathy of prematurity*, summarizing the old and new neuropathologic findings, mechanisms of pathogenesis through animal models,[84] and the characteristics of this type of lesions in modern neuroimaging.

Neuropathology of White Matter Injury

Historical View

Congenital encephalomyelitis was the term first used by Virchow in 1867 to describe a disease in newborns who demonstrated pale softened zones of degeneration within the periventricular white matter at autopsy. Microscopically, these lesions were characterized by glial hyperplasia, with the presence of foamy macrophages and signs of tissue destruction with necrosis. Interestingly, Virchow related the disease to acute infection, as many of the cases were seen in infants of infected mothers.[155] Clinically, he suggested that these lesions might be related to a disease described earlier by Little,[99] in which the patients suffered from spasmodic limb contractures, diplegia, and mental retardation, occasionally with an additional epileptic condition. Parrot, in 1873, first linked the pathologic entity to premature birth and proposed that the lesions were caused by a particular vulnerability of the immature white matter, as a result of nutritional and circulatory disturbances resulting in infarction.[124] Much later, Rydberg again proposed a hemodynamic etiology with a reduction of cerebral blood flow to the vulnerable regions of the immature white matter.[136] Banker and Larroche, in 1962, first introduced the term *periventricular leukomalacia* to define this characteristic lesion that they found in 20% of autopsies of infants deceased prior to 1 month of age and described the macroscopic and microscopic neuropathology in more detail.[12]

Periventricular Leukomalacia

Macroscopic Neuropathology

The topography of the lesions is uniform, primarily affecting the white matter in a zone within the subcallosal, superior fronto-occipital, and superior longitudinal fasciculi; the external and internal border zones of the temporal and occipital horns of the lateral ventricles; and some parts of the corona radiata.[55] These areas appear pale, usually bilateral, but without definite symmetry (Fig. 52.1). Although not unanimously accepted, it has been noted that the anatomic distribution of PVL correlates with the development of perforating medullary arteries and areas that represent the arterial borders or end zones, that arise between ventriculopetal and ventriculofugal arteries within the deep white matter (Fig. 52.2).[75] Immunohistochemical studies further confirm low vessel density in the deep white matter between 28-36 weeks' gestation, whereas in the subcortical white matter, the vessel density is low between 16 and 24 weeks and thereafter increases (Fig. 52.3).[114]

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Abstract

This chapter presents the current concepts of injury to the immature brain, which has been termed *encephalopathy of prematurity*, and summarizes the old and new neuropathologic findings, mechanisms of pathogenesis through animal models, and the characteristics of this type of lesions in preterm infants with modern neuroimaging. Brain injury in the premature infant is composed of multiple lesions, traditionally described as germinal matrix intraventricular hemorrhage (IVH) with or without parenchymal involvement, posthemorrhagic hydrocephalus (PHH), and periventricular leukomalacia (PVL). These mostly focal lesions mainly affecting white matter have, in recent years, been recognized to be associated with various other brain alterations, such as cortical and subcortical neuronal loss and distant alteration of white matter integrity. It is, therefore, no longer a static brain lesion but very much a dynamically evolving injury with modification of the subsequent developmental steps all the way through to adulthood.

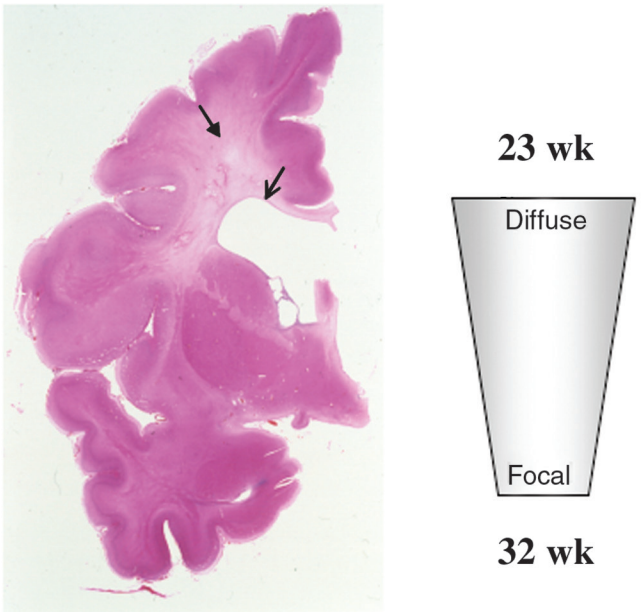
Keywords

encephalopathy of prematurity
periventricular leukomalacia
intraventricular hemorrhage
pathogenesis
neuroimaging

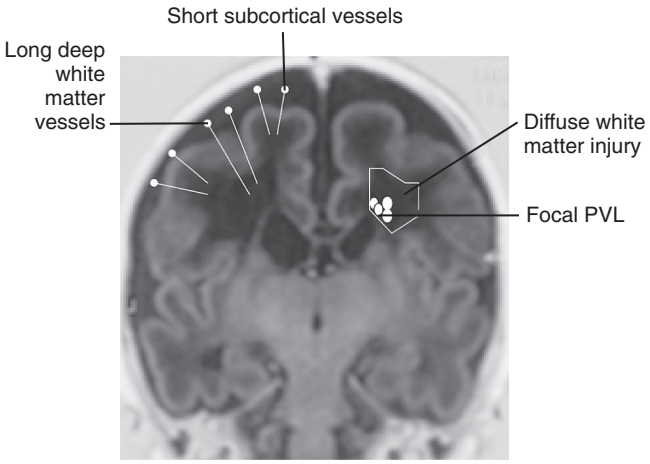
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Microscopic Neuropathology

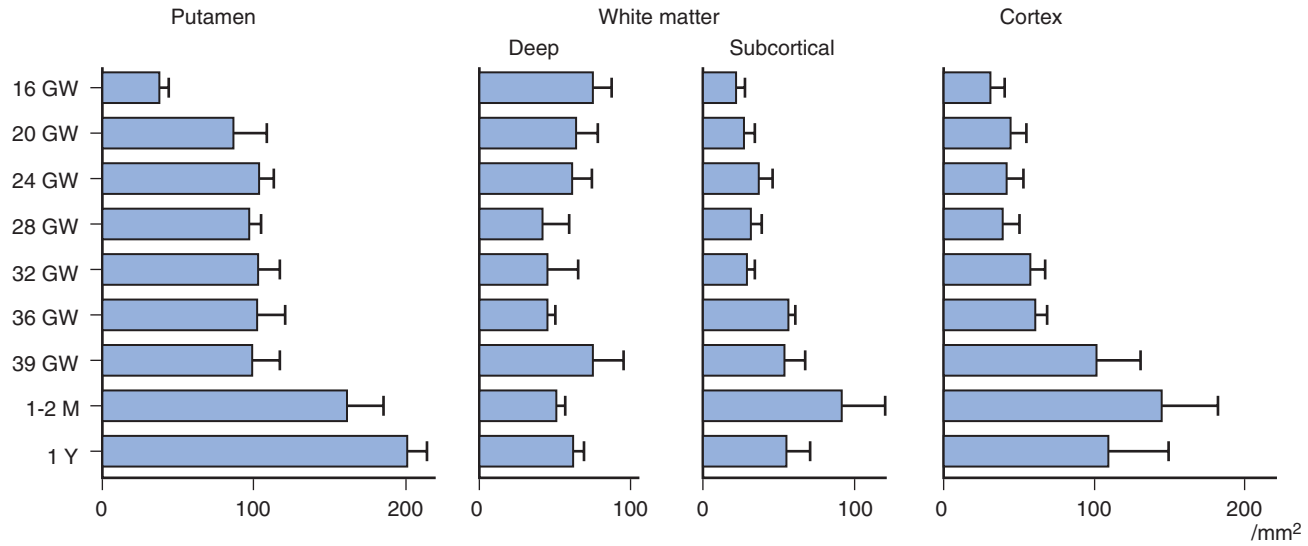
The earliest recorded changes are of coagulation necrosis of all cellular elements, with loss of cytoarchitecture and tissue vacuolation.[34] Axonal swelling and intense activated microglial reactivity and proliferation have been observed as early as 3 hours after an insult.[35,109] In addition, in the periphery of these focal lesions, a marked astrocytic and vascular endothelial hyperplasia characterize the brain tissue reaction at the end of the first week. After 1-2 weeks, macrophage activity, with characteristic lipid-laden macrophages, is predominant over the astrocytic reactivity, with progressive cavitation of the tissue and cyst formation thereafter. During subacute and chronic stages of PVL, swollen axons calcify, accumulate iron, and degenerate particularly at the periphery of the injured zone.[146] Additional minor changes are also found within gray matter, with some diffuse neuronal loss especially in the lower cortical layers, the hippocampus, and the cerebellar Purkinje cell layer. Many conventional neuropathology studies subsequently



• **Fig. 52.1** Neuropathology showing periventricular lesions primarily affecting the white matter and characterized by pale softened zones of degeneration (hematoxylin preparation) (*closed arrow*) and thinning of the corpus callosum with ventriculomegaly (*open arrow*). Lesions detected in infants with very low gestational age at birth tend to be diffuse, with more focal cystic lesions in infants with higher gestational age at birth.



• **Fig. 52.2** Schematic representation of vascular supply characterized by short subcortical end-arteries and long deep end-arteries and their relation to the diffuse and focal component of immature white matter injury. (From Rorke LB. Anatomical features of the developing brain implicated in pathogenesis of hypoxic-ischemic injury. *Brain Pathol.* 1992;2:211.)



• **Fig. 52.3** Developmental changes in vessel density in the human brain illustrate decrease in vessel density in long deep white matter arteries between 28 and 36 weeks. Low density of subcortical end arteries below 32 weeks. (From Miyawaki T, Matsui K, Takashima S. Developmental characteristics of vessel density in the human fetal and infant brains. *Early Hum Dev.* 1998;53(1):65-72.)

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have noted widespread diffuse central cerebral white matter astrocytosis, often with abnormal glial cells,[95] which were termed *perinatal telencephalic leukoencephalopathy*. On the basis of these studies, Leviton and Gilles described, for the first time, a differentiation between focal and diffuse white matter damage.[94]

New Neuropathologic Insights

This diffuse white matter damage is macroscopically characterized by a paucity of white matter; thinning of the corpus callosum; ventriculomegaly and delayed myelination in the later stages; and, as shown in recent studies, reduction of thalamic, striatal, and hippocampal size and cortical gray matter.[84] With the use of immunocytochemical techniques, the assessment of autopsy tissue has allowed for further localization of cell-specific injury in white matter damage. The deep periventricular white matter is prone to showing focal necrosis regionally, consistent with the presumed vascular end zones/border zones, whereas in the peripheral white matter, diffuse injury could be characterized by preferential death or injury of late oligodendrocyte progenitors and immature oligodendrocytes (preoligodendrocytes [pre-OLs]; see Chapter 51).[9] This leads to a proliferative response of early pre-OLs, but their differentiation into mature cells remains partly arrested.[137,140] Postmortem data support the hypothesis that in very preterm infants, blockade of maturation of oligodendrocytes, rather than their death, is the key neuropathologic hallmark in diffuse white matter damage.[49,154] In addition, more recent neuropathologic studies on human preterm material have shown the extensive involvement of axonal damage,[63] especially thalamocortical fibers and damage to white matter neuronal populations (GABAergic interneurons),[85,86,135] and damage to the cerebellar white matter.[83]

These new neuropathologic features lead to the well-discussed hypothesis that the encephalopathy of the preterm infant is an amalgam of damage and disrupting development.[32,158]

Vulnerability of Oligodendroglia Cell Line

Several lines of evidence implicate damage to immature oligodendrocytes during a specific window of vulnerability as a significant underlying factor in the pathogenesis of PVL (see section on Models of Encephalopathy of Prematurity below). Oligodendrocyte progenitor cells proliferate and die by apoptosis (programmed cell death) (see Chapter 51), regulated by trophic factors, such as platelet-derived growth factor and insulin-like growth factor.[13] The activation of cytokine receptors on the surface of oligodendrocytes can lead to the death or maturation blockade of these cells. Studies in vitro have shown that the inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN- gamma) are toxic to cultured oligodendrocyte progenitor cells.[5] Selective injury to oligodendrocytes is mediated by induction of "death" receptors, such as Fas on the surface of oligodendrocytes. Direct axonal contact appears to be another important factor for the survival and maturation of oligodendrocytes.[24] Oligodendrocytes are further susceptible to oxidative damage mediated by free radicals, such as reactive oxygen and nitrogen species, and as a consequence of the depletion of the main antioxidant, glutathione are subject to epigenetic alterations.[8,115] Injury-induced swelling and disruption to axons within white matter leads to locally elevated glutamate, which also induces oligodendrocyte cell death and/or injury. Glutamate toxicity depends on the maturational stage of the oligodendrocyte and is mediated via the alpha-3-amin o-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and potentially through N-methyl-D-aspartate (NMDA) receptors.[36,80]

Experimental data show, however, an important increase in NG2 (high-molecular-weight, integral membrane chondroitin sulfate proteoglycan)–positive oligodendrocyte progenitor cells within the area of the injury.[138,140] The role of this increase in NG2 cells is currently unknown, but this population is distinct from neurons, oligodendrocytes, astrocytes, and microglia. This cell population could comprise multipotent cells capable of differentiating into any other type of cells and playing a role in axonal growth and myelination and in regeneration after injury with functional integration in neural circuitry.[57]

Microglial Activity

Specific immunocytochemical markers (e.g., CD68) have identified a marked increase of activated microglia in diffuse white matter injury.[154] Microglia are already widely dispersed throughout the immature white matter by 22 weeks' gestation. These cells are fully capable of producing potentially toxic inflammatory mediators, free radicals, and reactive oxygen intermediates.[131] The phagocytic activity of microglia and their capacity for oxidative mediated injury are potently enhanced by inflammatory mediators (IFN-gamma, TNF-alpha, interleukin-beta [IL-beta], and bacterial lipopolysaccharide [LPS]).[1,60] Studies of pre-OLs of the same maturational stage as those populated in the immature white matter of the human premature infant show that cells are exquisitely vulnerable to attack by reactive oxygen species and reactive nitrogen species produced by activated microglia.[143] The presence of activated microglia inducing cell death in immature white matter, both in pre-OLs and in astrocytes, has been widely confirmed.[40,145] So far, it also seems that microglia and resident mononuclear phagocytes are the primary sources for the proinflammatory cytokines in PVL brains.[48]

More recently, a translational experimental study has linked genetic polymorphisms controlling proinflammatory proteins in microglia to the microstructural changes in the brain of preterm infants.[89]

Neuronal/Axonal Damage

Previous studies have performed indirect assessment of axonal damage in classic PVL by immunostaining for beta-amyloid precursor protein, a neuronoaxonal protein. Immunostaining of damaged axons was found to be

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predominant in the acute phase of PVL and was no longer detectable in the chronic stage.[109] Swollen axons calcify (probably owing to glutamatergic overactivation), accumulate iron, and degenerate; this has been shown to occur without overt coagulation necrosis of all tissue components.[65] Axons from the corticospinal tract (CST), thalamocortical fibers, optic radiation, superior occipitofrontal fasciculus, and superior longitudinal fasciculus may be affected and result in deficits in motor, sensory, visual, and higher cortical functions. Thalamocortical projections that course through the white matter develop prior to the functional development of cortical neurons. Therefore the ensuing disruption to these circuits and to the subcortical plate may affect not only the function but also the density, survival, and organization of the cortical neurons and the cortex itself[74,88] (see section on Subplate Damage).

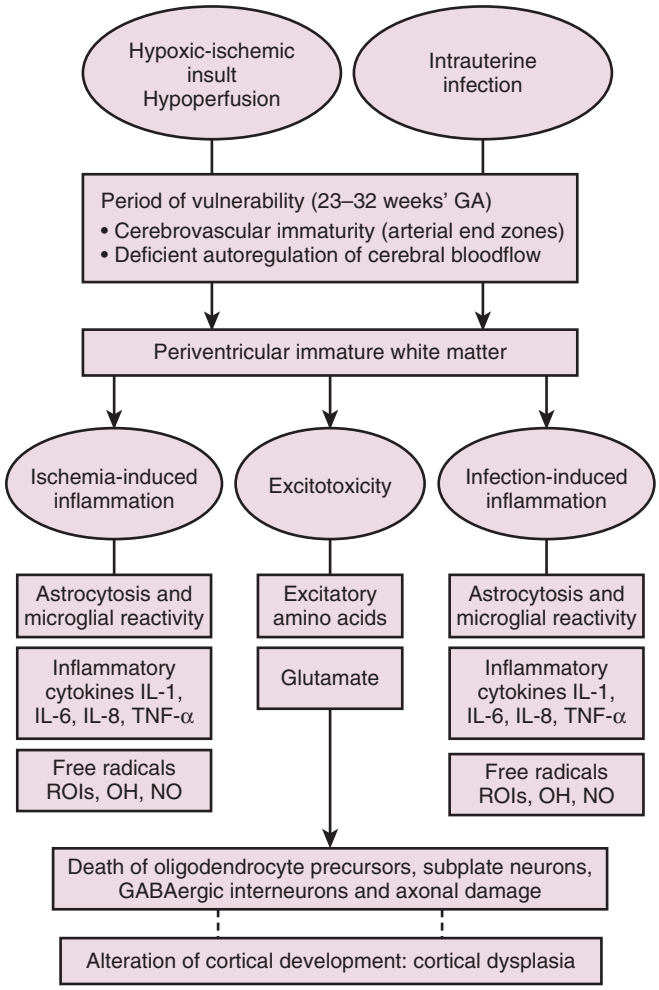
In addition, there is evidence for cell death of the progenitor cells, not of the neural stem cells in the subventricular zone after hypoxia–ischemia.[50] These destructive effects occur in parallel with potential trophic reactions, such as the proliferation of potentially pluripotent progenitor cells, also called *polydendrocytes* in the area of injury.[140] These cells are known to differentiate into oligodendrocytes and, to a lesser extent, into gray matter astrocytes and potentially even neurons.[120]

Studies have also suggested that preterm delivery decreases the number of interneurons in some cortical areas, indicating that the production, migration, and/or survival of interneurons is impaired.[25] Wnt signaling has been shown to be implicated in this neuronal migration arrest and responsible for subsequent alteration of circuit formation, relevant for both somatosensory as well as social behavior development.[20] Activated microglia in white matter could contribute to impairment of migration and/or survival of interneurons.

Subplate Damage

Damage to the early developing subplate neurons, with their critical role for the organization of the cortical plate (see Chapter 51), has long been postulated as a possible mechanism by which injury to the immature brain results in long-lasting motor and cognitive deficits.[156] McQuillen et al.[107] were able to show specific cell death in subplate neurons after hypoxia–ischemia in very immature animals. Lack of guidance for the thalamocortical connections ensued by the loss of subplate neurons may represent one of the major developmental disturbances after injury to the immature brain.[87] A recent model of induced mild apoptosis in cortical layer IV resulted in cortical anisotropy changes similar to those in preterm infants, hypomyelination in the subcortical white matter, and activated microglia, which indicates that subtle neuronal cell death can trigger white matter changes.[129]

The current concept of pathogenesis of encephalopathy of prematurity is based on the combination of destructive and developmental disturbances, which are presented schematically in Fig. 52.4.

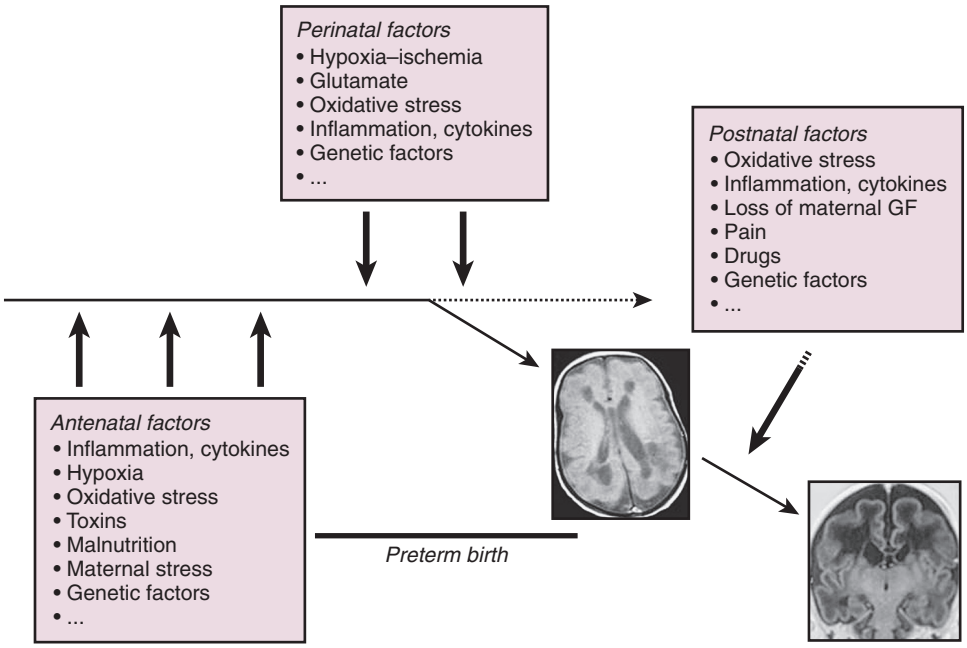


• **Fig. 52.4** Schematic representation of the current main pathogenetic factors involved in immature white matter injury. (Adapted from Rezaie P, Dean A. Periventricular leukomalacia, inflammation and white matter lesions within the developing nervous system. *Neuropathology.* 2002;22:106-132; and Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol.* 2009;8:110-124.)

Models of Encephalopathy of Prematurity: Implications for Pathogenesis

As mentioned, the etiology of white matter injury and encephalopathy of prematurity in human neonates has been widely described as multifactorial rather than being linked solely to cardiovascular instability and hypoxia–ischemia. The many preconception, prenatal, perinatal, and postnatal factors potentially implicated in the pathophysiology of these lesions include hypoxia–ischemia and hypercapnia, maternal infection with overproduction of cytokines and other proinflammatory agents, endocrine imbalances, genetic factors, growth factor deficiency, abnormal competition for growth factors, overproduction of free oxygen radicals, exposure to toxins, maternal stress, and malnutrition. Although some of these potentially noxious factors may suffice to permanently injure the developing brain, some researchers have developed a two-hit hypothesis, which

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• **Fig. 52.5** Schematic representation of the multiple-hit hypothesis, in which a combination of two or more environmental or genetic factors occurring during the prenatal, perinatal, or postnatal period induces or modulates brain lesions. GF, growth factors.

suggests that early exposures increase the susceptibility of the brain to subsequent insults (Fig. 52.5).

The development and characterization of distinct, yet complementary, animal models should help to unravel the complex cellular and molecular pathophysiologic mechanisms underlying the occurrence of perinatal white matter lesions and encephalopathy of prematurity. In available animal models or in vitro paradigms, the insults most often used to induce white matter damage or oligodendrocyte cell death, respectively, are generally hypoxia, hypoxia–ischemia, infection, inflammatory factors, oxidative stress, or excitotoxic agents. The relevance of white matter damage produced in these animal models to human white matter injury is largely based on neuropathologic data, although some studies are also based on magnetic resonance imaging (MRI) parameters or on neurologic and behavioral deficits.[37]

The following section focuses on the most studied models of perinatal white matter damage, highlighting their major contributions to the understanding of the pathophysiology of these lesions. The interested reader can find more information and a more comprehensive bibliography in published reviews on this topic.[61,111,152]

Hypoperfusion and Hypoxia–Ischemia

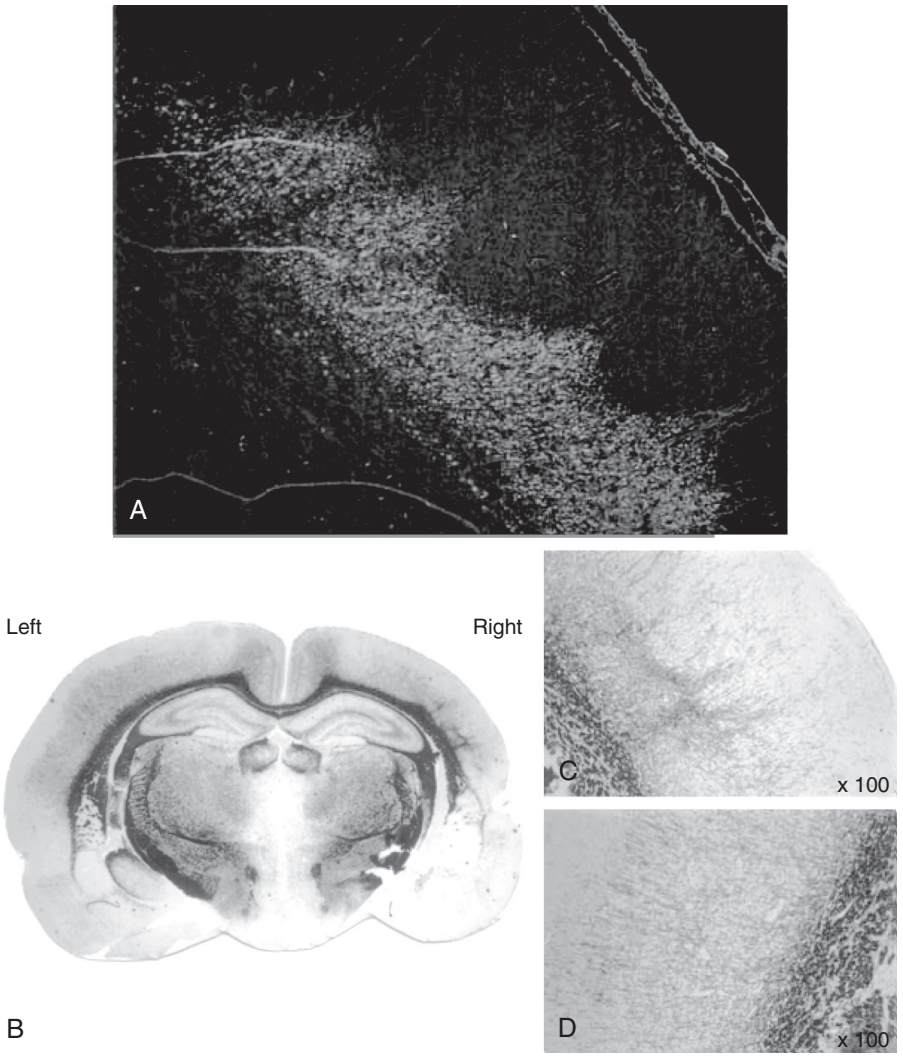
Hypoxic–ischemic or hypoperfusion insults have been used in a large variety of neonatal species, including rats, mice, rabbits, pigs, and dogs. In most cases, these insults produce specific gray matter damage (mimicking lesions observed in human full-term infants), which has been the focus of most of these studies, whereas observed white matter damage is generally considered an extension of gray matter damage in the most severe cases. However, notable exceptions highlight some potentially important features of perinatal white matter damage.

In canine pups, hypoxic–ischemic insult by bilateral carotid ligation selectively induces white matter damage mimicking human PVL.[164] This selective vulnerability of white matter could underlie a genetic predisposition of the dog to white matter hypoxic–ischemic damage. Modern tools of genomics could unravel important genes involved in the pathophysiology of perinatal white matter damage.

In rats, the classic Rice-Vannucci model performed on postnatal day 7 or 9 predominantly leads to gray matter lesions. However, analyses have shown involvement of the periventricular white matter with involvement of immature oligodendroglial and progenitor cells.[53,132,141] More important, adaptation of this paradigm to more immature newborn rats (postnatal days 1 or 3) has allowed for production of important lesions in the periventricular white matter with relative sparing of the classic intracortical injuries (Fig. 52.6).[23,107,138] These studies have also highlighted the specific involvement of subplate neurons in brain damage. Altogether, these data obtained in newborn rats further support the notion of an ontogenic window of white matter sensitivity and subplate vulnerability to such insults as hypoxia–ischemia.

Asphyxia of sheep fetuses (around 65% of gestation) has been shown to induce periventricular (focal and diffuse) and subcortical (diffuse) white matter disease, accompanied by acute astrocyte and oligodendrocyte loss, as well as marked reactive microgliosis.[104] These studies support the concept of the association of focal (e.g., cystic lesions) and diffuse (e.g., diffuse microglial activation) white matter lesions,

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• **Fig. 52.6** Pattern of injury after hypoxic–ischemic injury in the postnatal day 3 (P3) rat brain. **A,** Degenerating neurons 24 hours after hypoxic–ischemic insult at P3 stained with Fluoro-Jade. Ipsilateral brain with severe damage: A columnar aspect of positive cells is present with confluence of positive cells in the deep cortical layers (magnification 100×). The outer cortical layers remained unaffected. **B,** Myelin basic protein immunostaining of the brain at P21 after hypoxic–ischemic injury at P3. Coronal section of brain at the level of the dorsal hippocampus (10×): a reduction of the cortical and myelinated areas in the ipsilateral right hemisphere extending from the cingulum to the rhinal sulcus can be seen. **C, D,** At 100× magnification, the alteration of the myelin pattern in the deep cortical layers is noticed in the ipsilateral right cortex (**C**) when compared with the left normal cortex (**D**).

the pathophysiology of which is potentially distinct. Furthermore, it has been shown by using microdialysis that white matter glutamate levels were significantly increased after asphyxia, supporting a role of excitotoxicity in the pathogenesis of such white matter lesions (see section on Excitotoxicity).[101]

Exposure of pregnant rats[16] or postnatal murine pups[149] to hypoxia induces pathologic changes in the periventricular white matter that are reminiscent of human periventricular leukomalacia, with inflammation, astrogliosis, and myelination delay in the prenatal model, and white matter atrophy, ventriculomegaly, and alteration of synaptic maturation in the postnatal paradigm. Although the initial insult is pure hypoxia, the observed effects are likely the result of the combination of different mechanisms, such as hypoperfusion, ischemia, inflammation, and/or oxidative stress induced by protracted hypoxia and the subsequent reoxygenation phase.

Infection and Inflammation

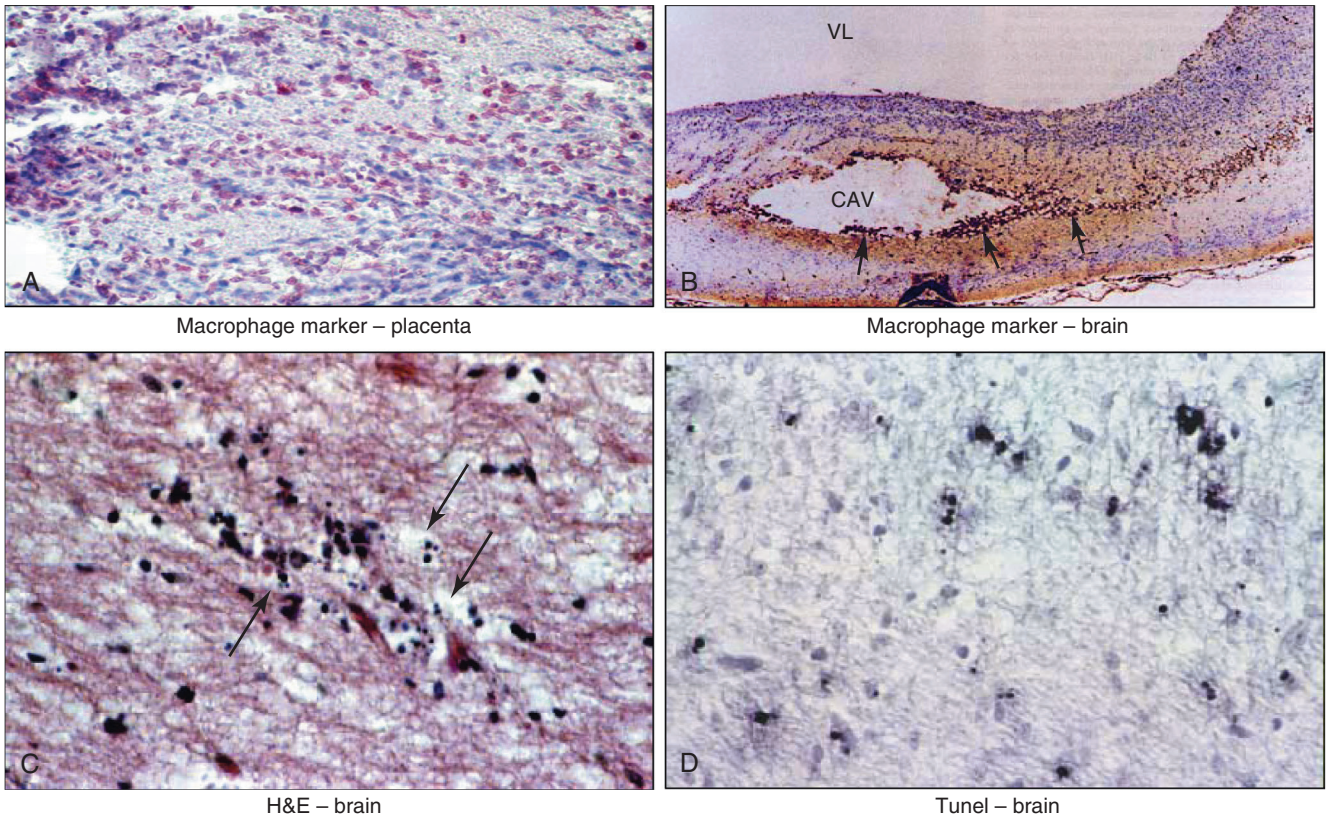
Systemic administration of LPS to immature cats, dogs, or rabbits induces white matter lesions.[4,54] Systemic administration of LPS can induce marked systemic inflammation and immune changes in the central nervous system, such as increased expression of CD14. Furthermore, high doses of LPS can induce hypotension, hypoglycemia, hyperthermia, and lactic acidosis, all potential factors predisposing to

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brain damage. However, low doses of LPS, which do not induce significant hypotension, were also shown to induce white matter damage in fetal sheep.[61,103] In fetal sheep, the comparison of white matter damage induced by cord occlusion and by LPS injection revealed distinct patterns of microglia–macrophage activation, suggesting separate or partly separate underlying mechanisms.[103] However, systemic administration of LPS to newborn rats failed to induce detectable white matter lesions, although increased cytokine production and microglial activation were observed in white matter.[22,47] These data suggest that species differences that might be linked to species-related genetic susceptibility of the developing white matter to infectious–inflammatory factors. Interestingly, in vitro studies have shown that macrophages are necessary for LPS to induce pre-OL cell death.

Live infectious agents have also been used by a few research groups to produce models of white matter lesions. In pregnant rabbits, ascending intrauterine infection with *Escherichia coli* (*E. coli*) caused focal white matter damage in 6% of live fetuses,[163] whereas direct inoculation of *E. coli* in the uterine cavity combined with early antibiotics produced focal white matter cysts in about 20% of live fetuses and diffuse white matter cell death in almost all live fetuses (Fig. 52.7).[33] Cystic lesions are accompanied by macrophage–microglia activation and reactive astrogliosis, whereas diffuse white matter cell death does not induce such glial responses. These results suggest that these two types of brain damage have distinct pathophysiologic mechanisms.

In addition, a study has shown that infection of pregnant mice with *Ureaplasma parvum*, an organism rather frequently isolated in chorioamnionitis, induces central microgliosis and disrupted brain development, as detected by decreased numbers of calbindin-positive and calretinin-positive neurons in the neocortex, as well as myelination defect in the periventricular white matter.[121]



• **Fig. 52.7** Intrauterine infection with *Escherichia coli* in pregnant rabbits induces a combination of placental and brain abnormalities. **A,** Macrophage activation is observed in all placentas. The numerous red blood cells correspond to activated macrophages labeled with a specific antigen. **B,** Focal cystic periventricular white matter lesions with macrophage activation are detected in some fetuses. Cells identified by *arrows* correspond to activated macrophages/microglia labeled with a specific antigen. CAV, cystic lesion; VL, lateral ventricle. **C** and **D,** Diffuse white matter cell death without detectable inflammatory response is observed in all fetuses on hematoxylin and eosin stained sections. (**C,** *Arrows* points to examples of apoptotic nuclei in the periventricular white matter) and on Tunel (a marker of fragmented DNA and of accompanying cell death) stained sections. **D,** Purple blue nuclei correspond to diffusely distributed dying white matter cells). (**A,** from Debillon T, et al. Intrauterine infection induces programmed cell death in periventricular white matter. *Pediatr Res.* 2000;47:736-42; **B-D,** from Debillon T, et al. Patterns of cerebral inflammatory response in a rabbit model of intrauterine infection-mediated brain lesion. *Brain Res Dev Brain Res.* 2003;145:39-48.)

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Intrauterine inoculation of Border disease virus to pregnant sheep induces decreased expression of white matter molecules, including myelin basic protein in the fetuses.[3] However, the virus also infects the thyroid and the pituitary gland, raising the question of the precise etiology of the white matter damage (low thyroid hormones versus infectious–inflammatory insult).

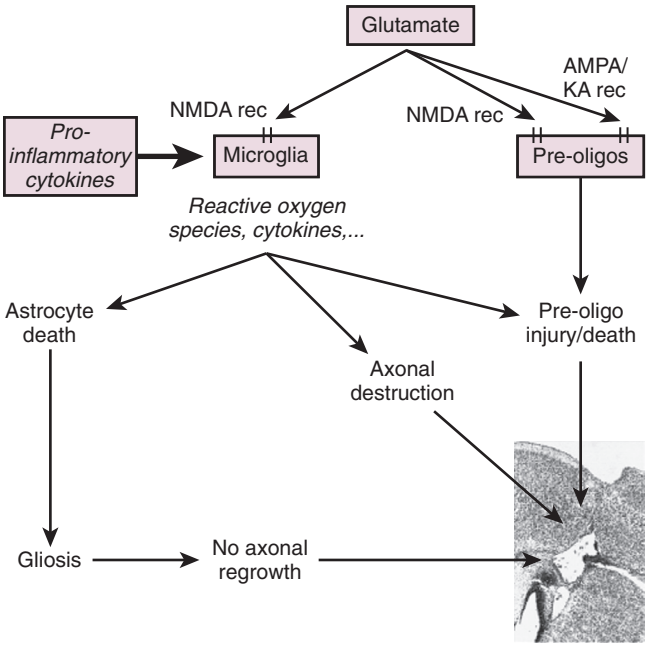
Exposure of newborn mice to low doses of systemic IL-1-beta induces a moderate and transient inflammatory response during the neonatal period that is sufficient to disrupt oligodendrocyte maturation, myelin formation, and axonal development.[49] These white matter abnormalities are moderate during the developmental period but do persist until adulthood. They lead to permanent deficiencies in cognition tests. The underlying molecular mechanisms include blockade of microglial activation, oligodendrocyte maturation blockade, and alterations of the transcription of genes implicated in oligodendrogenesis, myelin formation, and axonal maturation.

Excitotoxicity and Oxidative Stress

Glutamate can act on several types of receptors, including NMDA, alpha-3-amino-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate, and metabotropic receptors. Excess release of glutamate has been suggested to represent a molecular mechanism common to some of the risk factors for brain lesions associated with cerebral palsy. In keeping with this possibility, injection of glutamate agonists into the striatum, neocortex, or periventricular white matter of newborn rodents (rats, mice, or hamsters), rabbits, or kittens produces, according to the stage of brain maturation, histologic lesions that mimic those seen in humans with cerebral palsy, such as neuronal migration disorders, polymicrogyria, cystic periventricular leukomalacia, and hypoxic–ischemic or ischemic-like cortical and striatal lesions.[1,53]

Studies exploring the pathophysiology of these excitotoxic white matter lesions in newborn rodents and rabbits have permitted the following contributions (Fig. 52.8)[39,53,130,145]:

1. Both NMDA and AMPA–kainate agonists can induce periventricular cystic white matter lesions.
2. NMDA receptor–mediated white matter lesions involve an early microglia–macrophage activation and astrocyte cell death, whereas AMPA–kainate receptor–mediated lesions involve pre-OL cell death; in addition, NMDA receptors expressed by pre-OLs could participate to the injury of these pre-OLs.
3. The periventricular white matter of newborn rodents and rabbits exhibits a window of susceptibility to excitotoxic insults.
4. Transient expression of NMDA receptors on white matter microglia–macrophages and transient expression of high levels of AMPA–kainate receptors on pre-OLs are likely important factors to explain the window of sensitivity of white matter to neonatal excitotoxic insults.
5. The study of NMDA receptor–mediated white matter lesions in newborn rabbits revealed that the excitotoxic white matter lesion extended into the subplate, but not in the overlying neocortical layers. With use of antioxidant molecules, excitotoxic white matter lesions involve excess production of reactive oxygen species, which play an important role in the pathophysiology of the lesions.



• **Fig. 52.8** Schematic representation of the potential cellular and molecular pathways by which excess release of glutamate and proinflammatory cytokines may lead to white matter lesions. KA, Kainate; oligo(s), oligodendrocyte(s); Rec, receptors.

Extensive in vitro studies have confirmed the exquisite susceptibility of pre-OLs to AMPA–kainate agonists and to oxidative stress.[80]

Combined Insults

To further support the hypothesis of a multifactorial hypothesis of perinatal brain damage (see Fig. 52.5), different studies have induced combined insults in newborn rodents.

Pretreatment of newborn mice with systemic proinflammatory cytokines (e.g. IL-1-beta, IL-6, or TNF-alpha) before an excitotoxic insult significantly exacerbates excitotoxic white matter lesions, demonstrating a causative link between circulating proinflammatory cytokines and white matter damage.[38] Results of various studies have suggested that this effect of proinflammatory cytokines is more pronounced with NMDA receptor agonists when compared with AMPA–kainate receptor agonists (see Fig. 52.8). The precise mechanism by which these cytokines systemically act on white matter excitotoxicity remains to be determined but could potentially involve activation of brain cyclooxygenase or activation of microglia with increased white matter production of reactive oxygen species and cytokines.

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Similarly, systemic pretreatment with IL-9, a T-helper 2 (Th2) cytokine, was shown to exacerbate NMDA receptor–mediated white matter lesions.[38,126] The mechanism of IL-9 toxicity involves brain mast cell degranulation and excess release of histamine. Interestingly, increased circulating levels of IL-9 around birth was demonstrated in a subgroup of human infants who later developed cerebral palsy.[119] Chronic mild stress of pregnant mice has been shown to induce a significant exacerbation of excitotoxic white matter lesions in pups. LPS was also used to sensitize the newborn brain to hypoxia–ischemia. A low dose of this endotoxin, given 4 hours before a mild hypoxic–ischemic insult in postnatal day 7 rats induced extensive brain damage, whereas each insult given separately did not induce any detectable brain lesion.[47]

Several experimental paradigms have emerged for the study of white matter diseases of the preterm infant. These animal models have permitted identification of some of the potentially key cellular (e.g., pre-OLs, microglia–macrophages) and molecular (glutamate, cytokines, and other inflammatory mediators, reactive oxygen species, etc.) players involved in the pathophysiology of perinatal brain damage. These studies have also delineated potential targets for neuroprotection through the neurotrophic action of erythropoietin.[66,153] Future studies should incorporate imaging and behavioral studies to facilitate comparisons with human cases. Although it is clear that studies with rodents, because of their low cost and easy availability, are absolutely necessary to generate and test multiple hypotheses, the use of larger models, such as sheep, pigs, and monkeys, continues to be important for testing the relevance of the obtained data in a more reliable fashion for human cases.

Neuroimaging of White Matter Injury

Neonatal Sonography

Neonatal sonography is the one major bedside technique to image the neonatal brain. Leviton et al. postulated, in 1990, that ultrasonographic white matter echodensities and echolucencies in low birth weight infants predicted later handicap more accurately compared with any other antecedent.[96] Unlike intraventricular hemorrhage, damage to the white matter can have different appearances, and depending on the timing of the injury, the imaging characteristics can be nonspecific, with generally an increase in echogenicity in the acute phase of the injury (Fig. 52.9). In clinical practice, at least in the older preterm infant, the condition of white matter is judged by its echogenic potential compared with that of the choroid plexus. Generally, the echogenicity found in early periventricular leukomalacia is similar in intensity to that of the choroid plexus. The echogenicity is bilateral but slightly asymmetric in appearance, can be sharply delineated, and may have nodular components. This has to be differentiated from normal peritrigonal flaring, which is perfectly symmetric and has a radial appearance. Evolution of such hyperechogenicity can be twofold, either complete disappearance or evolution into cysts and/or ventricular dilatation. Cyst formation analogous to neuropathology is a process typical for the second week (10-40 days) after the insult. De Vries et al.[31] proposed an ultrasound-based classification of four grades for PVL. Increasing grades are associated with increasing neurodevelopmental handicap. Grade I is defined as transient (>7 days) periventricular densities without cyst formation. If cysts develop and are few in number, localized primarily in frontal and frontoparietal white matter, this is classified as grade II. When they are widespread and extend into the parieto-occipital region they are referred to as grade III; these may grow and gradually disappear, leaving an irregularly dilated lateral ventricle. Grade IV cysts are present all the way into the subcortical area, resembling porencephaly (Table 52.1). In a pooled analysis based on data from 15 published studies, 11% of infants with small ultrasound-defined white matter echolucencies, 35% of those with medium echolucencies, and 60% of those with large echolucencies had an intelligence or developmental index less than 70,[67] which underscores the importance of potentially associated microstructural alterations in cortical development after white matter injury.

Ultrasonography may be perceived as the ideal mode of imaging to detect cystic PVL but has very limited value for detecting diffuse white matter injury and the processes leading to encephalopathy of prematurity as shown in studies comparing neonatal ultrasonography with MRI.[25,77,133] MRI has been found to be less sensitive for such pathologies as lenticulostriate vasculopathy or calcifications.[92]

Conventional Magnetic Resonance Imaging

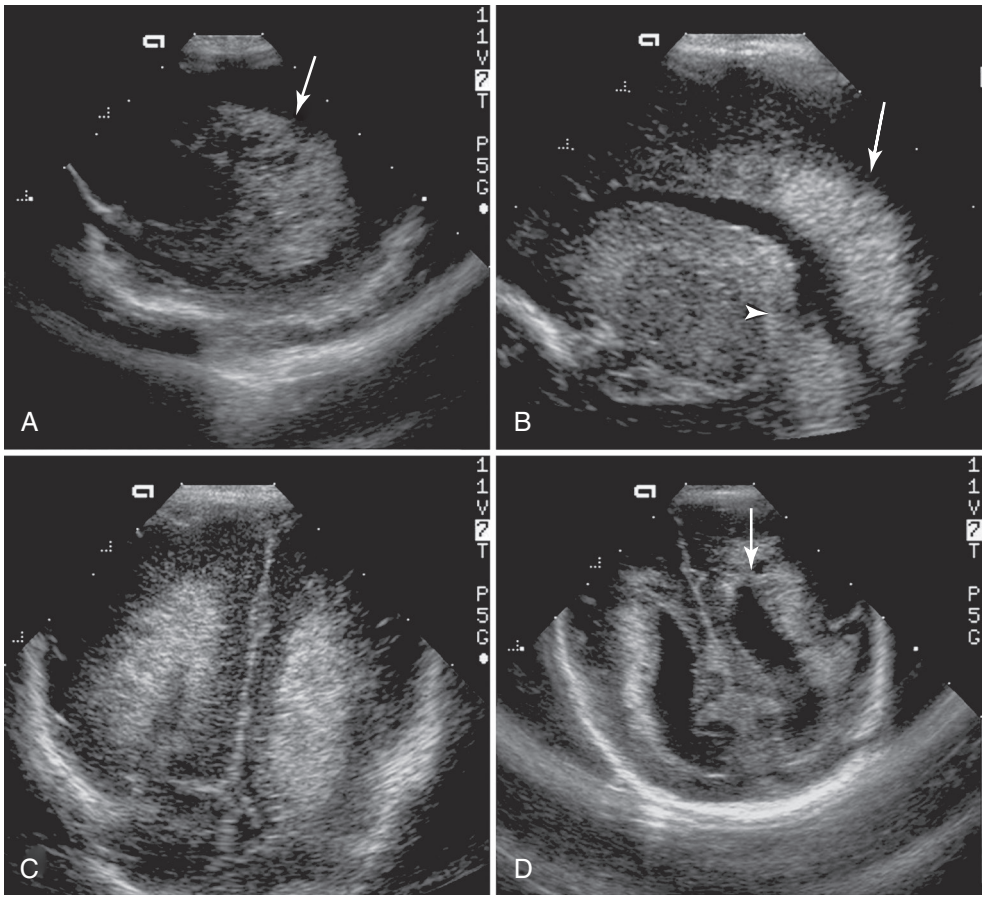
Conventional T1- and T2-weighted imaging can show signal abnormalities in the periventricular white matter that are different from the cystic lesions detected by ultrasonography. The typical conventional MRI pattern in the subacute phase consists of punctate periventricular areas

TABLE 52.1 Ultrasound Classification of Periventricular Leukomalacia

Grade I	Transient periventricular echodensities (PVEs) (>7 days)
Grade II	PVE evolving into localized frontoparietal cystic lesions
Grade III	PVE evolving into extensive periventricular cystic lesions
Grade IV	Echodensities evolving into extensive periventricular and subcortical cysts

Classification needs longitudinal assessment with daily to weekly ultrasound evaluations.
Data from Counsell SJ, et al. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. *Pediatrics.* 2003;112:1-7.

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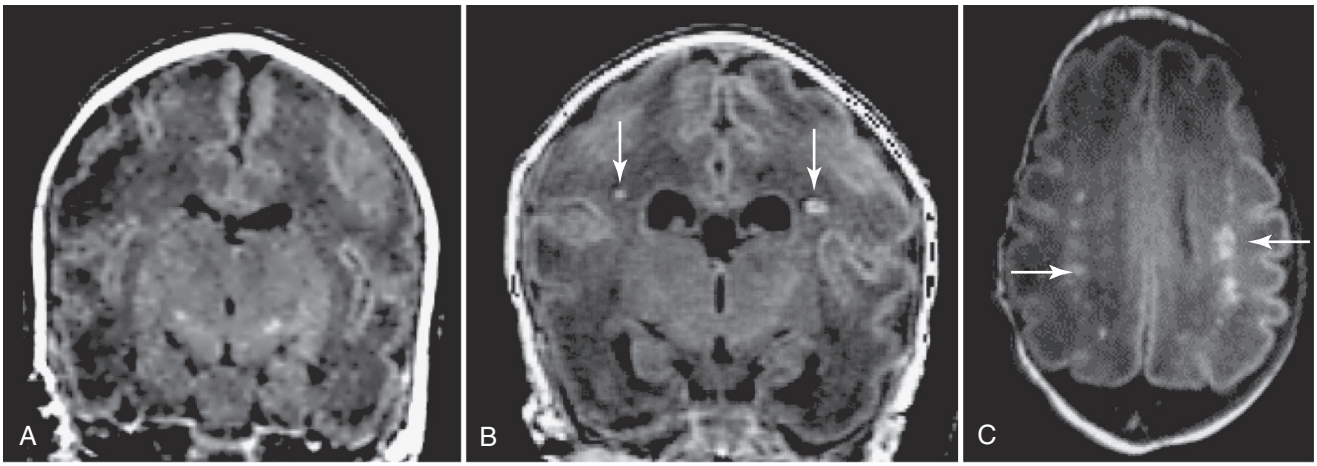
• **Fig. 52.9** Ultrasonography scans of periventricular echodensity in a preterm infant born at 27 weeks' gestational age with premature rupture of membranes and neonatal sepsis. **A** and **B,** Bilateral echodensities in sagittal view at 5 days of age (*arrows*). **B,** Echogenicity of similar intensity to echogenicity of choroid plexus (*arrowhead*). **C,** Bilateral echodensities in coronal view. **D,** Echolucency developing at 12 days in sagittal view (*arrow*) representing cystic transformation.

of T1 signal hyperintensities and T2 signal hypointensities (Fig. 52.10). The precise neuropathologic correlate of these signal abnormalities is not completely known but may be caused by some hemorrhagic components of the lesions and most likely represents the cellular reaction of glial cells and macrophages, which are known to contain lipid droplets (see section on Models of Encephalopathy of Prematurity) accounting for the high signal intensity on T1-weighted MRI scans. These abnormalities have been associated with the presence of markers of oxidative stress in cerebrospinal fluid (CSF).[76] Most of these lesions disappear by term age and then have little significance for later neurodevelopmental problems.[45] For the punctate T1 hyperintensities that persist to term age and are present in significant numbers (more than one or two isolated lesions), data indicate an association with subsequent neurodevelopmental delay in motor development as well as in cognitive development.[30,81]

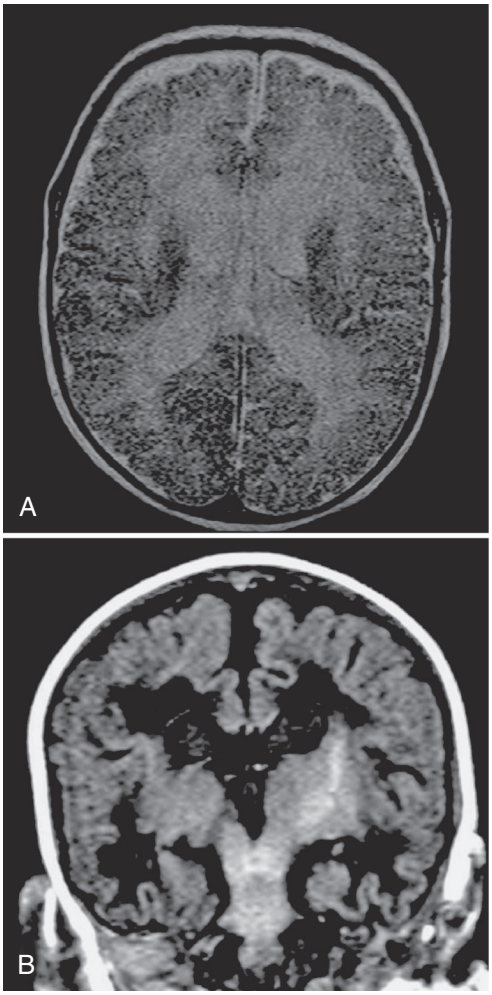
A study of over 500 MRI scans obtained from preterm infants at term-equivalent age revealed that a large number of preterm infants had punctate white matter lesions (24%) that have not been seen on ultrasonography and had no other cerebral or cerebellar lesions on MRI. An increasing number of punctate lesions was associated with lower thalamic volumes and altered microstructure in CSTs and a significant association with impaired motor outcome, but this had a limited positive predictive value.[150]

Conventional MRI features of chronic white matter injury in the immature brain are characterized by cysts, comparable with those demonstrated not only by ultrasonography but also, more importantly, by a persistent high signal intensity of white matter on T2-weighted MRI representing higher water content or loss of white matter microstructural elements (Fig. 52.11).[28,72] This imaging characteristic can later be associated with thinning of the corpus callosum and loss of white matter volume, resulting in deep prominent sulci (see section on Impairment of Brain Growth). In several studies on the brain of the preterm infant, diffuse excessive high signal intensity (DEHSI) in the cerebral white matter on T2-weighted MRI was reported to be present in up to 40%-75% of low birth weight preterm infants imaged at term[102] and, combined with white matter loss, showed negative associations with neurodevelopmental outcome (Fig. 52.12).[45] Carefully designed studies aimed at assessing the risk of neurodevelopmental delay in specific neonatal white matter lesions have shown that DEHSI

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• **Fig. 52.10** A normal preterm infant at 31 weeks' gestational age. **A** and **B,** Conventional T1-weighted magnetic resonance imaging (MRI) scans in coronal and **(C)** axial plane; **B** and **C,** Bilateral periventricular lesions with high signal intensities (*white arrows*). If these lesions persist to term age and are numerous in the periventricular white matter, they are associated with increased risk for motor developmental delay.



• **Fig. 52.11** Magnetic resonance imaging (MRI) scan in a child who had been born at 25 weeks' gestational age imaged at age 40 weeks, with severe bronchopulmonary dysplasia and repetitive episodes of severe hypoxia. **A,** Conventional T2-weighted MRI shows widespread markedly increased T2 signal intensity in the central white matter and **(B)** low signal intensity on the inversion recovery (IR) MRI with T1-weighted signal characteristics in the central white matter, representative of diffuse white matter injury.

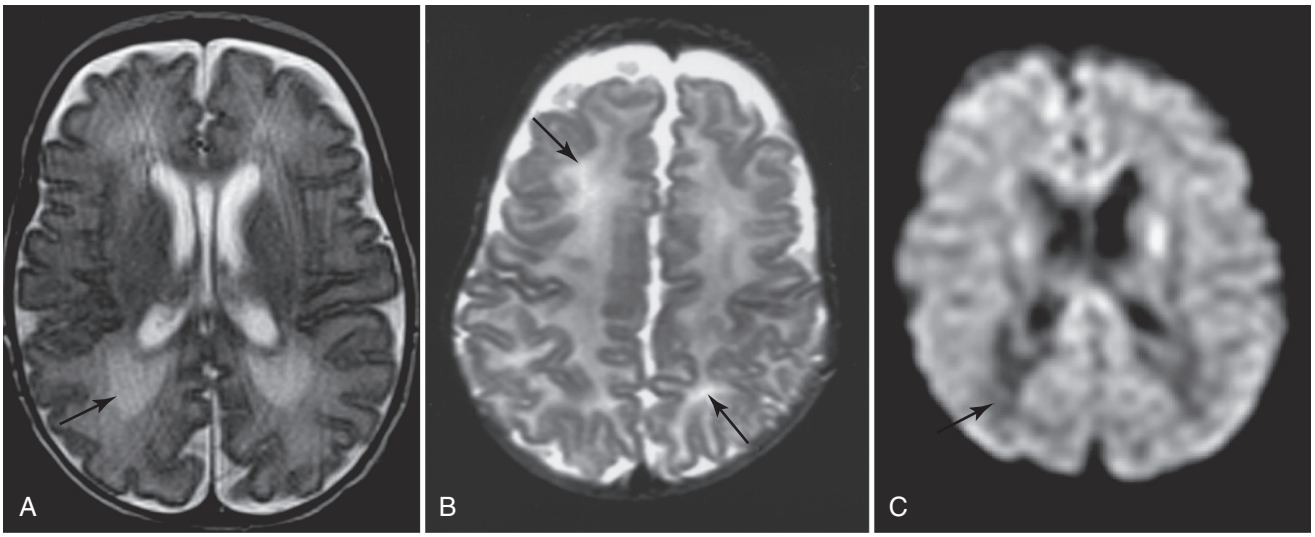
alone is not associated with significant neurodevelopmental delay.[30,62,82] Use of MRI is ideal to assess delayed myelination as well. The absence of myelination in the posterior limb of the internal capsule (missing T1 high signal intensity, T2 low signal intensity) at term age is a good indicator of later neuromotor impairment (Fig. 52.13). Woodward et al.[162] showed that 21% of preterm infants at term age had MRI-defined moderate to severe white matter abnormalities, but an even larger proportion of 49% had gray matter abnormalities characterized by poor cortical development. Furthermore, about half the preterm infants showed mild white matter abnormalities, and these infants had only marginal mental developmental indexes at age 2 years (Table 52.2). A recent neuroprotective trial with erythropoietin showed a reduction of MRI-based biomarkers of encephalopathy of prematurity in 1 of 7 preterm infants,[93] but neurodevelopmental outcome at 2 years was not significantly different in the two groups.[117] Generally, MRI-based biomarkers in the preterm infant at term-equivalent age have high negative predictive values for neurodevelopmental outcome, but much less positive predictive power.[90]

Diffusion Magnetic Resonance Imaging

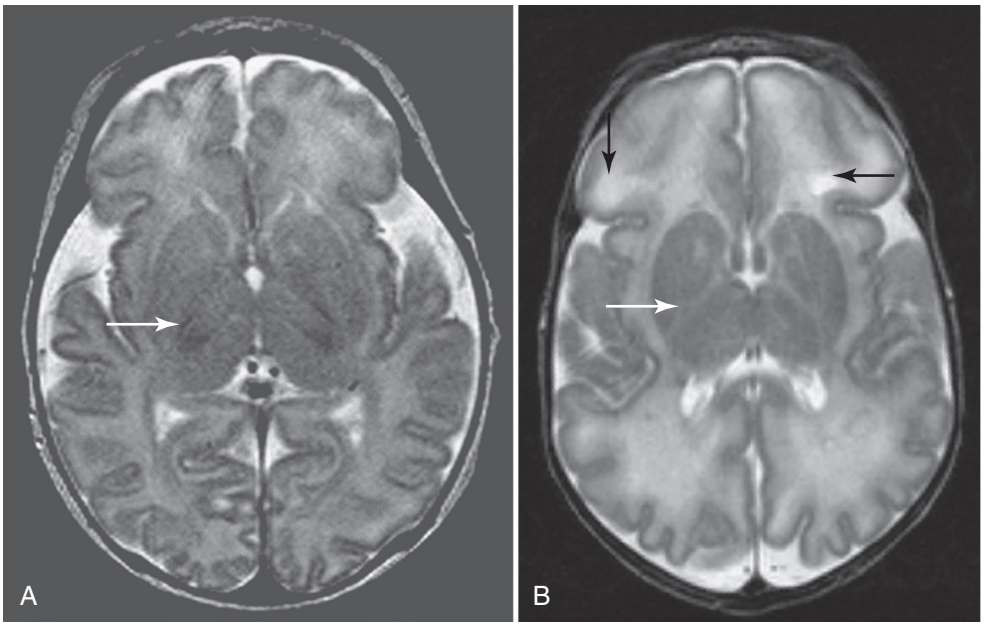
Diffusion-weighted imaging (DWI) or diffusion tensor imaging (DTI) measures the self-diffusion of water. The two primary pieces of information available from DWI studies—water apparent diffusion coefficient (ADC) and diffusion anisotropy measures—change dramatically during development, reflecting underlying changes in tissue water content and cytoarchitecture (see Chapter 51).

Parameters of DWI also change in response to brain injury. The ADC decreases in acute injury, and possible mechanisms leading to this decrease are decrease in extracellular fluid due to cellular swelling (cytotoxic edema), swelling of mitochondria and reduction of cytoplasmic diffusion, axonal swelling, and other mechanisms, such as membrane changes resulting from fatty acid peroxidation.

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• **Fig. 52.12** Conventional T2-weighted magnetic resonance imaging (MRI) scan. **A** and **B,** Diffuse excessive high signal intensity (DEHSI) (*black arrows*). **C,** T2-weighted hypersignal is associated with low intensity on diffusion-weighted imaging (*black arrow*). This can indicate chronic white matter injury, but if mild, is not associated with neurodevelopmental impairment alone.



• **Fig. 52.13** Normal full term infant. **A,** Conventional T2-weighted magnetic resonance imaging (MRI) scan with thin area of low signal on the T2-weighted MRI scan, corresponding to myelin deposition in the posterior limb of the internal capsule (*white arrow*). **B,** Corresponding T2-weighted MRI with diffuse white matter lesions (*black arrows*) and missing signal change in the posterior limb (*white arrow*) of the internal capsule, indicating delay in myelination.

Early DWI assessment of periventricular white matter in preterm infants can reveal bilateral periventricular diffusion restriction similar to the typical distribution of PVL when ultrasonography and conventional MRI show no or nonspecific abnormalities (Fig. 52.14).[21] A reduced ADC in an otherwise normal preterm brain is considered an early indicator of white matter damage (just as a reduced ADC is seen shortly after the onset of an acute cerebral ischemic lesion in adults). The typical histologic changes in the acute phase of PVL outlined previously are characterized by some of the same mechanisms leading to restriction of water diffusivity. These changes are responsible for the diffusion changes described earlier in that they considerably change the microstructure of white matter and, therefore, change in water diffusivity.

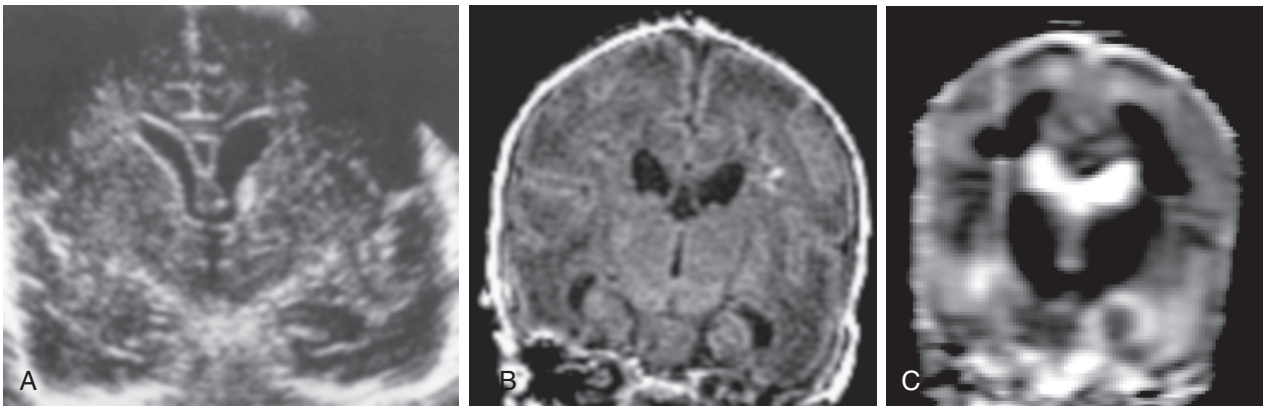
The chronic phase of white matter injury again is characterized by cyst formation (Figs. 52.15 and 52.16) and by T2-weighted hyperintensities of the white matter for which studies demonstrate higher ADC values in the area of T2 hyperintensities, and this confirms the locally higher

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TABLE 52.2 Neurodevelopmental Outcomes at 2 Years' Corrected Age

Outcome Measure	White-Matter Abnormality, *N* = 167				*P* Value
	None *N* = 47 (28%)	Mild *N* = 85 (50%)	Moderate *N* = 29 (17%)	Severe *N* = 6 (3.5%)	
MDI score (mean ± SD)	92.50 ± 15.63	85.32 ± 15.46	77.93 ± 19.16	69.67 ± 25.30	<0.001
Severe cognitive delay (%)	7	15	30	50	0.008
PDI score (mean ± SD)	94.63 ± 13.45	90.73 ± 12.75	80.11 ± 18.18	56.17 ± 23.50	<0.001
Severe motor delay (%)	4	5	26	67	<0.001
Cerebral palsy (%)	2	6	24	67	<0.001
Neurosensory impairment (%)	4	9	21	50	0.003
Any neurodevelopmental impairment (%)*	15	26	48	67	<0.001
Number of impairments	0.22 ± 0.47	0.40 ± 0.71	1.15 ± 1.20	2.33 ± 1.97	<0.001

MDI, Mental development index; PDI, psychomotor development index.
*Presence of severe impairment defined as MDI or PDI score less than 70, cerebral palsy, or hearing or visual impairment.
Adapted from Woodward LJ, Anderson PJ, Austin NC, et al. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med.* 2006;355:685.

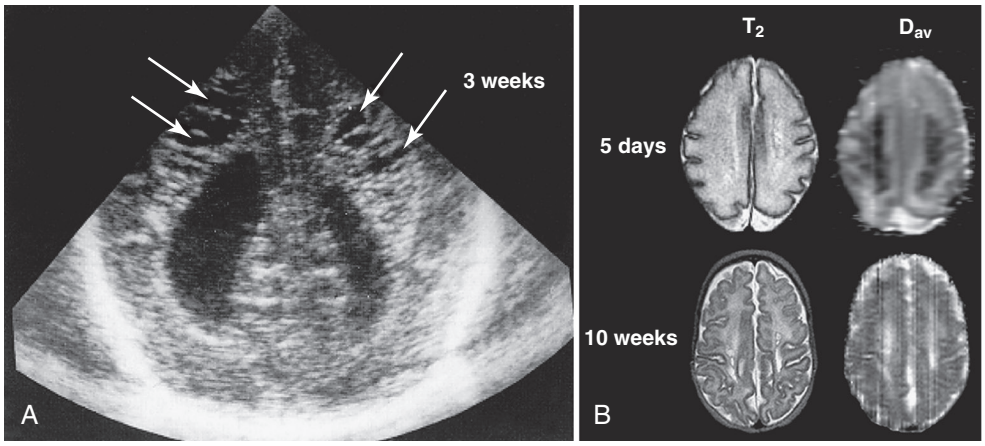


• **Fig. 52.14** Infant of 30 weeks' gestation at 5 days of age. **A,** Normal ultrasonography image. **B,** T1-weighted magnetic resonance imaging (MRI) scan in the coronal plane with a small possibly hemorrhagic lesion in the left periventricular white matter. **C,** Apparent diffusion coefficient maps in coronal plane on diffusion weighted imaging illustrates bilateral periventricular lesions with low D_{av} (0.8 μm²/ms) (*circle*) indicating acute periventricular leukomalacia (PVL). (**B** and **C,** from Inder T, et al. Early detection of periventricular leukomalacia by diffusion-weighted magnetic resonance imaging techniques. *J Pediatr.* 1999;134:631).

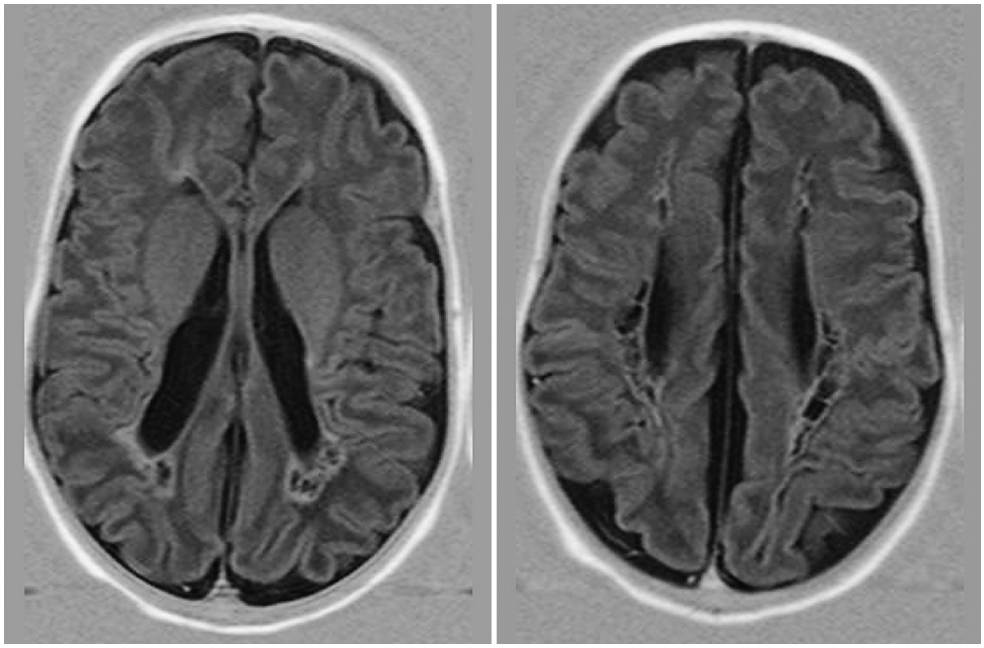
tissue water content in those areas (see Fig. 52.12).[27,113] These high ADC values are similar to those seen in the very immature healthy white matter; therefore a potential explanation for the failure of ADC to decline from high levels in the extremely premature infant to lower levels in the term infant might be related to prior injury with destruction of normal cellular elements (i.e., pre-OLs) as discussed in the models of white matter injury.[157] Further quantitative measures of diffusion at term among premature infants with perinatal white matter lesions (both T2 hyperintensities as well as T1 hyperintensities [punctate lesions]), compared with preterm infants without white matter injury, showed lower anisotropy values not only in the area of the previous injury (i.e., central periventricular white matter) but also in the underlying posterior limb of the internal capsule (Fig. 52.17).[71,118] The lower anisotropy in the injured cerebral white matter suggests that the white matter fiber tracts were destroyed or their subsequent development was impaired. Whether this effect involves axon bundles per se, their packing density, or their encasement by premyelinating oligodendroglia is unknown. The lower anisotropy in the internal capsule further suggests a disturbance in the development of the descending CSTs.[6,14,70]

Fiber tracking is another technique applied to study quantitative assessment of specific pathway maturation in white matter in the developing brain.[2,44,159] Berman et al.[17] were able to show significant differences in the maturational changes in fractional anisotropy and transverse diffusion

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• **Fig. 52.15** Ultrasonography image showing **(A)** bilateral cystic *(arrows)* periventricular leukomalacia (PVL). **B,** Evolution of the lesions identified on diffusion-weighted imaging (D_{av}) at 5 days of age with the development of cystic lesions on T2-weighted magnetic resonance imaging (MRI) and apparent diffusion coefficient map (D_{av}) at 10 weeks of age. (**A,** from Inder T, et al. Early detection of periventricular leukomalacia by diffusion-weighted magnetic resonance imaging techniques. *J Pediatr.* 1999;134:631).

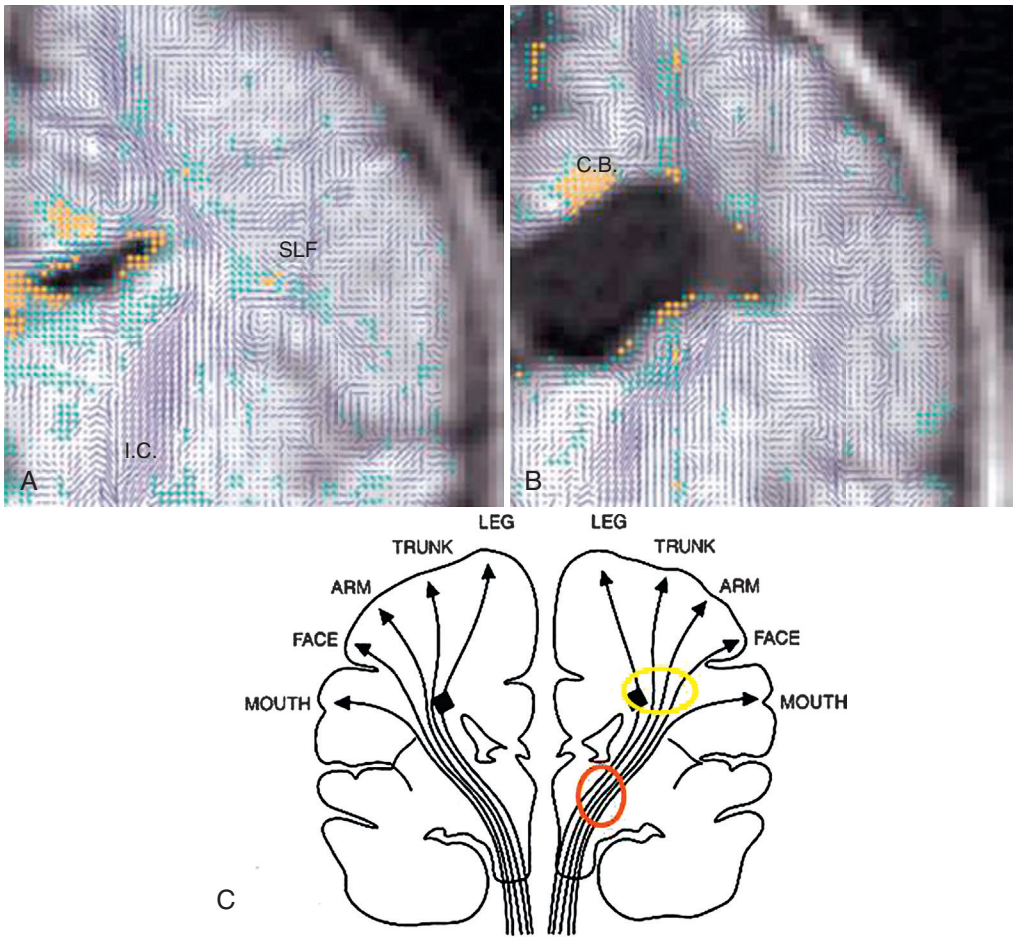


• **Fig. 52.16** Axial inversion recovery magnetic resonance imaging (MRI) scans with T1-weighted contrast illustrating chronic phase of periventricular leukomalacia (PVL), with multiple bilateral cystic lesions with high signal gliotic scars and calcifications in the periphery of the cystic lesions. Note also the loss of white matter volume with cerebral atrophy.

between the motor and somatosensory pathways in premature infants between 30 and 40 weeks' gestational age. This approach further allowed for the measurement of diffusion changes across multiple levels of the functional tract and, thus, the assessment of myelination progress over a given white matter fiber tract.[17,125]

The subsequent neurologic deficits after cerebral white matter injury are grouped together under the term *cerebral palsy*. Structural correlates of cerebral palsy have been assessed using DTI in the newborn period, adding to prognostication of cerebral palsy in the newborn period.[7,29,69] Tract-specific evaluation of children with cerebral palsy after PVL identified most frequent alterations in white matter fiber tract development in the retrolenticular part of the internal capsule, posterior thalamic radiation, superior corona radiata, and in commissural fibers of the corpus callosum.[116] In another study, regional measurements in the primary site of white matter lesions showed increased average diffusivity (D_{av}) values and decreased fractional anisotropy values suggesting primary degeneration, whereas the CST ipsilateral showed secondary degeneration with increased D_{av} and decreased fractional anisotropy; contralateral CST

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• **Fig. 52.17** Diffusion vector maps overlaid on coronal diffusion weighted images for **(A)** a premature infant at term with no white matter injury and **(B)** a premature infant at term with perinatal white matter injury. The posterior limb of the internal capsule (IC) in **(A)** shows more homologous directed vectors that are longer and more densely packed than in the internal capsule of **(B)**. Anteroposterior-oriented white matter fibers in the area of the superior longitudinal fasciculus (SLF; yellow and green dots with yellow representing higher anisotropy than green) in **(A)** indicate the presence of fiber bundles that are missing or are less prominent in **(B)**. The only discrete anteroposterior fiber bundles that definitely are present in **(B)** are the cingulate bundle (CB). Fibers of the corona radiata appear less well-organized in **(B)** than in **(A)**. (Reproduced by permission of the American Academy of Pediatrics.) **C,** Schematic illustration of loss of axons in the central white matter (*yellow area*) and the posterior limb (*red area*), as outlined above, will result in neuromotor disturbances. (**A** and **B**, from Hüppi P, et al. Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. *Pediatrics.* 2001;107:455; **C,** from Volpe JJ. *Neurology of the newborn*. St Louis: Elsevier; 2008).

showed increased D_{av} but an increase in fractional anisotropy, suggesting reorganization of sensorimotor tracts.[148]

The clinical relevance of injury and related modification of white matter architecture detected in this fashion is not yet known, and long-term follow-up studies of prematurely born children are under way, linking functional outcome to structural white matter development assessed by DTI.[6,15,26,41,56,90,142,151]

Given the diffuse character of neuropathologic features of encephalopathy of prematurity described earlier, the overall wiring of the brain, which is assumed to occur mostly during the second part of pregnancy, is most affected. Newer whole brain assessment methods, such as tract-based spatial statistics (TBSS), have enabled to show significant fractional anisotropy reductions in preterm infants with chronic lung disease at term-equivalent age in comparison with term newborns, despite any evidence of focal lesions on conventional MRI, in several white matter regions.[10] Neuroprotective interventions that aim at preventing and decreasing the long-term effects of the encephalopathy of prematurity, such as postnatal neuroprotection with the growth factor erythropoietin or the antenatal neuroprotective action of magnesium sulfate, have shown positive effects on brain connectivity in the preterm brain.[2,123] DWI with diffusion tensor analysis has provided new insights into the microstructural white matter development and seems to be

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an ideal tool to assess alteration of white matter pathways in the developing brain of the preterm infant.[44]

Functional Magnetic Resonance Imaging—Functional Connectivity

The process of establishing permanent functional connectivity is influenced by several factors (e.g., neuron survival, competition for trophic factors, electrical activity of axons, and afferent inputs).[86] Functional connectivity can be studied even in the newborn period by resting state functional MRI and analysis of regional time course of blood-oxygenation-level-dependent (BOLD) fluctuations. Functional MRI uses deoxygenated hemoglobin as an endogenous contrast agent to produce a BOLD signal. By utilizing these BOLD signals in neonates, it is possible to identify networks with synchronous neuronal activity in sleeping neonates to study resting state functional connectivity. Studies indicate that aberrant functional connectivity relevant for cognitive outcome is observed in preterm infants[11] and depends on the severity of the brain injury.[64,144]

Magnetic Resonance Spectroscopy

One of the essential contributors to the progress in noninvasive detection of tissue metabolism and in vivo biochemistry has been magnetic resonance spectroscopy (MRS), which gives specific chemical information on the biochemistry of numerous intracellular metabolites. The biochemical characteristics of white matter damage in preterm infants have been studied in vivo by using MRS.[134] Similar to the high diagnostic value of MRS in term asphyxia, MRS in acute phase immature white matter injury can detect indicators of anaerobic glycolysis with increased intracerebral lactate. Data from studies suggest that white matter damage in the preterm infant studied around term gestational age resulted in high Lac/Cr and high Myo-Inositol/Cr ratios.[134] The increased presence of lactate at this chronic stage was not associated with changes in pH,[134] whereas N-acetylaspartate as a marker of neuroaxonal integrity was reduced in the damaged periventricular white matter. As outlined in Chapter 51, astrocytes further play a variety of complex nutritive and supportive roles in relation to neuronal metabolic homeostasis. For example, astrocytes take up glutamate and convert it to glutamine. This removal of glutamate from the extracellular space protects surrounding cells from excitotoxicity from glutamate. Glutamate uptake into astrocytes further stimulates glycolysis within the astrocyte with production of lactate that can be used by neurons as energy substrate. Given that chronic phase white matter injury is characterized by widespread cerebral white matter astrocytosis, this change in metabolite composition might be an expression of altered cellular composition and substrate utilization. A study found links between elevated glutamate and the occurrence of punctate white matter lesions, indicating their biomarker role for cellular injury.[161]

There are other metabolites that become visible with short echo-time spectroscopy, such as the macromolecules/lipids at 0.9 parts per million (ppm) and 1.3 ppm (see Fig. 52.8). These resonances show important changes in adult hypoxia–ischemia[58] and in experimental data on in vitro apoptosis.[19] Preliminary data have suggested that these metabolites are also present in acute periventricular white matter injury of the immature brain and may represent metabolites from membrane peroxidation. Consistent with the observation of these resonances, one study found elevated neonatal levels of lipid peroxidation and oxidative protein products in the CSF of infants with PVL, as documented by MRI.[76]

Impairment of Brain Growth and Long-Term Development

Periventricular white matter injury has been strongly associated with long-term neurodevelopmental deficits in preterm infants.[127,128] The significance of abnormalities in myelination in relation to functional (neurologic) development has been extensively studied. Correlation was found between neurodevelopmental delay and delay in myelination. The major long-term morbidity of the focal component of periventricular leukomalacia is spastic diplegia (Box 52.1). This motor disturbance has as its central feature a spastic paresis of the extremities with greater effect on lower than upper limbs. More severe lesions, with lateral and posterior extension into the centrum semiovale and corona radiata, are associated with effects on the upper extremities or visual and cognitive deficits (see Box 52.1).

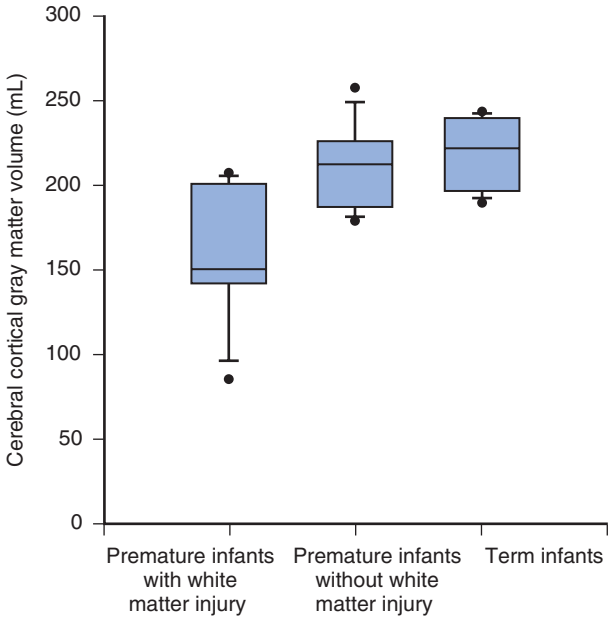
The development of three-dimensional MRI methods, combined with image postprocessing techniques, has allowed volumetric assessment of brain development and an absolute quantitation of myelination.[160] Despite the challenging methods of mathematical morphology-based segmentation, these techniques have improved the reliable quantification of myelinated versus unmyelinated white matter tissue from in vivo MR images of the newborn.[59] These techniques allow for exact definition of brain volume and can, therefore, accurately monitor brain growth, measure CSF volume, and detect volume changes in cortical gray matter. Three-dimensional MRI volumetric techniques were used to evaluate the effect on subsequent brain development of

• BOX 52.1 Clinical Correlates of Immature White Matter Injury

Long-term sequelae of periventricular white matter injury, including corticospinal tracts, optic radiation, and association fibers:

- Spastic diplegia/quadriplegia
- Visual deficits
- Cognitive deficits

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• **Fig. 52.18** Figure illustrating the effects of perinatal white matter injury on subsequent cortical gray matter development at term with a significantly lower cortical gray matter volume determined by three-dimensional magnetic resonance imaging (MRI) with postacquisition image analysis in a group of preterm infants with perinatal white matter injury compared with control preterm and full-term infants. (From Inder T, et al. The postmigrational development of polymicrogyria documented by magnetic resonance imaging from 31 weeks' postconceptional age. *Ann Neurol.* 1999;45:798).

early white matter injury in premature infants. Three groups of infants were studied at 40 weeks' postconceptional age: premature infants with preceding evidence for periventricular white matter injury by cranial ultrasonography and MRI; premature infants who had no prior evidence of white matter injury; and control term infants (Fig. 52.18). In premature infants with preceding white matter injury, the volume of myelinated white matter at term was significantly lower than in premature infants without prior white matter injury and infants born at term, measuring the degree of delay of myelination. Furthermore, this study showed a marked decrease in cortical gray matter volume in preterm infants with prior periventricular white matter injury, indicating impaired cerebral cortical development. This finding is in line with the neuropathologic findings of encephalopathy of prematurity and may explain the intellectual deficits associated with both cystic and noncystic periventricular leukomalacia in preterm infants.[79] Assessing moderately preterm infants without signs of white matter injury, cortical development was similar to full-term infants.[165] Regional assessment of white matter myelination in preterm infants further revealed particular delay in myelination in the central and posterior parts of the brain.[112] When assessing cerebellar volume at term, there was a significant reduction in cerebellar volume of preterm infants compared with that in term infants.[97] Unilateral cerebral white matter lesions resulted in contralateral reduction of cerebellar volume, indicating the trophic interplay resulting from loss of cerebrocerebellar connectivity.[98]

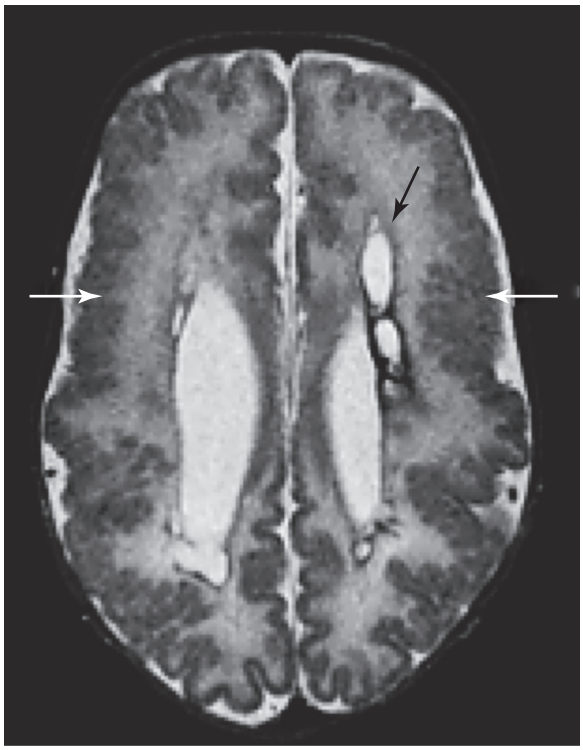
Long-term follow-up studies of preterm infants have confirmed the permanent character of these disruptive/adaptive changes in brain development. Evaluations with volumetric brain assessment of 8-year-old children who had been born prematurely showed persistence of cortical gray matter reduction accompanied by a reduction in the volume of hippocampus, which correlated with cognitive scores indicating long-term functional consequences.[100] Both cortical volume and cortical thickness were shown to be reduced in 15-year-old adolescents born prematurely.[106] Studying a larger cohort of preterm subjects at the same age, Nosarti[122] noted widespread alterations in both gray and white matter volumes throughout the brain. Of note, several gray matter regions, including the middle temporal gyrus, the superior temporal gyrus, and the sensorimotor region, as well as the precentral and postcentral gyri, were linearly related to gestational age for the preterm group. Furthermore, decreases in both gray and white matter volumes in the middle temporal gyrus were associated with cognitive impairment in the preterm group. With the development of whole brain connectivity analysis, specific long-term effects of prematurity and associated brain injury have been defined, affecting not only sensorimotor connectivity[68] but, more importantly, the prefrontal and the limbic cortico-basal-ganglia-thalamocortical loops as well, tightly linked to performance in executive function and social behavior.[51] New mathematical modeling techniques, such as graph model theory, have further evaluated the efficiency of brain networks in those born prematurely, indicating that their network efficiency can be altered both globally and regionally.[52] Neuroimaging has defined new biomarkers of later neurofunctional outcome and has become a useful adjunct to clinical practice.[110]

Human brain development is characterized by several interrelated steps. Neuronal and radial glial proliferation and migration are early events in brain development that are followed by a series of organizational events that result in the complex circuitry of axons and dendrites characteristic of the human brain. The immature cortex is characterized by radial organization seen both in rodents[139] and humans. The preterm cortex at term-equivalent age reveals a persisting fetal radial organization that can be characterized by DTI-based analysis (higher fractional anisotropy) and is associated with decreased cortical folding, which is more pronounced in preterm infants with signs of white matter injury.[46,108] Elaboration of dendritic and axonal ramifications and attainment of proper alignment and orientation is most likely one of the driving forces for the folding of the cerebral cortex during development. Several authors have investigated the influence of preterm birth on primary cortical folding. Biagioni[18] studied preterm infants of less than 30 weeks' gestational age and demonstrated that the degree of cortical folding significantly increased with postmenstrual age. Dubois et al.[42,43] observed a trend toward lower cortical surface areas and smaller cortical and white

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matter volumes, but equivalent sulcation in female preterm infants compared with male preterm subjects. Furthermore, preterm neonates with intrauterine growth restriction had more pronounced reduction of volume in relation to surface area and increased sulcation with resultant changes in cortical thickness, which correlated with impaired behavioral functions. Infants with early white matter lesions at birth showed a trend to increased sulcation in overlaying cortex.[43] Early alteration of white matter connectivity and ensuing disruption to the white matter circuits and to the subcortical plate may, therefore, alter subsequent density, survival, and organization of the cortical neurons. In severe cases, secondary polymicrogyria after primarily early white matter injury have been described (Fig. 52.19).[78] Neuropathology of the cerebral cortex in preterm infants has revealed cortical dysplasia in cortical areas overlaying white matter destruction.[105] These abnormalities of cortical development are found secondary to disturbances of afferent input to and efferent output from areas of the cortex by disruption of the respective white matter axons.[105] Cortical volume changes in three-dimensional MRI, as described earlier, are probably representative of these cortical alterations and may explain the increased risk of cognitive impairment and epilepsy in infants with classic motor deficits (spastic diplegia) after injury to the immature white matter.

Many studies confirm the potential long-term effect of the earlier described brain abnormalities and make encephalopathy of prematurity one of the major concerns in neonatology.[73,90]



• **Fig. 52.19** Axial T2-weighted magnetic resonance imaging (MRI) scan in a preterm infant 25 weeks' gestational age at birth imaged at 31 weeks' gestational age showing cystic lesions in the periventricular white matter (*black arrow*) associated with bilateral polymicrogyria (*white arrows*). (From Inder T, et al. The postmigrational development of polymicrogyria documented by magnetic resonance imaging from 31 weeks' postconceptional age. *Ann Neurol.* 1999;45:798.)

Key Points

- Encephalopathy of the preterm infant is an amalgam of damage and disrupted development.
- Hypoxia–ischemia and intrauterine infection during a vulnerable period of 23-32 weeks' gestation may both contribute to white matter injury via axonal injury and aberrant oligodendrocyte maturation.
- Glutamate acting on its various receptors plays a key excitatory role in the molecular mechanisms contributing to brain injury.
- Neonatal ultrasonography clearly identifies cystic periventricular leukomalacia but is of very limited value for detecting diffuse white matter injury.
- DWI can identify early periventricular white matter injury, and newer imaging techniques will enable characterization of molecular and functional components of brain integrity.
- Periventricular white matter injury with accompanying motor deficits is frequently accompanied by reduced gray matter volume and intellectual delay.

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53

Intracranial Hemorrhage and Vascular Lesions in the Neonate

LINDA S. DE VRIES

Germinal Matrix Hemorrhage–Intraventricular Hemorrhage

Incidence

Germinal matrix hemorrhage–intraventricular hemorrhage (GMH-IVH) mainly occurs in premature infants, and the risk is higher with decreasing maturity. A 2003 study, however, also showed that IVH, sometimes associated with a thalamic hemorrhage, can be seen in full-term infants, and this can be associated with a sinovenous thrombosis.[136] The first studies using computed tomography (CT) and ultrasonography were performed between 1978 and 1983 and showed an incidence of 40%-50% in infants with birth weights less than 1500 g. In the 1990s and more recently, several groups noted a decline in the incidence to approximately 20% of infants with very low birth weight,[47] but this decline has not been confirmed by others, and the decrease in severe GMH-IVH shown in a cohort of the Vermont Oxford Network was of borderline statistical significance.[49] In a recent study from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network in 34,636 infants with a gestational age between 22 and 28 weeks, a decline in the incidence of severe IVH was seen from 19%-15% with the following trends between 1993 and 2012: A significant reduction was seen for those with a gestational age of 26-28 weeks (adjusted relative risk [RR] for the change per year, 26 weeks 0.987) (95% confidence interval [CI] 0.974-0.999), 27 weeks 0.964 (95% CI 0.971-0.997), and 28 weeks 0.973 (95% CI 0.958-0.989).[21,112]

Since the early 1980s, the incidence of intraparenchymal hemorrhage has also shown a decline, although this decline was not found in all studies. The average incidence for intraparenchymal hemorrhage is now 5%-11%.[21,25] An even lower incidence of 3% was reported in a French population-based cohort.[64,105] The decrease in the incidence of GMH-IVH is mainly attributed to the increased use of antenatal corticosteroids and postnatal use of surfactant.[47,98]

Timing of the Hemorrhage

Accurate timing of GMH-IVH is possible only when sequential ultrasonography is performed. A diagnosis of a hemorrhage of antenatal onset can be made only when the first ultrasonography is performed on admission, within a few hours after delivery. Many studies have shown that almost all hemorrhages develop within the first week after birth, and many of them within the first 48 hours after birth. Progression of a GMH-IVH over 1-2 days is not uncommon, and this applies especially to an IVH progressing to an intraparenchymal hemorrhage.[21] Impaired venous drainage of the medullary veins in white matter leading to venous infarction is the most likely underlying mechanism for this progression (see section on Neuropathology). Only approximately 10% of cases of GMH-IVH occur beyond the end of the first week, in contrast to periventricular leukomalacia, wherein late onset is not uncommon.[25]

Neuropathology

Pathologists have noted GMH-IVH developing after hemorrhage in the subependymal germinal matrix, a structure that is most prominent between 24 and 34 weeks of gestation and that has almost completely regressed by term. Germinal matrix tissue is abundant over the head and body of the caudate nucleus but can also be found in the periventricular zone. More recently, magnetic resonance imaging (MRI) has confirmed just how extensive this tissue is in preterm infants. The germinal matrix contains neuroblasts and glioblasts that undergo mitotic activity before migrating to other parts of the cerebrum. Bleeding into the caudothalamic part of the germinal matrix is predominant, but using a new MRI sequence, susceptibility weighted imaging (SWI), it has been noted that many cases also have bleeding into the temporal or occipital germinal matrix outer zones.[92] Using this MRI sequence, it has also been observed that preterm infants with GMH-IVH have a higher variability in anatomy of subependymal veins which may be a predisposing factor for GMH-IVH.[119] The germinal matrix

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Abstract

Even though white matter damage is now considered the main determinant of cerebral palsy later in infancy, germinal matrix hemorrhage–intraventricular hemorrhage (GMH-IVH) is still a serious condition in premature infants, associated with a high mortality rate. Large IVHs, complicated by posthemorrhagic ventricular dilatation or associated with a unilateral parenchymal hemorrhage, are associated with an increased risk of adverse neurologic sequelae. The widespread use of cranial ultrasonography since the early 1980s has shown a gradual decrease in incidence of IVH and has helped with the identification of risk factors. The increased use of magnetic resonance imaging (MRI) has helped better define the site and extent of the lesion and to visualize associated white matter damage and cerebellar hemorrhages. The second part of this chapter is about extra-axial hemorrhages in the full-term infant and about perinatal stroke, including sinovenous thrombosis and perinatal arterial ischemic stroke (PAIS).

Keywords

germinal matrix/intraventricular hemorrhage
posthemorrhagic ventricular dilatation
intracerebellar hemorrhage
hydrocephalus
perinatal stroke

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receives its blood supply from a branch of the anterior cerebral artery known as the *Heubner artery*. The rest of the blood supply is derived from the anterior choroidal artery and the terminal branches of the lateral striate arteries. Vessels in the germinal matrix are primitive and cannot be classified as arterioles, venules, or capillaries and are often referred to as the *immature vascular rete*. Venous drainage of the deep white matter occurs through a fan-shaped leash of short and long medullary veins through which blood flows into the germinal matrix and subsequently into the terminal vein, which is positioned below the germinal matrix. The anatomic distribution of parenchymal lesions associated with GMH-IVH suggests venous infarction resulting from obstruction of this vein.

Germinal Matrix Hemorrhage

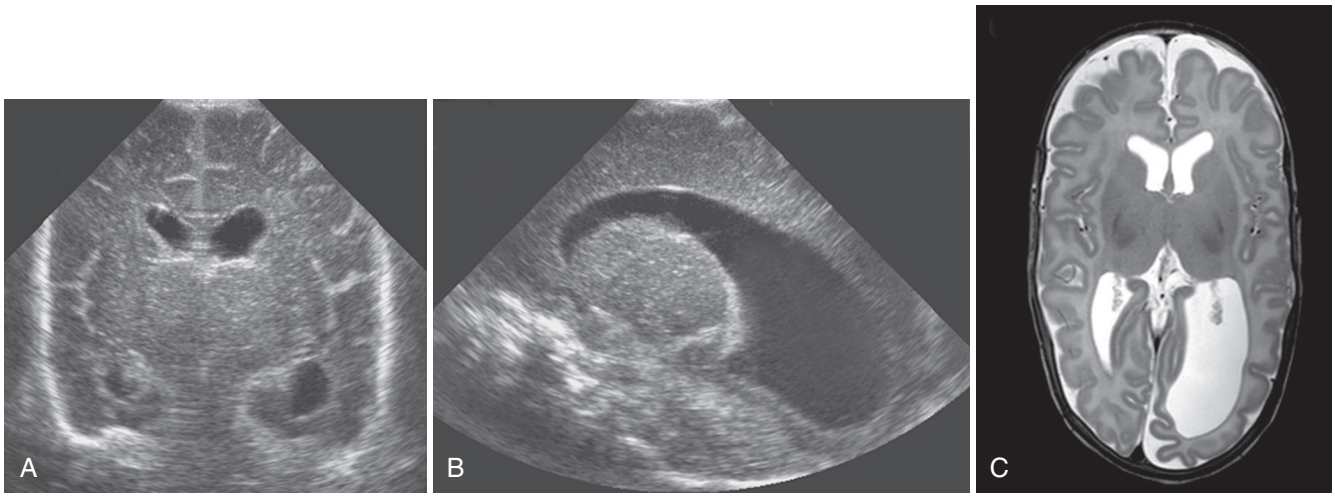
Most GMHs arise in the region of the caudate nucleus. Although GMHs at the level of the caudate nucleus are identified with ultrasonography, MRI using the SWI sequence has shown that GMH also occurs in the germinal matrix in the roof of the temporal horn.[92] The size of the GMH changes with the maturity of the infant: The less mature the infant, the larger the GMH. The site also varies with maturity, with occurrence over the body of the caudate nucleus in the less mature infant and over the head of the caudate nucleus in the more mature infant. A GMH can result in suppression of cell proliferation of the human ganglionic eminence.[26] When the GMH is followed longitudinally with ultrasonography, a subependymal cyst is seen as a sequel after several weeks, and this cyst is often still present at term-equivalent age and is better visualized with cranial ultrasonography than with MRI.

Intraventricular Hemorrhage

Hemorrhages occurring in the germinal matrix often rupture through the ependyma into the lateral ventricle and are then referred to as an *IVH*. These hemorrhages can vary considerably in size and, if large, can lead to acute distension of the lateral ventricle. Large clots can be present, seen as casts at postmortem examination or with cranial ultrasonography, and these can sometimes change position with repositioning of the infant. The blood can fill part of or the entire ventricular system, spreading through the foramen of Monro, the third ventricle, the aqueduct of Sylvius, the fourth ventricle, and the foramina of Luschka and Magendie to collect eventually around the brainstem in the posterior fossa. Clot formation can lead to outflow obstruction at any level, but most commonly at the level of the aqueduct of Sylvius or more diffusely at the level of the arachnoid villi. More gradual progressive ventricular dilation occurs especially in those with a large GMH-IVH; this is known as *posthemorrhagic ventricular dilation.* This can be transient or persistent. In a small group, it can be rapidly progressive and noncommunicating, usually because of obstruction at the level of the aqueduct of Sylvius or the outlet foramina of Luschka and Magendie. Unilateral outflow obstruction at the level of the foramen of Monro can lead to unilateral hydrocephalus (Fig. 53.1). In cases of communicating progressive posthemorrhagic ventricular dilation, the increase in ventricular size is more gradual and is considered to be caused by an obliterative arachnoiditis resulting from blood collecting in the subarachnoid spaces of the posterior fossa, leading to an imbalance between cerebrospinal fluid (CSF) production and reabsorption.[99]

Parenchymal Hemorrhage

The most severe type of hemorrhage involves the parenchyma. This type of lesion occurs in approximately 3%-15% of all hemorrhages.[64] A study by Dudink et al. described the different veins involved in this type of lesion.[28] Direct extension into the parenchyma from pressure of blood in the ventricle is now considered unlikely. Some still take the view



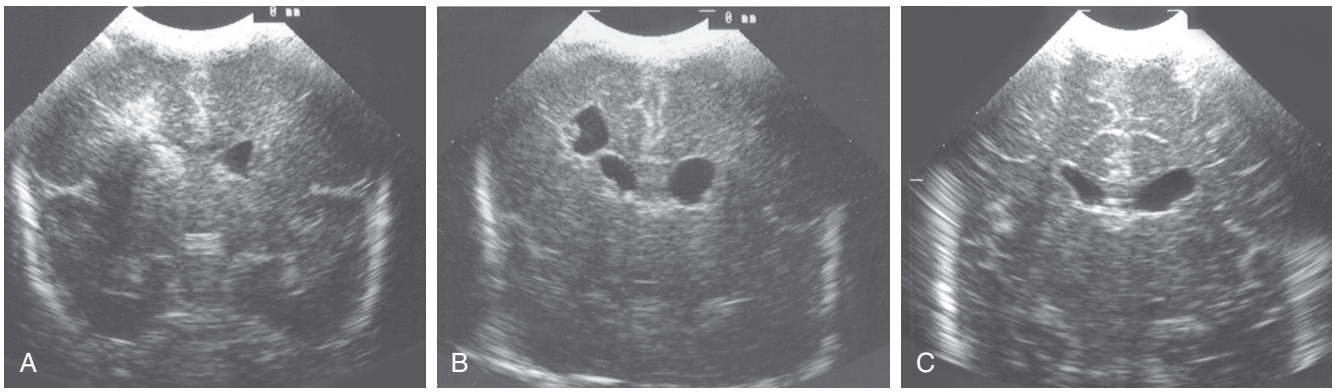
• **Fig. 53.1** **A,** Cranial ultrasonography, coronal view, shows posthemorrhagic ventricular dilation after a large left-sided hemorrhage. **B,** Note isolated enlargement of the left occipital horn on the parasagittal view. **C,** The magnetic resonance image, T2-weighted, spin-echo sequence still shows evidence of enlargement of the left occipital horn and enlargement of the frontal extracerebral space. Myelination of the posterior limb of the internal capsule (PLIC) is symmetric and seen as low signal intensity.

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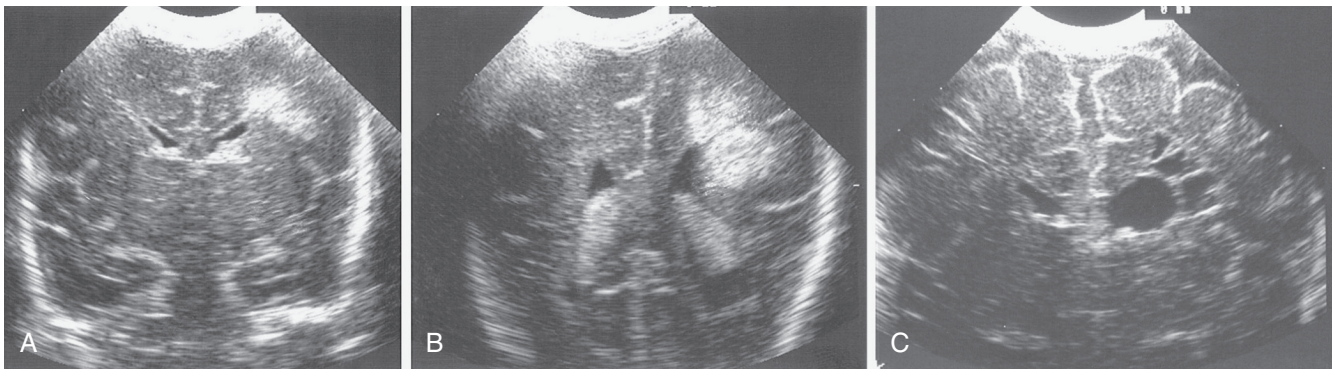
that all parenchymal hemorrhages are originally ischemic in origin, with any bleeding being a secondary complication. However, most agree that a unilateral parenchymal lesion accompanying GMH-IVH is most often caused by the presence of the GMH leading to impaired venous drainage and venous infarction. Gould et al.[41] showed that the ependyma remained intact, indicating that there had not been an extension of the preceding IVH. These lesions almost invariably show a moderate to large IVH on the ipsilateral side. The parenchymal hemorrhage is mostly unilateral but can occur in both hemispheres and is associated with a worse neurodevelopmental outcome.[73] A score was introduced, taking into account whether the lesion is unilateral or bilateral, the presence of a midline shift, and the number of regions that are involved.[5] The appearance of the intraparenchymal hemorrhage has changed since the early 1990s. Instead of a unilateral globular hemorrhagic lesion in continuity with the lateral ventricle and evolving into a single porencephalic cyst, a smaller, triangular parenchymal lesion can be seen with the tip of the triangle toward the lateral ventricle. There may be partial or even no communication of the parenchymal hemorrhage with the lateral ventricle, and an evolution into a few cystic lesions, separate from or partially in communication with the lateral ventricle, can be seen after several weeks (Figs. 53.2 and 53.3).[21] This type of lesion is sometimes classified as *unilateral periventricular leukomalacia* (PVL), but in view of the later MRI appearance, with very focal gliosis instead of diffuse gliosis, this appears to be incorrect. With the use of sequential ultrasonography, the underlying problem can be better understood because unilateral cystic lesions occurring after an ipsilateral IVH are more likely to be caused by a venous infarction rather than cystic PVL. It is possible that improvement in neonatal care is associated with the change in appearance of the unilateral parenchymal hemorrhage seen over time.

Intracerebellar Hemorrhage

Cerebellar hemorrhage was always considered uncommon, but the increased use of routine MRI in preterm infants has shown that this condition is more common than previously thought. This problem is especially common in very immature infants. The condition has been reported in 2.5% of high-risk preterm infants, but with the increased use of neonatal MRI, the diagnosis is more often made, and the reported incidence is now reported to be between 2% and 19%.[69,111,115] The high incidence includes all punctate lesions, which are not seen with ultrasonography, which is unable to recognize lesions less than 4 mm, but only with MRI.[21,111,115] Ultrasonography performed through the mastoid window is more successful in making the diagnosis,

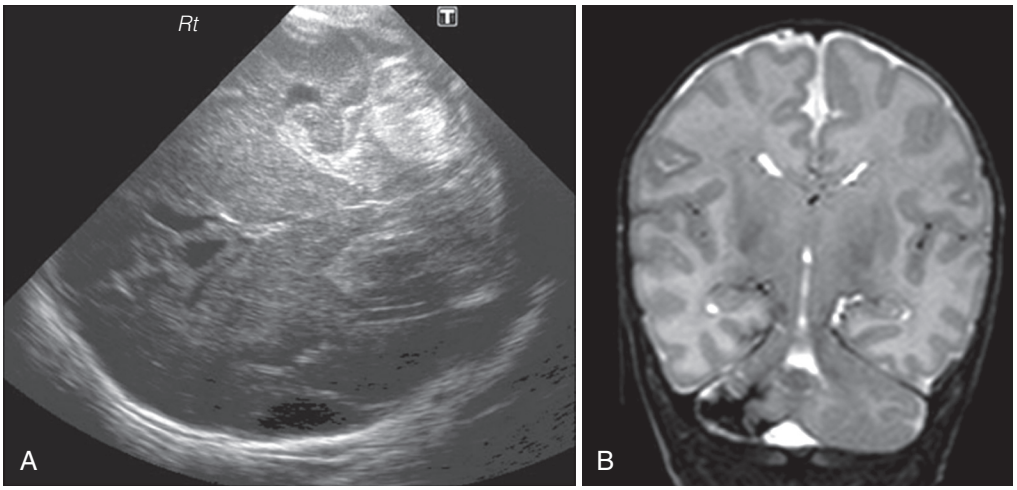


• **Fig. 53.2** **A,** Cranial ultrasonography, coronal view, shows intraventricular hemorrhage and parenchymal hemorrhage not in communication with the lateral ventricle. **B,** Three weeks later, a single cystic lesion is present after resolution of the hemorrhage. **C,** At term, the cyst is no longer seen.



• **Fig. 53.3** **A** and **B,** Cranial ultrasonography, coronal view, shows intraventricular hemorrhage and parenchymal hemorrhage not in communication with the lateral ventricle. **C,** At term age, multiple cysts are seen adjacent to the lateral ventricle.

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• **Fig. 53.4** **A,** Cranial ultrasonography, axial scan through the temporal bone, shows a large right cerebellar hemorrhage. **B,** The magnetic resonance imaging (MRI) scan, T2-weighted, spin-echo sequence still shows evidence of blood (low signal intensity) at term equivalent age, as well as atrophy of the right cerebellar hemisphere.

but is still inferior to MRI (Fig. 53.4).[93] Cerebellar hypoplasia without an apparent cerebellar hemorrhage has also been reported as a common sequel of severe immaturity. Reduced cerebellar volumes were only shown on three-dimensional MRI in preterm infants at term-equivalent age in association with supratentorial pathology, such as hemorrhagic parenchymal infarction, intraventricular hemorrhage with dilation, and periventricular white matter damage.[109,136] More recent studies have confirmed significantly slower cerebellar growth at term-equivalent age in the presence of severe supratentorial IVH,[57] but no reduced cerebellar growth in the presence of associated white matter injury.[115]

Pathogenesis

The precise nature and origin of GMH-IVH remain uncertain. Although some groups have suggested that the capillaries in the germinal matrix do not rupture easily, others have suggested that they can because the vessels are immature in structure with little evidence of basement membrane protein and they are of relatively large diameter. Early neuropathologists considered subependymal bleeding to be entirely venous in origin. This theory was rebutted by Wigglesworth and Pape,[134a] who suggested, on the basis of their injection studies, that capillary bleeding was more prominent than terminal vein rupture. There has been a return to the concept that most parenchymal hemorrhages are caused by venous infarction[41] or by reperfusion injury after an ischemic insult. An anatomic analysis of the developing cerebral vasculature did not show precapillary arteriole-to-venous shunts.[4]

Prenatal Factors

Histologic signs of amniotic infection have been shown by some to increase the risk of GMH-IVH,[35,117] but not by others.[103] This fits in well with acute inflammatory placental lesions and increased serum levels of interleukin (IL)-1-beta, IL-6, and IL-8, noted to be associated with severe IVH in extremely premature infants.[45,117,138] In one of these studies, a correlation was shown between blood cytokine concentrations and altered hemodynamic function.[138] Cord blood IL-6 concentration correlated inversely with newborn systolic, mean, and diastolic blood pressures. The number of infants with an IVH was limited, but in the five infants with IVH, the placenta significantly more often showed evidence of fetal inflammation.[138] An increase in total leukocytes during the first 72 hours after birth, as well as an increased ratio of immature-to-total white blood cells (WBCs), was also recognized as an independent risk factor for GMH-IVH.[138]

Maternal preeclampsia has been associated with a reduced risk of GMH-IVH.[36] The protective effect appears to be a result of enhanced in utero maturation of the fetus. In a recent study, intrauterine growth restriction (IUGR) did not lead to increased neonatal brain injury on cranial ultrasonography but was associated with increased mortality.[74] Administration of antenatal corticosteroids is, according to several studies, the most important protective factor against development of GMH-IVH.[98] The effect may be caused by a direct maturational effect on the brain, but other factors, such as the reduction of the severity of lung disease and the decreased need for inotropes, may also be involved. Several studies have shown that male gender is associated with a high incidence of IVH and an increased rate of severe IVH.[54,83]

Intrapartum Factors

Whether the mode of delivery plays a role is still uncertain.[42] A reduced mortality, but not a reduced risk of a GMH-IVH, was reported in a Swedish population-based study for preterm infants with a gestation of 25-36 weeks, when avoiding vaginal breech delivery.[46] When specifically

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studying the mode of delivery in 2885 small for gestational age (SGA) infants, no significant difference in IVH was noted between the cesarean delivery and vaginal delivery groups. Cesarean delivery compared with vaginal delivery was associated with increased odds of respiratory distress syndrome.[130] A vaginal breech delivery is, in some studies, associated with a higher risk of large GMH-IVH, but this effect was not found in a multivariable analysis.[97] In a population-based study from Israel, the rate of severe GMH-IVH was 7.7% for infants delivered by cesarean section compared with 13.6% in vaginal delivery ($P < 0.001$). In the multivariable model, cesarean delivery had no effect on the odds for severe IVH (odds ratio [OR] 0.98; 95% CI 0.77-1.24). Similar data were found in another study with a higher incidence of severe IVH in the vaginal delivery group (16.2%) versus 6.8% in the cesarean section group. The association was only seen in those born after less than 28 weeks' gestation (OR 2.05 [1.29-3.25].[37] Neonatal transport for infants born outside a tertiary center has also been shown to be a risk factor.[84] This was confirmed in another study, in which the overall incidence of IVH in the sample was 14.7%, and the transport group had more IVH compared with the inborn group (27.4% versus 13.4%): adjusted OR 1.75 (85% CI 1.64-1.86; $P < 0.001$). Severe IVH was higher in the transport group compared with the inborn group (44.1% versus 32.9%): adjusted OR 1.44 (95% CI 1.22-1.70; $P = .001$). It was recently suggested that the reason may not be the transport itself, but the association with underlying clinical variables.[128]

Delayed cord clamping was initially reported to be associated with a reduction in GMH-IVH as demonstrated by five infants (14%) in the delayed clamping group compared with 13 infants (36%) in the nondelayed group ($P = 0.03$).[78] The impact of delayed cord clamping on IVH was evaluated adjusting for gestational age and cesarean section. The final model indicated that the IVH rate was more than three times higher in the immediate cord clamping group (OR 3.5; 95% CI 1.1-11.1). In a meta-analysis of 18 randomized controlled trials (RCTs), there was significant reduction for infant deaths (RR 0.69; 95% CI 0.52-0.91), but no reduction in the incidence of IVH.[32] A recent RCT enrolling enrolled 1,566 infants with gestation of less than 30 weeks was unable to show a difference for the combined outcome of death or major morbidity at 36 weeks of gestation and no difference was found for development of GMH-IVH.[116] Being born outside office hours increased the risk of development of GM-IVH (OR 1.39; 95% CI 1.23-1.57).[51]

Neonatal Factors

Respiratory problems and respiratory distress syndrome (RDS), in particular, have been recognized as important risk factors in the development of GMH-IVH. This association is most likely not causal but results from complications, such as hypercarbia, pneumothorax, and acidosis, occurring during mechanical ventilation for RDS.[53,124] Because of improvement in ventilatory techniques, including an increased use of nasal continuous positive airway pressure, hypercarbia, and severe acidosis have become less common. Hypercarbia, a potent cerebral vasodilator, especially when combined with a severe acidosis, has been noted to be associated with GMH-IVH.[124]

Cardiovascular Factors

The immature brain is considered vulnerable to fluctuations in blood pressure because of limitations in autoregulation of cerebral blood flow. Impaired autoregulation renders the cerebral circulation "pressure passive" and, hence, unprotected from any wide swings or changes in blood pressure. This applies especially to sick preterm infants. Data initially obtained by using a radioactive xenon tracer showed a direct linear relationship between blood pressure and cerebral blood flow in a small number of infants. Similar findings were obtained by using near-infrared spectroscopy.[120] With use of these techniques, it was shown that routine caregiving procedures in critically ill preterm infants are associated with major circulatory fluctuations and that these cerebral hemodynamic changes were associated with early parenchymal ultrasound abnormalities.[70] Looking at a selected population of ventilated infants with evidence of asynchronous respiratory efforts, a significant reduction in IVH (any grade and severe IVH) was found, using muscle paralysis.[14] The fluctuating pattern may be exaggerated in hypovolemia. Hypotension is common in infants with severe RDS, and in the presence of a pressure-passive cerebral circulation may lead to hypoxia–ischemia of the germinal matrix. It has been shown that arterial hypotension precedes the development of GMH-IVH,[124] with the hemorrhage occurring during a period of reperfusion. In a study using continuous near-infrared spectroscopy and mean arterial blood pressure (MABP) measurements, MABP–regional cerebral oxygen saturation ($rScO_2$) correlation suggested more pressure-passive brain perfusion in infants with IVH.[3] In another study measuring flow in the superior vena cava, a low flow was detected during the first few hours of life before IVH occurs.[91] Delayed cord clamping was noted to be associated with a higher flow in the superior vena cava, and antenatal administration of steroids is associated with a reduction in the need for blood pressure support. Next to a reduction in the severity of RDS, this effect on blood pressure may be most protective for the development of a GMH-IVH. Early administration of fresh frozen plasma does not reduce the incidence of GMH-IVH.[63,90] A reduction in GMH-IVH has been seen during an era of closer attention to blood pressure, gentle handling, synchronous ventilation, and less severe RDS because of antenatal steroid and postnatal surfactant therapy, rather than because of any specific drug used as prophylaxis.

Genetic Factors

Thrombophilic disorders, including factor V Leiden mutation, which renders factor V resistant to cleavage by activated protein C, and prothrombin G20210A mutation, which was found to be associated with raised plasma

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concentrations of prothrombin, were suggested to play a role in the development of GMH-IVH,[102] but a large prospective study was unable to confirm previously reported associations of hemostasis gene variants and development of severe IVH in infants with very low birth weight, except for an increased prevalence for the methylenetetrahydrofolate reductase 1298A>C variant.[2] In preterm infants with an atypical time of onset, either antenatal or beyond 96 hours after birth, an association was noted with polymorphism in the factor V Leiden gene.[44] Antenatal porencephaly was reported to be associated with a mutation in the collagen 4A1 gene (*COL4A1)* encoding procollagen type 4a1, a basement membrane protein in two preterm siblings and preterm twins.[8,20] The diagnosis can be made before birth and should be considered in the presence of a parenchymal hemorrhage, especially when associated with a cerebellar hemorrhage.[67]

TABLE 53.1 Grading System for Neonatal Intraventricular Hemorrhage*

Description	Generic Term
Grade I: Germinal matrix hemorrhage	GMH
Grade II: Intraventricular hemorrhage without ventricular dilation	GMH-IVH
Grade III: Intraventricular hemorrhage and with acute ventricular dilation (clot fills >50% of the ventricle)	GMH-IVH with acute dilatation
Intraparenchymal lesion—size, location	Intraparenchymal hemorrhage

*This represents an evolution of the system described in Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of the subependymal intraventricular hemorrhage: a study of infants with birth weights less than 1,500 grams. *J Pediatr.* 1978;92:529.
GMH, Germinal matrix hemorrhage; IVH, intraventricular hemorrhage.

Diagnosis

With ultrasonography largely available in neonatal units, most high-risk preterm infants undergo routine ultrasonography soon after admission or within the first few days after birth. Three clinical syndromes, however, can be recognized in preterm infants not paralyzed or heavily sedated on the ventilator.[127] The first is known as *catastrophic deterioration*, noted by a sudden deterioration in the infant's clinical state, such as an increase in oxygen or ventilatory requirement, a fall in blood pressure, or acidosis. More often, however, a drop in hematocrit is seen without a clear change in the infant's condition. The *saltatory syndrome* is more common and gradual in onset, presenting with a change in spontaneous general movements. The third and most frequent presentation is *asymptomatic*; 25%-50% of infants with GMH-IVH have no obvious clinical signs.

A classification system suitable for describing early and late ultrasonography appearances, based on that suggested by Volpe,[127] is given in Table 53.1.[91a]

Ultrasonography is a noninvasive bedside technique that uses the anterior fontanel and increasingly also the posterior and mastoid fontanel as acoustic windows. The posterior fontanel improves detection of small IVHs.[15] The mastoid window allows for detection of cerebellar hemorrhages with a diameter of at least 4 mm.[111] Good correlations of GMH-IVH signs on ultrasonography with autopsy findings have been reported for the more severe hemorrhages. With the increased use of MRI, it has become apparent that GMHs at sites other than at the level of the caudate nucleus, such as the roof of the temporal horn, are not always identified with ultrasonography.[93] With ultrasonography, it also is not always possible to be certain about the presence or absence of a small associated IVH.[92] In contrast to MRI, immediate access to ultrasonography, as well as the fact that the examination can be repeated as often as indicated, still makes this technique the first-choice method.

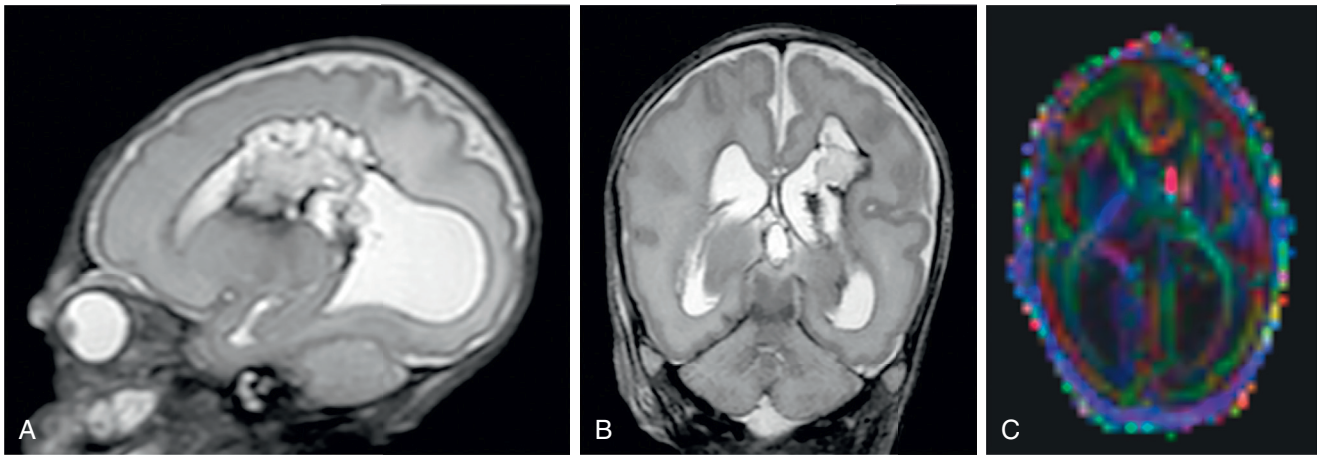
Timing of the examination depends on the questions raised. An examination within hours after delivery helps in timing the lesion as antenatal or postnatal. When trying to determine risk factors, sequential scans until the GMH-IVH is diagnosed are also important. A single scan at the end of the first week shows 90% of all hemorrhages as well as their maximum extent. Further ultrasound examinations (up to two to three times weekly) are required in infants with any degree of hemorrhage to detect the occurrence of posthemorrhagic ventricular dilation (PHVD), which occurs in approximately 30%, and the occurrence of associated PVL.[88] The more severe the hemorrhage, the higher is the risk for development of PHVD, which tends to occur 10-20 days after the onset of GMH-IVH.[9]

Unilateral intraparenchymal hemorrhage associated with a bilateral or ipsilateral GMH-IVH is now considered to be caused by impaired drainage of the veins in the periventricular white matter, resulting in venous infarction.[21,41] This type of lesion is classically triangular or fan shaped, with the apex at the outer border of the lateral ventricle. In some cases, the lesion is globular, with the apex of the triangle at the midline and a smooth outer border. The globular type of lesion (usually unilateral) evolves over 2-3 weeks into a porencephalic cyst (Fig. 53.5), whereas those intraparenchymal hemorrhages that are clearly separate from the ventricle at the start often form multiple small cysts (see Fig. 53.3).[21]

Management

Clinical management of children who have GMH-IVH is not different from that of other at-risk preterm infants. Minimal handling, prevention of fluctuations in blood pressure or carbon dioxide (CO_2) levels, prevention of breathing against the ventilator, and optimization of any coagulopathy may be warranted in an attempt to prevent extension of the initial hemorrhage. A blood transfusion may be needed in the case of a large IVH associated with a drop

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• **Fig. 53.5** Magnetic resonance imaging (MRI) scans. T2-weighted sequence in sagittal plane (**A**) and coronal plane (**B**), with a large intraventricular and intraparenchymal hemorrhage. **C,** Diffusion tensor imaging, direction-encoded color map only shows the descending corticospinal tract on the unaffected side (blue).

in the hemoglobin level. Continuous electroencephalography (EEG) monitoring may be helpful in the detection of subclinical seizures (see Chapter 55). The use of fibrinolytic therapy in an attempt to resolve the initial clot has been disappointing because it can even result in rebleeding.[99] Repeat scanning with ultrasonography is indicated to diagnose PHVD. Ventricular dilation seen on cranial ultrasonography usually precedes the development of clinical symptoms by several weeks. The clinical signs are a full fontanel, diastasis of the sutures, and a rapid increase in head size. "Sun setting" of eyes is a late sign. PHVD is transient in approximately half the infants and is persistent or rapidly progressive in the remaining cases.[88] Once it is recognized that the ventricles have begun to enlarge, the baseline size should be measured by using ultrasonography. The most widely adopted measurement system is that of Levene and Starte.[66] This "ventricular index" is the distance between the midline and the lateral border of the ventricle measured in the coronal view in the plane of the third ventricle. Another useful measurement is the depth of the frontal horn taken just in front of the thalamic notch, with height greater than 3 mm being used to define ventriculomegaly and one greater than 6 mm to suggest PHVD.[23] Measuring the occipital horn in a sagittal plane can also be useful because there can be a discrepancy between the anterior and posterior horn widths (see Fig. 53.1). Any measurement greater than 24 mm also suggests severe PHVD. The ventricular index graph of Levene indicates a gestational age range of 27-40 weeks. New reference values for the ventricular index, anterior horn width, and thalamo-occipital distance have been published, with an age range of 24-42 weeks.[10] Accurate measurement of CSF pressure is required to distinguish infants with progressive hydrocephalus (i.e., those with raised intracranial pressure) from those in whom the dilation is due to cerebral atrophy (low pressure). Raised CSF pressure can cause symptoms, including visual disturbance, seizures, feed intolerance, and apneas. In the long term, pressure-induced destruction of neuronal tissue can lead to motor handicap and cognitive impairment. Short-term adverse effects on the nervous system have been confirmed with use of somatosensory and visual evoked potentials, Doppler estimates of cerebral blood flow velocity, and near-infrared spectroscopy (NIRS).[62] Soul et al.[108] demonstrated a pronounced effect of CSF removal on cerebral perfusion regardless of the opening pressure and the amount of fluid removed. In another study of nine infants with PHVD, NIRS was used and a significant cerebral blood flow increase was measured (15.6%) following a ventricular tap (14.6 ± 4.2 to 16.9 ± 6.6 mL/100 g/min), but without a corresponding change in cerebral metabolic oxygen requirement ($CMRO_2$) (1.02 ± 0.41 mL O_2/100 g/min).[76] CSF hypoxanthine levels of IL-8, IFN-gamma, and sFas (soluble Fas) were noted to be raised in infants with PHVD and especially so in those with associated PVL.[104,106] Other CSF biomarkers were found to be increased in infants with PHVD (amyloid precursor protein [APP], soluble APP-alpha [sAPP-alpha]), L1 cell adhesion molecule (L1CAM), APP, and total protein were selectively increased in PHH (all $P < 0.001$) compared with preterm controls or infants with an IVH but without PHVD.

There is some evidence that early drainage of CSF alters the natural history or outcome of PHVD. In a large, retrospective, observational study, a significant reduction in the need for shunt placement was noted when intervention was started before the 97th percentile + 4 mm line of the graph of Levene and Starte[66] was crossed and when the threshold for inserting a subcutaneous reservoir was low.[9] A more recent retrospective study comparing two centers, treating early, on the basis of ultrasonography measurements, or treating late, on the basis of clinical symptoms, showed a worse outcome at 2 years in the latter group.[65] The initial data of the drainage, irrigation, and fibrinolytic therapy (DRIFT) study showed a reduced need for

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shunt insertion: 22% compared with approximately 60% in previous multicenter studies.[134] A subsequent RCT showed a high risk (33%) of rebleeding in the group allocated to DRIFT without an apparent positive effect on the need for a ventriculoperitoneal shunt.[133] When these children were seen at 2 years' corrected age, 21 of the 39 (54%) infants assigned to DRIFT died or were severely disabled versus 27 of 38 (71%) in the standard group (adjusted OR 0.25 [95% CI 0.08-0.82]). Among the survivors, 11 of 35 (31%) in the DRIFT group had severe cognitive disabilities versus 19 of 32 (59%) in the standard group (adjusted OR 0.17 [95% CI 0.05-0.57]).[133] An interesting observation was that the use of quantitative cranial ultrasonography measurements was useful for predicting outcome.[50] Neither ventricular area nor ventricular width correlated with developmental quotient (DQ) in grade III IVH, but the intraventricular echodensity area correlated with motor DQ in infants with periventricular hemorrhagic infarction, and the parenchymal lesion area correlated significantly with later mental and motor DQ. A prospective international randomized study, randomizing for early or later placement of a subcutaneous reservoir, showed no difference in ventriculoperitoneal shunt requirement, but the percentage of shunts inserted was the lowest reported so far—19% when treatment was started when the P97 line was crossed and 23% when treatment was started once the p97 + 4 mm line was crossed.[21a] Even in infants started early, an effect on volume of the central gray nuclei ([95% CI]: −1.4 cc [−2.3; −0.5]), cerebellum (−2.7 cc [−3.8; −1.6]), ventricles (+12.7 cc [7.9; 17.4]), and extracerebral CSF (−11.2 cc [−19.2; −3.3]), and with apparent diffusion constant (ADC) values in occipital, parieto-occipital, and parietal white matter (beta: +0.066 to −-0.119 × 10(−3) mm^2/sec) was noted on term-equivalent age MRI (TEA-MRI) ($P < 0.05$).[11]

Neurodevelopmental Outcome

Data on long-term neurologic and developmental outcomes mainly are from children who had a large IVH with or without parenchymal involvement. These follow-up data are still mainly based on neonatal ultrasonography findings. Associated PVL may have been missed with use of this technique, especially in children with posthemorrhagic ventricular dilation, where the periventricular white matter is more difficult to visualize. Children with small hemorrhages were not considered to be at increased risk for development of a major handicap, even though MRI was performed in the majority of the infants to additionally assess subtle white matter injury and cerebellar hemorrhages.[96] In one study, these infants did not develop more handicaps but scored lower on tests assessing visual–motor integration.[126] Three-dimensional volumetric imaging studies, however, have shown reduced gray matter volumes at term-equivalent age[123] associated with a reduced mental development index (MDI) on the Bayley Scales of Infant Development (BSID)-II, but this was only significant in the most immature infants with less than 30 weeks' gestation. In a recent meta-analysis, outcome was poorer in preterm infants with mild GMH-IVH compared with those without a hemorrhage. Among survivors, the odds of moderate-to-severe neurodevelopmental impairment (NDI) were higher with mild GMH-IVH in both unadjusted (1.75; 1.40-2.20; 3 studies) and adjusted (1.39; 1.09-1.77; 3 studies) pooled analyses. Adjusted odds of cerebral palsy and cognitive delay were higher with severe but not mild GMH-IVH.[86] Another study using advanced imaging techniques, including tract-based spatial *statistics* (TBSS) showed lower fractional anisotropy (FA) and higher radial diffusivity (RD) of the corpus callosum, limbic pathways and cerebellar tracts, especially in those with gestational age less than 29 weeks. These *diffusion tensor imaging* (DTI) abnormalities were associated with poorer locomotor, eye–hand coordination, and performance outcomes at 24 months.[118] The risk of a poor outcome increases significantly with the presence of post-hemorrhagic ventricular dilation (50%) and even further in those who require shunt insertion (75%).[94,118]

Children with ventriculomegaly present at term are at higher risk of a poor outcome. Outcome data from children with a unilateral parenchymal hemorrhage show a major neurodevelopmental disability in approximately 50%-80%, depending on the size and especially the site of the lesion. The most common handicap is a hemiplegia contralateral to the side of the parenchymal hemorrhage. Ten infants with a porencephalic cyst following a parenchymal hemorrhage were followed up into adolescence.[105] At all ages assessed, rates of motor, cognitive, and overall impairment were significantly higher compared with those in preterm control subjects ($P \leq 0.002$ for all tests). Six of the 10 children who were ambulatory when seen at 16-19 years required learning assistance in school and had social challenges. In a retrospective hospital-based population study, outcome was considerably better than reported previously, with cerebral palsy occurring in only 7.4% of the infants with a large IVH (grade III) compared with 37 (48.7%) of the 76 infants with a parenchymal hemorrhage ($P < 0.001$).[9] Data from the study by Leijser et al. support that this better neurodevelopmental outcome was related to earlier treatment of PHVD. The data from this retrospective observational study[65] are very much in contrast to those of another study looking at a large group of infants with a grade III/IV hemorrhage with and without a shunt.[1] Of the 562 infants with a grade III hemorrhage, 103 (18%) needed a ventriculoperitoneal shunt compared with 125 of the 436 (29%) with a grade IV hemorrhage. Children with severe IVH and shunts had significantly lower scores on the BSID II compared with children with no IVH and children with IVH of the same grade and no shunt. An MDI less than 70 was found in 183 of 424 (43%) infants with a grade III hemorrhage without a shunt compared with 59 of 99 (60%) in those with a shunt. In those with a grade IV hemorrhage without a shunt, 143 of 295 (48%) had an MDI less than 70, compared with 87 of 115 (76%) of those requiring a shunt. Infants with shunts were at increased risk for cerebral palsy

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and head circumference at less than the 10th percentile at 18 months' adjusted age. Infants with a grade III hemorrhage without apparent associated white matter involvement are more likely to do well or may develop diplegia, whereas those with a periventricular hemorrhagic infarction are more at risk of developing hemiplegia, depending on the site and extent of the lesion.

In a study by Goldstein et al.,[38] it was noted that neurodevelopmental impairment differed by gestational age in infants with a grade III hemorrhage, but not with grade IV hemorrhage. Contributors to neurodevelopmental impairment in infants with a severe hemorrhage included male gender, surgical necrotizing enterocolitis, and posthemorrhagic ventricular dilatation requiring a shunt.

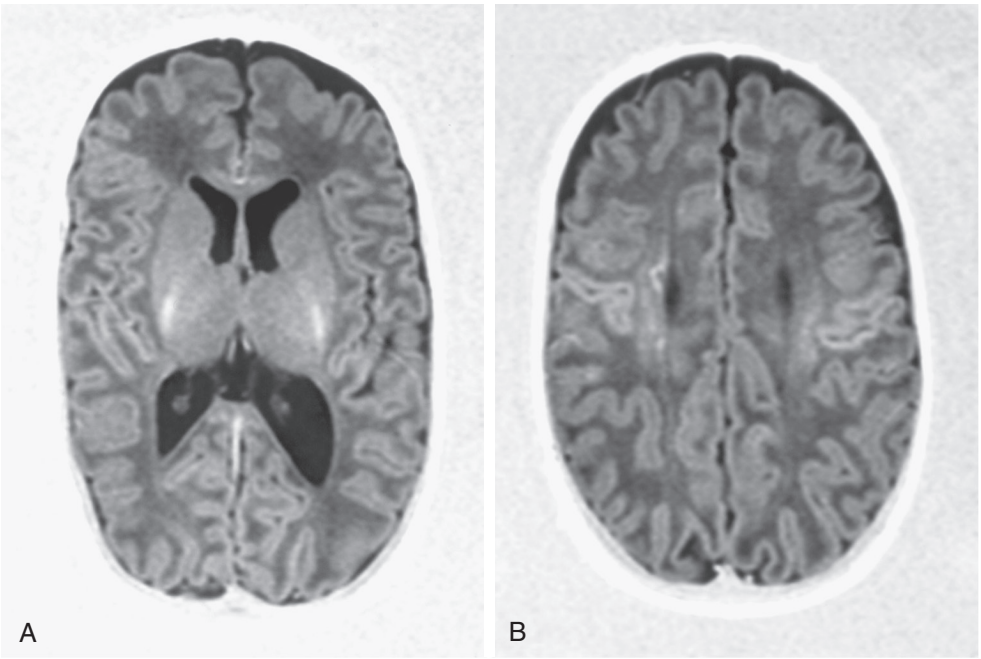
Early prediction of development of a hemiplegia is now possible with use of neonatal MRI. At term, myelination of the posterior limb of the internal capsule should be present (Fig. 53.6). In infants in whom hemiplegia subsequently developed, asymmetry and even lack of myelination of the posterior limb of the internal capsule were noted (Fig. 53.7).[24] Using DTI, visualization of the tracts is also possible at an earlier stage.[101]

Outcome data from preterm infants with cerebellar hemorrhage have caused some concern.[68] Neurologic abnormalities were present in 66% of infants with isolated cerebellar hemorrhage compared with 5% of the control group. Compared with controls, infants with isolated cerebellar hemorrhagic injury had significantly lower mean scores on all tested measures performed at a median age of 32 months, including severe motor disabilities (48% versus 0%), expressive language (42% versus 0%), delayed receptive language (37% versus 0%), and cognitive deficits (40% versus 0%). The study concluded that cerebellar hemorrhagic injury in preterm infants is associated with a high prevalence of long-term pervasive neurodevelopmental disabilities. Outcome of infants who had small and punctate lesions in the cerebellum, which can only be recognized on MRI, appears not to be abnormal, at least during the preschool period.[49a,115]

Prevention

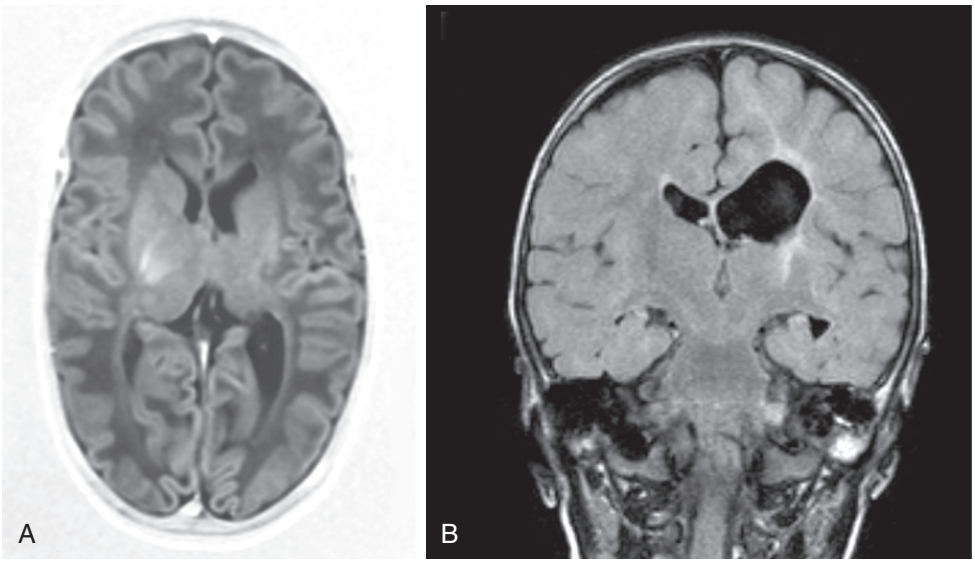
Both prenatal and postnatal pharmacologic prophylaxis have been used to reduce the incidence of GMH-IVH. With improvement in general neonatal care, a reduction has also been reported in many large neonatal units without the use of any drugs. Neonatal intensive care unit (NICU) characteristics were shown to affect the incidence of severe GMH-IVH, with NICUs with high patient volume and high neonatologist-to-staff ratio having a lower rate of severe GMH-IVH.[114]

The most promising specific prophylactic drugs are antenatal steroids. A systematic review published in 2017 involving more than 6000 babies showed a significant reduction in the risk for GMH-IVH, as diagnosed by ultrasonography (RR 0.55; 95% CI 0.40-0.76). There was no clear benefit toward improved long-term neurologic outcome (RR 0.64; 95% CI 0.14-2.98).[98] It is not certain whether the effect is mainly due to increased lung maturation and, therefore, less severe RDS, stabilization of postnatal blood pressure, or perhaps a direct protective effect on the brain. Betamethasone instead of dexamethasone is recommended because



• **Fig. 53.6 A,** Magnetic resonance imaging (MRI) scan, T1-weighted sequence, at term age, in same infant as in Fig. 53.2. A symmetric high signal at the level of the posterior limb of the internal capsule is seen. **B,** At a higher level, a small triangular area of high signal intensity is still seen as a sequel of the parenchymal hemorrhage.

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• **Fig. 53.7** Magnetic resonance imaging (MRI) scan, T1-weighted sequence, at term age, in same infant as in Fig. 53.3. **A,** There is no symmetric high signal at the level of the posterior limb of the internal capsule. **B,** A fluid-attenuated inversion recovery (FLAIR) sequence at age 18 months shows high signal intensity suggestive of gliosis adjacent to the porencephalic cyst and across the internal capsule.

dexamethasone has been associated with an increased incidence of PVL. However, a more recent Cochrane review showed a reduced risk of IVH when dexamethasone rather than betamethasone was used (RR 0.44; 95% CI 0.21-0.92; 4 trials, 549 infants).[12]

Antenatal phenobarbital was shown to be protective in some but not all studies. The quality of some of these studies was not good because of lack of randomization or a placebo group. When these studies were excluded from a systematic review, no protective effect could be shown.[17]

Studies of antenatal administration of magnesium sulfate have yielded different results. A systematic review published in 2009 involving over 6000 babies substantially reduced the risk of cerebral palsy (RR 0.68; 95% CI 0.54-0). The number of women needed to be treated to benefit one baby by preventing cerebral palsy is 63 (95% CI 43-87).[27] In a multicenter RCT, no significant reduction was found for the incidence of a large GMH-IVH (2.1% versus 3.2 %; RR 0.64; 95% CI 0.38-1.06). Moderate or severe cerebral palsy occurred significantly less frequently in the magnesium sulfate group compared with the control group (1.9% versus 3.5%; RR 0.55; 95% CI 0.32-0.95).[100]

Maternal vitamin K administration was associated with a nonsignificant reduction in the overall rate of GMH-IVH (RR 0.76; 95% CI 0.54-1.06) and a significant reduction in severe GMH-IVH (grades 3 and 4) (RR 0.58; 95% CI 0.37-0.91).[18] Phenobarbital was the first drug used postnatally in the prevention of GMH-IVH. Although the first studies were promising, a meta-analysis of 12 trials was unable to show a reduction in either all GM-IVH (typical RR 0.91; 95% CI 0.77-1.08), or severe IVH (typical RR 0.77; 95% CI 0.58-1.04).[107]

Indomethacin has been the most promising prophylactic drug administered postnatally. The results of a meta-analysis involving 19 trials and a total of 2872 infants showed a significant reduction in the incidence of grades III and IV hemorrhage (pooled RR 0.66; 95% CI 0.53-0.82).[33] The children of the original cohort were assessed at 8 years of age, and no effect of indomethacin on long-term outcome was seen.[126] Analysis of the original cohort by gender, however, showed that indomethacin reduced the incidence of IVH by half, eliminated parenchymal hemorrhage, and was associated with higher verbal scores at ages 3-8 years in boys.[77] A meta-analysis of ibuprofen involving 33 studies did not show a reduction in the incidence of IVH in a subgroup of 571 infants (typical RR 1.21; 95% CI 0.74-1.98).[89]

Other Hemorrhages

Subdural and subarachnoid hemorrhages are probably underdiagnosed because they are difficult to recognize with use of cranial ultrasonography (see also Chapter 29). Clinical signs may be mild or absent. A significant subdural hemorrhage is most often related to birth trauma, but a small subdural hemorrhage was noted to be a common occurrence in an MRI study looking at 111 consecutive full-term infants.[132] A subdural hemorrhage occurred in nine infants—after a normal vaginal delivery in three (6.1%), after forceps-assisted delivery after an attempted ventouse delivery in five (27.8%), and after traumatic ventouse delivery in one (7.7%). Similar results were found on MRI in another study on 88 neonates with a mean age of 21 days). Sixteen infants had subdural hemorrhage, two subarachnoid hemorrhage, and six parenchymal hemorrhage. All neonates had been delivered vaginally, with a rate of intracranial hemorrhage of 26%. In this group, no association was seen with traumatic or assisted birth compared with uncomplicated vaginal births, and in all cases, the infants were

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asymptomatic.[71] Underlying mechanisms can be tearing of the dura, occipital diastasis, or rupture of the bridging veins. Tearing of the dura can occur after a precipitous delivery or from use of instrumentation, both of which are not very common with preterm delivery. A dural tear results in extensive bleeding from the adjacent sinus. Occipital diastasis can occur during a vaginal breech delivery with excessive extension of the neck of the infant, although vaginal breech deliveries are not commonly performed on the basis of the results of several multicenter, randomized studies.[48] Rupture of the bridging veins is the most common etiology of subdural hemorrhage and may be seen in association with subarachnoid hemorrhage. Children are usually born at term and present with a full fontanel, lethargy, apnea, or seizures. In cases of severe hemorrhage, a midline shift may be seen, and surgery needs to be considered. Percutaneous needle aspiration of the subdural hematoma may be attempted, and a study showed that it was successful in five of seven infants and recommended it as the treatment of choice.[125] This was confirmed in another study, with successful intervention in eight infants.[14a] The diagnosis usually is made by using CT or MRI (Fig. 53.8). Hydrocephalus can develop from outflow obstruction and may require temporary external drainage, sometimes followed by permanent drainage.

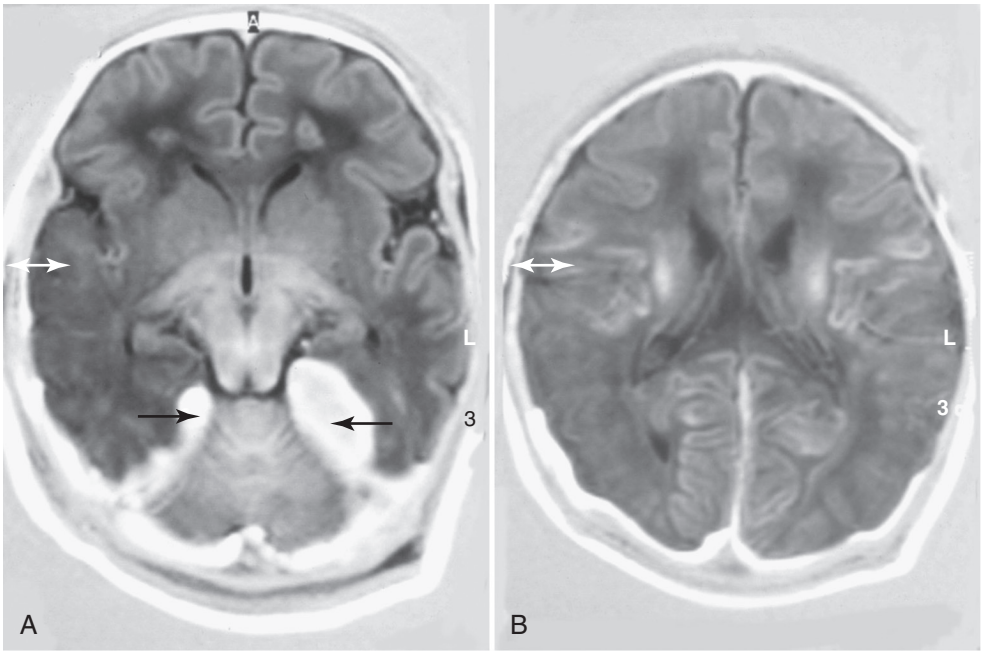
Small subarachnoid hemorrhages, which are usually asymptomatic, are sometimes seen in preterm infants at postmortem examination. Blood can leak into the subarachnoid space after IVH by flowing through the aqueduct into the fourth ventricle and subsequently through the foramina of Luschka and Magendie into the subarachnoid space. Once again, the diagnosis is hard to make with ultrasonography unless the lesion is large and causes compression of brain tissue. Hydrocephalus is less commonly seen than in children with a subdural hemorrhage.

Cerebral Artery Infarction

Because of increased access to neonatal MRI, infarction of a major artery, or a branch arising from it, is better recognized. This condition is often referred to as *neonatal stroke* or *perinatal arterial ischemic stroke*.[59,95] Information about incidence is becoming available with the introduction of neonatal registries.[58] Newborn infants are susceptible to neonatal stroke because of a number of factors present around the time of delivery, such as the hypercoagulable state of the mother, mechanical stress during delivery, the transient right-to-left intracardiac shunt, and the risk of dehydration during the first few days after delivery often associated with a high hematocrit and blood viscosity[58,123] In another study, male gender (OR 2.8), family history of seizures (OR 6.5) or neurologic diseases (OR 4.9), and 1 or greater (OR 5.8) and 2 or greater (OR 21.8) intrapartum complications were independently associated with neonatal stroke.[75] Neonatal stroke can be classified into sinovenous thrombosis and arterial ischemic stroke.[22] Both conditions are still not always detected because presenting symptoms may not always be clear and appropriate imaging is not always performed. Arteriovenous malformations are discussed in Chapter 76.

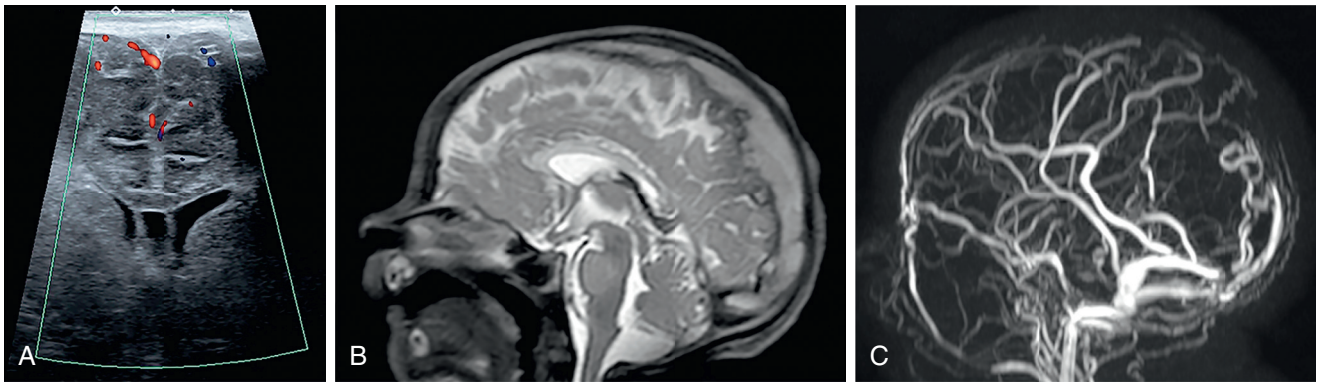
Sinovenous Thrombosis

An incidence of 41 per 100,000 newborn infants with sinovenous thrombosis was found in the Canadian Pediatric



• **Fig. 53.8** **A,** Magnetic resonance imaging (MRI) scan, T1-weighted sequence, shows a large collection of blood in the posterior fossa with blood along the tentorium bilaterally (*black arrows*). **B,** At a higher level, extensive cortical highlighting is seen posteriorly and in the region of the sylvian fissure (*white arrows*).

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• **Fig. 53.9** Magnetic resonance imaging (MRI) scans obtained at age 12 days, after development of seizures on day 9. **A,** Doppler ultrasound does not show any flow in the superior sagittal sinus. **B,** On the midsagittal T2-weighted sequence, a large thrombus is seen at the level of the superior sagittal sinus. **C,** Magnetic resonance venography image shows loss of flow at the level of the superior sagittal sinus and straight sinus.

Ischemic Stroke Registry but was higher in a population-based study performed in the Netherlands.[7,22] Most cases (66%) come to medical attention within 48 hours of birth, although symptoms can also develop 10-14 days after delivery, sometimes associated with dehydration or infection.[7,85] Almost half the children (43%) with sinovenous thrombosis in this registry were newborns. Seizures are the most common presenting symptom and were reported in 70% of the infants from the Canadian Registry. Lethargy is also commonly present. The fontanel may be full, and the scalp veins may be prominent.

During the birth process, molding of the skull and overriding of the sutures of the different parts of the skull may occur and affect the underlying sinus, resulting in the occurrence of sinovenous thrombosis. Perinatal asphyxia is a commonly associated risk factor, as reported in 24% of the cases in the Canadian Registry. The superior sagittal sinus and the lateral sinuses are most commonly involved, but in the study by Berfelo et al.,[7] the straight sinus was most commonly affected, and an associated thalamic hemorrhage was common. Involvement of the straight sinus, the vein of Galen, and the internal cerebral vein has also been reported. The occurrence of associated IVH, especially a unilateral thalamic hemorrhage or periventricular congestion, may help clarify the diagnosis.[56,136] Wu et al.[136] noted that sinovenous thrombosis was significantly more common in full-term infants with IVH and unilateral thalamic hemorrhage (4 of 5) compared with newborns with IVH only (5 of 21). They strongly recommend the diagnosis of sinovenous thrombosis be considered in any full-term neonate presenting with IVH.

Risk factors for cerebral sinovenous thrombosis during the first 28 days of life include dehydration, infection, maternal fever/chorioamnionitis, hypoxic–ischemic injury, and thrombophilia.[7,119] In another study, risk factors were analyzed in 30 full-term infants with sinovenous thrombosis.[137] They reported that 29% of these newborn infants had been on extracorporeal membrane oxygenation and that 23% had congenital heart disease. Only seven infants were tested for a genetic thrombophilia, and four of these seven were found to be positive.

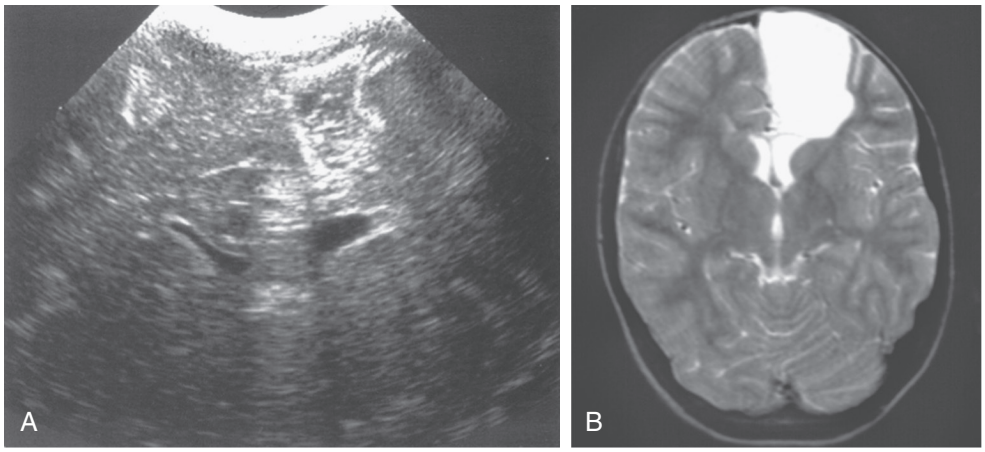
A diagnosis can be made by using Doppler flow ultrasonography, which may demonstrate absent or decreased flow in the affected sinus.[81] Contrast-enhanced CT can also be used and shows the so-called empty delta sign—the lack of contrast filling. The best modality is MRI, especially magnetic resonance venography, which helps make a definitive diagnosis by demonstrating a reduction or absence of venous flow in the affected venous sinus (Fig. 53.9).

There is no agreement about the use of antithrombotic therapy in this age group, even though recommendations in favor of its use have been made recently. Studies show that regional practices with regard to antithrombotic therapy show considerable variability.[52] Different treatment policies were noted, with physicians in the United States being less likely to treat neonates with cerebral sinovenous thrombosis with antithrombotic medications compared with physicians at centers in other countries—25% of these neonates being treated in the United States versus 69% in other countries.[52] About 25% of the infants show propagation of the thrombus.[85] Whether early anticoagulation therapy in those with involvement of the straight sinus may prevent development of a thalamic hemorrhage still needs to be assessed, but the use of antithrombotic therapy was shown to be safe in a study from the Netherlands.[7] Development of electrical status epilepticus during sleep is not uncommon after associated thalamic hemorrhage.[55] The number of infants with cerebral sinovenous thrombosis is limited; therefore enrollment in many centers will be required to be able to conduct a randomized study.

Greater than 90% of newborns with sinovenous thrombosis survive, with 48%-61% of survivors having moderate to severe disabilities and 9% experiencing a recurrence of cerebral or systemic thrombosis.[7,85]

In the retrospective study by Fitzgerald et al. who assessed 42 newborn infants, 57% presented with seizures and 60% had associated parenchymal infarcts, which were mainly hemorrhagic.[31] Of these 42 infants, 79% had any

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• **Fig. 53.10** Preterm infant, gestational age 32 weeks. **A,** Routine ultrasonography image obtained at 2 weeks shows an area of cystic evolution in the region of the left anterior cerebral artery. Mild ex vacuo dilation of the left ventricle is also present. **B,** T2-weighted magnetic resonance imaging (MRI) scan, spin-echo sequence, at age 7 years shows the parenchymal cavity in the same distribution.

form of impairment, with 59% having cognitive impairment, 67% cerebral palsy, and 41% epilepsy. Infarction was associated with the presence of later impairment.

Perinatal Arterial Ischemic Stroke

Cerebral infarction in the neonate has been defined as a severe disorganization or even complete disruption of both gray matter and white matter caused by embolic, thrombotic, or ischemic events.[61,95] In infants dying in the acute stage of the condition, the hemisphere is swollen and deeply congested. There is involvement of both white matter and the cortex, with secondary hemorrhagic infarction in some cases. In infants who survive for longer, contraction of the affected area is seen with softening and multiple cystic degeneration, giving a honeycomb appearance on sectioning. It is recommended that a distinction be made between a unilateral parenchymal hemorrhage, which usually occurs in the preterm infant and evolves into a porencephalic cyst, and an infarct in the region of the middle cerebral artery, which usually occurs in a term newborn and evolves into an area of parenchymal cavitation. A porencephalic cyst occurring after parenchymal hemorrhage of antenatal onset has, however, been referred to as *fetal stroke*, and small porencephalic cysts occurring after antenatal venous infarction have also been included within the spectrum of presumed perinatal stroke.[60]

Lesions involving the left hemisphere are three to four times more common than those of the right hemisphere. This may be the result of hemodynamic differences early after birth in association with the patent ductus arteriosus or a preferential flow across the left common carotid artery. Middle cerebral artery infarction occurs twice as often as involvement of any other artery.[58]

A classification system based on the main artery involved can be used. Infarcts in the territory of the middle cerebral artery were further subdivided into main branch, cortical branch, and lenticulostriate branch infarction.

Incidence

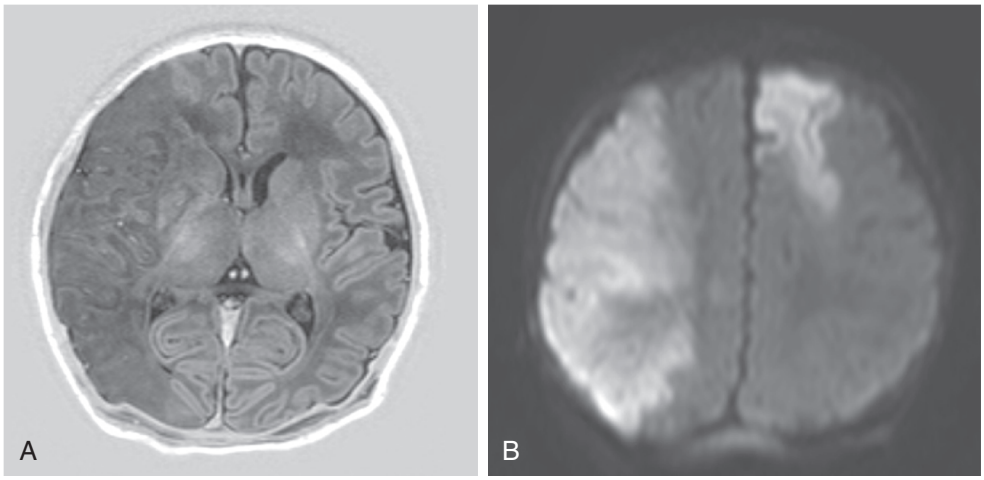
In the Canadian Registry, the incidence of perinatal arterial ischemic stroke was as high as 93 per 100,000 newborn infants, which is much higher than reported previously. Neonatal stroke is the second most common cause of neonatal seizures. Data about focal infarction in preterm infants are scarce. In a hospital-based study, an incidence of 7 per 1,000 was found in preterm infants with gestational age less than 35 weeks.[6]

Seizures are the most common presenting symptom.[58] They are usually of the focal clonic variety, but multifocal tonic or subtle seizures also may be seen (see Chapter 55). Many of the infants show no major clinical neurologic abnormality between seizures. The largest population reported, to date, is that of 248 infants, of whom 72% presented with seizures, which were focal in almost all,[58] and 26% were admitted because of respiratory problems.[58] Symptoms can be very subtle, especially in the preterm infant,[6,29] and the diagnosis can be easily missed. Presentation with a hand preference later in infancy may lead to a diagnosis, with an area of cavitation on CT or MRI suggestive of a perinatal or in utero arterial ischemic stroke, which is now referred to as *presumed perinatal stroke*.[60]

Diagnosis

When a newborn without an obvious history of perinatal asphyxia presents with focal seizures, care should be taken to not miss the diagnosis of arterial ischemic stroke. The middle cerebral artery is most commonly involved, and the infarct occurs more often on the left than the right side.[58] Arterial infarcts of the anterior and posterior cerebral artery are less often diagnosed, possibly because of the lack of clinical symptoms in the neonatal period[121] (Fig. 53.10). Involvement of the smaller branches of the middle cerebral artery is more often seen in preterm infants, whereas obstruction of the main branch is less common in this age group.[6,29] Infarcts can be hemorrhagic

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• **Fig. 53.11** Full-term infant, magnetic resonance imaging (MRI) scans obtained at age 4 days. **A,** T1-weighted sequence shows low signal intensity in the distribution of the right middle cerebral artery suggestive of main branch involvement. **B,** Diffusion-weighted imaging scan shows high signal intensity in the same area, as well as a smaller area of high signal intensity in the distribution of the left anterior cerebral artery.

in 20%, and bilateral infarcts can be seen in 10%-15% (Fig. 53.11).

In the absence of abnormalities on ultrasonography, MRI is recommended to confirm or exclude the diagnosis. Ultrasonography has not been considered reliable in making a diagnosis; this applies especially when the examination is made soon after the clinical presentation. By the end of the first week of life, a wedge-shaped area of echogenicity, often with a linear demarcation line, restricted to the territory of one of the main arteries, usually becomes apparent.[16] Cystic evolution can take place over the next 4-6 weeks, often associated with ex vacuo dilation of the ipsilateral lateral ventricle. Doppler ultrasonography can show asymmetry of arterial pulsations. Decreased pulsations on the affected side can be seen in the acute phase, whereas an increase in size and number of visible vessels in the periphery of the infarct and increased mean blood flow velocity in vessels supplying or draining the infarcted areas is often seen a few days later, and this is considered to result from luxury perfusion.

The threshold for performing MRI should be low in infants presenting with neonatal seizures.[129] The use of MRI plays an important role in making the diagnosis. If performed early after clinical presentation, diffusion-weighted imaging (DWI) is very helpful. This technique reveals abnormalities, indicating cytotoxic edema, at a very early stage, preceding abnormalities seen on conventional MRI. This technique also enables visualization of acute damage to the corticospinal tracts at the level of the midbrain.[61] Several studies have shown that these findings predict Wallerian degeneration and development of subsequent hemiplegia.[61] A repeat scan can show asymmetry at the level of the mesencephalon, which can be seen as early as 4-6 weeks after onset of the infarction and is referred to as *Wallerian degeneration*. Magnetic resonance angiography, which allows for investigation of the main vascular bed, can be used and can sometimes show dissection or occlusion of one of the main vessels. This may be rare, however, and this technique may also fail to show small vessel occlusion. Early assessment of structure–function relationship is possible with use of functional MRI. EEG showing focal electrographic and electroclinical seizures with ipsilateral suppression of the background activity and focal sharp waves are strongly suggestive of the presence of perinatal stroke.[72] Mercuri et al.[80] found an abnormal background pattern, even when recorded on two-channel EEG, to be the best early predictor of an adverse neurologic outcome.

Reorganization of the somatosensory cortex can be followed using a combination of transcranial magnetic stimulation and functional MRI.[30,37,110,122] Staudt et al.[110] showed that when a lesion abolishes the normal contralateral corticospinal control over the paretic hand, the contralesional hemisphere develops (or maintains) fast-conducting ipsilateral corticospinal pathways to the paretic hand. This reorganization with ipsilateral corticospinal tracts can mediate useful hand function. Normal hand function, however, seemed only possible with preserved crossed corticospinal projections from the contralateral hemisphere. Ipsilesional reorganization is less effective in the restoration of good motor function as opposed to contralesional reorganization.

Risk Factors

Perinatal complications have been reported in more than 50% of newborn infants who had suffered a perinatal stroke.[43,58,75] Perinatal stroke is multifactorial in origin, and when risk factors were compared with those in infants with neonatal encephalopathy, many were present in both groups; and cardiotocography results were abnormal in 67% of those with perinatal stroke and 77.5% of the infants with neonatal encephalopathy.[75] Stroke among infants admitted with neonatal encephalopathy is an uncommon

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observation. Cardiac disease, extracorporeal membrane oxygenation, and portal vein thrombosis have all been reported as associated risk factors. Stroke was especially common (31%) among infants with transposition of the great arteries, and this was associated with balloon septostomy.[82] Maternal cocaine abuse has also been considered as a cause of perinatal stroke. An underlying genetic prothrombotic disorder is not considered likely, and extensive investigations should not be routinely performed.[19] Population-based studies using case-matched controls found diverse etiologic factors responsible for perinatal arterial stroke in term infants. Infertility, preeclampsia, prolonged rupture of membranes, chorioamnionitis, and hypoglycemia have been identified as independent maternal risk factors.[43] A recurrence risk of 1.2% was reported among 84 newborn infants with perinatal stroke.[34] Association with elevated maternal antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulants) has also been reported. Data on risk factors in preterm infants are scarce.[6,29] Using case-matched controls (three controls per case, matched for gestational age), etiologic factors responsible for perinatal arterial stroke in preterm infants were studied, and it was noted that these were different from those in infants born at term. Twin–twin transfusion syndrome (19% versus 3%; OR 31.2; 95% CI 2.9-340.0; $P = 0.005$), fetal heart rate abnormality (58% versus 26%; OR 5.2; 95% CI 1.5-17.6; $P = 0.008$), and hypoglycemia (42% versus 18%; OR 3.9; 95% CI 1.2-12.6; $P = 0.02$) were identified as independent risk factors for preterm stroke.[6]

Prognosis

The outlook in most cases is relatively good. Published follow-up data from case reports suggest that the majority of the infants achieve independent walking before 13 months and that more than half of all infants surviving neonatal stroke are found to be doing well at age 12-18 months.[39,120] Spastic hemiplegia is the most important sequela, particularly after infarction of the main branch of the middle cerebral artery. There is an increased incidence among male infants. In a cohort studied by Mercuri et al., hemiplegia developed in only 5 of 24 infants (20%). Hemiplegia or asymmetric tone tended to develop only in those cases with involvement of the hemisphere, basal ganglia, and internal capsule on the first scan. At school age, 30% showed a hemiplegia, and another 30% showed some neuromotor abnormality. Involvement of the internal capsule was always associated with some motor disturbance.[79] The overall prevalence of cerebral palsy is approximately 1 in 2,000 children. On the basis of the estimated incidence of perinatal cerebral vascular infarction, it might be expected that this condition is the cause of the neurologic deficit in up to 20% of children with cerebral palsy. This is supported by data showing that 22% of 377 infants with cerebral palsy showed focal arterial infarction on head imaging.[135]

Two thirds of children with hemiplegia are of normal intelligence when seen at a young age. Deficits in higher-level cognitive skills may first become apparent during school, and this is more common in males, with development of epilepsy and involvement of the central gray nuclei.[87,131] Homonymous hemianopia may follow posterior cerebral artery infarction.[121]

Outcome data depend very much on the threshold for performing MRI, on the artery involved, and on whether the main branch is involved or only a cortical branch or one of the lenticulostriate branches.[127a]

Several groups have now shown that involvement of the lenticulostriate branches was more common in preterm infants.[6,29] Only three of 16 infants with involvement of a cortical branch or one or more lenticulostriate branches had cerebral palsy, in contrast to all five survivors with main branch involvement.[6]

Seizures are a common complication and occur beyond the neonatal period in 25%-67% of affected infants.[40] An infarct on prenatal ultrasonography and a family history of epilepsy were significantly associated with post-neonatal epilepsy in the univariate analysis. Because epilepsy may first develop later in childhood, the rate of epilepsy will be higher when follow-up is longer. In a recent study, the mean follow-up was 8 years and 5 months, and 16.4% of the patients developed post-neonatal epilepsy. The mean age at first post-neonatal seizure was 4 years and 2 months (range 1-10 years and 6 months).[113]

Even though the focus is often on motor outcome, other outcome parameters are also important and in a national cohort study, language was impaired in almost half (49%) of the children. Cerebral palsy, low academic skills, active epilepsy, and global intellectual deficiency were present in 32%, 28%, 11%, and 8%, respectively. Eventually, 59% of children were affected by at least one of the aforementioned conditions.[13]

Key Points

- Germinal matrix hemorrhage–intraventricular hemorrhage (GMH-IVH) is still a common problem in the extremely preterm infant.
- Posthemorrhagic ventricular dilation (PHVD) is an important complication of especially large IVH.
- Data are accumulating to suggest that PHVD should be treated prior to the onset of clinical symptoms.
- *Cerebral venous sinus thrombosis* should be suspected when an IVH with or without a thalamic hemorrhage is seen in a full-term infant.
- Perinatal arterial ischemic stroke occurs in about one in 2,300 full-term infants and usually presents with (hemi) convulsions.

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54

Hypoxic–Ischemic Encephalopathy

FLORIS GROENENDAAL AND LINDA S. DE VRIES

Hypoxic–ischemic encephalopathy (HIE) following severe perinatal asphyxia (also referred to in the literature as *perinatal hypoxia–ischemia* or *asphyxia neonatorum*) has an incidence of 1-2 per 1,000 live births in the Western world and is far more common in developing countries (see Chapter 8). Although metabolic disorders may mimic perinatal asphyxia, and genetic and placental factors may contribute to the clinical picture, brain imaging techniques have demonstrated acute changes in the brain of the term neonate after perinatal asphyxia occurs.

The chance of irreversible damage or death after severe perinatal asphyxia is high—up to 65% of patients enrolled in trials of neuroprotective strategies. Therapeutic hypothermia is neuroprotective, as has been demonstrated in several trials, and is standard therapy for (near-) term neonates with severe perinatal asphyxia and encephalopathy.[33] Ongoing studies will aim at additive strategies to augment the neuroprotection of hypothermia.[26]

Experiments in animals have demonstrated that the immature brain is more resistant to hypoxia–ischemia than the brain of the term neonate. The several reasons to explain this difference are a lower cerebral metabolic rate; lower sensitivity to neurotransmitters with potential neurotoxicity; and the greater plasticity of the immature central nervous system. Nevertheless, in the fetus and in the preterm neonate, cerebral hypoxia–ischemia is a major cause of acute mortality and, in survivors, morbidity. However, the neuropathology will be different from that of the full-term neonate (see Chapters 52 and 54).

Definitions

Hypoxic–Ischemic Encephalopathy

The term *HIE* describes abnormal neurologic behavior in the neonatal period after perinatal hypoxia–ischemia occurs. Previously, the term *post-asphyxial encephalopathy* was used, and some suggest that the term *neonatal encephalopathy* is best used because the cause of encephalopathy is not always obvious. This has also been suggested by the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy.[18]

The severity of HIE can be defined as mild, moderate, or severe, depending on clinical findings, as described by Sarnat and Sarnat[61]; this classification is widely used and is summarized in Table 54.1. Other clinical scoring systems have been developed to assess the severity of HIE and are used to select infants for therapeutic hypothermia[77] (Table 54.2).

Hypoxia or Anoxia

This denotes a partial (hypoxia) or complete (anoxia) lack of oxygen supply to the brain or blood. Hypoxemia denotes lack of oxygen in blood.

Ischemia

Ischemia refers to reduction (partial) or cessation (total) of blood flow to an organ (e.g., the brain), compromising both oxygen and substrate delivery, such as glucose to the tissue. Global ischemia may occur as a result of reduced cardiac output, as in circulatory failure. Focal brain ischemia, or ischemic stroke, has been demonstrated more commonly during the last decade in both term and preterm neonates with the increased use of cranial magnetic resonance imaging (MRI), which is a sensitive technique to demonstrate stroke.

Perinatal Asphyxia

The term *asphyxia*, from the Greek word for suffocation, is used to describe the interrupted supply of oxygen through the placenta and umbilical cord to the fetus, leading to combined hypoxemia and hypercapnia. In case of total interruption of oxygen, within minutes, anaerobic glycolysis will occur and lactic acidosis, and thereby metabolic acidosis, will be produced. This can be measured by blood gas analysis. In addition, (fetal) bradycardia will develop and will add ischemia to the process and augment cerebral hypoxia and hypercapnia.

Pathophysiology

Systemic Adaptation to Hypoxic–Ischemic Insult

Severe fetal hypoxic–ischemic injury affects the entire organism, and these effects have been well studied in animal

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Abstract

Hypoxic–ischemic encephalopathy (HIE) occurring after severe perinatal asphyxia has an incidence of 1 to 2 per 1,000 live births in the Western world and is far more common in developing countries. Although metabolic disorders may mimic perinatal asphyxia and genetic and placental factors may contribute to the clinical picture, brain imaging techniques have demonstrated acute changes in the brain of the term neonate after perinatal asphyxia occurs.

Keywords

hypoxic–ischemic encephalopathy
perinatal asphyxia
resuscitation
therapeutic hypothermia
neuroprotection
electrophysiology
magnetic resonance spectroscopy

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TABLE 54.1 Clinical Staging of Hypoxic–Ischemic Encephalopathy

Variable	Stage I	Stage II	Stage III
Level of consciousness	Alert	Lethargy	Coma
Muscle tone	Normal or hypertonia	Hypotonia	Flaccidity
Tendon reflexes	Increased	Increased	Depressed or absent
Myoclonus	Present	Present	Absent
Seizures	Absent	Frequent	Frequent
Complex Reflexes			
Suck	Active	Weak	Absent
Moro	Exaggerated	Incomplete	Absent
Grasp	Normal or exaggerated	Exaggerated	Absent
Doll's eye	Normal	Overactive	Reduced or absent
Autonomic Function			
Pupils	Dilated, reactive	Constrictive, reactive	Variable or fixed
Respirations	Regular	Variations in rate and depth, periodic	Ataxic, apneic
Heart rate	Normal or tachycardia	Bradycardia	Bradycardia
Electroencephalogram	Normal	Low voltage, periodic paroxysmal	Periodic or isoelectric

Modified from Sarnat HB, et al. Hypoxic-ischemic encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol*. 1976;33:695.

TABLE 54.2 Thompson Score

	Score						
Sign	**0**	**1**	**2**	**3**	**Day 1**	**Day 2**	**Day 3**
Tone	Normal	Hypertonic	Hypotonic	Flaccid			
Level of consciousness	Normal	Hyper alert stare	Lethargic	Comatose			
Fits	None	Infrequent <3/day	Frequent >2/day				
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate			
Moro	Normal	Partial	Absent				
Grasp	Normal	Poor	Absent				
Suck	Normal	Poor	Absent ± bites				
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)			
Fontanel	Normal	Full, not tense	Tense				
				Total score per day			

IPPV, Intermittent positive-pressure ventilation.
From Thompson CM, et al. The value of a scoring system for hypoxic–ischaemic encephalopathy in predicting neurodevelopmental outcome. *Acta Paediatr*. 1997;86:757-761.

models. In particular studies, instrumented fetal sheep and monkeys in the 1960s and 1970s have been used to describe the physiologic and pathologic changes in the brain after hypoxia has occurred.[14,47] Hypoxic–ischemic injury may occur at any time during pregnancy, the birth process, or the neonatal period. The pattern of brain damage is reflected by the gestational age of the fetus at the time that the injury occurs. Fetal hypoxic–ischemic injury may result from maternal, uteroplacental, or fetal problems (Box 54.1). The fetus may survive maternal hypoxia–ischemia, such as transient hypoxia or hypotension. Correctable placental factors include hyperstimulation with oxytocic agents or intermittent cord compression, but these may cause irreversible brain damage before recovery occurs.

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• BOX 54.1 Causes of Fetal Hypoxic–Ischemic Insult

Maternal

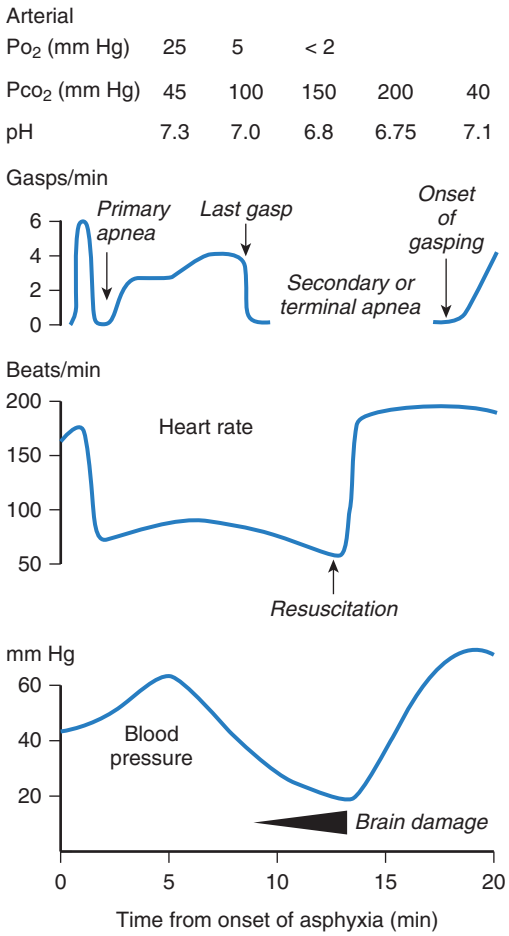
- Cardiac arrest
- Asphyxiation
- Severe anaphylactoid reaction
- Status epilepticus
- Hypovolemic shock

Uteroplacental

- Placental abruption
- Cord prolapse
- Uterine rupture
- Hyperstimulation with oxytocic agents

Fetal

- Fetomaternal hemorrhage
- Twin-to-twin transfusion syndrome
- Severe isoimmune hemolytic disease
- Cardiac arrhythmia



• Fig. 54.1 Physiologic responses of rhesus monkeys during asphyxia and on resuscitation. Brain damage was assessed histologically weeks or months after asphyxia. (From Dawes GS, ed. *Foetal and neonatal physiology: a comparative study of the changes at birth*. Chicago: Year Book Medical Publishers, Inc.; 1969.)

Fetuses with brain damage occurring as a result of early in utero hypoxic–ischemic insult do survive, but in the majority of cases, severe maternal hypoxia in the second trimester of pregnancy will result in fetal death. Occasionally, there is a history of a catastrophic maternal illness, such as suffocation, anaphylaxis, or major physical trauma. In other situations, the antecedent pathogenic event is confined to the fetus, sometimes resulting in symmetric thalamic lesions, with or without an associated abnormality of the uteroplacental unit. Whatever the cause of the cerebral hypoxia–ischemia, the neuropathologic consequence is often devastating.

In the more mature fetus, a period of mild to moderate hypoxemia produces a consistent pattern of responses (Fig. 54.1). Initially, there is fetal bradycardia with an immediate rise in blood pressure and, in particular, an increase in perfusion to the brain and other vital organs at the expense of the rest of the body. With ongoing hypoxemia, the fetal heart rate will decrease further, apnea will occur, and permanent brain injury occurs after 10-15 minutes. The fetus is very resistant to milder hypoxemia, and normal cardiovascular function will be maintained for up to an hour even with a partial pressure of oxygen (PaO_2) of 15 mm Hg (normal fetal PaO_2 is 25 mm Hg). With prolonged moderate hypoxia, cerebral perfusion will remain normal, but (asymmetric) fetal growth restriction will occur. In fetuses with such prolonged moderate hypoxia, lactate levels may be elevated, indicating that anaerobic glycolysis has occurred in some tissues. The rapid changes in blood gas values have been documented in numerous experiments (Fig. 54.2).

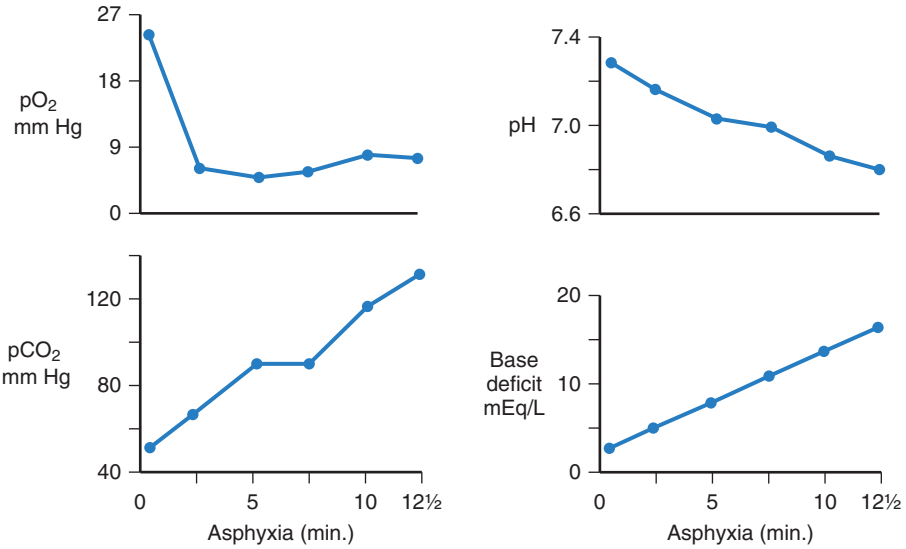
As the hypoxic insult becomes more severe, changes in regional cerebral blood flow occur. The brainstem is able to extract sufficient oxygen to maintain metabolism despite very low PaO_2 at the expense of the cerebrum. Failing myocardial function may cause a fall in cardiac output, and the watershed areas of the cerebral hemispheres are most exposed to damage (see section on Vascular Territories).

An acute hypoxic–ischemic insult, often referred to as a sentinel event, as may occur during cord prolapse or uterine rupture, is likely to damage the basal ganglia and brainstem, in contrast to the more chronic insult, which leads to damage in the cerebrum (see section on Neuropathology).[47]

Preconditioning

Preconditioning describes reduced sensitivity of the immature brain to injury, depending on whether it has been exposed to previous nondamaging hypoxic events some hours before the main hypoxic–ischemic insult. Preconditioning of immature rat pups by exposure to moderate hypoxia or inflammation before hypoxia–ischemia appears to be neuroprotective. Preconditioning may work through stabilizing hypoxia-inducible factor-1-alpha (HIF-1-alpha) during hypoxia. When dimerized with HIF-1-beta to HIF-1, it acts on hypoxia response elements in the promoter of hypoxia-responsive genes, which will lead to

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• **Fig. 54.2** Changes in blood gas values in the term monkey fetus after acute, total asphyxia. (Adapted from Myers RE. Two patterns of perinatal brain damage and their conditions of occurrence. *Am J Obstet Gynecol*. 1972:112:246-276.)

induction of genes encoding erythropoiesis, angiopoiesis, and antiapoptosis.[35]

Perinatal Hypoxic–Ischemic Brain Damage

During the last decades, the processes leading to neuronal death in the neonate have been described in more detail. This knowledge is important when considering neuroprotective strategies (see section on Specific Neuroprotective Strategies).

In contrast to adult ischemic stroke, neonatal hypoxia–ischemia is characterized in most cases by a combination of cerebral hypoxia (and ischemia during bradycardia), followed by reperfusion and potential excessive distribution of oxygen. The contribution of reperfusion to cerebral injury is recognized and has led to the restricted use of supplemental oxygen during neonatal resuscitation.[88]

An acute hypoxic–ischemic insult leads to events that can be broadly categorized as early (primary) and delayed (secondary) neuronal death. Previously, two different patterns of cell death were reported in neonates.[52] *Necrosis* is lytic destruction of cells, whereas *apoptosis* is programmed cell death, which is driven by adenosine triphosphate (ATP). More recently, these cell death patterns have been recognized to be in continuum. The final pathway is dependent on tissue circumstances such as oxygen content.

Early or primary neuronal damage occurs as a result of cytotoxic changes caused by failure of the microcirculation, inhibition of energy-producing molecular processes, increasing extracellular acidosis, and failure of Na^+/K^+–adenosine triphosphatase (ATPase) membrane pumps, which result in excessive leakage of Na^+ and Cl^- into the cell with consequent accumulation of intracellular water (cytotoxic edema). Free radical production is also initiated, which further compromises neuronal integrity. If not reversed, these processes lead to neuronal death of the necrotic type within a short time of the acute insult.

Recovery and reperfusion, as occur with resuscitation, fuel the pathways to late (secondary) neuronal damage through a relatively large number of pathophysiologic mechanisms.

It has been demonstrated in experimental settings that secondary energy failure starts within 6-8 hours after the primary insult. The term *energy failure* reflects the fact that high energy phosphates are reduced as can be demonstrated in vivo using phosphorus magnetic resonance spectroscopy (^{31}P-MRS). This technique uses the intrinsic magnetic properties of some atomic nuclei, such as ^{31}P. The peaks described for the ^{31}P spectrum are beta-ATP, alpha-ATP, gamma-ATP, PCr, phosphodiesters, inorganic phosphate (Pi), and phosphomonoesters. Depletion of ATP and an increase in Pi, associated with a change in the PCr/Pi ratio, have been reported using ^{31}P-MRS.[42] Secondary energy failure is a result of changes in mitochondria and may last up to 72 hours or even longer after the acute insult. Timing of moderate hypothermia for neuroprotection is based on this "therapeutic window" of 6 hours before the onset of secondary energy failure.

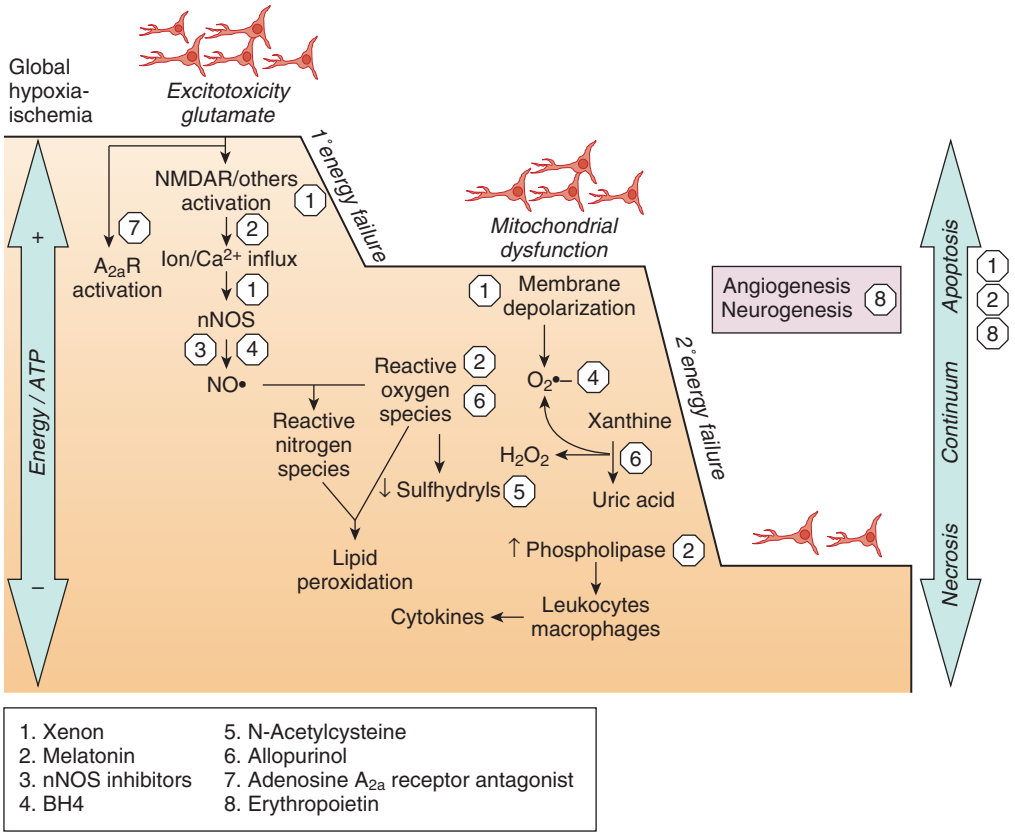
Secondary Neuronal Death

A complicated cascade of intracellular events is triggered by the initial hypoxic–ischemic insult, which results in either cell necrosis or apoptosis (Fig. 54.3).

Glutamate Injury (Excitotoxicity)

Excessive neuroexcitatory activity occurs as a result of the asphyxial event, and this is mediated through glutamate toxicity. Glutamate activates N-methyl-D-aspartate (NMDA)

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• **Fig. 54.3** Intracellular neurotoxic cascade and potential targets for neuroprotection after hypoxia–ischemia. After global hypoxia–ischemia, glutamate-induced excitotoxicity proceeds via N-methyl-D-aspartate receptor (NMDAR) activation, producing calcium ion (Ca^{2+}) influx and therefore activation of Ca^{2+}-dependent nitric oxide synthase (NOS), particularly neuronal NOS. At high concentrations, $NO^{\bullet}$ reacts with superoxide ($O^{\bullet-}$) to produce peroxynitrite ($ONOO^{-}$), which, in turn, induces lipid peroxidation and mitochondrial nitrosylation. During the acute energy depletion, some cells undergo primary cell death. After reperfusion, the initial hypoxia-induced cytotoxic edema and accumulation of excitatory amino acids typically resolve in 30-60 minutes, with apparent recovery of cerebral oxidative metabolism. Mitochondrial failure is a key step leading to delayed cell death. Potential neuroprotective targets are indicated. (Adapted from Robertson et al. Which neuroprotective agents are ready for bench to bedside translation in the newborn infant? *J Pediatr*. 2012;160:544-552.[58])

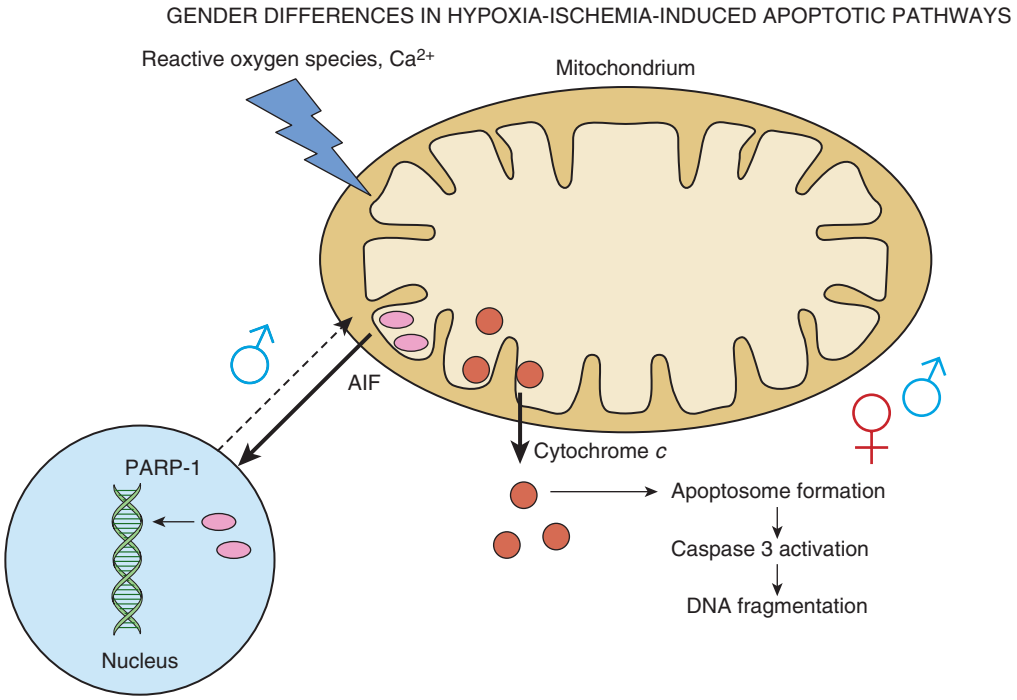
receptors, which, in turn, cause calcium channels to open in an unregulated manner with excess entry of intracellular calcium ions (Ca^{2+}). The high concentrations of this ion activate lipases, proteases, endonucleases, and phospholipase C, which, in turn, break down organelle membranes. This sets up a variety of abnormal processes with release of free radicals, including nitric oxide (NO•) and superoxide ions. This has further adverse effects on cell membranes and leads to mitochondrial failure with the release of caspase-3 and eventual DNA fragmentation, poly(ADP-ribose) polymerase, which causes further energy failure of intracellular membrane function. This process also triggers an apoptotic response in the cell.[26] The process of cell death is very different from that seen in adults, requiring specific neonatal animal models in the research of perinatal asphyxia.

Furthermore, cell death pathways differ between male and female rat pups (Fig. 54.4).[57] Some compounds like erythropoietin appear to be more protective in female than in male pups. The relevance of this gender difference for human neonates is not yet established. Clinical trials of erythropoietin for neuroprotection after perinatal asphyxia or stroke are ongoing.[35]

Free Radical Formation

Oxygen free radicals cause peroxidation of unsaturated fatty acids, and because the brain is especially rich in polyunsaturated phospholipids, it is especially susceptible to free radical attack. Mechanisms for quenching and inhibiting free radical production exist within the brain, but in the immature organ these mechanisms may be underdeveloped. Consequently, the human neonatal brain is at particular risk for oxygen free radical–induced injury.[56] Brain arteriole endothelium is the main source of free radical production by the action of xanthine oxidase, but free radicals are also produced by activated neutrophils, microglia, and intraneuronal structures. During reperfusion, free radical production from the arteriolar endothelium results in blood–brain barrier leakage and release of platelet-activating factor, platelet adhesion, and neutrophil accumulation, which may

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• **Fig. 54.4** Pathways of apoptosis in neonatal male and female animals. AIF, apoptosis-inducing factor; PARP, poly(ADP-ribose) polymerase. (Courtesy of CHA Nijboer, PhD, Laboratory of Neuroimmunology and Developmental Origins of Disease, University Medical Center, Utrecht, The Netherlands).

contribute to cellular damage. Resuscitation of human neonates with 100% oxygen has led to prolonged changes in oxidized glutathione as a result of excessive production of oxygen free radicals.[88]

A particularly important mechanism that exposes the newborn brain to oxygen free radical attack is the presence of free iron. Non–protein-bound ("free") iron is found in higher concentration in the immature animal because of low transferrin levels. Free iron catalyzes mildly reactive oxygen species to more toxic free radicals through the Fenton reaction. There is evidence that after a hypoxic–ischemic insult, there is an increased presence of intraneuronal free iron within the first 24 hours that persists for several weeks.

The second important mechanism that leads to (nitrogen) free radicals is the production of neuronal-derived NO•.[56] NO• is produced by three isoforms of the enzyme nitric oxide synthase (NOS): designated *neuronal* (nNOS), *endothelial* (eNOS), and *inducible* (iNOS). Production of NO• is accelerated by intracellular Ca^{2+} influx and NO• is neurotoxic in excessive concentrations. It is thought that up to 80% of NMDA toxicity is mediated through NO•. NO• also combines rapidly with superoxide to produce peroxynitrous acid, which gives rise to the free radical peroxynitrite. Excessive NO• can cause DNA strand breaks and induce neuronal apoptosis mediated through caspase-3 activation, and iNOS, produced during inflammatory processes, has also been reported to aggravate injury in the immature brain. However, NO• from endothelial cells (eNOS) is essential in maintaining cerebral perfusion. For neuroprotection, only nNOS- (and iNOS-) specific inhibitors can be used.

Apoptosis

Apoptosis (see Chapter 51), or programmed cell death, is perhaps the most important cause of neuronal death in the neonate following hypoxia–ischemia and resuscitation. It can be distinguished histologically from necrosis by shrinkage of affected cells with retention of the cell membrane. By contrast, necrosis is associated with cell rupture, which induces secondary inflammatory processes. DNA degradation develops in the apoptotic cell, giving a characteristic ladder appearance on gel electrophoresis.

Apoptosis is a gene-regulated process, and both proapoptotic and antiapoptotic genes, including *BCL2*, *Bax*, *APAF1*, and the caspase gene family, influence the process. A major role in the apoptotic mechanism is played by the caspase family of proteins, with caspase-3 identified as the execution protein. Inhibitors of caspase can block apoptosis and attenuate injury.

Apoptotic pathways have been shown to differ between males and females. Apoptosis via an apoptosis inducing factor–dependent pathway was demonstrated in cultured XY neurons, whereas a cytochrome c-dependent pathway was seen in XX neurons.[49,51,57]

Cytokines

There is evidence that some proinflammatory cytokines (tumor necrosis factor-alpha, interleukin [IL]-1-beta, and IL-18) are activated after a hypoxic–ischemic insult in immature experimental animal models, and they may have

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neurotoxic properties. After hypoxic–ischemic insult, widespread expression of caspase-1 and IL-18 protein in microglia is found. These data suggest that hypoxic–ischemic insult may initiate an inflammatory response in the absence of infection, leading to neuronal injury.

Studies in animals and humans have shown that exposure to infection (gram-negative bacteria or lipopolysaccharide [LPS] in animal models)[82] and chorioamnionitis in pregnant women significantly exacerbate clinical and neuronal injury.[71]

Human Studies

Studies in human neonates have confirmed the presence of secondary energy failure after perinatal asphyxia. ^{31}P-MRS in affected term infants were usually normal within the first 6 hours after birth, suggesting that mitochondrial phosphorylation had initially recovered with resuscitation. After 8 hours, there was a significant decline in the high energy phosphates, such as phosphocreatine and ATP, with a further decline in the most severely affected infants at 48-72 hours. In some infants, recovery occurred to normal values within 7 days. The delayed fall in phosphocreatine/inorganic phosphate (PCr/Pi) ratio represents secondary energy failure.[32]

In addition, proton magnetic resonance spectroscopy (^{1}H-MRS) may show some lactate in the neonatal brain on very early scans, but higher levels of lactate could be demonstrated after 48 hours in most affected infants.[6,38] Studies using near-infrared spectroscopy (NIRS) have shown reduced oxygen uptake, and higher brain oxygen saturations in neonates with perinatal asphyxia, suggesting secondary energy failure.[39] Diffusion weighted imaging (DWI) studies have demonstrated reduced diffusion of water molecules represented as the apparent diffusion coefficient (ADC), suggestive of cytotoxic edema returning to normal ADC values after approximately 1 week. In cystic areas, these ADC values will increase to above-normal values.[1]

Doppler studies of major intracranial arteries demonstrated loss of normal carbon dioxide (CO_2) reactivity with high diastolic blood flow, first seen 12-24 hours after birth.[4] Recently, MRI studies using arterial spin labeling (ASL) have demonstrated higher perfusion values in neonates with HIE and an adverse neurodevelopmental outcome.[15]

Selective Vulnerability

In the human neonate, as well as in animal experiments, different patterns of brain injury following HIE have been demonstrated, depending on the developmental stage of the fetus, and severity and duration of the hypoxic–ischemic insult. The factors influencing brain injury after perinatal hypoxia–ischemia can be summarized as follows:

- Cellular susceptibility
- Maturity
- Vascular territories
- Regional susceptibility
- Type of hypoxic–ischemic insult
- Others, such as genetic predisposition and placental factors

Cellular Susceptibility

In the term neonate, the neuron is the most sensitive cellular element to hypoxic–ischemic insult. In the preterm neonate, neurons as well as precursors of oligodendrocytes are sensitive cell types.

Maturity

Gestational age plays an important role in the changing susceptibility of cerebral structures to hypoxic–ischemic insult for a number of reasons, including rapid changes in neuronal development, changing vascular watersheds, and biochemical variables within cells, such as relative proportions of excitotoxic and inhibitory expression. In addition, a low susceptibility of the immature myocardium compared with that of the term neonate may result in a more preserved cerebral perfusion during hypoxia.

Hypoxic–ischemic insults before 20 weeks' gestational age, as may occur as the result of severe maternal illness, may lead to neuronal heterotopia or polymicrogyria because the insult to the fetal brain occurs during the stage of neuronal migration, which is not complete until 21 weeks of gestation. Insults affecting the brain during midgestation (26-36 weeks) predominantly damage white matter, leading to cystic periventricular leukomalacia, and may have secondary negative effects on growth of the deep gray matter or may increase the risk of intracranial hemorrhage. Primary hypoxic–ischemic injury to the basal ganglia and thalamus in preterm infants has been reported and resulted in a poor outcome. Insults near or at term (35 weeks and beyond) result predominantly in damage to the deep gray matter or the watershed areas of the brain.[73]

Vascular Territories

Watershed injury refers to tissue damage that occurs in regions that are most vulnerable to reduction in cerebral perfusion as the result of having the most tenuous blood supply. These tissues are at the farthest points of arterial anastomoses and are exposed to damage when perfusion pressure falls, usually as the result of impaired cardiac output and low blood pressure. Watershed areas change with advancing development.

In the term brain, a cortical watershed area (the parasagittal region) is present among the three main arteries supplying each hemisphere. Volpe et al. used positron emission tomography (PET) to measure regional cerebral blood flow in 17 full-term newborns who had suffered asphyxia and found a consistent decrease in blood flow to the parasagittal region of both cerebral hemispheres in most of the infants.[89] Modern techniques, such as DWI, have demonstrated these watershed-type lesions in the full-term neonate (see section on Neuroimaging).[13]

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The depths of the sulci are also sensitive to hypoxic–ischemic insult as the result of being watershed areas at term. Reduction in perfusion in small vessels at the base of sulci during hypoxia–ischemia leads to columnar necrosis and may lead to ulegyria in the older child's brain.[73]

Ischemic infarction (stroke) has been recognized more commonly with the increased use of MRI in neonates with or even without encephalopathy. Although infarction of a major cerebral artery has been found in neonates with a hypoxic–ischemic insult, thrombosis and embolus, vasospasm, maternal smoking, or hypoglycemia are more common etiologic factors.[28,59] The location of the lesions and neurodevelopmental outcome is dependent on the cerebral artery involved.[89a]

Regional Susceptibility

Some regions of the brain are particularly sensitive to hypoxic–ischemic insult as a result of certain vascular factors, as discussed previously, but high metabolic rates of individual nuclei may predispose them to damage during cerebral hypoxia and hypoperfusion. This may account for the susceptibility of the posterior and lateral thalamic nuclei and lentiform nuclei to damage after acute total asphyxia in the term neonate. Another factor accounting for regional variability to hypoxia–ischemia is the distribution of glutamate excitotoxic receptors. Regional cerebral glucose use has been investigated with PET after perinatal cerebral hypoxia–ischemia. Occipital regions of the brain appear to be particularly vulnerable to hypoglycemia in full-term infants.

Types of Hypoxic–Ischemic Insult

Animal studies on primates have modeled two different patterns of hypoxic–ischemic insult and have shown different patterns of neuronal injury, depending on the type of insult.[47] Acute total asphyxia was produced in fetal monkeys by clamping the umbilical cord and preventing the animal from breathing. This produced injury to the thalamus, brainstem, and spinal cord structures. The longer the duration of the acute insult, the more extensive the damage occurred in these regions. Little damage was reported in higher structures.

The second model attempted to mimic a prolonged, partial asphyxial insult lasting 1-5 hours. This produced damage predominantly in the cerebral hemispheres and particularly in the watershed distribution (see section on Vascular Territories), often with sparing of the brainstem, hippocampus, and temporal and occipital lobes. Damage was also seen, not uncommonly, in the basal ganglia and the cerebellum.

Others

Other types of hypoxic–ischemic insults include maternal fever during labor, which may accelerate fetal brain injury, fetal starvation with reduction in intracerebral glucose availability, sepsis, and twinning. The effects of these factors may act through one or a number of the variables discussed previously.

There has been much debate as to the role of pre-existing antenatal factors in exacerbating intrapartum HIE. Recently, placental changes were seen in full-term neonates with encephalopathy who suffered asphyxia. Chronic villitis was associated with the basal ganglia/thalamus pattern of injury, whereas decreased placental maturation was linked to white matter and watershed injuries.[20,30] Polymorphisms of the *MTHFR* gene were demonstrated more often in neonates with HIE and cerebral lesions of the watershed type.[27]

An MRI study of term infants with hypoxic–ischemic encephalopathy has suggested that the majority of the brain damage present in these infants occurred in the immediate perinatal period and was not the result of long-standing damage. DWI is a technique that visualizes the motion of water molecules. Increased use of DWI in human infants has demonstrated restricted diffusion in cytotoxic edema during the first week after perinatal asphyxia, indicating absence of long-standing injury.[1,7,12]

Neuropathology

The neuropathologic features of hypoxic–ischemic injury vary, depending on the type and duration of the insult and the gestational age of the child at the time of the insult. The pathologic features evident on examination also depend on the interval between the insult and death. The neuropathologic features become more apparent as they develop in a temporal sequence. Some of the more consistent features of hypoxic–ischemic injury are discussed below. Of course, findings on neuropathology are biased by the fact that these neonates have died. Thus, these findings will show different patterns when compared with those on imaging studies, for example, MRI findings, in a cohort of neonates who survived after hypoxic–ischemic encephalopathy. In addition, MRI is less sensitive in detecting cerebral hypoxic–ischemic changes compared with histology.[2]

Cerebral Edema

Brain edema is thought to occur frequently in infants who have sustained a severe cerebral hypoxic–ischemic insult and is widely reported in autopsy studies. Cellular edema develops rapidly and resolves by 7 days after its onset, although imaging cannot reliably detect edema until 24 hours after the event because of the higher water content of the neonatal brain. In primate studies of intrapartum asphyxia, partial intermittent hypoxia–ischemia with marked and prolonged hypoxemia was associated with severe edema in all cases, whereas brain swelling was not a feature of severe, acute, total hypoxic–ischemic insults. If the brain damage has been widespread and severe, on gross examination, the brain appears swollen, with slitlike lateral ventricles, widening and flattening of the cerebral gyri with

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associated obliteration of the sulci, and herniation of hippocampal structures. In the most severe cases, herniation of the cerebellar tonsils and vermis through the foramen magnum has been described, but this is seen rarely in clinical practice. Brain edema is seen mainly in the most severe ("near total") pattern of neonatal brain injury after perinatal asphyxia.[13]

Cellular Responses

Different cell lines in the brain react in varying ways to an acute hypoxic–ischemic insult. Neurons may undergo either necrosis or apoptosis (see section on Pathophysiology). The nature of these two mutually exclusive processes can be distinguished to some extent by histologic staining. In necrosis, sections stained with hematoxylin and eosin (H&E) show changes 5-6 hours after the injury. Nuclear membranes degenerate, with release of nuclear chromatin and a secondary inflammatory reaction.

Activated microglia express a number of cytotoxic cytokines. Although microglial cells respond rapidly after a hypoxic–ischemic insult and undertake the function of ingesting and lysing dead tissue, CD68-positive cells, indicating activated microglia and macrophages, were seen not earlier than at least 24 hours after the hypoxic–ischemic insult in a cohort of 22 full-term neonates who died as a result of severe perinatal asphyxia.[25] In this paper, caspase activity could be seen in the brain examined within 24 hours of the hypoxic–ischemic insult. In addition, nitrotyrosine staining, considered the product of NO• toxicity, was present in brain and spinal cord tissues.

Hemoglobin released from damaged red blood cells (RBCs) is mobilized in this way, leaving residual hemosiderin present in the macrophage. Microglial cells present in the dentate gyrus are a reliable indication of previous hypoxic–ischemic insult in infants younger than 9 months of age.

Glial cells respond to hypoxic–ischemic insult by enlarging, proliferating, and later developing fibrillary processes with the expression of glial fibrillary acidic protein, which can be recognized by specific staining. A glial response occurs from 17 weeks of gestation.[73]

Calcification

Deposition of calcium in damaged neurons is commonly seen after hypoxic–ischemic insult and, if extensive enough, may be apparent on brain imaging. Insults other than those caused by hypoxia–ischemia may also cause extensive calcification, including viral infection and certain metabolic disorders.

Chronic Lesions

Cerebral atrophy is the end stage of cellular loss in the brain. Atrophy affects particularly vulnerable areas of the brain (described earlier under section on Selective Vulnerability). Various specific forms of end-stage pathologic lesions have been recognized in the brain for many years.

Status marmoratus describes a patchy, marble-like appearance of the basal ganglia and thalamus that may develop approximately 6 months after a severe perinatal hypoxic–ischemic insult. Histologic study shows abnormal myelination of glial bundles rather than neurons.

Ulegyria refers to a particular form of pathology seen in the depths of the cortical sulci and is probably caused by particular watershed vulnerability (see section on Vascular Territories). The chronic phase of this process produces the appearance of mushroom-like gyri because of loss of the deep gray matter in the sulci.[73]

Assessment Tools

Many different tools have become available to aid in the more precise prediction of neurodevelopmental outcome in the full-term infant with HIE.

Clinical Examination

Previous studies have described in detail the clinical changes in the term neonate with encephalopathy. The Sarnat classification is based on clinical and electroencephalography (EEG) findings 24 hours after the insult. It has been modified to be used shortly after the insult for neonates to determine eligibility for therapeutic hypothermia.[61]

The Thompson score is based on several clinical items and results in a quantitative score (see Table 54.2).[77] Classification systems have been used not only for clinical purposes but also for inclusion of patients in clinical trials, as well as for stratification of patients within those trials. Although the predictive value for long-term neurodevelopment of mild and severe encephalopathy is good (no handicaps following mild encephalopathy, almost invariably poor outcome after severe encephalopathy), the predictive value for moderate encephalopathy is poor.

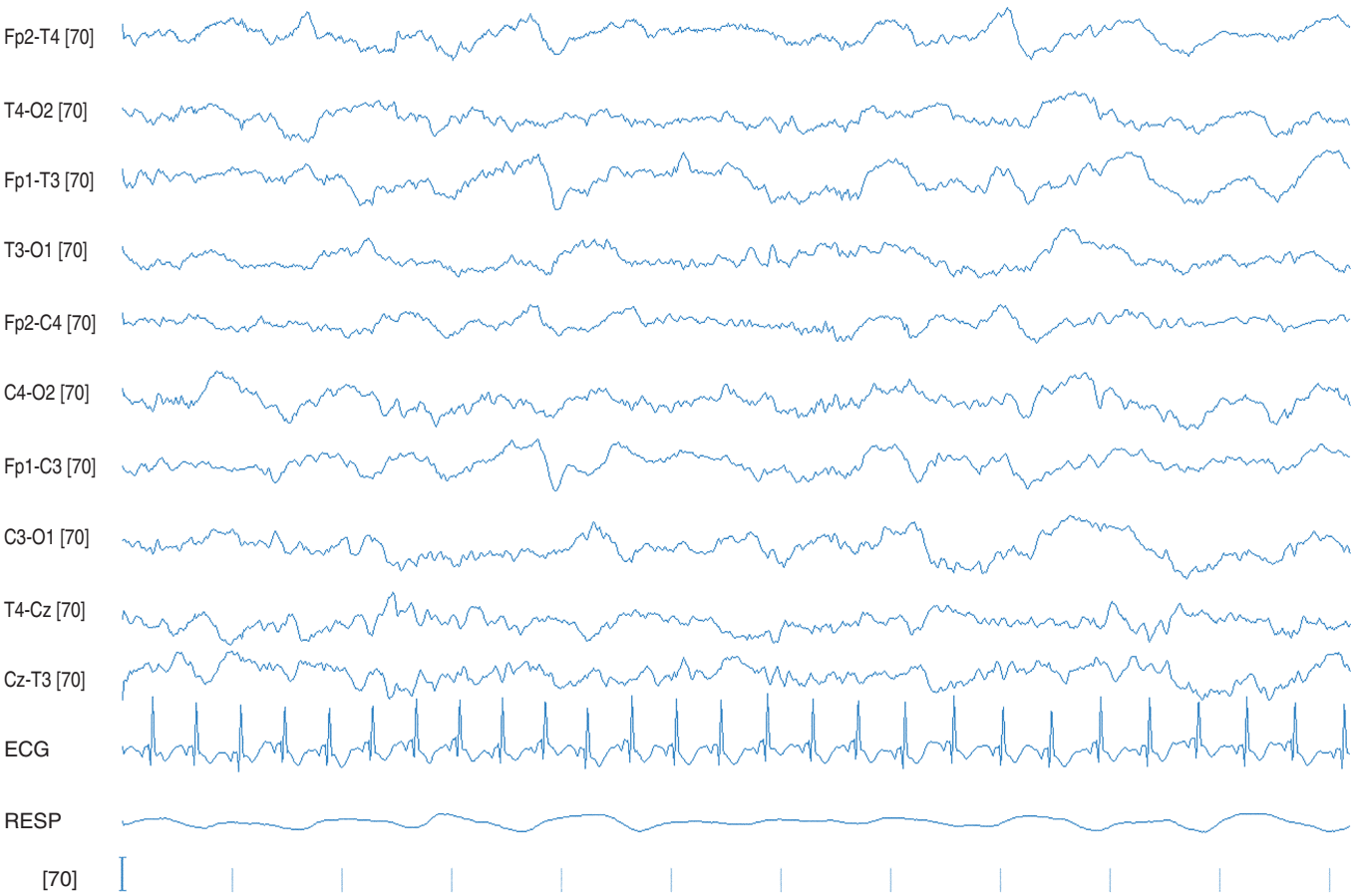
Neurophysiology

Electroencephalography

Neonatal EEG is a well-recognized method to assess brain integrity after hypoxia–ischemia that results in hypoxic–ischemic encephalopathy. In newborn infants, EEG commonly uses 16 channels; it requires skilled technicians and highly trained and experienced neurophysiologists to interpret the recordings. The 16-channel EEG provides detailed information and, when performed with simultaneous video recording, helps make a distinction between clinical and subclinical seizures. In 2011, the American Clinical Neurophysiology Society published guidelines on continuous EEG monitoring in neonates.[70] Although it is clear that using continuous full EEG with video recording is optimal, this can, at present, be achieved only in a limited number of centers. With use of these guidelines, data of 426 consecutive neonates with clinically suspected

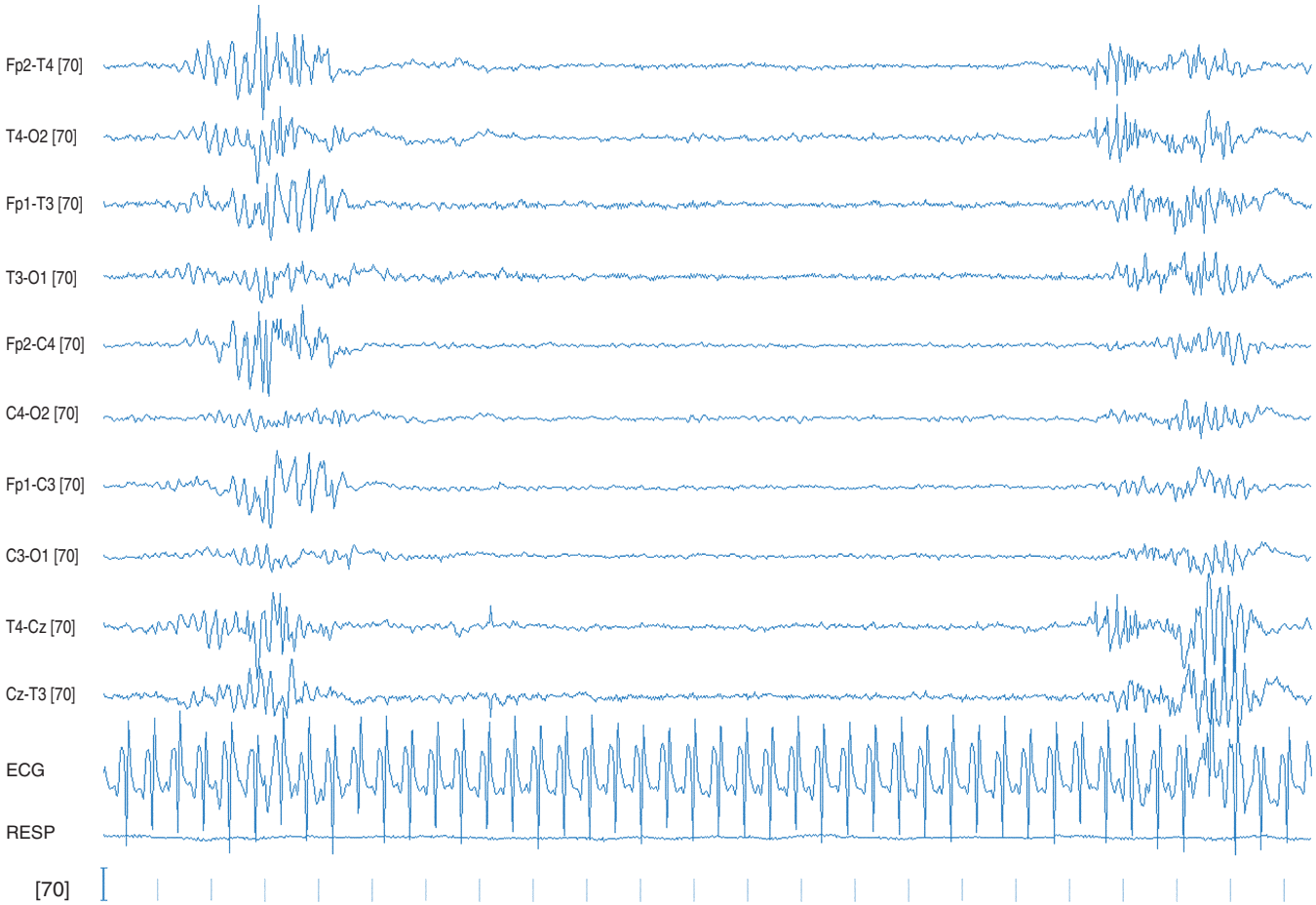
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seizures and/or electrographic seizures were studied in seven tertiary centers.[21] In agreement with findings from previous studies, the most common seizure etiologies were HIE (38%), ischemic stroke (18%), and intracranial hemorrhage (11%). There was a high seizure burden, with 59% having ≥7 electrographic seizures and 16% having status epilepticus; 52% received ≥2 antiepileptic drugs. During admission, 17% of the neonates died; 49% of survivors had abnormal neurologic examination at hospital discharge. In an adjusted analysis, high seizure burden was a significant risk factor for mortality, length of hospital stay, and abnormal neurologic examination findings at discharge. One study made it very clear that continuous EEG or amplitude-integrated EEG (aEEG) is required to accurately diagnose seizures. Those authors showed that less than 10% of neonatal seizures were correctly identified by the neonatal staff, compared with simultaneous video-EEG recordings (see Chapter 55).[46] With the use of continuous aEEG or continuous EEG (cEEG) monitoring, a reduction in the use of antiepileptic medication was noted, when compared with a period when intermittent EEG was used.[34] Normal and severely abnormal results on EEG are of important predictive value. Normal traces almost invariably predict a normal outcome, whereas persistent, severely abnormal traces predict an adverse outcome (Fig. 54.5). Prediction in children with mild to moderate EEG abnormalities is less reliable and requires sequential recordings. EEG activity is fully differentiated in full-term infants. During quiet sleep, a discontinuous pattern (*tracé alternant*) alternates with a high-voltage continuous delta pattern. In wakefulness, the EEG is characterized by low-voltage mixed theta–delta activity. In active sleep, a mixed medium-voltage delta–theta activity is seen. Abnormalities on the EEG can be classified as background abnormalities, ictal abnormalities, and abnormalities in the organization of states and maturation. Background pattern abnormalities are highly predictive of outcome (Fig. 54.6). One should take into account the fact that antiepileptic drugs can (transiently) affect sleep states and the background pattern, especially in children with severe encephalopathy. The following background patterns can be recognized: isoelectric and extremely low voltage (less than 5 μV); burst suppression pattern with long periods of inactivity (usually longer than 10 seconds) mixed with bursts of abnormal activity. Outcome is especially poor with long periods of inactivity and brief periods of bursts (<6 seconds) with small-amplitude bursts and interhemispheric asymmetry and asynchrony.[8] Among a group of 90 infants undergoing therapeutic hypothermia 43 (48%)



• **Fig. 54.5** Standard 16-channel electroencephalogram showing a normal continuous-voltage background pattern. (Courtesy of AC van Huffelen, PhD, Department of Neurophysiology, University Medical Center, Utrecht, The Netherlands).

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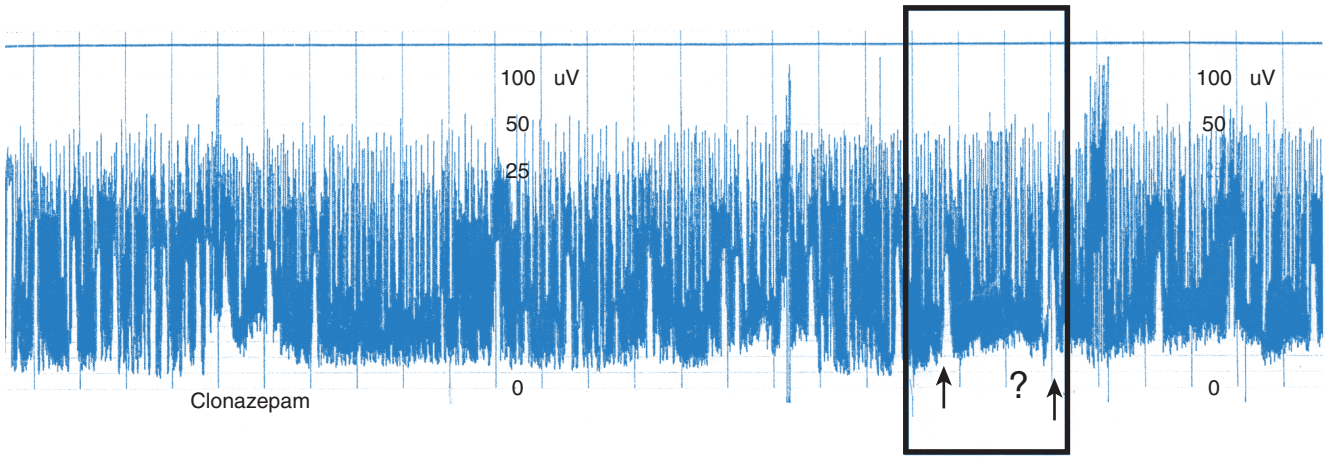


• **Fig. 54.6** Standard 16-channel electroencephalogram showing a typically abnormal burst suppression background pattern. (Courtesy of AC van Huffelen, PhD, Department of Neurophysiology, University Medical Center, Utrecht, The Netherlands).

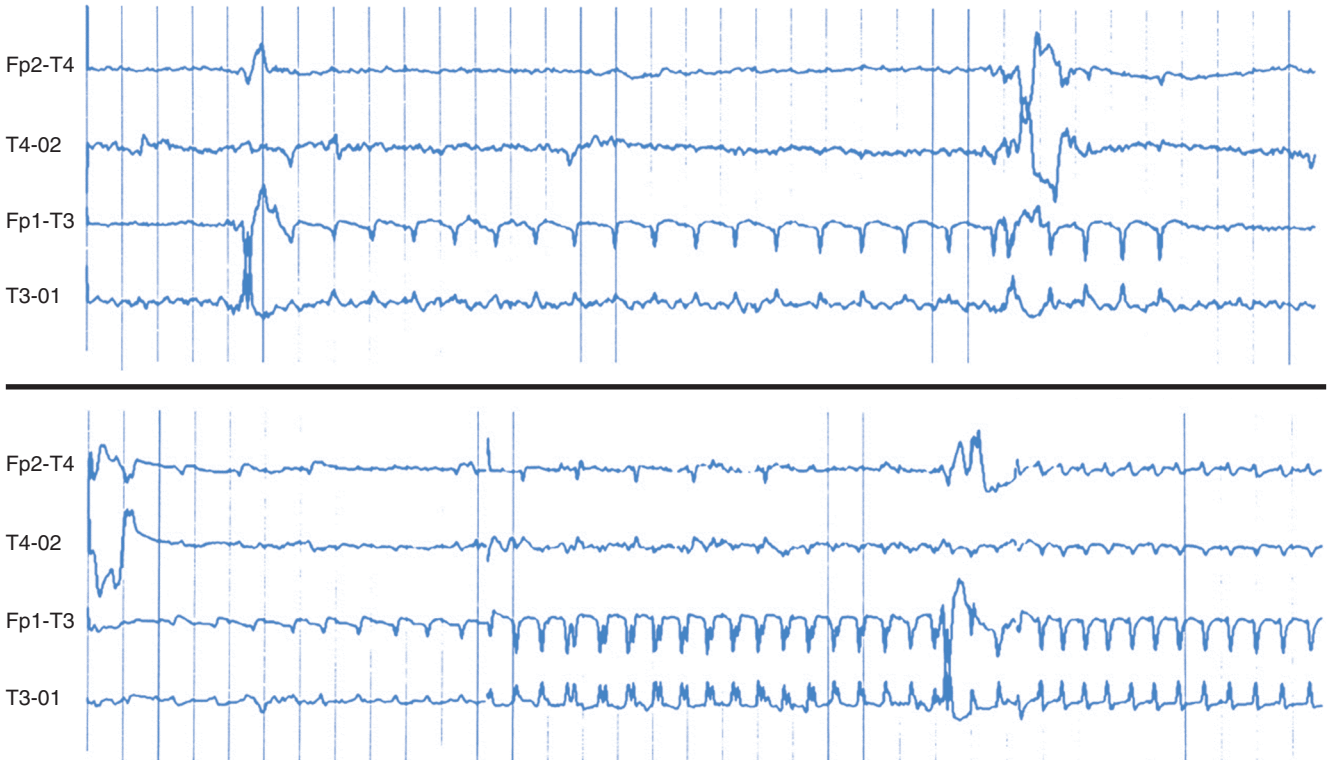
had electrographic seizures, including 9 (10%) with electrographic status epilepticus. Abnormal initial EEG background classification (excessively discontinuous, depressed and undifferentiated, burst suppression, or extremely low voltage) was strongly associated with seizures.[22]

To overcome the problem of difficult access and lack of continuity, a continuous monitoring device, the aEEG, is now increasingly being used.[80] This simple device was initially used as a single-channel EEG from a pair of parietal electrodes. The EEG signal is first amplified and passed through an asymmetric band-pass filter that strongly attenuates activity below 2 hertz (Hz) and above 15 Hz to minimize artifacts from electrical interference. The EEG processing involves semilogarithmic amplitude compression, rectification, smoothing, and time compression. The digital devices also provide raw EEG data and can use more than a single channel. Easy around-the-clock access and easy interpretation based on pattern recognition have led to an increase in continuous monitoring of brain activity in the neonatal intensive care unit (NICU). Several groups have compared simultaneous aEEG with a 16-channel EEG recording. A good correlation was noted for the background pattern (Fig. 54.7). Seizures that will not be detected with aEEG are short seizures, low-amplitude seizures, and focal discharges (Fig. 54.8). Sensitivity of seizure recognition can be considerably improved when using a two-channel bilateral centroparietal aEEG recording with access to the corresponding raw EEG data. The sensitivity for detecting seizures in one- or two-channel aEEG recordings without access to the raw EEG data was 27%-56%, whereas 76% of the seizures were detected by using two aEEG channels, with corresponding raw EEG data.[64] Performing at least one 16-channel EEG during the aEEG recording is, therefore, strongly recommended. Use of continuous aEEG recording provided information about the improvement that can occur in infants with very poor background patterns immediately after delivery. Recovery of a burst suppression pattern within the first 24 hours was sometimes noted to be associated with a normal outcome. However, children with a continuous voltage pattern could deteriorate after 24 hours during a period of secondary energy failure, showing deterioration of their background pattern and late onset of seizures. In most infants, however, a good prediction of later neurodevelopmental outcome could be made on the basis of the aEEG background pattern obtained at 6 or even 3 hours after birth. The early predictive value of the background pattern assessed with this technique has led to its use for selection of newborn infants in intervention

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• **Fig. 54.7** Same child as in Fig. 54.6 showing burst suppression pattern on amplitude-integrated electroencephalography (aEEG). The box indicates a period of simultaneous EEG recording. The two arrows indicate an electrical discharge recognized by aEEG, and the question mark indicates a period when a focal discharge was seen only on the standard EEG.



• **Fig. 54.8** *Top,* Focal discharge, origin left temporal, not detected on amplitude-integrated electroencephalogram. *Bottom,* Focal discharge with spread. (From Toet MC, et al. Comparison between simultaneously recorded amplitude integrated EEG [cerebral function monitor] and standard EEG in neonates. *Pediatrics.* 109:772, 2002, with permission).[79]

studies, such as therapeutic hypothermia.[78] A longer recording will also allow for assessment of the presence, quality, and time of onset of sleep–wake cycling (SWC). The presence, time of onset, and quality of SWC reflects the severity of the hypoxic–ischemic insult to which newborns have been exposed. The time of onset of SWC helps predict neurodevelopmental outcome on the basis of whether SWC returns before 36 hours (good outcome) or after 36 hours (bad outcome).[53] It has been shown that recovery of background activity tends to be slower during hypothermia, and care should be taken when predicting outcome. The positive predictive value (PPV) for predicting a poor outcome during the first 3-6 hours was only 59% in the infants receiving hypothermia compared with 84% in those with normothermia. Infants with a good outcome normalized their background pattern by 24 hours, but by 48 hours if treated with hypothermia.[78] This observation has been confirmed by others.

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The presence of subclinical seizures can be better evaluated using aEEG, and it was noted that newborns very often show electroclinical dissociation, especially after administration of the first drug given for clinical seizures. Scher et al. found that 58% of infants with seizures persisting after treatment with phenobarbital or phenytoin showed uncoupling of electrical and clinical seizures.[62] Status epilepticus (ongoing seizure activity for at least 30 minutes) is not uncommon and was noted in 18% in a cohort monitored with continuous aEEG. In this study, there was a significant difference in background pattern, as well as in duration of the status epilepticus between infants with a poor outcome and those with a good outcome.

Efficacy of treatment of seizures was noted to be poor, as already reported by others using intermittent 16-channel EEGs. The most commonly used drugs (phenobarbital and phenytoin) were shown to treat seizures effectively in less than 50% of the patients when given as a single drug. Other drugs, such as lidocaine, were noted to be more effective but are not yet widely used.[91] Antiepileptic drugs, such as levetiracetam and topiramate, are increasingly used in newborn infants. Similar to the cEEG study mentioned above, a high seizure burden on two-channel aEEG was independently associated with greater injury on MRI (odds ratio [OR] 5.00; 95% confidence interval [CI] 1.47-17.05).[65] The same group also used the aEEG and raw EEG data to calculate discontinuity and showed that a mean discontinuity greater than 30 sec/min–long epoch had a specificity and PPV of 100%, sensitivity of 71% and a negative predictive value (NPV) of 88% for unfavorable neurodevelopmental outcome at a 10-μV threshold.[16]

Evidence that neonatal seizures themselves can lead to damage of the immature neonatal brain is accumulating in the literature.[87] Electroclinical and electrographic neonatal seizures produce an increase in cerebral blood flow velocity. It is suggested that electrographic seizures are associated with disturbed cerebral metabolism and that treatment of neonatal seizures until electrographic seizure activity is abolished may improve outcome.

Animal studies have shown that neonatal seizures can permanently disrupt neuronal development.[31] Seizures superimposed on hypoxic ischemia in rat pups were noted to significantly exacerbate brain injury. However, antiepileptic drugs are not without side effects, and data have shown apoptotic neurodegeneration in the developing rat brain at plasma concentrations relevant for seizure control in humans.

Long-term outcomes in children who had neonatal seizures vary considerably in reports. This is probably because of differences in inclusion criteria and methods of diagnosing neonatal seizures. Postneonatal epilepsy is not uncommon (20%-50%), also after subtle seizures. In studies using aEEG and treating clinical as well as subclinical seizures, postnatal epilepsy developed in less than 10% of the survivors.[80] In a study of 151 neonates undergoing therapeutic hypothermia, 8 (6%) were diagnosed to have epilepsy (International League against Epilepsy definition, www.ilea.org), of whom 3 (2%) received antiepileptic drugs. Of the 103 children seen at age 4-8 years, 14 (13%) had developed epilepsy, with 7 (7%) receiving treatment with antiepileptic drugs.[40] There is little data about the best time to discontinue antiepileptic drugs given for acute symptomatic seizures during therapeutic hypothermia. Seizures after hospital discharge were rare and only seen in 4 of 35 infants who had acute symptomatic seizures. There was no increased risk in the development of postneonatal epilepsy when antiepileptic drugs were discontinued prior to discharge.[19]

Evoked Potentials

Evoked potentials can further aid in the prediction of neurodevelopmental outcome of full-term infants with HIE.[81] Brainstem auditory evoked potentials (BAEPs) or brainstem evoked response and visual evoked potentials (VEPs) are technically easier to perform than somatosensory evoked potentials (SEPs).

The BAEPs are responses generated in the auditory brainstem pathway after an acoustic stimulus (see Chapter 59). They are used to assess both the peripheral sensitivity and the neurologic integrity of the auditory pathway. Seven positive waves can be recognized; these are indicated with Roman numerals. BAEPs are regarded as the most objective and reliable method of evaluating peripheral auditory function in neonates. Because perinatal asphyxia is a well-known risk factor for sensorineural hearing loss, hearing should always be assessed in the neonatal period. This may be performed using automated auditory brainstem response (AABR) or BAEPs. The incidence for a permanent hearing impairment ranges from 5%-10%.[72] Using logistic regression, the high incidence of 10% was noted to be associated with a high trough level of gentamicin, which was present in 90% of those with hearing impairment, a low cord pH, and hypoglycemia within an hour after birth (<46.8 mg/dL).

Initial studies using BAEPs to predict neurodevelopmental outcome were not as consistent as those using SEPs and VEPs. BAEPs are not often used in the prediction of outcome in infants with HIE.

The VEP is a gross electrical signal generated by the occipital area of the cortex in response to a visual stimulus. The stimulus can be either a diffuse flashing light or a patterned visual stimulus. In the neonatal unit, light-emitting diode goggles or small light-emitting diode screens are most widely used. The P200 and the N300 are the major components that can be recognized in the neonatal period. Flash VEPs (FVEPs) are good predictors of cerebral visual impairment after perinatal asphyxia in non-cooled infants. A high correlation between FVEPs and neurodevelopmental outcome was found by the same group. Absent FVEPs carried a poor prognosis, whereas persistently abnormal FVEPs also predicted an abnormal outcome. Normal FVEPs, however, were not always associated with a good outcome, and FVEPs appeared to be more resistant than SEPs. When FVEP recording was performed within 6 hours after birth, a PPV of 77% was found, slightly lower than

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for SEPs (82%) or aEEG (84%).[17] With use of FVEPs in the prediction of outcome in infants receiving therapeutic hypothermia, no response was found in infants with a severely abnormal EEG.[50]

Technically, SEPs are the most difficult to perform and, by far, the most time consuming. The median nerve is usually stimulated because this is better tolerated than stimulation of the tibial nerve. At the scalp, contralateral to the site of stimulation and overlying the primary somatosensory cortex, wave N19 is recorded, which is considered cortically generated. In the newborn, this component is usually referred to as N1. The predictive value of SEPs in full-term infants with HIE has been confirmed since by several groups.[81] A group of 56 infants with HIE who had neonatal aEEG and SEPs underwent a full neuromotor and neurocognitive assessment and an MRI at 9-10 years.[36] A normal SEP latency performed during the first 5 days after birth was associated with a normal neuromotor outcome, and a prolonged day 3 latency with lower childhood intelligence quotient (IQ). The presence of multiple seizures in the aEEG, as well as a moderate or severe injury on the neonatal MRI, was associated with a poor neuromotor score.

When comparing FVEPs and SEPs, some studies showed SEPs to be superior in the prediction of neurodevelopmental outcome. Because the predictive value within the first 6 hours after birth was noted to be similar for aEEG and evoked potentials, aEEG is preferred because of easy access, application, and interpretation. Recently, several studies have shown that SEPs and FVEPs persist during hypothermia and are still of predictive value in infants who are exposed to therapeutic hypothermia.[50] In the study by Nevalainen et al.,[50] 28 of the 50 infants included were treated with hypothermia. The FVEPs and SEPs were performed between 15 hours and 10 days, simultaneously with the routine EEG. The prediction accuracy was highest with SEPs (98%), followed by EEG (90%), and lowest with VEPs (84%). Those authors only looked at absent responses, rather than delayed or absent responses, which were outcome measures in prehypothermia studies. In the subgroup of newborns that received therapeutic hypothermia, the prediction accuracy of SEPs was 100% and that of EEG 96%. In a larger group of 58 infants, all treated with hypothermia, similar values were found by using neonatal MRI rather than neurodevelopmental outcome.[74] Bilaterally absent responses were obtained in 10 (17%) of the 58 neonates, and all showed moderate or severe MRI abnormalities; 36 (75%) of 48 neonates with present SEPs had normal MRI results. The PPV of SEPs for MRI outcome was of 1.00, whereas the NPV was 0.72. The data obtained in another study that included 26 cooled infants were less promising, with an abnormal outcome in only 4 of 11 infants with bilateral absent SEPs (PPV 0.36). The NPV was, however, high, with correct prediction of a normal outcome in 14 of 15 infants (0.93).

Overall, the predictive power of evoked potentials and aEEG for neurodevelopmental outcome is good and may especially be of additional value in those with moderate HIE and moderately abnormal EEG background activity.[81]

Neuroimaging

As discussed earlier, certain regions of the brain are preferentially affected under different circumstances. Different imaging modalities can be used, but recent data have shown MRI to be superior to ultrasonography and computed tomography (CT).[24]

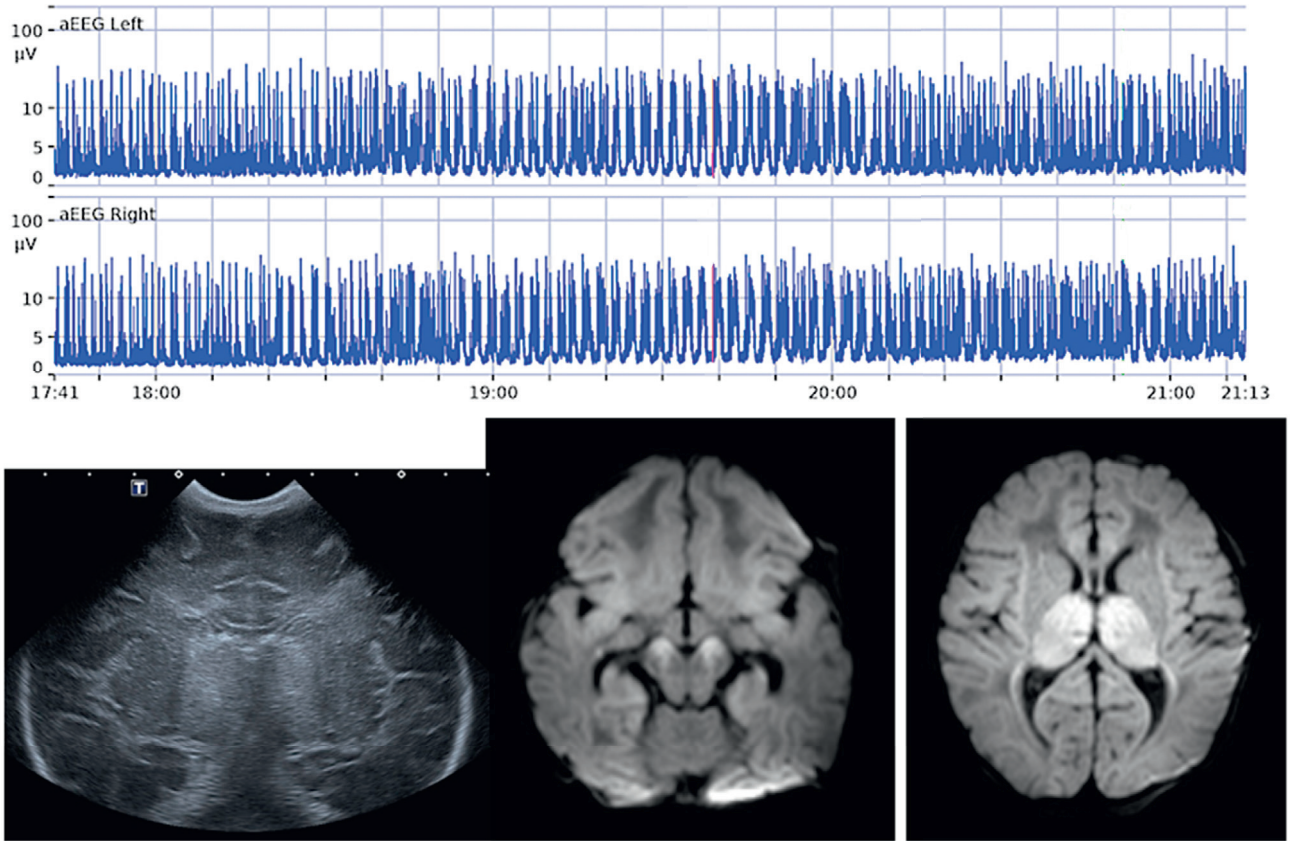
Cranial ultrasonography has a poor reputation when it comes to assessment of abnormalities of the brain of the full-term infant with HIE. Ultrasonography can be helpful, especially when performed sequentially during the first week after birth (Fig. 54.9). Changes in the thalami and basal ganglia may be subtle but usually become clearer by the end of the first week.[24] Alterations of the signal in white matter can sometimes be seen on admission, suggesting that the insult is of antenatal onset. More often, echogenicity develops gradually over a period of days. In severe cases, the ventricles are difficult to visualize because of edema and are described as "slitlike." A Doppler signal can be obtained during ultrasonography, at the level of the anterior or preferably the middle cerebral artery. Several studies have shown that an increase in diastolic flow, resulting in a reduced resistance index (<0.55) and an increase in cerebral blood flow velocity (>3 standard deviations [SDs]), is associated with a poor neurodevelopmental outcome. Changes usually developed after the first 24 hours after birth.[4] Color Doppler flow across the sagittal sinus can be used to diagnose or exclude a sinovenous thrombosis.

CT is less sensitive than MRI for detecting changes in the central gray nuclei, which is the most common problem in full-term infants with HIE. A decrease in attenuation of white matter may be difficult to differentiate from normal unmyelinated white matter. CT is only useful in an infant admitted after a very traumatic delivery and suspected of having extra-axial hemorrhage. In such cases, ultrasonography may miss these blood collections unless they are large, with an associated midline shift. Furthermore, CT may be more accessible than MRI, and in the likelihood of possible emergency surgical intervention, CT can be performed soon after admission.

The most appropriate technique to use is MRI because it can show different patterns of injury. After an acute sentinel event, the basal ganglia and thalami are most commonly involved.[13] An altered, sometimes reversed signal at the level of the posterior limb of the internal capsule can be seen during the second half of the first week in term infants, and this has been noted to be of very high PPV for neurodevelopmental outcome.[44] Signal changes in the basal ganglia and thalami have also been reported in preterm infants after a sentinel event.[41]

With the use of DWI, abnormalities in the thalami and basal ganglia can often be seen within days after birth, but the alterations in signal intensity may be more pronounced

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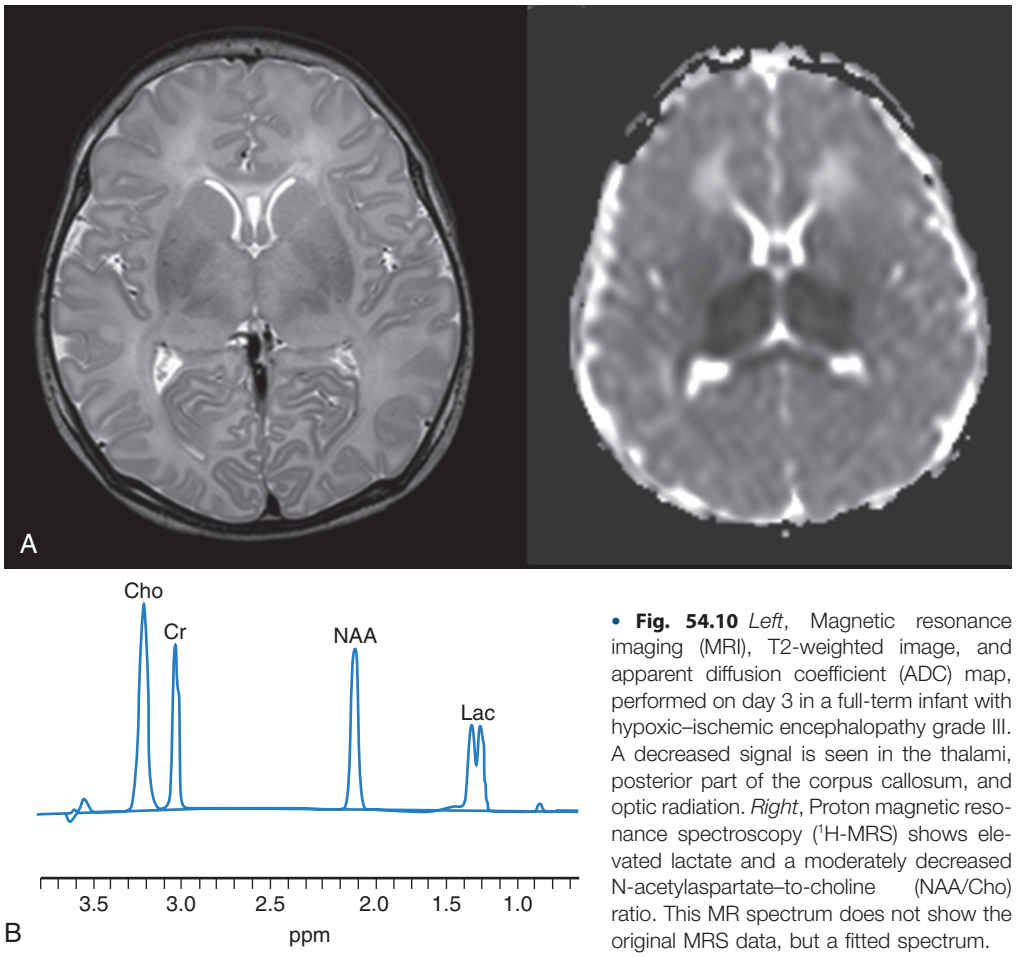
• **Fig. 54.9** *Top,* Bilateral amplitude-integrated electroencephalography (aEEG) showing a status epilepticus on day 1 in a full-term infant with perinatal asphyxia. *Bottom left,* Cranial ultrasonography performed on day 2 showing echodensities in the basal ganglia and thalami. *Bottom middle and right,* Diffusion weighted imaging (DWI) on day 3 showing severe abnormalities in the cortex, white matter and cerebral peduncles (*middle*), as well as in the thalami (*right*).

later in the first week (Fig. 54.10). Calculation of ADC is important to assess the severity of the insult. DWI changes and the ADC show so-called pseudonormalization after the first week of life, which decreases the predictive value of this technique after the first week of life, although this process may be a few days delayed by therapeutic hypothermia.[1,7] Changes in the basal ganglia are often seen together with changes at the level of the central gyrus, and this combination carries a poor prognosis. Dyskinetic cerebral palsy is a result of injury to these brain areas. Additional lesions in the pons will result in feeding problems, whereas signal changes involving the cortex may be followed by epilepsy. Additional MRI abnormalities in the occipital white matter are likely to result in cerebral visual impairment.[45]

The second most common pattern of injury is to the watershed regions, which is especially well recognized with DWI.[13] The severity of white matter abnormalities can be different from that of focal lesions, often with punctate white matter lesions, and these were recently noted to be especially common in infants with milder encephalopathy. White matter lesions can also be very diffuse with loss of gray matter–white matter differentiation, preceding cystic evolution. These more severe white matter abnormalities can be seen in isolation or in association with abnormalities of the basal ganglia. Early changes on MRI correlate well with neonatal EEG findings, later MRI findings, and the neurodevelopmental outcome. Early cognitive and motor outcome in infants with extensive watershed lesions without involvement of the basal ganglia is often more favorable than expected, but these children need to be seen until school age because they may grow into their deficits.[29] Although cerebral injury in infants with hypoxic–ischemic encephalopathy was reduced by therapeutic hypothermia, the PPV of MRI for subsequent neurologic impairment was maintained.[1] Punctate white matter lesions are commonly seen in infants with cardiac and noncardiac congenital malformations. The pattern of cerebral involvement appears to be influenced by the presence and type of placental pathology (see section on Selective Vulnerability).

Focal ischemic lesions are also well detected with use of this technique. The middle cerebral artery, most often the left branch, is most commonly affected. DWI allows for detection of the area involved at a time when conventional MRI may not yet be very reliable. Involvement of the descending corticospinal tracts can be well visualized with DWI and is referred to as *pre-Wallerian degeneration*, which is highly predictive of subsequent Wallerian degeneration and development of a hemiplegia. Diffusion tensor imaging

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• **Fig. 54.10** *Left*, Magnetic resonance imaging (MRI), T2-weighted image, and apparent diffusion coefficient (ADC) map, performed on day 3 in a full-term infant with hypoxic–ischemic encephalopathy grade III. A decreased signal is seen in the thalami, posterior part of the corpus callosum, and optic radiation. *Right*, Proton magnetic resonance spectroscopy (^{1}H-MRS) shows elevated lactate and a moderately decreased N-acetylaspartate–to-choline (NAA/Cho) ratio. This MR spectrum does not show the original MRS data, but a fitted spectrum.

(DTI) and tractography may aid in the prediction of asymmetric neuromotor development.[85]

Magnetic resonance angiography (MRA) can further aid in the visualization of abnormal flow across the artery involved in case of an embolism or dissection. The area of cavitation noted on a repeat scan performed a few months later usually is smaller than expected on the basis of the area of abnormal signal intensity seen on the initial scan, but the tissue surrounding the cavity is altered and shows gliotic scarring later in infancy. Sinovenous thrombosis was considered a rare condition, but with the introduction of MRI and magnetic resonance venography (MRV), it is more often diagnosed.[24] Conventional MRI shows an increased signal in the sinus on a T1-weighted image, and MRV shows lack of flow across the sinus. The sagittal sinus, straight sinus, or the deep veins of the basal ganglia can be affected. An associated unilateral thalamic hemorrhage can be present. Novel techniques, such as arterial spin labeling, have been used to demonstrate hyperperfusion in infants with severe perinatal asphyxia. Higher arterial spin labeling perfusion values in full-term infants with HIE were associated with a worse neurodevelopmental outcome.[15]

Metabolic assessment with use of ^{1}H-MRS or ^{31}P-MRS can be performed during MRI examination. The most commonly used nucleus for clinical applications is ^{1}H because it is the most abundant and the strongest nucleus. N-acetylaspartate, creatine/phosphocreatine, choline-containing compounds, myoinositol, glutamine and glutamate, and lactate can all be recognized within the proton spectrum. A decrease in N-acetylaspartate and a high lactate peak have been reported for ^{1}H-MRS. A recent meta-analysis comparing conventional MRI diffusion-weighted imaging and ^{1}H-MRS as potential early biomarkers found the deep gray matter Lac/NAA ratio to be the most accurate quantitative MR biomarker within the neonatal period for prediction of neurodevelopmental outcome after hypoxic–ischemic encephalopathy. This predictive value of ^{1}H-MRS was retained after therapeutic hypothermia.[1,36a]

A comparison of ^{1}H-MRS and DWI performed on the first day after birth showed that ^{1}H-MRS was better in accurately depicting the severity of injury at this very early stage.[38]

PET has been infrequently used. A study of regional cerebral metabolic rates of glucose (CMRgl) showed localized increases, which were in good agreement with changes seen with other neuroimaging techniques, whereas in another study, the deep subcortical areas, thalamus, basal ganglia, and sensorimotor cortex were identified as the most metabolically active brain areas. Total CMRgl were inversely related to the severity of HIE.[24]

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Chemical Biomarkers

Numerous compounds were tested to be used as biomarkers of adverse neurodevelopmental outcome. These tests included analysis of blood gases; early lactate levels; liver enzymes, such as lactate dehydrogenase; erythroblastosis; cytokines in cerebrospinal fluid (CSF); hypoxanthine in CSF; isoprostanes; and more specific brain proteins, such as creatine kinase (BB), S-100B, and neuron-specific enolase.[75] Although these compounds may reflect the severity of hypoxia–ischemia, or even the severity of brain involvement, they have limited value for the prediction of long-term neurodevelopment because of lack of a specific origin within the brain.

Management

Primary Prevention

Prevention of fetal asphyxia is, by far, preferable to the prospect of managing the newborn who has suffered a hypoxic–ischemic insult during birth. The aim of modern obstetrics is to recognize the compromised fetus before irreversible organ damage occurs and rescue it from the hostile environment.

Electronic fetal monitoring (EFM) is widely used to identify infants with hypoxia (see Chapter 12). A Cochrane Review of 13 randomized controlled trials (RCTs) showed a statistically significant decrease in the number of neonatal seizures in the infants born in the EFM group (relative risk [RR] 0.50; 95% CI 0.31-0.80). This effect was noted in only two of the larger studies, where the option of pH estimation was available for unfavorable traces. There was no significant difference in overall perinatal death rate (RR 0.86; 95% CI 0.59-1.23). These studies also showed a significantly increased risk of delivery by cesarean section in the EFM group (RR 1.63; 95% CI 1.29-2.07). Follow-up data from the surviving infants was available in two studies, but both failed to show any reduction in long-term neurologic adverse effects.[3]

Fetal electrocardiography (ECG) waveforms have been evaluated as a more sensitive method for the detection of fetal hypoxia rather than EFM. Two different methods have been studied: the PR to R-R ratio and the ST waveform. In the PR to R-R ratio, there is normally a positive correlation between the PR interval and the R-R interval so that when the heart rate increases, both PR and R-R intervals shorten. The hypoxemic heart behaves differently, with shortening of the PR interval and lengthening of the R-R interval so that change in the PR to R-R ratio is a predictor of fetal heart hypoxic compromise. An alternative method assesses changes in the ST waveform in much the same way as exercise ECG assessment in adults with myocardial disease.

A Cochrane analysis of seven RCTs of fetal ECG use in labor has been reported by Neilson. All trials assessed fetal ECG as an adjunct to EFM alone during birth. The studies of ST waveform resulted in no fewer infants born with severe metabolic acidosis (pH <7.05; base deficit [BD] >12 mmol/L), or babies with neonatal encephalopathy. There were fewer operative vaginal deliveries, but no difference in admissions to the NICU. The author concluded that there was "little strong evidence that ST waveform analysis had an effect on the primary outcome measures."[48] Other fetal monitoring strategies, such as fetal pulse oximetry, fetal scalp lactate values, fetal movement counting, and use of NIRS, have been investigated, but without beneficial effects (see www.cochrane.org; accessed December 21, 2017).

In summary, intrapartum assessment of severe hypoxia may result in improved condition at birth and reduce the risk of hypoxic–ischemic encephalopathy, but there is little evidence to support the notion that hypoxic–ischemic brain damage can be prevented.

Resuscitation

The key to resuscitation (see Chapter 31) is to restore adequate oxygenation and perfusion of vital organs, particularly the brain. Systemic acidosis developing as a result of intrapartum asphyxia impairs cardiac contractility, but its effect on cerebral function is less clearly understood. Infants may be born in unexpectedly poor condition and require immediate resuscitation. Most infants born in suboptimal condition can be anticipated (Box 54.2), and staff trained in neonatal resuscitation should be available at the birth. It is estimated, however, that approximately 20% of infants who require resuscitation do not fall into this group. The importance of expert resuscitation has been recognized, and every infant, wherever born, must have personnel available with expert resuscitation skills and all the appropriate equipment in good working order. The introduction of obstetric emergencies training courses can result in a significant reduction in low 5-minute Apgar scores and HIE. With continued training, it is possible to sustain this improvement.

During the last decade, novel insights have been developed into the technique of neonatal resuscitation. This has led to a change in guidelines. Most recent guidelines suggest the use of as little oxygen as needed.[55] Further research is aimed at the benefit of delayed cord clamping, especially in preterm infants.[76]

Systemic Management

The diving reflex occurs during experimental asphyxia to maintain blood flow to vital organs, such as the brain, at the expense of less-vital organs. This is the basis of systemic complications after a clinically significant hypoxic–ischemic insult, and the heart, kidneys, and liver are the most vulnerable organs. Almost all infants with HIE show compromise in at least one organ system other than the brain.[67] The clinical course after a hypoxic–ischemic event in labor is unpredictable, so problems should be anticipated and the infant appropriately observed by trained staff in a clinical environment. Hypoxic–ischemic insult affects the whole

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• BOX 54.2 Conditions in Which the Need for Resuscitation at Birth May Be Anticipated

Prelabor Factors

Maternal

- Toxemia (eclampsia)
- Diabetes mellitus
- Drug addiction
- Cardiovascular disease
- Infectious disease
- Collagen vascular disease

Uteroplacental

- Placental abruption
- Umbilical cord prolapse
- Placenta previa
- Polyhydramnios
- Premature rupture of the membranes

Intrapartum Factors

- Isoimmunization
- Multiple birth
- Preterm birth
- Cardiopulmonary abnormalities
- Abnormal presentation
- Precipitous delivery
- Fetal distress
- Thick meconium staining
- Prolonged labor
- Difficult forceps delivery
- Intrauterine growth restriction
- Prolonged pregnancy

organism, and any organ system may be compromised. Brain-oriented management is discussed later; the following section discusses management of systemic complications.

Renal System

Renal impairment is reported to occur in 23%-70% of asphyxiated infants.[67] Acute renal failure (plasma creatinine >130 μmol/L [1.2 mg/dL] for at least 2 consecutive days) is reported in 19% of asphyxiated infants of gestation age greater than 33 weeks. In a study using a more sensitive measure of renal tubular function (N-acetylglucosaminidase), there was a relationship between elevated N-acetylglucosaminidase levels and degree of HIE in the infant.[67] Because of the fear of renal failure and fluid overload, many clinicians have adopted a policy of fluid restriction in newborns with asphyxia, but there is no evidence that normal fluid volumes contribute to cerebral edema in the newborn. Fluid restriction is necessary in infants who have inappropriate antidiuretic hormone secretion or those with known renal tubular impairment. Fluid intake in these infants should be titrated against measurements of the infant's serum and urinary electrolytes.

Oliguria is managed by careful maintenance of fluid balance with daily measurement of plasma and urinary creatinine levels, and serum and urinary electrolytes, as well as daily assessment of the infant's weight. Acute renal failure and anuria lasting more than a day should be initially managed conservatively (see Chapter 92). Chronic renal failure and the need for dialysis are extremely rare in severely full-term infants with asphyxia.

Cardiovascular System

Myocardial contractility is impaired after hypoxic–ischemic insult, causing a significant reduction in cardiac output, hypotension, and further impairment of cerebral blood flow and perfusion of other organs. Myocardial dysfunction detected by Doppler ultrasonography has been shown to occur in many newborn infants with asphyxia. Other cardiac pathologic processes recognized to occur after a severe hypoxic–ischemic insult include acute cardiac dilation with functional tricuspid valve regurgitation, myocardial ischemia present on ECG assessment, and ischemic necrosis of papillary muscle. Cardiac biomarkers, such as troponin T, as markers for perinatal myocardial damage are currently under investigation. Although the risk of persistent pulmonary hypertension (PPHN) is not significantly increased by therapeutic hypothermia, PPHN is common when perinatal asphyxia is seen in combination with early-onset sepsis or meconium aspiration syndrome. PPHN may have a profound impact on brain oxygenation in term newborns with asphyxia treated with hypothermia during the first days after birth, and this can be assessed by using NIRS. In addition to inhaled NO, milrinone is used to improve circulation.

Hypotension is common after severe hypoxic–ischemic insult, and volume support is often ineffective in restoring normotension. Inotropes have been shown to be effective in restoring blood pressure in infants with asphyxia.

Hepatic and Gastrointestinal Systems

Elevated liver enzymes occur in 80%-85% of asphyxiated full-term newborn infants during the first week of life. Irreversible liver damage appears to occur very rarely after asphyxia at birth. Necrotizing enterocolitis is a well-recognized complication in infants with asphyxia but this etiology is relatively rare.

Hematologic System

Coagulation impairment is relatively common after a severe asphyxial insult. The bone marrow may be transiently damaged, leading to thrombocytopenia. Disseminated intravascular coagulation (DIC) occurring after birth asphyxia is also well recognized, with low levels of factor XIII and elevated thrombin–antithrombin complexes; D-dimer, fibrin, and fibrinogen degradation products; and soluble fibrin monomer complexes.

Coagulation impairment should be anticipated and screening for hematologic abnormalities undertaken in all severely asphyxiated newborn infants. Supportive treatment

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with platelets, vitamin K, or clotting factors may be indicated by specific abnormalities on the coagulation screen. The management of DIC is controversial, but there is no indication for systemic heparinization (see Chapter 79). Hypothermia has no effect on coagulation, but thrombocyte counts are lower during hypothermia.[33]

Brain-Oriented Management

Careful attention must be paid to maintain cerebral homeostasis by anticipation of complications that may have a direct or indirect effect on brain function and recovery after a severe hypoxic–ischemic insult. More standard brain-specific complications affecting the infant after a severe hypoxic–ischemic insult are discussed in the following section.

Glucose

Hypoglycemia has been shown to be an additional adverse factor for the immature brain in conjunction with a hypoxic–ischemic insult. Immature hypoglycemic animal models subjected to anoxia have a considerably increased mortality rate compared with anoxic, normoglycemic animals. The presence of ketone bodies as an alternative brain fuel ameliorates this effect despite low levels of circulating glucose. The facilitative glucose transporter proteins (GLUT1) transport glucose across the blood–brain barrier, and related proteins (GLUT3 and 45-kd GLUT3) mediate transport into the neuron and glial cells, but these proteins are in low concentration in the immature brain. Hypoxic–ischemic insult initially enhances both GLUT1 and GLUT3 expression in the brain, but GLUT3 decreases after 72 hours, in association with extensive cellular necrosis. Asphyxia initially increases the cerebral metabolic rates of glucose (CMRgl), and consumption of glucose during hypoxic–ischemic insult causes depletion of intracerebral glucose. Very limited numbers of infants have been studied after asphyxial insults by using PET, with conflicting results. In five term infants, CMRgl was increased 2-3 days after the insult, whereas another study of CMRgl in 20 human infants with asphyxia showed a high correlation between the more severe degree of HIE and lowest values of CMRgl. These low levels were obtained at a median age of 11 days, which was later than that in the first study and may account for the differences in values.

Studies have shown that there are major differences in the behaviors of the mature brain and the immature brain to glucose infusion. The infusion of glucose in the immature organism, unlike in adults, before a hypoxic–ischemic event, appears to have protective effects compared with subjects not given sugar supplementation. The pretreated hyperglycemic group had better preservation of PCr and ATP compared with the normoglycemic group. Preconditioning the animal before a major hypoxic–ischemic insult may afford protection, which appears to be caused by enhanced intracerebral glycogen levels, increased expression of GLUT1, and increased availability of alternative brain fuels. The clinical question of whether glucose infusion after hypoxic–ischemic insult is of value remains controversial.

Although routine use of high-concentration glucose is not advised after a hypoxic–ischemic event in the neonate, it is clear that hypoglycemia must be avoided. In addition, 3 decades ago, it has been shown that insulin levels are elevated in the hours after perinatal asphyxia, when stress hormones tend to decrease and the chance of hypoglycemia is considerable.[11] Regular blood glucose testing in neonates after resuscitation is of utmost importance. At present the importance of high glucose levels is not completely established.

Seizures

Seizures (see Chapter 55) occur in many infants who have sustained a significant hypoxic–ischemic insult; indeed, seizure is a feature of moderate and severe HIE. In general, the more severe or prolonged the hypoxia–ischemia, the more seizure activity the infant will have. In the past, there has been considerable debate as to whether seizure activity after a hypoxic–ischemic event confers an additional risk factor on the infant in terms of adverse neurodevelopmental outcome. Several studies have demonstrated adverse effects of repetitive seizures on the developing brain, and these should be treated, even if subclinical and demonstrated by using only EEG techniques.

A hypoxic–ischemic insult sets in train a cascade of intraneuronal events that may result in cell death. In animal studies, the induction of multiple short seizures over the first days of life does not result in neuronal loss but does result in morphologic changes involving cortical activation and cell density that are evident when the brain was examined in adult life. Furthermore, these animals exhibited impaired learning and lower seizure threshold in later life. In human neonates, there is often dissociation between clinically evident seizures and seizures recognized on EEG monitoring, so the frequency of seizure activity after a hypoxic–ischemic insult may well be underestimated by clinical observation. Therefore, asphyxiated infants are very likely to have a significant seizure burden that may be underestimated by clinicians. There is evidence that although the majority of irreversible neuronal injury after recovery from hypoxic–ischemic insult is due to the underlying cause of the condition, additional functional injury may ensue secondary to the seizure burden. This strengthens the case for effective management of seizure activity after a hypoxic–ischemic event.

Fully effective anticonvulsant therapy in the neonatal period is difficult, but some drugs, such as lidocaine as add-on therapy, are effective for controlling both clinical and electrographic seizures. Phenobarbital is still the drug of first choice. A study comparing the efficacy of phenobarbital against phenytoin in the management of EEG-diagnosed seizures found that in a single-blind RCT, there was complete seizure control in less than 50% of infants

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with either drug. When both drugs were given, complete seizure abolition occurred in only 50% of infants.[54]

In a study of term infants with asphyxia, high-dose phenobarbital (40 mg/kg) was associated with a significant reduction in severe neurodevelopmental disability. In many cases, the phenobarbital was given before the first evidence of seizure activity. A meta-analysis of five studies comparing barbiturates with conventional therapy after occurrence of hypoxic–ischemic encephalopathy found no difference in risk of death or severe neurodevelopmental disability in survivors. Phenobarbital has also been shown to have toxic effects on brain growth, neuronal toxicity, and adverse cognitive and behavioral effects when given to immature animals. Other anticonvulsants used to treat seizures occurring after a hypoxic–ischemic insult include phenytoin (no greater efficacy than phenobarbital), benzodiazepines (clonazepam, midazolam, lorazepam), lidocaine, thiopentone, sodium valproate, lamotrigine, and levetiracetam. These drugs have been evaluated in an uncontrolled manner, and the information on effect is largely anecdotal.

In Europe, lidocaine is more commonly used as a second- or third-line anticonvulsant; however, it should not be used if phenytoin has been administered because cardiotoxicity may occur. Lidocaine was more effective in abolishing (electroconvulsive) seizures when used as add-on therapy after phenobarbital than midazolam, especially during therapeutic hypothermia.[91] It is essential that new RCTs be started to evaluate the efficacy of the newer anticonvulsant drugs, such as levetiracetam or topiramate, in the management of seizures occurring after perinatal asphyxia. There has been accumulating evidence from animal studies that antiepileptic drugs have adverse effects, including apoptosis, inhibition of brain growth, and adverse behavioral and cognitive effects in adult life, when the drugs are administered at an early age. It is of interest that several studies have shown a decreased seizure burden in neonates with HIE who received cooling. This finding may explain some of the therapeutic benefits of cooling seen in term neonates with (moderate) HIE. As pharmacokinetics of anticonvulsants may be changed by therapeutic hypothermia, dose adjustments are needed, in particular for lidocaine and midazolam.[83,84]

The duration of anticonvulsant administration should be minimized to avoid the potential adverse effects of prolonged exposure. The optimal duration of anticonvulsants is unknown. Some clinicians withdraw treatment as soon as the neurologic examination normalizes. In case of serious cerebral injury documented with MRI, some clinicians continue phenobarbital administration for 2-3 months, but there is no evidence to support this.

Cerebral Edema

Cerebral edema may occur after a severe hypoxic–ischemic insult. Studies of intracranial pressure (ICP) monitoring in human infants who have suffered a severe hypoxic–ischemic insult have shown that severely raised ICP (>15 centimeters of water [cm H_2O]) was found in a minority of infants monitored by a median time of 26 hours. In this group of infants with asphyxia and raised ICP, successful treatment of the ICP, as judged by a significant benefit on outcome, was estimated to have occurred in less than 10% of cases. There is no evidence that routine monitoring of ICP is of benefit to the infant. Raised ICP is most probably an end result of the abnormal pathophysiologic processes that occur after hypoxic–ischemic insult and, in itself, is a marker of damage, rather than a cause of it. Consequently, the management of raised ICP becomes relatively less important.

Corticosteroids

There are few data to suggest that corticosteroids are effective in the management of hypoxia–ischemia. Animal studies on immature rat pups have shown that pretreatment with dexamethasone before a hypoxic–ischemic insult resulted in less severe injury than in untreated control animals, but treatment with dexamethasone after the insult was ineffective in alleviating cerebral edema. Steroids are routinely used in older children and adults with focal edema, as occurs in tumor or traumatic brain injury, but appear to be much less effective after a global hypoxic–ischemic insult.

There is concern about the long-term effects of large doses of dexamethasone given shortly after birth, particularly in preterm infants, in whom it is estimated that there is a significant increase in the risk of cerebral palsy. There is no scientific justification for the use of steroids after an intrapartum hypoxic–ischemic insult to treat cerebral edema.

Specific Neuroprotective Strategies

A number of studies have attempted to make preliminary investigations into the role of different strategies in neonatal brain protection after a hypoxic–ischemic insult, but few useful clinical data are currently available. Moderate hypothermia is the only specific neuroprotective therapy that is part of routine care.

Hypothermia

In recent years, interest in neuroprotection by brain cooling has shown benefit in both animals and humans. Studies in animal models have shown that in a variety of immature species, varying degrees of mild hypothermia (2°C-5°C below normal) for 3-72 hours were effective in maintaining brain function. Hypothermia has been suggested to have an effect by reducing cerebral metabolism and ATP consumption and downregulating many intracerebral metabolic processes associated with rapid expression of early gene activation.

Since the reports in 2005 of RCTs in full-term neonates with perinatal asphyxia, hypothermia has become standard of care for infants when perinatal asphyxia is followed by encephalopathy.[68] In the Cochrane analysis that

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has been updated frequently since then, no differences have been demonstrated between head cooling or whole body hypothermia.[33]

With whole body hypothermia, the rectal temperature is decreased to 33°C-34°C for 72 hours, whereas with the cooling cap perfused with a coolant solution at 10°C and body temperature is maintained between 34°C and 35°C. The primary outcome in the RCTs was death or disability at 18 months. All infants had been cooled within 6 hours of birth.

Despite the differences in the findings from the RCTs, the outcome at 18 months is remarkably consistent in showing improved survival without neurologic abnormality and significantly reduced cumulative outcome of death and severe disability (Fig. 54.11). Neuroprotection is better in neonates with moderate encephalopathy than in those with severe encephalopathy. Overall, with death or severe handicaps taken together as poor outcome, number to treat is approximately 7. Of interest, control infants in the trials who became hyperthermic had worse outcomes. The therapeutic effects of moderate hypothermia are sustained when examining these children at school age.

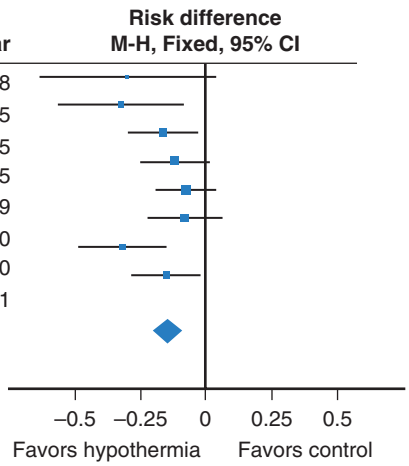
Reported complications of hypothermia are sinus bradycardia and thrombocytopenia (Fig. 54.12).[68] Anecdotal reports mention increased pulmonary hypertension and subcutaneous fat necrosis, but this has not been demonstrated in the RCTs and subsequent meta-analyses.

It is important to note that the temperature of the hypothermic babies needs to be maintained within preset limits, because more severe hypothermia (<33°C) may have detrimental effects, such as cardiac arrhythmia. Therapeutic hypothermia has been confined to studies in mature infants younger than 35 weeks' gestational age. Historical studies have shown a vast excess of deaths in very immature babies who became to chilled, and this form of treatment is at present not recommended in premature infants.

Both the therapeutic window, set at 6 hours, and the duration of therapy (72 hours) are based on the development

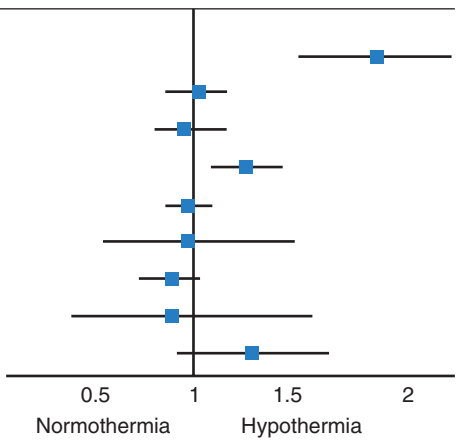
Study	Hypothermia Events	Hypothermia Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Gunn 1998	0	6	3	10	1.1%	–0.30 [–0.63, 0.03]	1998
Eicher 2005	14	27	21	25	3.9%	–0.32 [–0.56, –0.08]	2005
Shankaran 2005	45	102	64	106	15.6%	–0.16 [–0.30, –0.03]	2005
Gluckman 2005	59	108	73	110	16.4%	–0.12 [–0.25, 0.01]	2005
Azzopardi 2009	74	163	86	162	24.4%	–0.08 [–0.19, 0.03]	2009
Zhou 2010	41	100	46	94	14.6%	–0.08 [–0.22, 0.06]	2010
Simbruner 2010	27	53	48	58	8.3%	–0.32 [–0.48, –0.15]	2010
Jacobs 2011	55	107	67	101	15.6%	–0.15 [–0.28, –0.02]	2011
Total (95% CI)		**666**		**666**	**100.0%**	**–0.14 [–0.19, –0.09]**	
Total events	315		408				

Heterogeneity: Chi² = 9.81, df = 7 (P = 0.20); I² = 29%
Test for overall effect: Z = 5.29 (P < 0.00001)



• **Fig. 54.11** Meta-analysis of eight randomized controlled trials with follow-up to 18 months or more. Risk difference of death or major handicaps as events. CI, Confidence interval; RD, risk difference.

Outcome	Number of studies / number of participants	Relative risk
Arrhythmia	5 / 806	4.08 (1.55, 10.74)
Hypotension	8 / 1108	1.03 (0.93, 1.13)
Coagulopathy	7 / 1114	0.96 (0.80, 1.15)
Thrombocytopenia	4 / 638	1.28 (1.07, 1.52)
Seizure after enrollment	8 / 1102	0.96 (0.86, 1.06)
Renal failure	5 / 310	0.95 (0.53, 1.70)
Hepatic side effects	5 / 678	0.85 (0.69, 1.04)
Infection	7 / 544	0.86 (0.40, 1.88)
Pulmonary hypertension	5 / 636	1.36 (0.95, 1.96)



• **Fig. 54.12** Meta-analysis of eight randomized controlled trials with follow-up to 18 months or more. Safety outcomes. CI, Confidence interval; RR, relative risk. (From Shah PS. Hypothermia: a systematic review and meta-analysis of clinical trials. *Semin Fetal Neonatal Med*. 2010;15:238-246.)

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and duration of secondary energy failure in animal models. Starting hypothermia later than 6 hours after the insult is less effective.[37] Studies of longer or deeper therapeutic hypothermia did not show any benefit.[69] Therapeutic effects of moderate hypothermia in infants with milder encephalopathy have not yet been confirmed.

Other Strategies

A number of studies have attempted to make preliminary investigations into the role of different strategies in neonatal brain protection after a hypoxic–ischemic insult, but few useful clinical data are currently available.

The calcium channel blocker nicardipine was given to four infants who had sustained severe intrapartum hypoxic–ischemic insult. In 3 of 4, the mean arterial blood pressure dropped precipitously with a fall in cerebral blood flow. The systemic effects of the relatively nonspecific calcium channel blockers significantly limit their value for brain protection.

Magnesium sulfate ($MgSO_4$) is an NMDA receptor antagonist and has been proposed to be an effective agent for brain protection and is used extensively in preterm labor for fetal neuroprotection. Although studies have evaluated the role of $MgSO_4$ in term infants with asphyxia, no sustained benefits have been reported.

Potential neuroprotective agents for postnatal treatment are melatonin, erythropoietin (EPO), N-acetylcysteine, allopurinol, selective NOS inhibitors, and noble gases, such as xenon and argon and have been among the agents ranked highest. Melatonin is produced mainly by the pineal gland, allowing the entrainment of circadian rhythms of several biologic functions. Melatonin can also function as an antioxidant and has antiapoptotic effects. Although melatonin may have beneficial effects, more pharmacokinetic studies need to be performed. EPO messenger RNA expression is markedly increased in cerebral tissue neurons in response to hypoxia. EPO triggers several different signaling pathways. Neuroprotective effects have been associated with stimulation of production of growth factors, including vascular endothelial growth factor secretion and brain-derived neurotrophic factor. In one study, EPO appeared to improve neurologic outcomes in newborns with hypoxic–ischemic encephalopathy, but these patients did not receive hypothermia treatment. Studies combining hypothermia and EPO are ongoing.

Selective inhibitors of nitric oxide synthase (NOS), inhibiting neuronal and inducible, but not endothelial NOS, have been developed in preclinical studies, and pharmacokinetic studies with or without concurrent hypothermia are also ongoing.

N-acetylcysteine is a precursor of glutathione and can, therefore, act as an antioxidant and is also a scavenger of oxygen free radicals. In animal experiments, it has been used in combination with hypothermia, but clinical studies in humans have not yet been performed.

Allopurinol is an inhibitor of xanthine oxidase and has free radical scavenging action. The long-term effects of allopurinol after perinatal asphyxia in 23 neonates were published in 2011. At follow-up at a mean age of 5 years, no differences in long-term outcome between the allopurinol-treated infants and controls were demonstrated. However, subgroup analysis of the group with moderate asphyxia showed significantly less severe adverse outcome in the allopurinol-treated infants compared with controls (25% versus 65%; RR 0.40; 95% CI 0.17-0.94). In a trial, fetal levels of allopurinol could be achieved through maternal administration, and small effects were seen in a subgroup analysis. A neonatal trial is ongoing (NCT03162653).

Xenon, a noble gas, has been shown to be a very safe anesthetic and a potent neuroprotectant. Xenon is a noncompetitive antagonist of the NMDA subtype of the glutamate receptor, although other mechanisms of action have been reported. Xenon appears to be neuroprotective in animal models of perinatal asphyxia. At present, clinical trials are examining the neuroprotection by xenon in addition to hypothermia. Large-scale use of xenon may be limited by the excessive costs. A recent study did not show beneficial effects of xenon in combination with therapeutic hypothermia.[5] Argon, a cheaper alternative to xenon, has been used only in preclinical studies.

Stem cells or progenitor cells may have multiple beneficial effects on outcome after hypoxic–ischemic injury, as has been shown in preclinical studies. Trials of infusion of autologous cord blood are ongoing in several centers.

Prognostic Factors

Perinatal asphyxia is an important cause of neonatal mortality and morbidity, including dyskinetic cerebral palsy, cognitive deficits, behavioral problems, visual disturbance, deafness, and epilepsy. The outcome of infants with hypoxia–ischemia and encephalopathy is influenced by several factors, including the duration and severity of the insult to the brain; gestational age; presence of seizures; associated infectious, metabolic, and traumatic derangements; and effects of therapeutic hypothermia. Although the prognosis for any single newborn often is difficult to formulate, certain clinical and laboratory abnormalities, along with perinatal cerebral hypoxia–ischemia, are associated with a high risk of neurologic morbidity (Box 54.3). However, the value of some early prognostic factors that have been established previously has changed by the use of hypothermia.[60]

The degree of maturity at birth is an important predictor of mortality in infants suffering asphyxia at birth. In the early days of neonatal intensive care, Nelson and Ellenberg also reported an appreciably higher death rate in premature infants, but an increased risk for cerebral palsy in the full-term survivors. The lower morbidity among the premature infants was related, in part, to the small number of survivors in this group. Epidemiologic data in the present era of neonatal intensive care are only available for full-term neonates.[33]

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• BOX 54.3 Predictors of Mortality and Neurologic Morbidity After Perinatal Hypoxic–Ischemic Insult

- Apgar score ≤4 at 10 minutes
- Prolonged abnormal neonatal neurologic examination
- Abnormal brain imaging using ultrasonography and magnetic resonance imaging, and proton magnetic resonance spectroscopy (^{1}H-MRS)
- Abnormal electrophysiology: suppressed background pattern on electroencephalography (EEG) or amplitude-integrated EEG (aEEG), status epilepticus; abnormal evoked potentials (visual, brainstem auditory, and somatosensory)

Apgar Scores and Condition at Birth

Several studies have demonstrated the low sensitivity of the 1- and 5-minute Apgar scores in predicting long-term neurologic outcomes. However, the extended Apgar score is a reliable predictor of ultimate neurologic morbidity, especially when very low scores are obtained at 20 minutes.[10]

The time from birth until onset of spontaneous, sustained respirations also has been correlated with long-term neurologic function. Full-term infants who were apneic for 30 or more minutes were universally and severely damaged. Data have suggested that a prolonged delay in the initiation of spontaneous respirations is a reasonable indicator of irreversible brain damage. However, the predictive value has changed by the use of therapeutic hypothermia. In a recent study in Australia, 4 of 13 infants with a 10 minute Apgar score of zero were normal at 1 year.[66]

Acidosis

Obstetricians have long used blood acid–base status to ascertain the presence or absence of asphyxia in the fetus during the intrapartum period. Obstetricians concentrate on more severe degrees of acidosis and on the extent to which the altered pH reflects an underlying metabolic (lactic) acidosis. In the study of Goldaber et al., 2.5% of 3,506 full-term newborns exhibited an umbilical artery pH of less than 7.00, 66.7% of whom had a metabolic component to their acidosis. Significantly more of the severely acidotic newborns exhibited low (less than 3) 1- and 5-minute Apgar scores compared with infants with higher umbilical artery pH values.[23] In addition, neonatal death was significantly more frequent in the severely acidotic group. Low et al. compared 59 full-term fetuses exhibiting metabolic acidosis with 59 fetuses with normal umbilical blood acid–base status and 51 fetuses exhibiting only a respiratory acidosis at birth.[43] Various complications, including encephalopathy, were apparent in the majority of newborns experiencing metabolic acidosis, compared with very low complication rates in those infants with either respiratory acidosis or no acidosis at all. In addition, Low et al. had previously demonstrated a positive correlation between the severity and duration of intrapartum metabolic acidosis and neurodevelopmental outcome at 1 year. The predictive value of cord blood gases has been tested recently in infants treated with therapeutic hypothermia, and metabolic acidosis at birth was still associated with severe brain injury.[60]

Other Biochemical Predictors of Outcome

Prostanoids and non–protein bound iron represent specific plasma oxidative biomarkers reflecting oxidative stress injury to neuronal cells.[75] Activin A, glial fibrillary acid protein, neuron specific enolase, S100B, and adrenomedullin have all been suggested as biomarkers of brain damage and of the degree and extension of the lesion.[63]

Severity of Encephalopathy

Neurologic examination of the infant in the immediate newborn period provides a useful index for predicting later developmental outcome, especially in the full-term infant. Follow-up studies have shown that those infants assessed as having only mild HIE had virtually no risk of subsequent major neurodevelopmental disability, and in infants with moderate HIE, approximately 75% survived without major neurologic deficits. Infants with severe HIE had a very poor outcome, with 50%-100% mortality rate and severe disability incidence of 65%-75% in survivors.

A numeric scoring system based on features of hypoxic–ischemic encephalopathy has been shown to be able to predict, with a high degree of accuracy, outcome at 12 months of age.[77]

Electrophysiology and Imaging

In other sections of this chapter, the usefulness of electrophysiology and brain imaging in the assessment of the infant with perinatal asphyxia has been addressed. Abnormal findings of electrophysiology, such as abnormal evoked potentials, a high seizure burden, prolonged suppressed background patterns of the EEG, and delayed development of SWC are all associated with an adverse neurodevelopmental outcome.[78,81] Abnormal imaging findings with cranial ultrasonography, in particular to the deep grey matter, as well as abnormalities on DWI and ^{1}H-MRS of gray matter, are strongly associated with an adverse outcome and can be used to select patients for additional (experimental) treatment or in extreme cases to redirect care.[1,9,90]

Association Between Hypoxic–Ischemic Encephalopathy and Less Severe Neurodisability

It has become apparent that the outcome of HIE may be more heterogeneous than was previously thought. It has been suggested that if HIE caused damage in an infant, then the outcome involved severe cerebral palsy with or without

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intellectual impairment. There are published data on less severe forms of disability in older children who have survived a perinatal hypoxic–ischemic insult at term. Children with mild-to-moderate HIE, but without major neurologic deficit, had lower full-scale IQ values, minor neurologic dysfunction and/or perceptual motor difficulties, and attention deficit hyperactivity disorder requiring additional educational support.[86] Children who had suffered moderate hypoxic–ischemic encephalopathy in the neonatal period had a greater need for special education in school.

The prognosis for children with HIE depends on the severity and duration of the neurologic abnormality. To understand the development of HIE, an assessment of all potential contributing factors, including maternal medical history, obstetric antecedents, intrapartum factors (including fetal heart rate monitoring results, and issues relating to the delivery itself), and placental pathology is recommended.[18] Major neurodevelopmental problems occur only after moderate and severe HIE, and death is a significant risk and still common after severe HIE. Emerging data strongly support the observation that a significant number of children with perinatal hypoxic–ischemic insult previously considered to be without major problems do have significant perceptual–motor difficulties or a reduction in cognitive abilities. The predictive values of neuroimaging procedures and other investigative techniques have been described earlier. The use of MRI and EEG assessments provides the basis for the most accurate prediction of disability not only in later childhood but also after the introduction of treatment with hypothermia.

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Key Points

- Perinatal asphyxia, with the resulting encephalopathy, is still one of the major problems in full-term neonates.
- Brain monitoring at many centers using continuous or amplitude-integrated EEG provides important prognostic information for standard care of infants with encephalopathy.
- Therapeutic hypothermia has reduced adverse outcome in infants with HIE from approximately 65% to 45%.
- MRI and ^{1}H-MRS are good predictors of an adverse motor outcome.

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Seizures in Neonates

TERRIE E. INDER

Seizures are a common and important clinical manifestation of neurologic dysfunction in the newborn. Building on a traditional foundation of knowledge regarding seizures in the newborn, the last decade has brought new insights into the clinical-electroencephalographic correlates, pathophysiology, and treatment that will be reflected in this chapter.

The incidence of seizures varies with gestational age and birth weight and is most common in the very low birth weight (VLBW) infant. Estimated incidences are 58/1000 live births in the very low birth weight (VLBW) infant and 1-3.5/1000 live births in the term infant.[26,62] Seizures in the newborn differ in their clinical appearances, electrographic characteristics, etiologies, management, and outcomes compared to any other later developmental period. Thus recognition of seizures in the newborn period can be very difficult because of subtle or absent clinical manifestations. To assist in both the accurate identification of seizures in the newborn and successful treatment with antiepileptic drug therapy, electrophysiologic monitoring—either conventional or limited channel monitoring—now plays a critical role within the neonatal intensive care unit. Treatment of neonatal seizures is generally considered necessary since experimental and human evidence suggest seizures may lead to secondary brain injury and are associated with less favorable outcomes.

Pathophysiology of Newborn Seizures—Unique Maturational Features Increasing the Likelihood of Seizures in the Newborn

A seizure results from an excessive synchronous electrical discharge (i.e., depolarization) of neurons within the central nervous system.[48] Neuronal depolarization is produced by the influx of sodium (Na^+), and repolarization is produced by the efflux of potassium (K^+). Maintenance of the potential across the membrane requires an energy (adenosine triphosphate, ATP) dependent pump, which extrudes sodium and takes in potassium. In the newborn brain, it appears that excessive depolarization may occur because of the imbalance of neural excitation over inhibition. The factors contributing to this include developmental factors unique to the immature brain with an excess of excitatory neurotransmitters, particularly in relation to the principal excitatory neurotransmitter, glutamate, and a relative deficiency of inhibitory neurotransmitters. Developmentally, this enhanced excitation is important for activity-dependent synaptogenesis but predisposes to excitation and seizures. Secondly, the common pathologic processes in the newborn brain of hypoxemia-ischemia and hypoglycemia can result in failure of the ATP-dependent sodium-potassium pump disabling the cell from maintaining a stable membrane potential. Finally, other molecules can influence the membrane's sensitivity to depolarizations, such as calcium and magnesium that interact with the neuronal membrane to inhibit Na^+ movement. Thus, hypocalcemia or hypomagnesemia increase Na^+ influx resulting in depolarization.

In understanding why and how the seizure phenomena in newborns differ from those observed in older humans, it is important to understand that in the vast majority of neonatal seizures, electrical onset is focal or multifocal with the spread of the seizure occurring within one hemisphere and secondary generalization to the contralateral hemisphere occurring only rarely.[10] Thus, newborns rarely have well-organized, generalized tonic-clonic seizures, and premature infants have even less well-organized seizures than do term infants. The precise reasons for these differences relate to the status of neuroanatomical and neurophysiologic development in the perinatal period. Neuroanatomically, a propagation of seizures appears related to the completed cortical lamination and organization with myelination of cortical efferent systems and interhemispheric commissures.[101] The relatively advanced cortical development apparent in limbic structures in the human newborn infant and the connections of these structures to the diencephalon and brainstem may underlie the frequency and dominance of oral-buccal-lingual movements (e.g., sucking, chewing, or drooling), oculomotor movements, and apnea as clinical manifestations of neonatal seizures.

From a neurophysiologic viewpoint, the relation of excitatory to inhibitory synapses is important in determining the capacity of a focal discharge to both form and then to spread to contiguous and distant brain regions. Strong evidence indicates that the rates of development of the excitatory and inhibitory synaptic activities differ in

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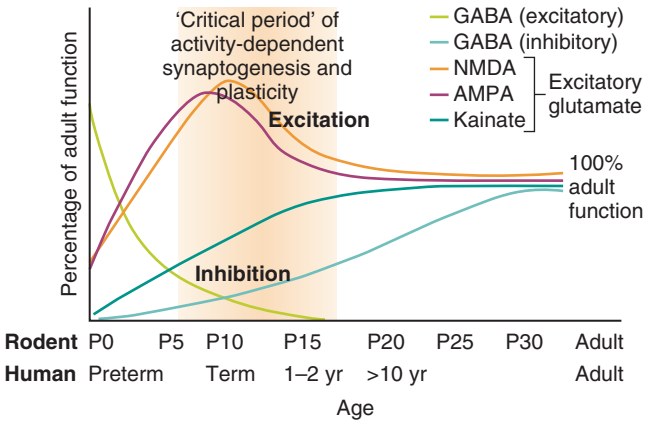
Abstract

Seizures in the newborn infant represent the most distinctive frequent manifestations of neurologic disease in the neonatal period. The incidence of seizures varies with gestational age and birth weight and is most common in the very low birth weight (VLBW) infant. Estimated incidences are 58/1000 live births in the very low birth weight (VLBW) infant and 1-3.5/1000 live births in the term infant. Compared to seizures at later developmental stages, seizures in the newborn differ in their clinical appearances, electrographic characteristics, etiologies, management, and outcomes. Since the majority of seizures during the newborn period are acute symptomatic seizures due to cerebral injury or dysfunction, seizures are an important manifestation to alert the clinician to underlying neurologic disorders. However, recognition of seizures in the newborn period can be very difficult due to subtle or absent clinical manifestations. To assist in both the accurate identification of seizures in the newborn and successful treatment with antiepileptic drug therapy, electrophysiologic monitoring—either conventional or limited channel monitoring—now plays a critical role within the neonatal intensive care unit. Treatment of neonatal seizures is generally considered necessary since experimental and human evidence suggest seizures may lead to secondary brain injury and are associated with less favorable outcomes. However, anti-seizure medications may have associated risks, and there are few data to guide evidence-based management. This chapter reviews the pathophysiology and clinical aspects of neonatal seizures with particular emphasis on the influence of the developmental characteristics of the immature brain.

Keywords

neonatal seizures
brain injury in the newborn
anticonvulsant therapy
electroencephalography
neurodevelopmental outcomes

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• **Fig. 55.1** Schematic depiction of maturational changes in glutamate and GABA receptor function in the developing brain. Equivalent developmental periods are displayed for rats and humans on the top and bottom axes, respectively. Activation of GABA receptors is depolarizing in rats early in the first postnatal week and in humans up to and including the neonatal period. Functional inhibition, however, is gradually reached over development in rats and humans. Before full maturation of GABA-mediated inhibition, the NMDA and AMPA subtypes of glutamate receptors peak between the first and second postnatal weeks in rats and in the neonatal period in humans. Kainate receptor binding is initially low and gradually rises to adult levels by the fourth postnatal week. (From Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. *Nat Rev Med*. 2009;5:380-391.) AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazole propionate; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; P, postnatal day.

the newborn cerebral cortex (Fig. 55.1). Excitatory activity is mediated by glutamate through two key receptor types, N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). These two excitatory receptors are the predominant neurotransmitter receptors found in the immature brain, with a relative paucity of the principal inhibitory receptors for gamma-aminobutyric acid (GABA). Indeed, the neonatal period is characterized by levels of excitatory neurotransmitter expression and function that exceed those observed in adult cortical neurons, while inhibition is not yet at adult levels (see Fig. 55.1).[58]

Moreover, properties of these two glutamate receptors enhance their excitatory function. NMDA receptors in the neonatal period exhibit prolonged duration of the NMDA-mediated excitatory postsynaptic potential, reduced ability of magnesium to block NMDA receptor activity, diminished inhibitory polyamine binding sites, and a greater sensitivity to glycine enhancement.[45] Similarly, AMPA receptors in the neonatal period are deficient in the GluR2 subunit responsible for rendering the AMPA channel impermeable to calcium. Thus these immature AMPA receptors are permeable to calcium and, as a consequence, enhanced excitation.[81] In addition, early in development, the principal inhibitory neurotransmitter, GABA, acts at the major postsynaptic $GABA_A$ receptor ($GABA_A$) to produce excitation rather than inhibition, as occurs later in development. Consistent with these developmental phenomena, it is easier to produce epileptic activity in the immature animal than in the adult.[58]

Insights into the critical developmental relationship between neuronal chloride (Cl^-) levels and Cl^- transport in the perinatal period have major implications for understanding the basis of GABA excitation and thus key clinical and therapeutic aspects of neonatal seizures. GABA activation of the major postsynaptic $GABA_A$ receptor causes Cl^- flux. In the mature neuron, there is Cl^- influx down an electrochemical gradient. However, in developing brains, at maturational stages comparable to the human perinatal period, GABA activation causes Cl^- efflux, and GABA activation is, therefore, excitatory.[17] The basis for this paradoxical effect relates to a developmental mismatch between the two Cl^- transporters that determine neuronal Cl^- levels. Thus in the perinatal period, in human cerebral cortex, the expression of the Na^+-K^+-Cl^- cotransporter (NKCC1) responsible for Cl^- influx reaches a peak, whereas the expression of the K^+-Cl^- cotransporter (KCC2) responsible for Cl^- efflux is relatively low.[61] The result is a high internal neuronal level of Cl^-, so when the $GABA_A$ receptor is activated there is efflux (rather than influx) of Cl^- resulting in depolarization and excitation. These findings may explain the therapeutic inconsistency of GABA agonists, such as phenobarbital and benzodiazepines, to be effective anticonvulsants in the newborn infant with seizures. The NKCC1 inhibitor, bumetanide, has potent antiseizure properties by enhancing GABA-mediated inhibition through blockage of Cl^- uptake and lowering of neuronal Cl^- levels (see later).[17] Moreover, because the maturation of the two cotransporters and neuronal Cl^- levels occurs in a caudal-rostral direction, spinal cord and brainstem motor neurons would be expected to exhibit GABA-mediated inhibition before the cerebral cortical regions. This maturational process could explain the frequent occurrence of electroclinical uncoupling/dissociation in which antiseizure medications with GABA agonist mechanisms (i.e., phenobarbital and benzodiazepines) suppress motor manifestations of seizures (by spinal cord and brainstem inhibition) but not cortical EEG manifestations (due to lack of cortex inhibition). The presence of a relative overexpression of NKCC1 versus KCC2 has been documented in postmortem human neonatal brain,[17] and combined with the efficacy in rodent neonatal seizure models, studies have been initiated to examine the safety and pharmacokinetics of the use of bumetanide as a combination anticonvulsant in human infants suffering from acute neonatal seizures. Results to date are conflicting on safety and efficacy (see later).

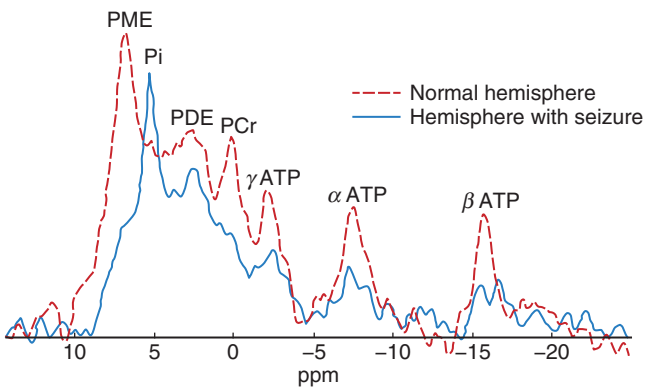
Biochemical and Physiologic Consequences of Seizures in the Immature Brain—Implications for the Clinician

The most prominent acute biochemical effects of seizures involve energy metabolism.[20] Seizures are associated with a greatly increased rate of energy-dependent ion pumping, which is accompanied by a fall in the concentration of ATP and phosphocreatine, the storage form of high-energy

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phosphate in brain. The resulting rise in adenosine diphosphate (ADP) leads to stimulation of glycolysis and to a shift of the redox state in the cytoplasm toward reduction (i.e., NADH). The excess of lactate has the beneficial effect of causing local vasodilation and a consequent increase in local blood supply and substrate influx.[14] In addition, seizures are associated with elevated blood pressure, which contributes to increased cerebral blood flow (CBF) and substrate influx.[55] This pressor effect is presumed to be a central autonomic component of the seizure, because it can be interrupted by section of the spinal cord or by administration of sympathetic ganglion-blocking agents.

Despite these important compensatory factors, in experimental animals, neonatal seizures are accompanied by reductions in brain glucose concentrations.[87] In the neonatal rat, rabbit, dog, and monkey, despite normal or slightly elevated blood glucose concentrations, brain glucose concentrations fall dramatically within 5 minutes of onset of seizure to nearly undetectable levels after 30 minutes. Concomitant with the fall in brain glucose is a rise in brain lactate, which is used readily as a metabolic fuel in the neonatal brain.[20,103] This fall in brain glucose concentration and rise in brain lactate are directly reminiscent of a hypoxic-ischemic brain insult and presumably relate to the accelerated rate of glucose utilization in an attempt to preserve supplies of phosphocreatine and ATP. Glucose conversion to lactate, which is accelerated with neonatal seizures, results in only two molecules of ATP for each molecule of glucose, as opposed to the 38 molecules of ATP generated when pyruvate enters the mitochondrion and is oxidized to carbon dioxide. MRS studies by Younkin and colleagues in the human newborns demonstrate the relevance of these experimental data to the clinical situation (Fig. 55.2).[104] Four newborns had seizures during MRS imaging. The seizures resulted in substantial (~50%) decrease in the phosphocreatine to inorganic phosphate (PCr/Pi) ratio. One newborn's seizures were successfully treated with intravenously administered phenobarbital, which caused an immediate increase in the PCr/Pi ratio. Further, newborns had PCr/Pi ratios of less than 0.8 during seizures and developed long-term neurologic sequelae, indicating that neonatal seizures may increase cerebral metabolic demands above energy supply, thereby causing or exacerbating injury. These observations indicate that seizures may lead to secondary brain injury in an already injured neonatal brain and, therefore, have important implications for prognosis and therapy.



• **Fig. 55.2** Magnetic resonance (phosphorus-31) spectra from a full-term infant during subtle seizure activity (oral-buccal-lingual movements, i.e., lip smacking and chewing). The electroencephalogram demonstrated seizure activity emanating from the left temporal region. The magnetic resonance spectrum from the nonictal hemisphere (*dotted line*) is normal. The spectrum from the ictal hemisphere (*solid line*) exhibits a marked decrease in phosphocreatine (PCr) and adenosine triphosphate (ATP) and a corresponding increase in inorganic phosphate (Pi). PDE, Phosphodiesters; PME, phosphomonoesters.

The deleterious effects of seizures may be divided into those related to prolonged seizures (in which the most prominent feature is cell loss) and those related to briefer recurrent seizures (in which the most prominent feature is altered development). While minimal data are available in human newborns, experimental studies are abundant, primarily in developing rodent models. Importantly, although the threshold for seizure generation is lower in the developing brain than in the mature brain, developing neurons are less vulnerable to injury from single prolonged seizures than are mature neurons. This may be due to a lower density of active synapses, lower energy consumption, and immaturity of relevant biochemical cascades to cell death.

For prolonged seizures, the best-documented mechanisms leading to brain injury include hypoventilation and apnea, which may result in hypoxemia and hypercapnia; cardiac dysfunction and diminished cardiac output as late complications of seizures, resulting in hypotension, diminished cerebral blood flow (CBF) and impaired energy metabolism. Importantly, increases in CBF have also been documented. In a study of 12 newborns with seizures, ictal measurements of regional CBF by single photon emission computed tomography showed a 50%-150% increase, and this increase occurred in newborns with subtle seizures and EEG-only seizures.[8] Although the increase in CBF with seizures may be initially an adaptive response to increase substrate supply to the brain at a time of excessive metabolic demand, this response could become maladaptive in some newborns. For example, depending on such factors as the gestational age of the newborn or the neuropathologic substrate for the seizures, some newborns may have highly vulnerable capillary beds, such as the germinal matrix in the premature infants or the margins of ischemic lesions in premature infants or asphyxiated term newborns.

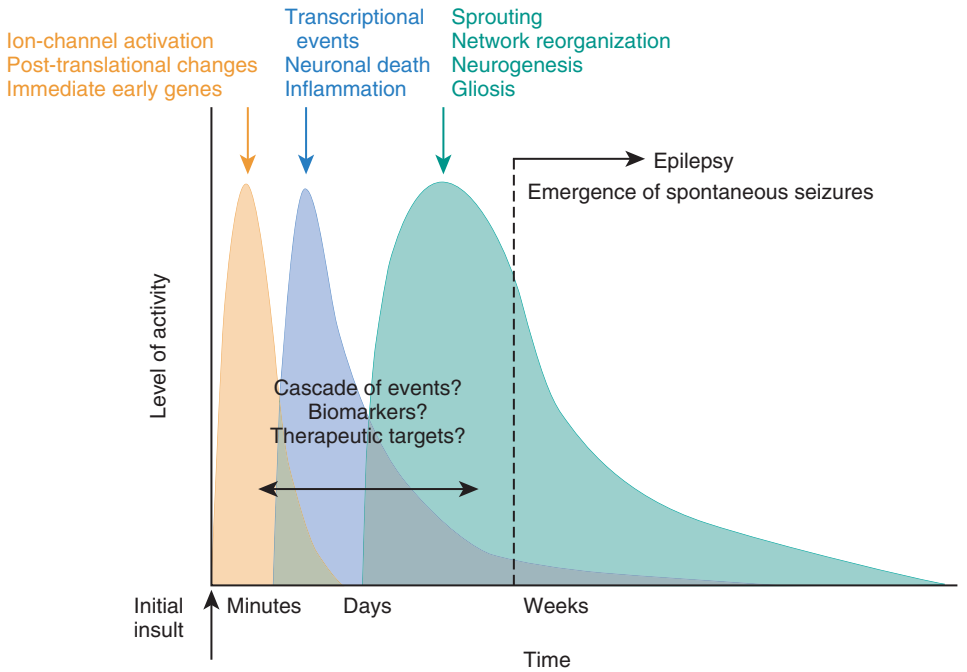
Repeated prolonged seizures may be deleterious for the brain, even in the absence of prominent disturbances of ventilation or perfusion. Such prolonged and repeated seizures eventually lead to decreases in brain ATP and phosphocreatine concentrations such that progressive and irreparable brain injury may result.[64] Nevertheless, most studies indicate that the neonatal brain is more resistant to seizure-induced neuronal necrosis than is the adult brain.

An additional mechanism for the genesis of brain injury with severe seizures relates to excitatory amino acids.[44] Injury to neuronal dendrites and cell bodies, the most prominent acute manifestations of injury from seizures, occurs particularly in limbic structures (e.g., hippocampus)

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and in distant sites intimately connected with limbic structures (e.g., selected areas of thalamus and cerebellum). When diminution of energy supplies is added, the energy-dependent reuptake systems for excitatory amino acids in presynaptic nerve endings and astrocytes are impaired, and the local accumulation of the neurotransmitters is accentuated. A particular vulnerability of the developing brain of the newborn may relate to the rich expression in the developing brain of glutamate receptors, which appear to play an important role in neuronal differentiation and plasticity.

Although most evidence does not suggest serious structural or functional defects from a single neonatal seizure, recurrent seizures, even if not prolonged, appear to be associated with long-term functional, morphologic, and physiologic deficits, particularly functional deficits in cognition.[35] Visual–spatial memory and learning have been particularly involved, and these deficits are consistent with the locus of the principal structural deficits in the hippocampus. The morphologic correlates of the functional disturbances involve neuronal developmental abnormalities rather than neuronal cell loss. The most severe disturbances occur in the hippocampus and include dendritic spine loss in CA3 pyramidal cells and a distinctive pattern of synaptic reorganization of axons and terminals of the dentate granule cells (i.e., mossy fibers).[35] The degree of this "sprouting" of mossy fibers correlates with the severity of the cognitive deficits. Additionally, dentate granule cell neurogenesis, which, unlike in other cortical areas, persists in the neonatal period, is impaired after recurrent seizures. Recurrent seizures also lead to physiologic and molecular alterations that favor subsequent neuronal excitability and, therefore, epileptogenesis (Fig. 55.3), as well as the occurrence of neuronal injury with subsequent insults.[35] Alterations include increases in excitatory amino acid receptors (NMDA and AMPA/kainate), decreases in GABA receptors, post-translational alterations in AMPA receptors (resulting in a decrease in the GluR2 subunit) that render them permeable to calcium, imbalanced excitatory and inhibitory systems, and altered intrinsic neuronal membrane properties, all of which favor excitation. A critical question, of course, is the extent to which these changes occur in the human newborn who experiences recurrent seizures and what seizure burden may produce such adverse neurobiologic consequences. Although this question remains unanswered, there is mounting evidence that seizures are associated with less favorable neurobehavioral outcomes.



• **Fig. 55.3** Time course of epileptogenesis. An initial insult, such as traumatic brain injury and/or status epilepticus, is followed by a latent period lasting weeks to months or even years before the onset of spontaneous seizures. During this latent period, a cascade of molecular and cellular events occurs that alters the excitability of the neuronal network, ultimately resulting in spontaneous epileptiform activity. The alterations that occur during the latent period might provide a good opportunity for biomarker development and therapeutic intervention. The cascade of events that are presently suggested by experimental evidence can be classified temporally following the initial insult. Early changes, including induction of immediate early genes and post-translational modification of receptor and ion-channel related proteins, occur within seconds to minutes. Within hours to days, there can be neuronal death, inflammation, and altered transcriptional regulation of genes, such as those encoding growth factors. A later phase, lasting weeks to months, includes morphologic alterations such as mossy fiber sprouting, gliosis, and neurogenesis. (From Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. *Nat Rev Med*. 2009;5:380–391.)

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Classification of Seizures in the Newborn

Seizure Types

A seizure is defined clinically as a paroxysmal alteration in neurologic function (i.e., behavioral, motor, or autonomic function). Such a definition includes clinical phenomena that are associated temporally with seizure activity identifiable on an EEG and, therefore, are clearly epileptic (i.e., related to hypersynchronous electrical discharges that may spread and activate other brain structures). The clinical seizure definition also includes paroxysmal clinical phenomena that are not consistently associated temporally with EEG seizure activity; how many of these clinical phenomena without identifiable EEG correlates are epileptic and just not identifiable on surface-recorded EEG and how many are nonepileptic is not resolved (see later discussion). The classification of neonatal seizures presented here categorizes clinical seizures and designates those clinical seizures likely to be associated with EEG seizure activity.

The classification schemes for neonatal seizures have varied over time and have been recognized to have common and uncommon electroencephalographic correlates (Table 55.1).[89] A consensus statement on neonatal EEG terminology by the American Clinical Neurophysiology Society defined three types of neonatal seizures: (1) clinical-only seizures in which there is a sudden paroxysm of abnormal clinical change that does not correlate with a simultaneous EEG seizure, (2) electroclinical seizures in which there is a clinical seizure coupled with an associated EEG seizure, and (3) EEG-only seizures in which there is an EEG seizure that is not associated with any outwardly visible clinical signs. EEG-only seizures are also referred to as subclinical, nonconvulsive, or occult seizures. Neonatal EEG seizures are described as having (1) a sudden EEG change; (2) repetitive waveforms that evolve in morphology, frequency, and/or location; (3) amplitude of at least 2 microvolts; and (4) duration of at least 10 seconds.[84]

TABLE 55.1 Classification of Neonatal Seizures

Clinical Seizure	Electroencephalographic Seizure Correlate	
	Common	Uncommon
Subtle	+	
Clonic		
Focal	+	
Multifocal	+	
Tonic		
Focal	+	
Generalized		+
Myoclonic		
Focal, multifocal		+
Generalized	+	

Electrographic seizure definitions are summarized in Box 55.1. It is important to distinguish between electrographic seizures and other related EEG patterns. While a seizure on EEG is comprised of an evolving pattern of epileptiform discharges, not all epileptiform discharges are seizures. Epileptiform discharges are brief abnormalities that stand out from the EEG background, usually because of a peaked or sharp appearance. They are sometimes referred to as "sharp waves" or "spikes" because of this EEG appearance. It is normal for newborns to have some sharp waves, and many newborns with epileptiform discharges do not experience seizures. However, epileptiform discharges that occur in runs or are clustered in one brain region are associated with an increased risk of seizure occurrence.[84]

For those seizures with a clinical correlate, the organization of this chapter will retain emphasis of the classification of clinical seizures noted in Table 55.1. Despite great efforts to carefully describe the appearance of neonatal seizures, inter-rater agreement in neonatal seizure identification by clinical observation is suboptimal. Malone and colleagues presented clinical data and video clips of abnormal neonatal movements from 20 newborns to 137 observers, including 91 physicians from seven neonatal intensive care units. Observers classified the movements as seizure or nonseizure. The average number of correctly classified events was only 50%, as compared to the gold standard of EEG classification. Further, interobserver agreement was poor for both physicians and other health care professionals.[42] Similarly, in a study of staff observing high-risk newborns, only 9% of 526 electrographic seizures were identified by clinical observation, indicating underdiagnosis of seizures occurred. Additionally, 78% of 177 nonictal events were incorrectly identified as seizures, indicating overdiagnosis of seizures occurred.[49] Problematically, the more difficult-to-diagnose seizure types tend to occur more often than the more readily diagnosed seizure types in newborns. A study of 61 seizures in 24 newborns classified seizures by their most prominent clinical features. Clonic and tonic seizures, which might be more readily identified, only occurred in 20% and 8%

• BOX 55.1 Electrographic Criteria for Neonatal Seizures

- Sudden change in EEG
- Repetitive waveforms that evolve in morphology, frequency, and/or location
- Amplitude: at least 2uV
- Duration: at least 10 seconds
- Seizures must be separated by at least 10 seconds to be considered separate.
- Clinical signs may or may not be present.

Adapted from Tsuchida TN, Wusthoff CJ, Shellhaas RA, et al. American Clinical Neurophysiology Society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society Critical Care Monitoring Committee. *J Clin Neurophysiol*. 2013;30:161-173, with permission.

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respectively, while orolingual, ocular, and autonomic features which might be more difficult to identify, were the main features in 55%.[50] Despite the limitations in clinical recognition of seizures discussed above, attempts at clinical recognition and classification of neonatal seizures are critical to diagnose seizures and differentiate them from nonictal events. Four essential clinically evident seizure types can be recognized: subtle, clonic, tonic, and myoclonic (see Table 55.1). Subtle seizures do not have a clear position in the most recent International League Against Epilepsy Seizure Classification Report,[4] but they are very common in newborns, and the term is used frequently throughout the literature. Thus the term is retained as part of the categorization system in this chapter. As discussed further below, a critical fifth seizure type to consider in newborns is a seizure with no observable clinical correlate, which have been referred to as EEG-only seizures, subclinical seizures, nonconvulsive seizures, and occult seizures.

An important initial distinction in classifying a seizure is whether it has a generalized or focal mechanism of onset. Focal seizures have a defined region of onset and electrical activity initially spreads through neural networks in that region, although the seizure may spread within the hemisphere or to the contralateral hemisphere with time. Generalized seizures may begin from a specific point but almost immediately involve bilateral neural networks, such that electrical activity appears on both sides of the brain simultaneously on EEG.[4] In the vast majority of neonatal seizures, onset is focal or multifocal. Spread of the seizure is less common in newborns than in older children because of the immaturity of the network connections in the newborn brain as discussed previously.

Subtle Seizures

The clinical manifestations of certain neonatal seizures may be overlooked even by skilled observers, and these paroxysmal alterations in neonatal behavior and motor or autonomic function are defined as subtle seizures. Available information from studies using EEG recording simultaneously with video recording or direct observation suggests that (1) subtle seizures are more common in premature than in full-term infants, and (2) some subtle clinical phenomena in full-term infants are not consistently associated with EEG seizure activity (i.e., clinical-only seizures). Common ictal clinical manifestations, confirmed by simultaneous abnormal EEG discharges, in a group of premature infants of 26-32 weeks of gestation included sustained opening of eyes, ocular movements, chewing, pedaling motions, and a variety of autonomic phenomena.[57] Similar subtle clinical phenomena occur in association with EEG seizure activity in full-term newborns, although slightly less commonly than in preterm newborns.[47] Thus, eye opening, ocular movements (often sustained eye opening with ocular fixation in premature infants and horizontal deviation in term newborns), peculiar extremity movements (e.g., resembling "boxing" or "hooking" movements), mouth movements, and apnea have been documented in association with EEG seizure activity.

The frequency with which subtle clinical seizure phenomena are associated with concomitant EEG seizure activity is uncertain. In one study, 22 newborns, approximately 85% of whom were of greater than 36 weeks of gestation, exhibited paroxysms of such ocular abnormalities as eye opening or blinking, oral-buccal-lingual movements, pedaling or stepping movements, or rotary arm movements with an "inconsistent association" with EEG seizure activity. Only tonic horizontal deviation of the eyes was consistently associated with EEG seizure activity.[47] In another report of 44 newborns (28 premature), subtle clinical phenomena accounted for 70%-75% of all clinical seizures with simultaneous EEG correlates.[66] It is more common for subtle clinical events to have an electrographic correlate (i.e., electroclinical seizures) if the newborn has other types of seizures; these events are somewhat less likely to be seizures when they are the only behavior of clinical concern.

The issue of apnea as a seizure manifestation deserves special consideration. Although apnea has been demonstrated as a seizure manifestation in the premature infant, most apneic episodes in premature infants are not epileptic in origin. However, apnea has been documented with electrical seizure activity, more commonly in the full-term newborn.[34] Of additional value in the clinical identification of apnea as a seizure is the observation that apnea accompanied by EEG seizure activity (i.e., convulsive apnea) is less likely to be associated with bradycardia than is nonconvulsive apnea.

Clonic Seizures

A clonic seizure is defined as a seizure characterized by "rhythmic movements of muscle groups in a focal distribution, which consist of a rapid phase followed by a slow return movement." Clonic seizures appear as repetitive and rhythmic jerking movements that can affect any part of the body, including the face, extremities, and even diaphragmatic or pharyngeal muscles. Clonic seizures represent the clinical seizure type associated most consistently with EEG seizure activity.[47]

Clonic seizures in the newborn are often classified as focal or multifocal (see Table 55.1). Focal clonic seizures involve the face, upper or lower extremities on one side of the body, or axial structures (neck or trunk) on one side of the body. Newborns commonly are not clearly unconscious during or after a focal seizure. The neuropathologic condition often is focal (e.g., cerebral infarction), although focal clonic seizures may occur with metabolic encephalopathies. Multifocal clonic seizures involve several body parts, often in a migrating fashion, although the migration most often "marches" in a non-Jacksonian manner (e.g., left arm jerking may be followed by right leg jerking). Generalized clonic seizures (i.e., diffusely bilateral, generally symmetrical, and synchronous movements) are rarely, if ever, observed in newborns. Clonic seizures are often reliably recognized by clinical observation, but they must be distinguished from other repetitive movements such as jitteriness, tremulousness, and myoclonus. Unlike those nonepileptic

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movements, the muscle twitches of a clonic seizure cannot be suppressed with gentle pressure and occur spontaneously.

Tonic Seizures

Tonic seizures are defined as a "sustained flexion or extension of axial or appendicular muscle groups." Two categories of tonic seizures should be distinguished: focal and generalized tonic seizures (see Table 55.1). Focal tonic seizures consist of sustained posturing of a limb or asymmetrical posturing of the trunk or neck. Mizrahi and Kellaway also classified horizontal eye deviation as a focal tonic seizure, although some classify those events as subtle seizures.[47] Focal tonic seizures are associated consistently with EEG seizure discharges. Generalized tonic seizures are characterized by tonic extension of both upper and lower extremities (mimicking "decerebrate" posturing) but also by tonic flexion of upper extremities with extension of lower extremities (mimicking "decorticate" posturing). The possibility that such clinical seizures represent posturing and are not ictal has been raised because of the frequent association with severe intraventricular hemorrhage and the often poor response to antiseizure medication therapy.[68] Approximately 85% of such clinical seizures were not accompanied by electrographic activity or by autonomic phenomena. The 15% of generalized tonic seizures that were accompanied by electrographic seizure activity were also accompanied by autonomic phenomena.[37] Thus, these generalized tonic events may represent "brainstem release" phenomena and uninhibited extensor posturing that appears similar to tonic stiffening in patients with severe brain injury. As an additional mimic to generalized tonic seizures, episodes of generalized hypertonia provoked by minor tactile or other stimuli are characteristic of hyperekplexia.[37]

Myoclonic Seizures

Myoclonus is defined as a rapid, isolated jerk that can affect one or multiple muscle groups, can be ictal or nonictal in etiology, and can arise from injury to any level of the nervous system. Myoclonic seizures are clinical episodes that are usually not associated with EEG discharges (see Table 55.1).[47] Myoclonic movements are distinguished from clonic movements by the faster speed of the myoclonic jerk and the predilection for flexor muscle groups. There are three categories of myoclonic seizures: focal, multifocal, and generalized myoclonic seizures. Focal myoclonic seizures typically involve flexor muscles of an upper extremity. Of 41 focal myoclonic seizures studied by Mizrahi and Kellaway,[47] only 3 were associated with EEG seizures. Multifocal myoclonic seizures are characterized by asynchronous twitching of several parts of the body. In five episodes studied by Mizrahi and Kellaway,[47] none had associated EEG seizure discharges. Generalized myoclonic seizures are characterized by bilateral jerks of flexion of upper and occasionally of lower limbs. These seizures may appear identical to the infantile spasms observed in older infants. Generalized myoclonic seizures are more likely to be associated with EEG seizure discharges than are focal or multifocal myoclonic seizures. Of 58 generalized myoclonic seizures studied by Mizrahi and Kellaway, 35 had associated EEG seizure discharges.[47] All three varieties of myoclonic seizures may occur as a feature of severe neonatal epileptic syndromes.

Myoclonic seizures must be distinguished from nonepileptic myoclonus, which can occur with injury to any level of the nervous system and from normal physiologic myoclonus, which occurs in normal newborns. Unlike such other forms of myoclonus, myoclonic seizures are not induced by stimuli and cannot be suppressed by pressure to the affected body part. Furthermore, newborns with myoclonic seizures almost always have abnormal neurologic exams, whereas newborns with benign myoclonus are otherwise normal.

EEG-Only (Subclinical, Nonconvulsive, Occult) Seizures

A major issue with clinical diagnosis of seizures in newborns is the high incidence of EEG-only seizures in newborns.[98] Numerous studies have indicated that about 80%-90% of electrographic seizures do not have any associated clinical correlate and, therefore, would not be identified without continuous EEG monitoring, even by the most expert and observant bedside caregivers.[97] Clancy and colleagues evaluated 41 newborns with seizures occurring frequently enough to occur during a routine EEG. Only 21% of 393 seizures identified on EEG were accompanied by clinically evident seizure activity (i.e., electroclinical seizures), while 79% of the seizures identified on EEG were EEG-only seizures. Electroclinical seizures and EEG-only seizures had similar durations, and there were no differences in the degree of encephalopathy. The authors concluded that "unaided visual inspection of infants seriously underestimates true seizure frequency" and that "long-term EEG monitoring may be necessary in many infants to determine their real seizure frequency and to judge the adequacy of antiepileptic drug treatment."[12] In a related study, Murray and colleagues evaluated 51 term newborns with continuous video EEG. Nine newborns experienced a total of 526 electrographic seizures, and only 19% of the electrographic seizure time was accompanied by clinical manifestations. Further, only 9% of electrographic seizures were accompanied by clinical seizure activity that was identified by neonatal staff.[49] These data indicate that the majority of neonatal seizures are EEG-only, that is, identifiable only with EEG monitoring.

In newborns with clinically evident seizures, administration of antiseizure medications may lead to termination of the clinically evident seizures while electrographic seizures persist, an occurrence referred to as electromechanical uncoupling or electromechanical dissociation.[65] In the study by Clancy and colleagues, 79% of 393 electrical seizures recorded were not accompanied by clinical seizure activity monitored by direct observation; 88% of the total population of patients had been treated with one or more antiseizure medications.[12] Thus when clinically evident electroclinical seizures terminate following antiseizure medication administration, EEG monitoring may be needed to assess for ongoing EEG-only seizures.

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The reasons for electroclinical dissociation/uncoupling are probably multiple, but data concerning the development of Cl^- transporters in the perinatal human brain provide a rational explanation. As discussed earlier, a developmental mismatch occurs between the transporter responsible for Cl^- influx (NKCC1) and the transporter responsible for Cl^- efflux (KCC2), such that in human perinatal brain, neuronal Cl^- levels are likely high. Thus GABA activation results in Cl^- efflux with resulting depolarization and consequently excitation. Therefore, after treatment with common anticonvulsant medications such as phenobarbital and benzodiazepines, which are principally GABA agonists, electrographic seizures are not consistently terminated. However, because the maturation of the transporters occurs in a caudal-to-rostral direction, neuronal Cl^- levels in the brainstem and spinal cord motor systems would be expected to decrease to normal levels before cortical neuronal levels. Thus, GABA activation induced by antiseizure medications would eliminate the motor phenomena of the seizure but not the cortical electrographic component, resulting in electroclinical dissociation/uncoupling.

The findings described earlier have led to an increased reliance on EEG monitoring with either conventional EEG or amplitude-integrated EEG (aEEG) for three main reasons. First, many newborns experience solely EEG-only seizures, and EEG-only seizures constitute the majority of neonatal seizures. Second, even in newborns with clinically evident electroclinical seizures, administration of antiseizure medications may induce electromechanical dissociation/uncoupling with termination of clinically evident seizures but persistence of EEG-only seizures. Third, clinical events may be difficult to distinguish as seizure-based on clinical observation, potentially leading to unnecessary exposure of newborns to antiseizure medications for nonepileptic events. As a result, many neonatal intensive care units place increased importance on EEG monitoring, either using conventional EEG or aEEG, to identify neonatal seizures,[24] and, as noted earlier, an expanded role for EEG monitoring has been advocated by recent guidelines, consensus statements, and committee reports (see later discussion).[84]

Nonepileptic Movements

Nonepileptic neonatal movements can be difficult to distinguish from seizures by appearance alone, and EEG assessment may be required. Some nonictal movements are benign events while others, although not seizures, are nonetheless abnormal and indicative of underlying brain injury or dysfunction.

Jitteriness

Jitteriness is characterized by movements with qualities primarily of tremulousness but occasionally of clonus. The most consistently defined causes of jitteriness are hypoxic-ischemic encephalopathy, hypocalcemia, hypoglycemia, and drug withdrawal. Five characteristics aid in distinguishing between jitteriness and seizure (Table 55.2). First, jitteriness is not accompanied by ocular phenomena (i.e., eye fixation or deviation); seizures often are associated with ocular phenomena. Second, jitteriness is exquisitely stimulus sensitive; seizures generally are not stimulus sensitive. Third, the dominant movement in jitteriness is tremor (i.e., the alternating movements are rhythmic and of equal rate and amplitude); the dominant movement in seizure is clonic jerking (i.e., movements with a fast and slow component). Fourth, the rhythmic movements of limbs in jitteriness usually can be stopped by gentle passive flexion of the affected limb; seizures do not cease with this maneuver. Finally, jitteriness is not accompanied by autonomic changes (e.g., tachycardia, increase in blood pressure, apnea, cutaneous vasomotor phenomena, pupillary change, salivation, or drooling); seizures may be accompanied by one or more of these autonomic changes. These same distinguishing clinical features are useful in the clinical distinction of episodic movements other than jitteriness that may mimic a seizure.

TABLE 55.2 Distinguishing Between Jitteriness and Seizure

Clinical Feature	Jitteriness	Seizure
Abnormality of gaze or eye movement	0	+
Movements stimulus sensitive	+	0
Predominant movement	Tremor	Clonic jerking
Movements cease with passive flexion	+	0
Associated autonomic changes	0	+

0, Absent; +, present.

Nonepileptic Myoclonus

Nonepileptic myoclonus may be benign or pathologic. Healthy premature infants often demonstrate occasional spontaneous myoclonus. Benign neonatal myoclonus, alternately termed benign neonatal sleep myoclonus, can be pronounced, typically is most prominent in sleep, and can last up to several minutes. Benign neonatal myoclonus may be differentiated from pathologic myoclonus in that benign myoclonus can be stopped by rousing the infant and typically does not involve the face.[60] The episodes usually last for several minutes or more and occur only during sleep, particularly quiet (non–rapid eye movement) sleep. They can be provoked by gentle rocking of the crib mattress in a head-to-toe direction and cease abruptly with arousal. The EEG pattern during the episodes does not show an ictal correlate, and interictal EEG findings are either normal or show minor, nonspecific abnormalities. The episodes can be exacerbated or provoked by treatment with benzodiazepines and resolve within approximately 2 months. Neurologic outcome is normal.

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Pathologic Myoclonus

This is attributed to a brainstem release phenomenon from loss of cortical inhibition of lower circuits. It is frequently seen in infants with severe global brain injury from hypoxia-ischemia, severe intraventricular hemorrhage, and toxic-metabolic disturbances including drug withdrawal and glycine encephalopathy. These newborns have abnormal neurologic exams and abnormal background patterns on EEG.[36]

Hyperekplexia

Hyperekplexia is also known as startle disease or congenital stiff-man syndrome.[28] It is characterized principally by two abnormal forms of response to unexpected auditory, visual, and somesthetic stimuli—an exaggerated startle response and sustained tonic spasms. Additional features are generalized hypertonia and prominent nocturnal myoclonus. The "minor" form of hyperekplexia only involves excessive startle, while the "major" form is associated with additional problems, including generalized stiffness while awake, nocturnal myoclonus, and an increased risk of sudden infant death syndrome from apnea. Hyperekplexia may be caused by glycine receptor gene mutations, and clonazepam can be an effective treatment for excessive startle. The episodes usually cease spontaneously by approximately the age of 2 years. In some patients, the disorder is inherited in an autosomal dominant fashion, and the responsible gene is on chromosome 5 and known to encode the alpha-1 subunit of the glycine receptor.[1]

Does Absence of EEG Seizure Activity Indicate That a Clinical Event Is Nonepileptic?

Data from older children and adults, as well as in newborns, indicate that epileptic phenomena can occur in the absence of surface-recorded EEG discharges, and such phenomena can be generated at subcortical (i.e., deep limbic, diencephalic, brainstem) levels.[18] Thus one should continue to use some aspect of clinical judgment in the decision-making process of trials of anticonvulsant therapy or consider electroencephalographic silence as a key indicator of abnormality in a high-risk newborn.

Seizure Etiology

The majority of neonatal seizures occur in the context of acute neurologic disorders. Thus most neonatal seizures may be considered acute symptomatic seizures, which have been defined as seizures occurring at the time of a systemic insult or in close temporal association (often 1 week) with a documented brain insult.[3] The current International League Against Epilepsy classifies seizure causes as genetic, structural/metabolic, and unknown.[5] Within that classification scheme, the majority of neonatal seizures are structural/metabolic in etiology.

Determination of the seizure etiology is critical, because it affords the opportunity to provide specific treatment and important prognostic information. While there are many causes for neonatal seizures, a relatively limited group of etiologies accounts for the majority of affected newborns. The most common causes and their usual time of onset in premature or full-term infants are shown in Table 55.3. The most common underlying etiologies are hypoxic-ischemic encephalopathy, stroke, intracranial hemorrhage, intracranial infections, and cerebral dysgenesis.[82] Less common but important etiologies include inborn errors of metabolism and neonatal epileptic syndromes, such as benign familial neonatal epilepsy, benign nonfamilial neonatal seizures, early myoclonic epilepsy, early infantile epileptic encephalopathy, and malignant migrating partial seizures of infancy.

TABLE 55.3 Neonatal Seizure Etiologies in Relation to Time of Seizure Onset and Relative Frequency

	Time of Onset		Relative Frequency†	
Cause	0-3 Days	>3 Days	Premature	Full Term
Hypoxic-ischemic encephalopathy	+		+++	+++
Cerebrovascular stroke	+		+	+++
Intracranial hemorrhage	+	+	++	+
Intracranial infection	+	+	++	++
Developmental defects	+	+	++	++
Hypoglycemia	+		+	+
Hypocalcemia	+	+	+	+
Other metabolic	+			+
Epilepsy syndromes	+	+		+

†Relative frequency of seizures: +++, most common; ++, less common; +, least common.

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The Neonatal Seizure Registry consortium of seven tertiary care pediatric centers in the United States prospectively collected data related to etiology in a cohort of 426 newborns with seizures who underwent cEEG. The most common seizure etiologies were hypoxic-ischemic encephalopathy in 38%, ischemic stroke in 18%, neonatal onset epilepsy in 13%, intracranial hemorrhage in 11%, neonatal genetic epilepsy syndrome in 6%, congenital cerebral malformation in 4%, and benign familial neonatal epilepsy in 3%. Additionally, for all these etiologies, the seizure burden was high, with 59% of subjects having >7 electrographic seizures and 16% having status epilepticus. There was no significant difference in seizure burden between preterm and term newborns or among the three most common causes of seizure (hypoxic-ischemic encephalopathy, ischemic stroke, and intracerebral hemorrhage).[25] These etiologies were similar to those reported in a study by Weeke and colleagues of 378 newborns obtained over a 14-year period with seizures confirmed by EEG or aEEG from a level 3 neonatal intensive care unit. The most common etiologies identified were hypoxic-ischemic encephalopathy (46%), intracranial hemorrhage (12.2%), and perinatal arterial ischemic stroke (10.6%).[92] These etiologies are quite similar to those found in a study by Tekgul and colleagues in which 89 newborns underwent careful etiologic evaluation. The most common etiologies were global hypoxic-ischemic encephalopathy in 40%, focal ischemic injury in 38%, intracranial hemorrhage in 17%, cerebral dysgenesis in 5%, transient metabolic disturbance in 3%, infection in 3%, and an inborn error of metabolism in 1%. The etiology remained unknown in 12%.[82] Thus, in summary, three key conditions account for nearly 75% of neonatal seizures—hypoxic-ischemic brain injury (40%-50%), arterial stroke (10%-15%), and intracranial hemorrhage (10%-20%). The next two most common etiologies are intracranial infection (5%) and cerebral dysgenesis (5%). The remaining less common conditions, accounting for 5%-10% of all seizures, remain important due to potential therapeutic interventions in transient metabolic disorders and inborn errors of metabolism.

Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy is the most common cause of neonatal seizures in both full-term and premature infants, accounting for close to one-half of the causes. The seizure burden is often high in the term newborn with hypoxic-ischemic encephalopathy and may result in electrographic status epilepticus in between 10%-15% of cases. A multicenter observational study of 90 newborns treated with therapeutic hypothermia for hypoxic-ischemic encephalopathy and who underwent conventional EEG monitoring–identified electrographic seizures in 48%, including 10% with electrographic status epilepticus. Abnormal EEG background features (excessively discontinuity, depressed and undifferentiated patterns, burst suppression, or extremely low voltage) were associated with seizures, but no perinatal variables, including pH <6.8, base excess ≤−20, or 10-minute Apgar score ≤3, predicted seizure occurrence.[27] Similarly, an earlier single center of 26 consecutive newborns with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia and continuous conventional EEG monitoring identified electrographic seizures in 65%, which were entirely nonconvulsive in 47% with seizures and constituted electrographic status epilepticus in 23% with seizures.[99] Regarding the timing of seizures in hypoxic ischemic encephalopathy (HIE), conventional teaching has been that seizures generally occur in the initial 24 hours of life and become more frequent from 12-24 hours after birth. Recent studies using EEG monitoring in consecutive newborns with hypoxic-ischemic encephalopathy confirmed that seizures are most common in the initial 24 hours but that they can initiate during hypothermia, rewarming, and rarely after return to normothermia.[69] There is some evidence that therapeutic hypothermia may reduce electrographic seizure exposure in newborns. However, comparing seizure incidence on studies conducted prior to and after therapeutic hypothermia utilization may not reflect a reduction in seizures since most studies performed initially relied on clinical observation for seizure identification, while most studies performed later used EEG monitoring for seizure identification. Data obtained prior to the implementation of therapeutic hypothermia as a neuroprotective strategy reported electroencephalographic seizures in 22%-64% of newborns.[71] In newborns with moderate to severe hypoxic-ischemic encephalopathy managed with therapeutic hypothermia, seizures were identified in 30%-65%.[100]

Ischemic Stroke

Ischemic stroke is the second-most common cause of neonatal seizures in full-term newborns, accounting for between 10%-20% of cases.[25,82,92] The incidence of perinatal arterial stroke is approximately 1 in 1600-5000. At least half of neonatal stroke cases are not recognized in the neonatal period, but for those that are diagnosed in the neonatal period, up to 97% present with seizures and 50% have seizures as the only recognized sign.[30] Compared to newborns with more diffuse brain injury, such as hypoxic-ischemic encephalopathy, those with neonatal stroke as a cause of seizures are more likely to appear active and alert between seizures. Additionally, seizures caused by arterial ischemic stroke tend to occur after the first 12 hours of life, that is, somewhat later than those caused by hypoxic-ischemic encephalopathy. The risk of developing subsequent epilepsy ranges from approximately 10%-50%, depending on time to follow-up and inclusion criteria.[30]

Cerebral sinus venous thrombosis occurs less frequently than arterial stroke in newborns, affecting approximately 1 in 8000-38,000 children per year; 42%-78% of these newborns have experienced a venous infarct. Seizures are the presenting symptom or a complication of cerebral sinus venous thrombosis in 55%-80% of the cases, but affected

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newborns usually also manifest diffuse and focal neurologic deficits.

Intracranial Hemorrhage

Intracranial hemorrhage may be difficult to establish conclusively as a cause of seizures distinct from hypoxic-ischemic or traumatic injury because of the frequent association of one or both of these factors with the hemorrhage. Nevertheless, approximately 15% of term infants have intracranial hemorrhage as the primary cause of their seizure. In the contemporary, multicenter, neonatal seizure registry study described earlier, intracranial hemorrhage was the etiology in 12% of newborns with seizures,[25] and in the large previously described single-center cohort, 12% had intracranial hemorrhage as the etiology.[92]

Primary subarachnoid hemorrhage, although very common, is usually not of major clinical significance. Nevertheless, seizures can occur secondary to subarachnoid hemorrhage in the full-term infant, and in that context the spells most often have their onset on the second postnatal day. Newborns with subarachnoid hemorrhage in association with hypoxic-ischemic encephalopathy usually exhibit seizures on the first postnatal day, probably as a result of the encephalopathy rather than the hemorrhage. In the interictal period, newborns with seizures secondary to uncomplicated subarachnoid hemorrhage often appear remarkably well.

Germinal matrix-intraventricular hemorrhage, emanating from small blood vessels in the subependymal germinal matrix, is principally a lesion of the premature infant, occurring in the first 3 days of life. Seizures in association with this type of hemorrhage usually occur with severe lesions or with accompanying parenchymal involvement or both. Recent studies have documented a high incidence of seizures in the preterm infant in the first 72 hours of life and these were strongly associated with the presence of high-grade intraventricular hemorrhage (IVH).[88]

Subdural hemorrhage is often associated with a traumatic event, and it is probably the associated cerebral contusion that results in the convulsive phenomena. The most common variety of subdural hemorrhage is the convexity type, and the seizures in this setting are often focal. Historically, in one large series, convulsive phenomena occurred in 50% of newborns with subdural hemorrhage and appeared in the first 48 hours of life.[16] However, in more recent series with less severe hemorrhages, the vast majority of subdural hemorrhages are asymptomatic.[94] In most newborns with extra-axial hemorrhage, no neurosurgical intervention is required, and following resolution of the acute, symptomatic seizures, prognosis is excellent.

Intracranial Infection

Intracranial bacterial and nonbacterial infections are not uncommon causes of neonatal seizures. In the contemporary multicenter neonatal seizure registry study described earlier, infection was the etiology in 4% of newborns with seizures.[25] There is an equal incidence in preterm and term infants. Infections can include congenital infections (such as TORCH infection) or acute central nervous system infections. Of the bacterial infections, meningitides secondary to Group B *streptococci* and *Escherichia coli* are the most common pathogens. The onset of seizures in these instances is usually in the latter part of the first week and subsequent to that period. The relevant nonbacterial infections include the various neonatal encephalitides: toxoplasmosis, herpes simplex, coxsackievirus B infection, rubella, and cytomegalovirus infection. In intrauterine toxoplasmosis or cytomegalovirus infection that is severe enough to result in neonatal seizures, the episodes occur in the first 3 days of life. Seizures associated with herpes simplex encephalitis tend to occur after 7 days of life. Early-onset disseminated herpes simplex virus (HSV) disease does not usually present with seizures. Seizures are more common in term infants with localized CNS rather than disseminated disease. The infant with this variety of neonatal HSV infection usually has been discharged from the hospital before the illness begins. The usual signs are stupor and irritability, which evolve to seizures (often focal) and, perhaps, coma.

Developmental Defects

Many aberrations of brain development can result in seizures, which begin at any time during the neonatal period. In the contemporary, multicenter, neonatal seizure registry study described previously, brain malformations were the etiology in 4% of newborns with seizures.[25] Similarly, in prior studies, malformations of cortical development accounted for 5%-9% of neonatal seizures.[82] Common malformations include tuberous sclerosis, focal cortical dysplasia, hemimegalencephaly, lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia, schizencephaly, and polymicrogyria. Although these disorders may be the cause of a substantial percent of neonatal seizures, most patients with these malformations do not have seizures in the neonatal period. In tuberous sclerosis, only 5% of children develop seizures in the neonatal period. Outcomes depend primarily on the type and severity of malformation.

Metabolic Disturbances

In the contemporary, multicenter, neonatal seizure registry study described previously, the etiology was a transient metabolic disturbance in 4% and an inborn error of metabolism in 3% of newborns with seizures.[25]

Hypoglycemia

Hypoglycemia is most frequent in small newborns, most of whom are small for gestational age, and in infants of mothers who are diabetic or prediabetic. Hypoglycemia is thought to be responsible for approximately 3% of neonatal seizures, although the incidence has been falling with improved neonatal care. The most critical determinants for the occurrence

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of neurologic symptoms in neonatal hypoglycemia are the duration of the hypoglycemia and, as a corollary, the amount of time elapsed before treatment is begun. Neurologic symptoms consist most commonly of jitteriness, stupor, hypotonia, apnea, and seizures. The onset is usually the second postnatal day. Hypoglycemia significant enough to trigger seizures is often associated with adverse neurodevelopmental outcomes.[63]

Hypocalcemia

Hypocalcemia has two major peaks of incidence in the newborn. The first peak, which takes place in the first 2-3 days of life, occurs most often in low-birth-weight newborns, both of average and below-average weight for gestational age, and in infants of diabetic mothers. In a recent series, hypocalcemia was the cause of 3% of neonatal seizures.[25,92]

When hypocalcemia appears later in the neonatal period, without the complicated associated factors of early onset hypocalcemia, delineation of hypocalcemia as the major etiologic factor in the convulsive phenomena is easier. Classically, these hypocalcemic newborns are large, full-term infants who avidly consume a milk preparation with a suboptimal ratio of phosphorus to calcium and phosphorus to magnesium (e.g., cow milk or a high-phosphorus synthetic formula). Hypomagnesemia is a frequent accompaniment or more rarely may be present without hypocalcemia. The neurologic syndrome is consistent and distinctive, involving primarily the following: hyperactive tendon reflexes; knee, ankle, and jaw clonus; jitteriness; and seizures. The convulsive phenomena are often focal, both clinically and electroencephalographically. Later-onset hypocalcemia of the nutritional type is unusual in the United States. Later-onset hypocalcemic seizures are associated more commonly with endocrinopathy (maternal hyperparathyroidism, neonatal hypoparathyroidism) or with congenital heart disease (with or without DiGeorge syndrome).

Inborn Errors of Metabolism

Inborn errors of metabolism may also present with neonatal seizures. Disturbances of amino acid or organic acid metabolism may result in neonatal seizures, virtually always in the context of other neurologic features. The most common of these associated with neonatal seizures are nonketotic hyperglycinemia, sulfite oxidase deficiency, multiple carboxylase deficiency, multiple acyl-coenzyme A dehydrogenase deficiency (glutaric aciduria, type II), and urea cycle defect. Hyperammonemia or acidosis, or both, most commonly accompanies these disturbances. Transient disturbance of the glycine cleavage enzyme may cause neonatal seizures; the diagnosis can be missed if CSF glycine levels are not determined because plasma glycine levels may be normal. The process resolves spontaneously after approximately 6 weeks of age.[67]

Additional unusual causes of neonatal seizures in this context include mitochondrial or peroxisomal disturbance. Of the former, pyruvate dehydrogenase deficiency and cytochrome c oxidase deficiency, with elevated lactate in blood and CSF, are the most common. Although not strictly a "metabolic" disturbance, peroxisomal disease, especially Zellweger syndrome or neonatal adrenoleukodystrophy, associated with elevations of blood levels of very-long-chain fatty acids and other biochemical changes, is associated with severe neonatal seizures caused by associated cerebral neuronal migrational defects.

Pyridoxine dependency, a disturbance in pyridoxine metabolism, may produce severe seizures that are recalcitrant to usual therapy. Onset is usually in the first hours of life, but intrauterine seizures as well as onset after the neonatal period have been observed. Seizures are usually multifocal clonic and recalcitrant to all therapeutic modalities. There is an associated newborn encephalopathy, which may manifest as hyperalertness, tremulousness, or hypothermia. A prodrome of restlessness, irritability, and emesis preceding seizures has been described. A progressive encephalopathy and ultimately death ensue if treatment is not initiated. Clinical studies also indicate that the disorder may begin after days or weeks, that the seizures may respond initially to anticonvulsant medications, and that doses of pyridoxine greater than 100 mg may be necessary to stop the seizures.

Any suspicion of the disorder should lead to a therapeutic trial of pyridoxine. The diagnosis may be suspected from the EEG that usually shows an unusual paroxysmal pattern consisting of generalized bursts of bilaterally synchronous, high-voltage, 1- to 4-Hz activity with intermixed spikes or sharp waves. Diagnosis is supported by documentation of cessation of seizures and normalization of the EEG findings within minutes after intravenous injection of 50-100 mg of pyridoxine. The EEG findings may not normalize for several hours, even when a prompt seizure response is observed. Subsequently, complete control of seizures on pyridoxine monotherapy and recurrence on withdrawal established the diagnosis. Most infants have exhibited subsequent intellectual disability despite therapy from the first days of life. Nevertheless, early therapy may decrease the likelihood or severity, or both, of intellectual deficit; indeed, 8 of the 10 reported infants with normal intellect were identified and treated in the first month of life. The molecular defect involves the active form of pyridoxine, pyridoxal-5-phosphate necessary for the action of glutamic acid decarboxylase (GAD), which leads to the synthesis of the inhibitory neurotransmitter GABA.[91]

Pyridoxamine phosphate oxidase deficiency (PNPO) is a related neonatal epileptic disorder involving synthesis of pyridoxal-5-phosphate. The molecular defect involves PNPO, required for synthesis of pyridoxal-5-PO_4. The clinical presentation often includes fetal seizures, and infants are often premature and exhibit an encephalopathy as well as seizures. The disorder requires treatment with pyridoxal-5 phosphate; pyridoxine, not unexpectedly, is not effective therapy. Folinic acid–responsive seizures refer to a clinical syndrome of neonatal seizures with onset as early as the first hours of life, responsiveness to oral administration of folinic

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acid, and the presence on CSF analysis for monamine neurotransmitters of two unknown metabolic peaks. The disorder is accompanied by a discontinuous EEG pattern with multifocal sharp waves and progressive cerebral cortical and white matter atrophy. The seizures respond to oral folinic acid at doses ranging from 2-20 mg twice daily; the lowest doses have been used in the neonatal period. At least 50% of the infants have had subsequent cognitive deficits. Recent data indicate that folinic acid responsive seizures and pyridoxine-dependent seizures are syndromes caused by the same genetic defects.

A disorder of glucose transport from blood to brain is important to recognize, because prompt treatment can lead to cessation of seizures and improved neurologic development. This disorder is caused by an autosomal dominant, heterozygous mutation in the GLUT1 transporter (*SLC2A1* gene). Approximately 25% of cases have had onset of seizures in the first 2 months of life. The mean age of onset of seizures is 5 months. The striking metabolic findings are low glucose concentrations in CSF with normal blood glucose concentration. The mean ratio of CSF to blood glucose has been 37%. That the hypoglycorrhachia was not the result of increased glycolysis, but rather of impaired glucose transport, is shown by the consistent finding of a low (rather than high) lactate level in CSF. The impaired glucose transport is related to a defect of the glucose transporter (Glut1) responsible for the facilitative diffusion of glucose across the blood–brain endothelial barrier and across the neuronal plasma membrane. Treatment with a ketogenic diet, which supplies usable metabolic fuel for brain energy metabolism not transported by the glucose transporter, is generally effective in leading to seizure control and may blunt the impaired neurologic development that is a consistent feature of the disease. However, in general, the beneficial effect of the ketogenic diet is most apparent for seizure control.

DEND refers to a syndrome characterized by developmental delay, epilepsy, and neonatal diabetes. Characteristic features are a severe neonatal-onset epileptic encephalopathy and diabetes mellitus, associated with a channelopathy involving the endocrine pancreas and the brain. The molecular defect involves an ATP-dependent potassium channel (KATP), responsive to the ratio of intracellular ATP/ADP concentrations. This channel normally closes when the ATP/ADP ratio rises (i.e., in association with increased blood glucose). Thus potassium remains intracellular, and the cell depolarizes. The depolarization leads to Ca^{2+} influx and thereby to physiologic insulin release. This mechanism serves to regulate insulin release moment-by-moment in response to blood glucose. In DEND, the channels are unable to close properly. Treatment with insulin is inadequate and does not ameliorate the neurologic manifestations. However, sulfonylurea, an oral hypoglycemic agent, binds to the channel, promoting closure and physiologic insulin release. Prompt recognition and treatment of this syndrome with oral hypoglycemic agents, and not systemic insulin administration, is essential for a good neurologic outcome.

Drug Withdrawal

A rare cause of seizures is passive addiction of the newborn and drug withdrawal despite the increasing problem of neonatal abstinence syndrome. The drugs particularly involved are narcotic-analgesics (e.g., methadone), sedative-hypnotics (e.g., shorter-acting barbiturates), propoxyphene, tricyclic antidepressants, cocaine, and alcohol. The usual time of onset of seizures in this setting is the first several days of life.

Neonatal Epilepsy Syndromes

As described earlier, most neonatal seizures represent acute symptomatic (provoked) seizures, but there are rare newborns with epilepsy. Several neonatal syndromes are distinguished principally according to their clinical features. The current International League Against Epilepsy classification system defines several electroclinical syndromes with onset in the neonatal and infantile periods. An epilepsy syndrome was defined as "a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder." These distinctive disorders are identifiable on the basis of a typical age of onset, specific EEG characteristics, seizure types, and other factors that, when taken together, permit a specific diagnosis. The classification and terminology used to describe these syndromes have evolved over time. The five major neonatal epilepsy syndromes are discussed next.

Benign Familial Neonatal Epilepsy (BFNE)

This syndrome is an autosomal dominant condition manifesting with seizures in the first week of life.[76] Seizure onset is usually on the second or third postnatal day, and in the interictal period the newborn appears well. The seizures most often are focal clonic, focal tonic, or apneic, and may occur with a frequency of 10-20 per day or higher. The electroclinical characteristics are typical and consist of an initial brief period of EEG flattening, accompanied by apnea and motor activity, followed by a bilateral discharge of spikes and slow waves, accompanied by clonic activity. The disorder is usually self-limited, with cessation of seizures in 1-12 months. Neurologic development is usually normal. However, about 10%-15% of children develop epilepsy later in life. Family histories indicate autosomal dominant inheritance with incomplete penetrance. However, because of the benign course of the disorder, the history of previously affected family members may be overlooked unless specifically sought by direct questioning of parents and sometimes grandparents. Two separate chromosomal loci have been identified (i.e., chromosome 20q13.3 and chromosome 8q24). Both genes encode voltage-gated potassium channels (KCNQ2 on chromosome 20 and KCNQ3 on chromosome 8), which may function in the same heteromeric complex to regulate the threshold for neuronal excitability. BFNE has also been reported in patients with mutations in PRRT2 and genes coding for a sodium channel subunit

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TABLE 55.4 Early Onset Epileptic Encephalopathies Characterized by Burst-Suppression

Clinical Features	Early Myoclonic Encephalopathy (EME)	Early Infantile Epileptic Encephalopathy (EIEE) (Ohtahara Syndrome)
Major clinical seizure types at onset	Myoclonic (also focal motor clonic and tonic)	Tonic spasms (also focal motor clonic)
Electroencephalographic interictal pattern	Suppression burst	Suppression burst
Relation to sleep	Enhanced by sleep	Same asleep and awake
Evolution	Persistent suppression burst	Transition to hypsarrhythmia
Etiology	Metabolic (rarely structural or genetic)	Bilateral structural cerebral lesions (rarely metabolic or genetic)
Outcome	Unfavorable	Unfavorable
Genes	ERBB4, PIGA, SETBP1, SIK1, SLC25A22	STX BP1 in ~30%; KCNQ2 in ~20%; SCN2A in ~10%; AARS, ARX, BRAT1, CACNA2D2, GNAO1, KCNT1, NECAP1, PIGA, PIGQ, SCN8A, SIK1, SLC25A22

(SCN2A).[76] Mutations in these genes are associated with a spectrum of diseases, including neonatal epileptic encephalopathies. A study of 36 families that included 33 families with BFNE found that 27 of these families had KCNQ2 mutations, one had a KCNQ3 mutation, and two had SCN2A mutations.[29]

Benign Nonfamilial Neonatal Convulsions

This syndrome is also referred to as "fifth-day fits" or benign idiopathic neonatal seizures. It is characterized by the onset of seizures in the latter part of the first week of life in apparently healthy full-term infants. The peak time of onset is the fifth day, and approximately 80%-90% have had their onset between the fourth and sixth days of life. The seizures are usually multifocal clonic, often with apnea. Status epilepticus has occurred in approximately 80% of cases. Despite the abrupt onset and frequent status epilepticus, in most patients seizures cease after 24 hours and in all patients within 15 days. The patient is normal between seizures; diagnostic testing, including standard laboratory tests and neuroimaging, are normal; and the prognosis is consistently favorable. The interictal EEG is generally normal, although a nonspecific theta pattern referred to as "theta pointu alternant" has been described in some patients. Anticonvulsant medications are often administered acutely in view of status epilepticus, but long-term therapy is generally not needed in view of the self-resolution of seizures in these patients. The possibility that some cases of benign nonfamilial neonatal convulsions are related to de novo mutations of KCNQ2, the K^+ channel most commonly affected in benign familial neonatal seizures (described previously), is suggested by preliminary data.

Early Myoclonic Encephalopathy (EME) and Early Infantile Epileptic Encephalopathy (EIEE, Ohtahara Syndrome)

Early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy (EIEE) or Ohtahara syndrome, characteristically present clinically in the first weeks of life (Table 55.4).[2] However, in some patients, these may not present until several weeks, or rarely, even several months of life. Intrauterine onset has been documented. These disorders are characterized by severe recurrent seizures, principally myoclonic and clonic at the onset in EME and tonic spasms at the onset in EIEE, and a striking suppression-burst EEG pattern. Patients with EME tend to have myoclonic seizures involving any part of the body but may also experience focal motor seizures and tonic spasms. Patients with EIEE tend to have frequent clusters of tonic spasms but may also have focal motor seizures. However, the characteristics of the suppression-burst EEG pattern differ (see Table 55.4); in EME, the burst-suppression feature is enhanced by sleep and tends to involve high amplitude bursts followed by brief periods of suppression, whereas in EIEE, the pattern is not altered by sleep or waking and is a more typical burst-suppression pattern. Further, the evolution of the EEG pattern differs; in EME, the burst-suppression pattern persists, whereas in EIEE, the pattern evolves to hypsarrhythmia and West syndrome. The primary etiologies also differ; in EME, the causes are primarily metabolic (especially nonketotic hyperglycinemia but also other amino acid and organic acid disorders), whereas in EIEE, the causes are primarily structural (primarily dysgenetic [i.e., migrational defects, microencephaly, or hemimegalencephaly], but also encephaloclastic [i.e., hypoxic-ischemic disorders]). Definition of an etiologic mechanism is possible in most cases of EIEE, whereas as many as 50% of cases of EME are cryptogenic. Additionally, while structural malformations are the most common causes of EIEE, many genetic mutations have been reported to cause EIEE (Table 55.5). The predominant genetic defect in EIEE is STXBP1, found in 20%-30% of patients. STXBP1 promotes the formation of functional vesicle fusion complexes via interaction with two N-terminal domains of syntaxin 1a, and a loss of function mutation impairs this interaction. Patients with STXBP1 encephalopathy present in the neonatal period with severe

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TABLE 55.5 Genes Involved in Early-Onset Epileptic Encephalopathy

Gene	Type / Inheritance	Clinical Manifestation	Protein Function
ARX	EEIE1 / XLR	Ohtahara syndrome	Transcriptional repressor and activator
SLC25A22	EIEE3 / X homozygous	Ohtahara syndrome	Glutamate transport into mitochondrion
STXBP1	EEIE4 / AD	Ohtahara syndrome	Modulator of synaptic vesicle release
SCN1A	EEIE6 / X de novo	Dravet syndrome	Subunit of voltage-gated sodium channel
PNKP	EEIE10 / AR	Microcephaly, seizures, and developmental delay	Enzyme involved in DNA repair
PLCB1	EIEE12 / AR homozygous	Malignant migrating partial seizures in infancy	Phospholipase-C role in intracellular transduction of extracellular signals
KCNT1	EEIE14 / sporadic	Malignant migrating partial seizures in infancy	Sodium-activated potassium channel subunit

Data adapted from Hwang SK, Kwon S. Early-onset encephalopathies and the diagnostic approach to underlying causes. *Korean J Ped*. 2015;58:407-414.

epilepsy and a suppression burst pattern on EEG. While refractory seizures are typical, the core of the phenotypic spectrum is the encephalopathy, which is present in the neonatal period.

Diagnosis

Appropriate diagnostic procedures in the newborn infant with seizures can be surmised from the discussion of causes. However, the diagnostic evaluation often is made unnecessarily complicated, and many diagnoses can be strongly suspected by such uncomplicated maneuvers as obtaining a complete prenatal and natal history and performing a careful physical examination. The first laboratory tests to be performed are directed against the two disorders that are dangerous but readily treated when recognized promptly: hypoglycemia and bacterial meningitis. Thus, blood glucose determination and lumbar puncture should be performed as soon as clinically feasible. In addition, blood should be drawn for determinations of Na^+, K^+, calcium, phosphorus, and magnesium levels. Other imaging and laboratory studies should be directed by specific clinical features. Focal seizures should lead to neuroimaging because of the frequency of focal ischemic cerebral lesions, and MRI is preferred since many focal lesions may not be detected by cranial ultrasound evaluation. As noted earlier, the most common etiologies of neonatal seizures are hypoxic-ischemic encephalopathy, intracranial hemorrhage, and perinatal arterial ischemic stroke. In one study of 354 patients with MRI and ultrasound performed, the diagnosis of important brain lesions would be frequently missed by ultrasound alone. Additionally, MRI contributed information beyond ultrasound to the diagnosis in about 40%.[92] Similarly, in a large cohort registry study by the Vermont Oxford Network, the deficiencies of cranial ultrasound and CT scanning as compared to MR imaging for clinically relevant lesions of deep nuclear gray matter injury and focal cortical and white matter injury were highlighted.

Warning signs for inborn errors of metabolism as a cause of neonatal seizures include: (1) seizures beginning in the antepartum period, (2) seizures refractory to anticonvulsant medications, (3) progressive worsening of clinical and electroencephalographic abnormalities, (4) EEG showing burst suppression, (5) MRI showing prominent brain atrophy, or (6) findings of hypoxic-ischemic encephalopathy without any obvious hypoxic-ischemic event identified. When laboratory testing is performed, the presence of low CSF glucose but normal blood glucose should suggest glucose transporter defect; the presence of elevated CSF glycine despite normal blood amino acids should suggest transient or true nonketotic hyperglycinemia; and the presence of elevated CSF lactate should suggest a mitochondrial disorder.

Electroencephalogram and Electroencephalographic Monitoring

EEG provides important diagnostic and prognostic information. Moreover, increasingly, continuous EEG monitoring is performed in neonatal intensive care facilities for several important reasons. EEG data can assist in the determination of whether clinical events are correlated with electrical seizures requiring anticonvulsant medication or with nonepileptic events in which anticonvulsant medication administration can be avoided. As discussed earlier, some seizures have readily identifiable clinical manifestations (i.e., clonic or tonic components), while many seizures have more subtle manifestations (i.e., orolingual, ocular, or autonomic). Thus clinical diagnosis of seizures may be difficult and unreliable. As described earlier, when compared to the gold standard of electroencephalographic data, observers only classify clinical events correctly as seizures about half of the time, and there is poor interobserver agreement.

As a result of these data, there is increasing emphasis on continuous EEG monitoring to aid in management of seizures in newborns. Many neonatal intensive care units report using EEG monitoring, with conventional EEG or

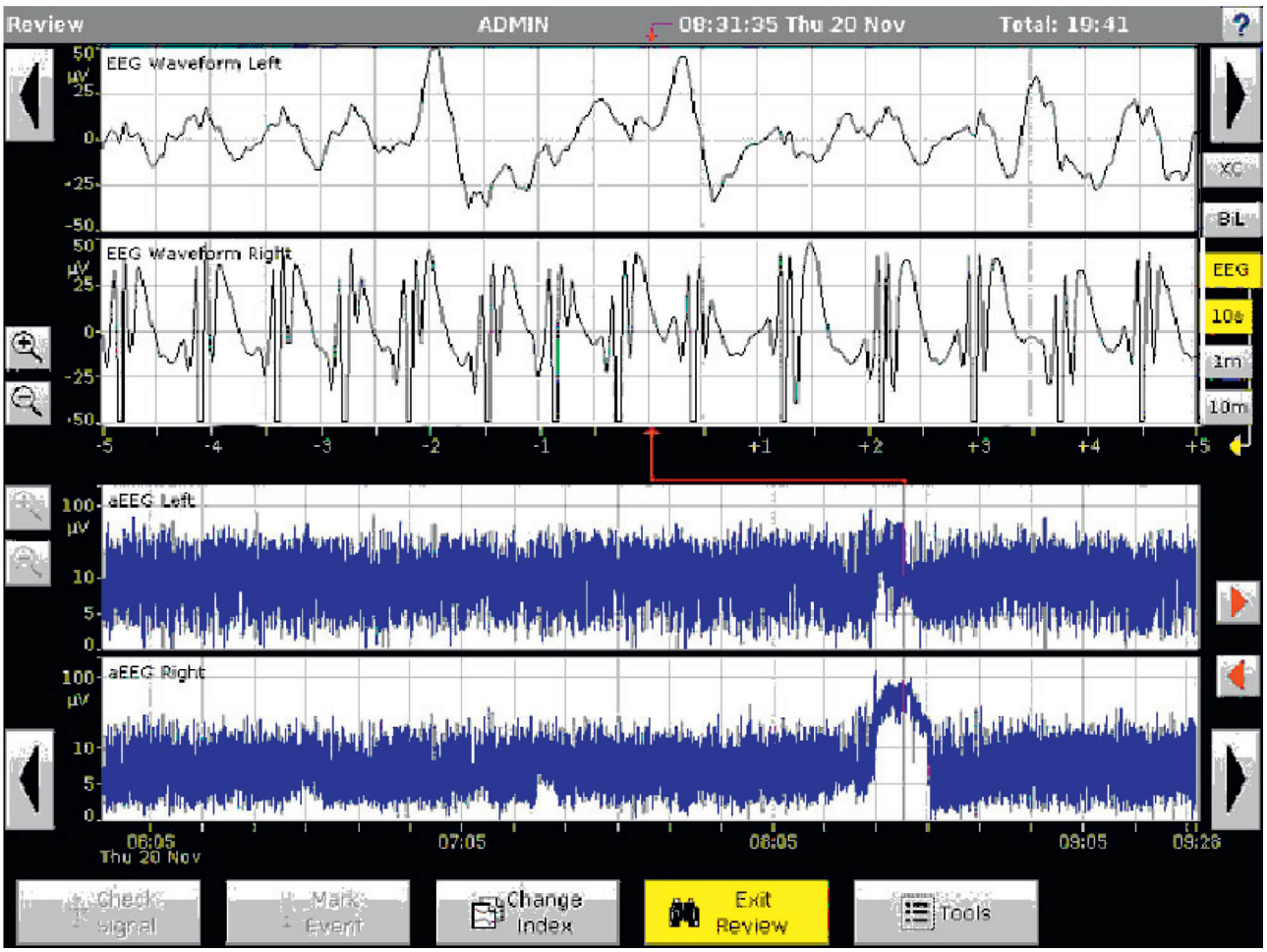
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aEEG, to identify and manage neonatal seizures.[9,70] Additionally, guidelines and consensus statements have advocated for EEG monitoring.[73] This recommendation has included the need for confirmation of seizures by EEG in specialized settings prior to therapy.

The most comprehensive guideline on continuous EEG monitoring in the newborn was produced in 2011 by the American Clinical Neurophysiology Society.[73] The guideline was created to standardize care and define best neuromonitoring practices in the neonatal population while recognizing that not all recommendations would be feasible or applicable across institutions. The guideline recommendations included that (1) electrodes be placed using the International 10-20 system with additional electrocardiogram, respiratory, eye, and electromyography leads; (2) at least 1 hour of recording be assessed to adequately assess cycling through wakefulness and sleep; (3) high-risk newborns be monitored for at least 24 hours to screen for the presence of electrographic seizures; and (4) in newborns with seizures, monitoring occur during seizure management and for an additional 24 hours after the last electrographic seizure. Video EEG recording was recommended for 24 hours rather than a briefer EEG recording, since many newborns will not have seizures in the first hour of recording but will experience electrographic seizures within the first day. Accurate delineation of seizure phenomena by EEG in the newborn requires experienced electroencephalographers with training in the normal developmental features of EEG in the newborn and skilled EEG technologists for the application of the EEG.

Amplitude-Integrated EEG (aEEG)

Amplitude-integrated EEG (aEEG) is in widespread use, especially by neonatologists, as a method to identify electrographic seizures at the bedside. The technique uses a reduced number of electrodes compared to a conventional EEG recording to generate a single channel (2 electrodes) or dual-channel (4 electrodes) EEG tracing. The EEG signal is modified and compressed using algorithms, which vary slightly between manufacturers to generate the final display showing several hours of aEEG data on a single screen. Electrographic seizures are characterized by upward arches (Fig. 55.4). The primary advantages of



• **Fig. 55.4** aEEG demonstrating typical seizure morphology with elevation of baseline and spike wave pattern seen on raw EEG above.

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aEEG relate to its relative ease of use. The limited electrode array can be applied by those without specialized training (i.e., not EEG technologists), and the display can be interpreted by bedside caregivers, generally without involvement of electroencephalographers or neurologists. As a result of these advantages and the resource intensity of conventional EEG monitoring, aEEG is widely used in neonatal intensive care units for seizure identification and management.

Some challenges with aEEG have been identified. For example, neonatologists may not have confidence in their ability to interpret the aEEG. In addition, aEEG may underestimate the true incidence of electrographic seizures. In a systematic review of 10 studies of aEEG in newborns for seizure diagnosis,[59] when aEEG was used with the raw EEG tracing available, the median sensitivity was 76% (range 71%-85%) and the median specificity was 85% (range 39%-96%). When aEEG was used without the raw EEG tracing, the results were worse; the median sensitivity was 39% (range 25%-80%), and the median specificity was 95% (range 50%-100%). Additionally, seizures that had low amplitude, were brief duration, or occurred distant from the aEEG recording sites were less likely to be identified. The American Clinical Neurophysiology Society's guidelines on EEG monitoring in newborns states that aEEG can be a "useful, initial complementary tool" to EEG monitoring, which remains the gold standard.

Despite the limitations of aEEG, some studies indicate that in comparison to use of clinical signs alone, aEEG may assist in recognition and management of seizures. In a study of 202 newborns, those who underwent aEEG monitoring had greater precision in the diagnosis of neonatal seizures than in contemporary controls with diagnosis by clinical signs alone.[72] Further, more accurate diagnosis of seizures and subsequent management may reduce seizure exposure in newborns. In a randomized study of 33 infants, neonatologists were allowed to view aEEG in their routine clinical care for 19 patients but were blind to the aEEG data for 14 patients. Among those newborns in whom aEEG was available to neonatologists, there was a trend toward reduced seizure exposure. Further, patients with lower duration of seizures exhibited less severe brain injury on MRI.[86] Similarly, a prospective single center study assessed 26 newborns who were randomized to have management guided by clinical data only (n = 16) or by clinical and electroencephalographic data including cEEG and aEEG (n = 10). The group with electroencephalographic data used for clinical management had a lower seizure burden and more rapid time to treatment completion. Additionally, newborns with increasing seizure burden had worse MRI injury scores and lower performance on cognitive, motor, and language composite Bayley scores.[79] More data with larger series will be of great interest, and two large randomized controlled trials of the impact of aEEG monitoring of newborns suspected of having seizures versus standard clinical evaluation are underway in Australia and the Netherlands.

Prognosis

General Outcomes

The major determinant of prognosis in newborn seizures is the neuropathologic process that underlies the seizures. However, two other considerations are of importance. The first is that although the outcomes of all high-risk newborns, including those with seizures, have improved, there continues a significant risk of disability. A recent review of 4538 children with a history of neonatal seizures demonstrated that 18% developed epilepsy, with nearly 70% having onset within the first year. Associated neurologic impairments were present in 81% of the children with epilepsy, including 18% with intellectual impairment, 6% with cerebral palsy, and 45% with both cerebral palsy and intellectual impairment.[54] The second key factor influencing outcome following seizures in the newborn is the gestational age of the infant. Clinical seizures in the preterm infant are commonly associated with severe brain injury and, thus, a poor prognosis.

Predicting Outcome in Individual Patients

The overall factors regarding prognosis discussed earlier do not answer the question that is most critical to the physician caring for a newborn with seizures: "How can I predict the outcome in my patient?" The two most important factors in predicting outcome for an individual infant are the infant's underlying neuropathology and the EEG pattern.

Relation of Neurologic Disease to Outcome

The most important determinant of neurologic prognosis is the nature of the neuropathologic process that underlies the seizures. The relationship of prognosis with the underlying disease producing the seizures is summarized in Table 55.6. Importantly, nearly all the data are based on follow-up periods that do not extend to school age; thus, the incidence of subtle but potentially important intellectual deficits is largely unknown. Additionally, in many studies, premature and term infants are considered together. The neurologic outcomes related to specific neurologic disorders are discussed in other chapters.

Relation of EEG to Outcome

Two aspects of the EEG are useful in assessment of outcome (i.e., the EEG background and the quantitation of seizure burden). A considerable amount of work has focused on the EEG background, proving that it is valuable for prognostic estimate with the qualification that evaluations of neonatal EEG findings are sometimes difficult and may vary among interpreters. Recent standardized terminology has been proposed by the American Clinical Neurophysiology Society.[84] In several careful studies, the background EEG pattern was found to correlate well with outcome in both full-term and premature infants with seizures. Most newborns with seizures occurring on a normal EEG background generally

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TABLE 55.6 Prognosis of Neonatal Seizures: Relation to Neurologic Disease

Neurologic Disease*	Normal Development†
Hypoxic-ischemic encephalopathy	50%
Intraventricular hemorrhage‡	10%
Primary subarachnoid hemorrhage	90%
Hypocalcemia	
Early-onset	50%§
Later-onset	100%#
Hypoglycemia	50%
Bacterial meningitis	50%
Developmental defect	0%

*Prognosis is for those cases with the stated neurologic disease when seizures are a manifestation.
†Values are rounded off to nearest 5%.
‡Usually, severe intraventricular hemorrhage.
§Typically in the first 72 hours of life.
#After 7 days of life.

have a normal outcome, while 90% of newborns with seizures on an abnormal EEG background (e.g., attenuation in voltage, burst-suppression, or excessive discontinuity) have an abnormal outcome. The burst-suppression pattern is particularly typical of the newborn with severe bilateral cerebral disease and is characterized by relatively long periods of voltage suppression (<5μV) or by no electrical activity at all in the intervals between the bursts of activity. Moderate background abnormalities, which generally account for approximately 15%-30% of the tracings, are associated with an intermediate likelihood of sequelae.

The preponderance of data concerning the predictive role of EEG concern newborns with hypoxic-ischemic encephalopathy. Normal EEG background, particularly in the first day of life, is associated with normal outcomes in 80%-100% of newborns, burst-suppression background is associated with unfavorable outcomes in 80%-100% of newborns, and an attenuated EEG background is associated with unfavorable outcomes in 90%-100% of newborns. Consideration of the impact of sedating medications on the EEG background is important; some newborns with backgrounds that predicted unfavorable outcome yet had favorable outcomes may have had their backgrounds worsened by phenobarbital. Additionally, since EEGs may evolve over time, repeat EEG tracings may be useful. EEGs that remain abnormal are more predictive of unfavorable outcomes.

The second major value of EEG in assessment of prognosis is quantitation of seizure burden. An important question is whether seizures in the newborn lead independently to brain injury and thereby worsen outcome. The answer to this question underlies decisions regarding the importance and aggressiveness of seizure identification and management. Data related to seizures and outcome in experimental animals were discussed in earlier sections. The extent to which seizures produce secondary brain injury versus serving as biomarkers of more severe acute brain injury in human newborns remains uncertain, and the relationship in an individual newborn is likely dependent on the etiology and severity of the acute brain injury, seizure burden, and seizure management strategies. Studies using univariate analyses show associations between seizures and less favorable outcomes, but such studies cannot determine whether the seizures contributed to the worse outcomes (i.e., led to secondary brain injury) or merely served as biomarkers of more severe brain injury and thus predicted worse outcomes. Studies using multivariate analyses may be more informative as to the impact of seizures on outcome. Several such reports have identified associations between seizures, particularly high seizure exposures, and unfavorable outcomes in models adjusting for variables reflecting acute brain injury etiology, acute brain injury severity, and critical illness severity. For example, in a study of 63 term-born infants with hypoxic-ischemic encephalopathy who were randomized to treatment of all seizures (clinical + aEEG) compared to treatment of only clinical seizures, a positive correlation was found between seizure duration and MRI injury severity across the entire cohort ($p < 0.001$).[86] Of note, this relationship was only significant for the newborns treated for only clinical seizures ($p = 0.001$), but not for those treated for both aEEG and clinical seizures ($p = 0.292$). In a similar study design of 69 term-born infants with moderate-severe hypoxic-ischemic encephalopathy and clinical seizures randomized to treatment with or without access to EEG data, an association between increasing seizure burden and worsened MRI injury scores ($p < 0.03$) was seen.[79] Of greater importance, an association was found between seizure burden and more adverse neurodevelopmental outcomes on Bayley Scales of Infant Development (cognitive composite $R = 0.502$, $p = 0.03$; motor composite $R = 0.497$, $p = 0.01$; language composite $R = 0.444$, $p = 0.03$). The infants in the aEEG-monitored group experienced a lower seizure burden, although neurodevelopmental outcomes were not shown to be statistically different. Larger data sets from current randomized controlled trials with aEEG monitoring that may lower seizure burden in monitored infants across diverse neuropathologies are required to definitely answer the question of the adverse impact of seizures in the newborn infant. However, the current data support that at least in some newborns, seizures may cause or accentuate secondary brain injury and subsequent worsening of neurobehavioral outcomes.

Management

Selection of Who to Treat

The selection of who to treat requires the accurate identification of the infant with epileptic seizures. As noted earlier, to accurately recognize a newborn infant with seizures requires continuous electrophysiologic monitoring with either gold standard, conventional video EEG, or, if

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unavailable, limited channel aEEG because of the very high incidence of clinically silent seizures. Why should the infant with seizures be treated with anticonvulsant medication at all? The answer relates to the potential adverse effects of seizures on ventilatory function, circulation, cerebral metabolism, and subsequent brain development, as discussed previously in the chapter. However, more recent reports, characterized by quantitation of electrographic seizures and multivariate analyses adjusting for severity of brain injury, suggest that seizures may accentuate brain injury, especially in newborns with hypoxic-ischemic brain injury. Although not unequivocally established in the human newborn, the balance of information indicates that repeated seizures should be stopped, because they may induce secondary brain injury and less favorable neurobehavioral outcomes. While there remains uncertainty as to the extent to which seizures worsen outcomes and in which patients, whether treatment actually improves outcomes, how aggressively to treat seizures, and what medications are optimal for seizure treatment, the large majority of clinicians treat neonatal seizures.[85] The World Health Organization guideline on neonatal seizures recommended treatment of all clinical and electrographic seizures.[95]

The value of implementation of a standardized treatment protocol has been documented in recent studies. One investigation evaluated neonatal status epilepticus management for 6 months before and 12 months after implementation of a standardized algorithm for therapy in newborn seizures.[32] This included a reduction in the maximum phenobarbital concentrations (57 versus 41 micrograms/mL), fewer patients progressing to status epilepticus (46% versus 36%), and decreased hospital length of stay by 10 days in survivors. Although increased attention to neonatal seizure management may lead to concern for overtreatment and elevated exposure to phenobarbital, there is some evidence that early treatment using a coordinated and consistent approach prevents overadministration of anticonvulsant medication. This conclusion is supported by a recent study of 108 newborns with hypoxic-ischemic encephalopathy cared for before and after implementation of a neonatal neurocritical care service. Nearly all newborns with seizures received phenobarbital at similar dosing (30-33 mg/kg). Although the era after implementation of the service had improved EEG monitoring and improved vigilance for seizures, after adjustment for seizure burden, newborns managed after implementation of the Neonatal Neurocritical Care Service received an average of 30 mg/kg less cumulative phenobarbital and were on maintenance therapy 5 fewer days.[96] These data indicate that even in the absence of an entirely evidence-based approach to neonatal seizure management, implementation of a logical and consistent plan may provide benefit.

Adequacy of Treatment

The decision to initiate seizure therapy and the assessment of the adequacy of treatment rely on accurate identification of seizures. The goal of therapy is the elimination of electrical seizure activity, based on the fact that many seizures in the newborn infant are clinically silent. In addition, the administration of anticonvulsant medications often leads to electromechanical uncoupling/dissociation in which there is cessation of clinical seizures despite persistence of EEG-only seizures. Given these difficulties in seizure identification, clinicians must rely on EEG monitoring as the only means for accurate determination of the adequacy of anticonvulsant therapy. A survey of 193 international neurologists, neonatologists, and specialists in neonatal neurology conducted in 2010 reported that the majority of centers used either EEG, aEEG, or a combination for newborns with seizures or at risk for seizures.[24] Thus the importance of electrophysiologic monitoring to determine accurately the presence of seizure activity appears essential in determination of the success of anticonvulsant therapy.

As management progresses, the goal of total elimination of electrical seizure activity may have to be adjusted based on individual circumstances. Although the goal of therapy is generally total or near-total elimination of electrographic seizures, in some newborns the doses of anticonvulsant medications required lead to potentially dangerous disturbances of cardiac function, blood pressure, and ventilation. For example, because a newborn with cardiovascular instability may not tolerate multiple anticonvulsant medications, the goal may evolve toward reducing seizure burden as much as possible without worsening cardiovascular function. Similarly, if a diagnosis of brain malformation or other neonatal-onset epileptic encephalopathy is made, the goal might be to reduce seizures as much as possible with an anticonvulsant medication regimen that retains acceptable alertness for long-term use.

Usual Sequence of Therapy

The infant exhibiting repeated seizure activity should be treated promptly. Although there are many knowledge gaps related to neonatal seizure management, a systematic approach to management is valuable. The lack of extensive, evidence-based information is notable however. For example, a 2004 Cochrane Database systematic review identified only two randomized controlled trials related to neonatal seizures, and the authors concluded that there were insufficient data to recommend one anticonvulsant medication over any other medication.[7] Similarly, a 2013 systematic review identified 571 publications related to neonatal seizure management but only two randomized controlled trials and only three additional studies with comparison groups. However, partially evidence-based treatment algorithms have been published (see Fig. 55.4).[77] Similar neonatal management algorithms have been developed by others.[33]

Phenobarbital is recommended as the first agent, and internationally phenobarbital is the most frequent initial medication administered for neonatal seizures. However, because of the lack of available data, there is substantial variability with regard to subsequent medication choices

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TABLE 55.7 Expected Response of Neonatal Clinical Seizures to Sequence of Therapy

Anticonvulsant Drug* (Cumulative Dose)	Cessation of Seizures (Cumulative Percentage)
Phenobarbital, 20 mg/kg	40%
Phenobarbital, 40 mg/kg	70%
Phenytoin, 20 mg/kg	85%
Lorazepam, 0.05-0.10 mg/kg	95%-100%

*All drugs administered intravenously.
Based largely on data of Gilman JT, Gal P, Duchowny MS, Weaver RL, et al. Rapid sequential phenobarbital treatment of neonatal seizures. *Pediatrics*. 1989;83:674-678; and on personal experience.

and the duration of therapy. A survey of 193 international neurologists, neonatologists, and specialists in neonatal neurology conducted in 2010 found that the most common first, second, and third line antiseizure medications were phenobarbital, phenytoin, and levetiracetam, respectively.[24] A typical sequence of therapy is provided in Table 55.7. There is varying familiarity and availability of these medications between institutions and countries, so practice is partially hospital specific.

Before reviewing the individual aspects of the sequence of therapy, it is important to emphasize that before instituting any anticonvulsant therapy, the physician should assess and manage ventilation and perfusion. Moreover, because the administration of certain anticonvulsant medications may impair ventilation, the necessary equipment for support of ventilation should be immediately available, with the expectation that the need for intubation is highly likely. If hypoglycemia is present and if the infant is having seizures, then 10% dextrose is given intravenously in a dose of 2 mL/kg (0.2 g/kg), and the newborn should be maintained on intravenous dextrose at a rate as high as 0.5 g/kg/hour (8 mg/kg/minute) if necessary.

Anticonvulsant Medications

Phenobarbital

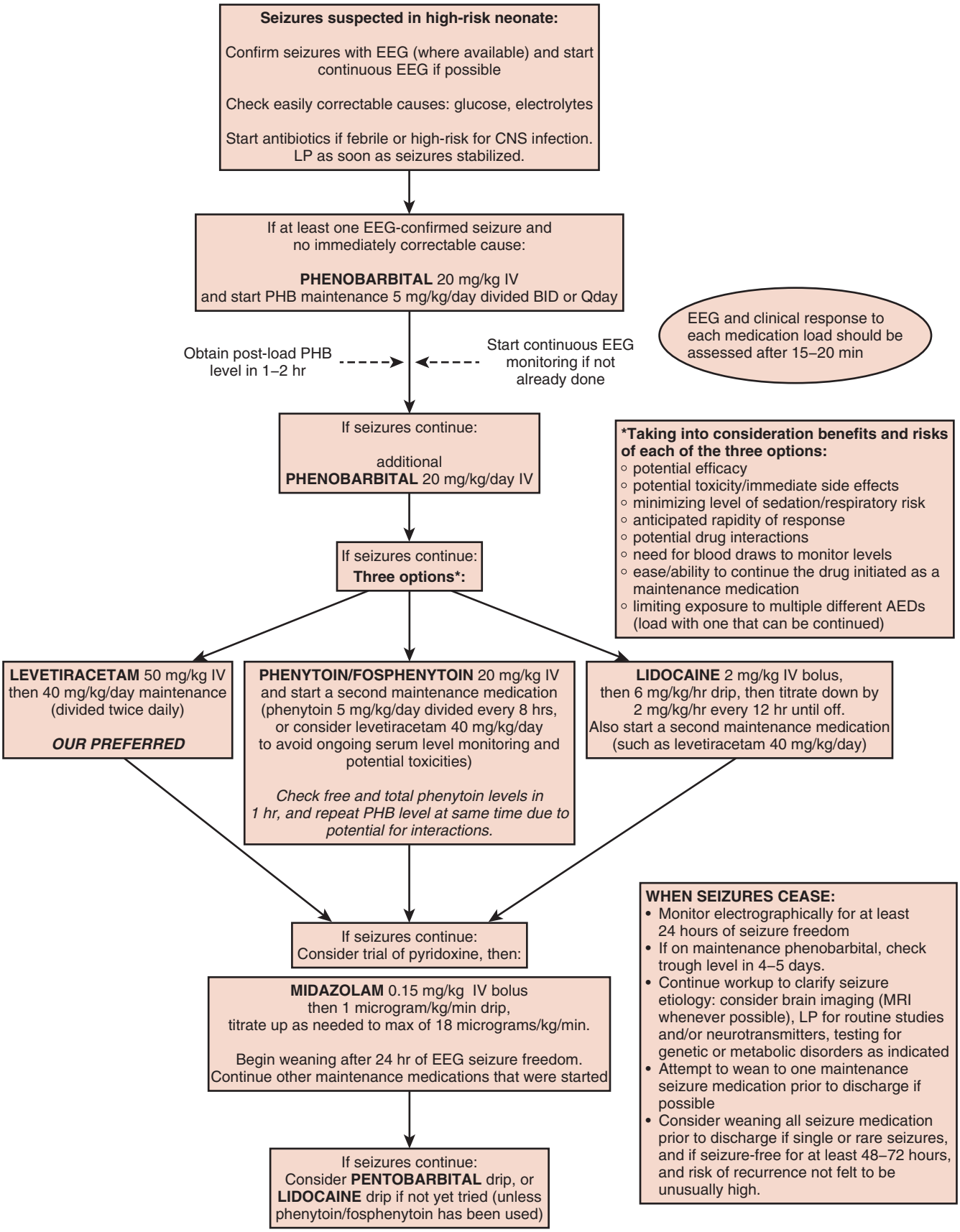
The initial anticonvulsant medication (Fig. 55.5) is most often phenobarbital administered intravenously in a loading dose of 20 mg/kg, which is generally delivered over 10-15 minutes. Careful surveillance of respiratory effort is important under these circumstances. This dosing is necessary to achieve a blood level of approximately 20 μg/mL, which achieves a clearly measurable anticonvulsant effect in the newborn. Weight or gestational age does not appear to influence the dose–blood level relationship appreciably, although infants less than 30 weeks' gestational age may require slightly lower doses to achieve the same blood level. If the initial 20 mg/kg dose of phenobarbital is not effective in controlling seizures, many clinicians administer additional doses of 5-10 mg/kg each until seizures have ceased, a total dose of 40 mg/kg has been administered, or the patient develops dose-limiting adverse effects. The goal is to achieve a phenobarbital blood concentration of approximately 40 μg/mL.

Using phenobarbital in approximately this manner, Gilman and colleagues[23] and Gal and colleagues[22] attained control of clinical seizures in approximately 70% of 71 newborns. Painter and colleagues used approximately similar doses in a later controlled study of 59 newborns, and the drug completely controlled electrographic seizures in only 43% of newborns.[51] An open-label randomized controlled trial in India also compared phenobarbital (20 mg/kg) to phenytoin (20 mg/kg) in patients with varied seizure etiologies. Seizures were controlled (defined as a seizure-free period of 24 hours) in significantly more newborns with phenobarbital (72%) than phenytoin (15%). If seizures persisted, newborns crossed over to the other drug. Overall seizure cessation occurred in significantly more newborns who received phenobarbital first than phenytoin first (91% versus 80%).[52] A retrospective study of newborns with electrographically confirmed seizures (but excluding newborns with status epilepticus) found that of 91 newborns who received phenobarbital, 63% responded completely (cessation of clinical and electrographic seizures), 17% responded partially (reduction but not cessation of electrographic seizures with the first bolus, response to the second bolus), and 21% did not respond.[78] The presence of EEG-only seizures and more abnormal EEG backgrounds predicted a lack of response to phenobarbital.[78]

Even with a favorable initial response to anticonvulsant medication, close observation is necessary since additional management may be needed. A study using EEG monitoring reviewed by experts calculated electrographic seizure exposure in 19 newborns for 1-hour epochs.[40] The seizure burden was compared in the hour before and subsequent hours after phenobarbitone administration. The seizure burden was reduced by 14 minutes (74% reduction) in the 1 hour after the administration of phenobarbitone, but the reduction was temporary and not significant within 4 hours following phenobarbitone administration. Additionally, only phenobarbitone doses of 20 mg/kg resulted in a significant reduction at 1 hour.[40] Total loading doses of phenobarbital in excess of 40-50 mg/kg generally do not provide additional benefit. Additionally, high levels appreciably sedate the newborn for several days, thereby impairing neurologic analysis, and may lead to toxic effects on the cardiovascular system.

Certain pharmacologic properties of phenobarbital are beneficial in the treatment of neonatal seizures. Thus the drug enters CSF (and presumably the brain) rapidly and with high efficiency (i.e., 30 minutes after an intravenous loading dose was administered, the CSF to blood ratio was 0.58 ± 0.07); the blood level is largely predictable from the dose administered; the agent can be administered intramuscularly as well as intravenously (preferably the latter) for acute therapy; and maintenance therapy is accomplished easily with oral therapy (see later discussion). Moreover,

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• **Fig. 55.5** An example of neonatal seizure management algorithm. (From Slaughter LA, Patel AD, Slaughter JL, et al. Pharmacological treatment of neonatal seizures: a systematic review. *J Child Neurol*. 2013;28:351-364). *Solid arrow* indicates next step if electrographically confirmed seizures are continuing (clinical or subclinical). AED, Antiepileptic drugs; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; IV, intravenous; LP, lumbar puncture; MRI, magnetic resonance imaging; PHB, phenobarbital.

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experimental data suggest that entrance of phenobarbital into brain is accelerated by the local acidosis associated with seizure.

Despite the concerning adverse profile of phenobarbital on neurons in experimental models, there are some data that phenobarbital-related reduction in seizures might yield more favorable neurobehavioral outcomes. A prospective cohort of 42 newborns with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia were either administered phenobarbital (20 mg/kg) prophylactically (20 newborns) or only if clinical seizures occurred (22 newborns). On univariate analysis, the use of prophylactic phenobarbital was associated with a decreased occurrence of seizure in the neonatal period (15% with prophylaxis versus 82% without prophylaxis, $p < 0.0001$) and decreased occurrence of seizures in the first 24 hours of life (5% with prophylaxis versus 64% without prophylaxis, $p < 0.0001$). On multivariate analysis, with birth weight and Apgar scores, the use of prophylactic phenobarbital was associated with more favorable neurodevelopmental outcomes.[46]

As discussed earlier, anticonvulsant medications with GABA agonist properties, such as phenobarbital (or benzodiazepines), may not be ideal agents because $GABA_A$ receptors are likely to be excitatory rather than inhibitory in most immature cortical neurons. More rational approaches might convert $GABA_A$ receptors from excitatory to inhibitory and thereby could enhance effectiveness of phenobarbital. Bumetanide inhibits NKCC1, the Cl^- cotransporter responsible for the elevated neuronal Cl^- levels and the depolarizing (excitation) rather than hyperpolarizing (inhibitory) response on $GABA_A$ receptor activation (see earlier). Blockade of NKCC1 decreases neuronal Cl^- levels and restores the inhibitory response of $GABA_A$ receptor activation. Bumetanide suppresses epileptiform activity in neonatal rat hippocampal slices in vitro and in neonatal rat brain in vivo. This drug has been used safely as a diuretic in the newborn, and an intravenous preparation is available.[39,80] These features have led to the hypothesis that bumetanide used concurrently with phenobarbital (or benzodiazepines) could be particularly effective, because bumetanide would allow the $GABA_A$ receptor activation produced by phenobarbital to lead to inhibition. A phase 2 feasibility study of combination bumetanide and phenobarbital therapy in newborns with hypoxic-ischemic encephalopathy and electrographic seizures enrolled 14 subjects.[56] Five had seizure reductions, but only two did not need additional rescue therapy. There were no acute adverse effects, but all 11 surviving newborns had hearing impairment. The trial was stopped early because of the concerns over the potential negative auditory adverse effects and limited evidence for efficacy by seizure reduction.[56] A second study of bumetanide for neonatal seizures is currently enrolling subjects.[13]

Phenytoin and Fosphenytoin

In the newborn who continues to experience electrographic or clinical seizures after as much as 40 mg/kg of phenobarbital, or in the severely asphyxiated infant in whom less than the full phenobarbital loading dose is deemed appropriate due to cardiopulmonary concerns, phenytoin or fosphenytoin is generally administered as second-line medication (see Fig. 55.5). Phenytoin's mechanism involves blocking of sodium channels and, therefore, represents an alternative mechanism to the action of barbiturates (i.e., phenobarbital) and benzodiazepines, which both act on chloride channels. The usual loading dose is 20 mg/kg for phenytoin or 20 mg phenytoin-equivalents/kg for fosphenytoin. When this approach is used in newborns who continue to exhibit electrographic seizures after 40 mg/kg of phenobarbital, approximately 15% more experience seizure cessation (i.e., to a total of nearly 60%). The cumulative response to the combined phenobarbital and phenytoin therapy is similar regardless of which medication is administered first. In the study by Painter and colleagues, when phenytoin was used as a first-line medication, 45% had seizure cessation.[51] If clinical seizure is the response endpoint, nearly 85% of newborns respond. However, as noted earlier, clinical seizure is not a suitable parameter for measuring seizure response. If 80% or more reduction of electrographic seizure is considered a favorable response, then the combination of phenobarbital and phenytoin achieves this level of benefit in fully 80% of newborns.

The 20 mg/kg loading dose of phenytoin results in a therapeutic blood level of approximately 15-20 μg/kg. The dose of phenytoin should be administered at a rate of no more than 1 mg/kg/minute to avoid disturbance of cardiac function, particularly cardiac rhythm. Cardiac rate and rhythm should be monitored during the infusion. Phenytoin should be administered directly into the intravenous line, because it is relatively insoluble in aqueous solutions and precipitates in standard dextrose intravenous solutions.

Fosphenytoin, a phosphate ester prodrug of phenytoin, has proved to be a major advance in therapy of status epilepticus and acute seizures. The drug's advantages include high water solubility and a pH value closer to neutral, ease of preparation in standard intravenous solutions, safe intramuscular administration, absence of tissue injury with intravenous infiltration, and a faster allowable rate of intravenous administration. Fosphenytoin is dosed in "phenytoin equivalents" (1.5 mg of fosphenytoin yields approximately 1 mg of phenytoin), and the effective dose is essentially identical to that described for phenytoin. The drug is converted to phenytoin, primarily by plasma phosphatases, in approximately 8 minutes. While fosphenytoin may be associated with fewer potential risks, it is more expensive and not readily available in some hospitals or countries.

Phenytoin has complicated pharmacokinetics, which make neonatal use complex. It is highly protein bound, so free levels can be difficult to achieve in newborns with renal or hepatic issues. It also induces hepatic metabolism of many other medications, including phenobarbital which is often concurrently administered. Thus levels of hepatically metabolized medications may need to be monitored. Further, maintaining an adequate and stable drug level is difficult, particularly for maintenance administration.

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Maintenance doses of 5 mg/kg/day divided twice per day (for intravenous formulations) or three times per day (for enteral formulations) are recommended. Drug levels should be followed closely as they can fluctuate substantially.

Benzodiazepines (Lorazepam, Diazepam, Midazolam)

Approximately 20% or more of newborns with electrographic seizures do not respond to the sequential administration of phenobarbital and phenytoin. Like barbiturates, benzodiazepines act on the GABA receptor and its chloride channel, thus hyperpolarizing the neuron. Thus benzodiazepines share the mechanistic problems related to GABA activation and chloride levels (see prior discussion) and the adverse effects associated with phenobarbital, including respiratory and, more rarely, cardiovascular depression.

Lorazepam is a benzodiazepine anticonvulsant medication of proven efficacy in older infants and children. Lorazepam enters the brain rapidly and produces a pronounced anticonvulsant effect in less than 5 minutes. Of importance, however, lorazepam is less lipophilic than diazepam, and thus lorazepam does not redistribute from brain as rapidly as diazepam. The duration of action for lorazepam is generally 6-24 hours (i.e., longer than diazepam). Moreover, lorazepam appears less likely to produce respiratory depression or hypotension than does diazepam. Lorazepam has been investigated in the newborn in several studies.[43] It has been effective in treatment of neonatal clinical seizures, whether as a second drug (after phenobarbital) or as a third drug (after phenobarbital and phenytoin). The onset of effect has been in 2-3 minutes, and the duration has extended to 24 hours. The effective dose is 0.05-0.10 mg/kg, administered intravenously in 0.05 mg/kg increments over several minutes. The half-life of lorazepam in asphyxiated newborns is approximately 40 hours (i.e., two- to threefold higher values than in the adult). This prolonged half-life could relate to decreased hepatic glucuronidation activity, a normal neonatal finding perhaps accentuated by asphyxial hepatic injury.

Diazepam is an effective anticonvulsant in the newborn but is less used than lorazepam for several reasons. First, diazepam is a poor drug for maintenance because of extremely rapid clearance from the brain (minutes after intravenous administration). Second, when used with barbiturate, diazepam carries an increased risk of severe circulatory collapse with respiratory failure. Third, the therapeutic dose is variable and is not necessarily less than the toxic dose (doses of 0.30 and 0.36 mg/kg have led to respiratory arrest). Fourth, the vehicle for intravenous diazepam, in many preparations, contains sodium benzoate, which is a very effective uncoupler of the bilirubin-albumin complex and theoretically could increase the risk of kernicterus.

Midazolam is a short-acting benzodiazepine in common use in the treatment of refractory status epilepticus in older infants and children. This drug has the advantage of less respiratory depression and sedation than lorazepam or diazepam. Reports suggest that midazolam is useful in refractory neonatal seizures. In a recent study of 13 newborns with electrographic seizures nonresponsive to phenobarbital with or without phenytoin, 8 responded to midazolam administered as a 0.15 mg/kg bolus followed by infusion of 0.4 mg/kg/hour.[11] The remaining 5 nonresponders responded after an additional bolus and somewhat higher infusion rates (maximum of 1.1 mg/kg/hour). Control of seizures generally was rapid (<2 hours), especially when treatment was begun promptly after failure of phenobarbital. Midazolam is usually started with a loading dose of 0.05-0.2 mg/kg and an infusion of 0.05-0.1 mg/kg/hour. If seizures persist, additional loading doses may be administered, and the infusion may be increased by 0.05-0.1 mg/kg/hour to maximum doses of about 0.5 mg/kg/hour.

Lidocaine

Lidocaine can be used as a second or third-line agent for refractory neonatal seizures. The medication has good central nervous system penetration and acts as a depressant, although its mechanism of action as an anticonvulsant medication is uncertain. Lidocaine is used much more frequently in Europe than in North America; one study has shown it to be the third-line agent of choice at multiple major European medical centers. A retrospective study of 319 term and 94 preterm newborns described the response rate to lidocaine for neonatal seizures confirmed by aEEG.[93] Lidocaine had a good (>4 hours with no seizures, no need for rescue medication) or intermediate (0-2 hours with no seizures, but rescue medication needed after 2-4 hours) effect in 71.4%. Full-term newborns had a better response rate than did preterm newborns (76% versus 55%). Additionally, among full-term infants the response to lidocaine was significantly better than to midazolam as second-line antiseizure medication (21% vs. 13%), and there was a trend toward lidocaine superiority as a third-line medication as well (68% vs. 57%).[93]

Because of the cumulative risk of toxicity, lidocaine must be stopped within 36 hours. Furthermore, the dose must be reduced in premature infants, or if the newborn is undergoing therapeutic hypothermia, as clearance decreases during hypothermia. Lidocaine can cause arrhythmias and bradycardia. The risk of such side effects can be significantly reduced by carefully following blood levels; the presumed threshold for cardiac and nervous system toxicity is >9 mg/L. It should be avoided in newborns who have congenital heart issues or have received other pro-arrhythmic drugs like phenytoin. In a retrospective study of lidocaine in 368 term and 153 preterm newborns with seizures described earlier,[93] a second analysis assessed cardiac events. Cardiac events were reported in 11 patients (2%) of the 521 patients, and in 7 patients a causal relationship was considered plausible. Risk factors for cardiac events were unstable serum potassium levels, cardiac dysfunction, and concurrent phenytoin use.

Levetiracetam (Keppra)

As a newer anticonvulsant medication, levetiracetam has become a medication used for the treatment of refractory

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neonatal seizures. In some centers, it is used as a second-line agent before using phenytoin, benzodiazepines, or lidocaine. Levetiracetam likely has a different mechanism of action from other anticonvulsant medications, since it prevents neurotransmitter release by binding to a presynaptic vesicle protein, SV2a. Experimental studies have yielded mixed results in terms of the impact of levetiracetam as a neuroprotective strategy, with some data indicating that it may be neuroprotective and other data indicating that in some situations (such as high-dose with hypothermia) the drug is associated with apoptosis.

While levetiracetam use is increasing, few data are available regarding efficacy. Clinical data consisting of mostly case reports and small series have reported that seizures terminate or decrease in frequency in about 52%-80% of newborns after receiving levetiracetam. Based on available data, levetiracetam does seem to have a reasonable safety profile with few side effects and without drug–drug interactions, and it is available in an intravenous formulation.[38,102] Many child neurologists report using levetiracetam off-label for neonatal seizures and often describe a beneficial response.[74] Optimal dosing is unknown, but common dosing involves intravenous loading doses of 30-50 mg/kg, with escalation to total intravenous loading doses of about 80-100 mg/kg if needed. Maintenance doses of 40-100 mg/kg/day divided twice or three times per day can be used. Blood levels typically are not followed, as they often take several days to return and are not clearly correlated with efficacy. There are ongoing studies of levetiracetam for treatment of neonatal seizures.

Topiramate

Topiramate is a blocker of the AMPA type of glutamate receptor and was shown in the neonatal rat to have potent anticonvulsant effects versus hypoxia-induced seizures, to have protective properties for neuronal or premyelinating oligodendrocyte injury, and not to exhibit neurotoxicity to developing neurons. Unfortunately, although case series describe benefit in some newborns, an intravenous preparation of topiramate is not yet available. Many child neurologists report using topiramate off-label for neonatal seizures and often describe a beneficial response.[74]

Other Drugs and Treatments

Valproic acid, administered orally as adjunctive therapy, led to control of neonatal seizures recalcitrant to phenobarbital (mean blood level >40 μg/mL) in five of six cases.[21] However, elevation of blood ammonia required cessation of therapy in three infants. Because of the uncertain risk of valproate hepatotoxicity in this age group, the value of this drug in the treatment of neonatal seizures is uncertain.

Carbamazepine was reported to be effective as an initial agent in the treatment of neonatal seizures in a study of 10 full-term infants with hypoxic-ischemic encephalopathy.[75] All patients showed an "excellent" clinical response. Therapeutic levels were achieved within 2-4 hours after a loading dose of 10 mg/kg administered by nasogastric tube. However, variability in blood levels suggests that more data are needed to determine the value of this agent.

There have been case reports of successful use of the ketogenic diet for refractory neonatal seizures of unclear etiology.[15] The ketogenic diet is the treatment of choice for patients with glucose transporter defects.

Other medications approved for the treatment of seizures in children or adults are often used in newborns with refractory seizures. These include oxcarbazepine, lamotrigine, felbamate, and vigabatrin. These medications are not available in intravenous formulations and can therefore be more difficult to administer in critically ill newborns. Furthermore, all of these medications are increased slowly over days to weeks, so they are not adequate for the rapid treatment of seizures.

Other Modes of Therapy

Metabolic Strategies

Seizures related to other metabolic disturbances or infection require therapeutic approaches that are better discussed in relation to these specific problems. Pearl has developed a useful clinical approach to neonatal or infantile onset epileptic encephalopathy,[53] and Ficicioglu and Bearden have described a useful treatment algorithm for neonatal seizures caused by some of the most common inborn errors of metabolism.[19]

Recurrent seizures that are not accompanied by any obvious associated findings to aid in diagnosis should raise the possibility of pyridoxine dependency. As noted earlier, the molecular defect involves an aldehyde dehydrogenase (antiquitin or ATQ) in the lysine degradation pathway; the gene involved is *ALDH7A1*. To interrupt seizures, a dose of 100 mg of pyridoxine-HCl is given intravenously accompanied by simultaneous monitoring of the EEG pattern, or orally/enterally with 30 mg/kg/day. Infants with pyridoxine dependency may exhibit hypotonia or even apnea after pyridoxine infusion perhaps because of an abrupt increase of synthesis of GABA in brain and activation of inhibitory GABA receptors in brain stem. Therefore, newborns should be monitored closely during and after the infusion. Any uncertainty regarding the response should provoke repeated 100-mg infusions of pyridoxine (to a maximum of 500 mg), a longer trial of oral pyridoxine (15-30 mg/kg/day), or both. To ensure that a late and masked response is not missed, treatment with oral/enteral pyridoxine should be continued until the aldehyde dehydrogenase deficiency is excluded by negative biochemical or genetic testing. Long-term treatment dosages vary between 15 and 30 mg/kg/day in infants or up to 200 mg/day in newborns and 500 mg/day in adults. As described earlier, some infants not responsive to pyridoxine may require pyridoxal-5-phosphate (PLP), the active form of vitamin B_6. In general, a dose of 50-100 mg/kg divided six times per day is administered for at least a 3-5 day trial. PLP is only available in enteral forms and has side effects similar to pyridoxine. In most of the PLP-responsive cases, PNPO (pyridox[am]

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ine phosphate oxidase) deficiency has been identified as the underlying genetic condition (see previous), but idiopathic PLP response occurs as well. has the potential to treat ATQ deficiency as well as PNPO deficiency. Some centers advocate the use of PLP (30 mg/kg/day divided into 3 dosages), as the first-line vitamin B_6, while other centers advocate the consecutive use when pyridoxine, given over 3 consecutive days, has failed to control seizures. Finally, pyridoxine-dependent epilepsy is an organic aciduria caused by a deficiency in the catabolic breakdown of lysine; a lysine restricted diet may assist in addressing the potential toxicity of accumulating metabolites.

Folinic acid responsive seizures (FARS) are genetically identical to ATQ deficiency and require specific therapy. FARS were first described in 1995 in patients with intractable seizures and encephalopathy who had two characteristic, but yet unidentified, peaks (peak X) in the HPLC chromatogram for CSF monoamine neurotransmitter analysis. Patients showed an improvement of seizures upon administration of folinic acid (3-5 mg/kg/day). Thus in refractile epilepsy unresponsive to pyridoxine a trial of folinic acid (leucovorin) should also be considered, with 3-5 mg/kg/day administered for at least 3-5 days.

Seizures associated with biotinidase deficiency tend to present slightly later, often in the second month of life, and there are often other symptoms such as an eczematous rash to suggest the diagnosis; in addition, the newborn screen captures at least some of these cases. Because treatment with biotin 10 mg/day can lead to favorable neurologic outcomes, this disorder should be considered in those newborns with intractable epilepsy of unclear etiology.

The ketogenic diet is the optimal treatment for newborns with a glucose transporter defect with onset of seizures in the neonatal period.

Maintenance Therapy

Typically, maintenance doses are begun 12 hours following administration of the loading dose. These are usually administered in divided doses every 12 hours.

For phenobarbital, intravenous, intramuscular, or oral administration are adequate, although the parenteral routes should be used in the seriously ill infant. Drug accumulation results within 5-10 days when maintenance doses of phenobarbital of 5 mg/kg/day are used. These rates are particularly slow in some asphyxiated infants, presumably secondary to hepatic involvement, renal involvement, or both, and lead more readily to drug accumulation than in nonasphyxiated infants. However, elimination rates do increase with increasing duration of therapy, and dose requirements may increase.

For fosphenytoin, intravenous administration is preferred, although fosphenytoin can be administered intramuscularly. For phenytoin, oral administration of phenytoin is less desirable than intravenous, although pharmacokinetic data have modified the prior notion that phenytoin absorption is poor in the newborn. Maintenance administration of phenytoin in the newborn is particularly difficult because of its nonlinear kinetics and rapid decrease in elimination rates in the first weeks of life. Thus the apparent half-life of the drug decreases from 57 hours in the first week of life to 20 hours in the fourth week. Careful attention to blood levels is particularly necessary when this drug is used for maintenance.

Carbamazepine may be a useful alternative to phenobarbital or phenytoin in maintenance therapy. Oral doses of 10-15 mg/kg/day were associated with good seizure control.

If medications used to control seizures initially are discontinued quickly and seizures recur, some clinicians initiate therapy with standard anticonvulsant medications such as levetiracetam or oxcarbazepine, which appear to have better tolerability, including less sedation, for long-term use than might occur with re-initiation of phenobarbital. However, more data are needed regarding the role of these newer anticonvulsant medications in young children.

Duration of Therapy

The optimal duration of anticonvulsant therapy for newborns with seizures relates principally to the likelihood of seizure recurrence if the drugs are discontinued. What is the risk of subsequent epilepsy in newborns with seizures? The overall incidence of subsequent epilepsy in neonatal seizure survivors has been reported as between approximately 10% and 30%.[83] This range can be refined by considering three important, readily identified determinants. The first of these is the neonatal neurologic examination. The risk of seizure recurrence is increased to approximately 50% when the neurologic examination at discharge is abnormal. The second determinant is the cause of the neonatal seizures. The risk of subsequent epilepsy after neonatal seizures secondary to perinatal asphyxia is approximately 30%-50%, and after seizures secondary to cortical dysgenesis, the risk is about 100%. However, simple, late-onset hypocalcemia has essentially no associated risk. Finally, the third determinant is the background EEG pattern. Of the 54 asphyxiated infants studied by Watanabe and colleagues, none developed subsequent epilepsy when the results of the neonatal interictal EEG tracing were normal or showed only "minimal" or "mild" depression. In contrast, 41% of infants with "marked" depression developed subsequent epilepsy.[90] The value of EEG patterns in determining the risk of subsequent epilepsy has been shown in other studies. Each of these factors should be assessed carefully to determine duration of therapy.

Phenobarbital is often maintained for several months because of concern that seizures may recur if the medication is discontinued early. However, there is growing concern about the sedating and potentially neurotoxic effects of anticonvulsant medications, particularly phenobarbital, which have led some clinicians, including ourselves, to attempt discontinuation of anticonvulsant medication as early as possible. Initial data suggest that early discontinuation of phenobarbital may not impact long-term outcomes. A

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study of 146 newborns compared 33 taking phenobarbital and 99 not taking phenobarbital at discharge from the neonatal intensive care unit and found no difference in seizure recurrence or neurologic development at 1-11 years.[31]

Experimental studies have raised the possibility that phenobarbital may have deleterious long-term effects on the developing brain. Initial studies involved rats and cultured cells of neural origin. The relation of these data to the human infant is unclear. The time period of the experiments in the rat corresponded to a period in the human from approximately the sixth month of gestation to years postnatally. Particularly concerning are studies in neonatal rats that showed pronounced apoptotic neurodegeneration within 24 hours after administration of phenobarbital, phenytoin, diazepam, clonazepam, and valproate.[6] Combinations of drugs produced greater effects. Doses and blood levels attained were generally comparable to those used in human infants. The neuronal death was associated with reduced expression of neurotrophins and survival-promoting proteins in the brain.

Some human data suggest possible risk associated with phenobarbital exposure. Studies of human children exposed in utero to several antiseizure medications, including phenobarbital and phenytoin, have demonstrated an increased risk of cognitive impairments in later childhood. A deleterious effect of phenobarbital on cognitive development of infants treated for febrile seizures raised further questions concerning potential toxicity of phenobarbital.

Some of these issues may be slightly less problematic with levetiracetam and topiramate.[58] In fact, experimental data suggest that levetiracetam can be anti-epileptogenic, and both may be neuroprotective in the setting of hypoxic-ischemic encephalopathy. A study of 280 newborns with comparable seizure etiology and neuroimaging characteristics, which adjusted for the number of electrographic seizures and gestational age, found that exposure to increasing doses of phenobarbital and levetiracetam were both associated with worse Bayley Scales of Infant Development scores at 24 months. However, the reductions were more pronounced with phenobarbital. Increased exposure to phenobarbital was associated with worse cognitive and motor scores (8.1- and 9-point decrease per 100 mg/kg; $P = 0.01$). Increased exposure to levetiracetam also was associated with worse cognitive and motor scores (but to a lesser extent than phenobarbital 2.2- and 2.6-point decrease per 300 mg/kg, $p = 0.01$). Increasing doses of phenobarbital were also associated with cerebral palsy while levetiracetam was not.[41]

Together, the facts that prolonged exposure to anticonvulsant medications may not provide benefits in terms of long-term neurodevelopment or epilepsy and may have associated risks suggest that attempts to wean such medications early are appropriate. A review by the World Health Organization recommends consideration of weaning of anticonvulsant medication after 72 hours of treatment if the neurologic examination and/or EEG are normal. The nature of the underlying neuropathology, including the nature and extent of neuroimaging abnormalities, may also assist in determining the risk-benefit of the duration of anticonvulsant therapy, although no formal studies using these guidelines have been undertaken. For those infants who required multiple medications for control, each drug should be weaned individually, with phenobarbital being the last to be discontinued.

Key Points

- Neonatal seizures are common in both the preterm and term born infant.
- Electroencephalography is essential to diagnose and treat neonatal seizures because of the frequency with which clinical signs are misinterpreted as seizures OR seizures or status epilepticus can be clinically silent.
- Seizures are a sign of neurologic dysfunction from a variety of etiologies, including hypoxic ischemia, such as stroke, and metabolic and infectious etiologies. Investigation to determine the etiology of neonatal seizures is necessary and often requires blood and cerebrospinal fluid sampling, electroencephalography, and magnetic resonance imaging.
- Therapy for neonatal seizures is important to limit both the short-term physiologic impact of the seizures and the potential contribution to long-term outcomes. Phenobarbitol remains first-line anticonvulsant therapy.
- Length of time with anticonvulsant therapy for neonatal seizures remains unknown, although more recent trends are to minimize exposure to anticonvulsants unless a protracted risk for seizures persists.

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56

Hypotonia and Neuromuscular Disease in the Neonate

NANCY BASS

Clinicians who care for newborns are often required to consider the possibility that a neuromuscular disorder might be present in a hypotonic infant. The ability to determine the normal expected tone of that infant is vital to assess what additional evaluation might be warranted. Hypotonia can be the result of an insult or disorder in any part of the nervous system, including the brain, spinal cord, and peripheral nervous system. The assessment begins with determination of the normal tone of the neonate. When placed in the supine position, the normal full-term infant shows active movement of flexed limbs. The hips are flexed 70-90 degrees and abducted approximately 10-20 degrees. If passive extension of the legs at the knees is attempted, resistance is met when the popliteal angle is approximately 90 degrees. When the child is pulled to the sitting from the supine position, only slight head lag is present, and on reaching the sitting position, the head should wobble in the midline for a few seconds. Similarly, a predominance of flexor tone is found in the upper limbs. When the infant is held under the axilla, normal tone prevents the infant from slipping through the examiner's hands, and the infant seems to sit in the air. In horizontal suspension, the limbs are flexed, the back is straight, and the head is maintained in the midline for a few seconds. These findings need to be modified for the premature infant who shows decreasing degrees of flexor tone depending on gestational age.[6,29]

The weak, hypotonic infant has a decrease in the expected resistance of muscle to stretch, and there is a decrease in spontaneous movement. If supine, the infant lies in a frog-like position with abduction of the hips and an abnormal extension of the limbs. When pulled to a sitting position, there is head lag with a lack of compensation when the sitting position is reached. In vertical suspension, decreased tone of the shoulder girdle causes the infant to slip through the examiner's hands, and the legs are more extended than flexed. On horizontal suspension, the back hangs over the examiner's hand, and the head and limbs hang loosely. (For further details, see Chapter 28.)

Diagnosis

Almost any condition that affects the central nervous system (CNS; brain or spinal cord) or peripheral nervous system of a newborn can be expressed by a reduction of tone. Furthermore, most acute or multisystem illness in neonates is accompanied by some degree of hypotonia. Therefore, the examiner initially must consider whether the infant is acutely ill from sepsis, organ failure, metabolic dysfunction, or other systemic illness. In addition, medications given to the mother in the time right before birth can have an effect on the infant's muscle tone. Most commonly implicated is magnesium sulphate to prevent preterm labor. If these illnesses are not present, the next step is to consider whether a primary disorder of the CNS or the peripheral nervous system is the cause. In general, a central cause leads to a reduction in tone out of proportion to the degree of muscle weakness, and the limbs demonstrate antigravity power.[30]

Although this finding is useful, there are exceptions. In some hypotonic neonates, there are abnormalities in both the central and peripheral nervous systems. Examples include congenital muscular dystrophy (CMD); congenital myotonic dystrophy; acid maltase deficiency; cervical spinal cord injury; and some mitochondrial, lysosomal, and peroxisomal disorders. In addition, some disorders that are primarily central may initially present with profound hypotonia and weakness. Examples are Prader-Willi syndrome and acute disease such as hemorrhage or infarction involving the deep central gray matter of the brain or spinal cord. Babies with near total asphyxia typically have involvement of the brainstem and at times the upper spinal cord, and thus typically present with profound hypotonia and absence of reflexes, similar to spinal shock seen in acute spinal cord injuries. Conversely, the infant with a mild congenital myopathy demonstrates some antigravity power in the limbs. Finally, hypotonia might be present in the infant without acute systemic or metabolic illness or abnormalities of the nervous system. In these children, there is an unusual

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Abstract

Diagnosis of a neuromuscular disorder in a newborn can be challenging. Hypotonia can result from an abnormality in the central or peripheral nervous system. In addition, conditions such as sepsis, chromosomal disorders, and acute multisystem diseases can also lead to hypotonia. Infants can be hypotonic with preserved strength or can manifest weakness. Those with weakness and hypotonia tend to be more likely to have a neonatal neuromuscular disorder. Many of these disorders present later in infancy or childhood whereas some do have their presentation in the neonatal period. As these diseases have varied presentations, accurate diagnosis is vital. These disorders include abnormalities of the anterior horn cell such as the spinal muscular atrophies, abnormalities of the peripheral nerves such as the hereditary motor sensory neuropathies, and abnormalities of the neuromuscular junction such as the congenital myasthenic syndromes. In addition, disorders of the muscles include congenital muscular dystrophies, congenital myopathies, and metabolic myopathies. Recently, there have been tremendous advances in the genetics of these disorders, which have led to many being diagnosed without the need for invasive procedures such as tissue biopsies. In addition, great progress has been made recently in the treatment of some of these disorders, which were previously considered progressive fatal diseases. This has potential implications for addition of these disorders to the newborn screening panel. These emerging therapies demonstrate the importance of accurate diagnosis of neonatal neuromuscular disorders.

Keywords

neonatal hypotonia
infantile spinal muscular atrophy
neonatal myasthenia
congenital muscular dystrophy
congenital myotonic dystrophy
congenital myopathies
infantile Pompe disease

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degree of ligamentous laxity such as that seen in Ehlers-Danlos syndrome and osteogenesis imperfecta.

The diagnosis of a neonatal muscle disorder requires a methodical approach similar to that used in the older infant or child. A detailed family, obstetric, and delivery history should be taken. Clues to the presence of a neuromuscular disorder include polyhydramnios, a decrease in fetal movement, and malpresentation, although these conditions can be present in any pregnancy with fetal akinesia (paucity of movement). Information should be obtained about whether there was any birth trauma or asphyxia and on the condition of the infant immediately after delivery.

The general examination begins with observation. Does the infant look sick or distressed? The skin should be examined for pallor, trauma, bruising, or petechiae. Any dysmorphic features or congenital defects of the head, neck, or spine should be noted, as should weight, length, and head size and shape. Each system is then examined with a particular emphasis on respiratory rate, pattern, and diaphragmatic movement; cardiovascular status; the presence of organomegaly; the genitalia; the hips; and the presence of contractures. On neurologic examination, initial observations include the degree of alertness and whether the infant fixes or follows. Posture and spontaneous movements are noted. In particular, movement against gravity should be sought, and the examiner should observe whether movement is greater proximally or distally. When formal examination of the cranial nerves is performed, particular attention should be paid to eye movements. These can be observed as spontaneous movements, elicited by a face or a red ball or induced by gentle rotation of the head (oculovestibular reflex). Caution should be taken when checking this reflex in an infant with possible high cervical cord injury. A lack of fixation or following, but movement with the oculovestibular reflex, suggests a lesion above the brainstem. If the infant is not in severe distress and there is no possibility of cervical spine injury, the degree of hypotonia is assessed by pulling the infant to a sitting position and holding him or her in vertical and horizontal suspension. Passive movement of the joints can assess power and tone in the limbs more gently. Resistance to gentle shaking of an arm or leg also provides a subjective assessment of tone.

On initial observation of a newborn, cerebral dysfunction should be suspected if there are abnormalities in primitive reflexes, poor arousal, paucity of movements in general, or fisting of the hands. Fisting can appear as a "cortical thumb" posture. This is where the thumb is flexed and lies under the first and second fingers. Persistence of this posture is felt to be associated with cerebral dysfunction.[34] The character of the deep tendon reflexes helps distinguish between an upper or lower motor neuron lesion. An upper motor neuron lesion involves descending motor tracts in the brain and spinal cord, whereas a lower motor neuron lesion involves the anterior horn cell, peripheral motor nerve, or muscle. If they are abnormally brisk with clonus, then an upper motor neuron lesion is suggested. Five to ten beats of ankle clonus is considered normal in the infant. Sustained clonus or that which is persistently asymmetric is typically abnormal and suggests an upper motor lesion.[84] If absent, a neuropathic lesion or a severe myopathy is more likely. As mentioned above, infants with near total asphyxia may have absent reflexes despite their lesion being of central origin. Assessment of sensation should be attempted, because this may indicate a spinal cord lesion. Although quite atypical to present in the newborn, abnormalities in sensation could point to a hereditary sensory neuropathy.[9]

Facial diplegia is a particular finding in some neuromuscular disorders and less likely in others. It is most commonly seen in such disorders as congenital myotonic dystrophy and the congenital myasthenic syndromes. It can also be an early feature of severe acute basal ganglia damage. Note should be made of the infant's ability to suck and swallow, the pooling of secretions, the character of the cry, and the presence of tongue fasciculations. The latter is most often seen in acute infantile spinal muscular atrophy (SMA) but can be seen in any condition in which there is hypoglossal motor neuron damage, examples of which include storage disorders such as acid maltase deficiency, hypoxic-ischemic damage, and infantile neuronal degeneration.

Neonatal Neuromuscular Disorders

Neonatal neuromuscular disorders are caused by lesions that affect specific parts of the nervous system, including the anterior horn cell, peripheral nerve, neuromuscular junction, or muscle (Box 56.1). Rapid and continuing advances are being made in our understanding of the molecular genetic basis of these disorders.

There are a number of CNS conditions in which hypotonia is of sufficient severity that a neuromuscular disorder should be suspected. These are not discussed in detail here, but they include chromosomal disorders such as Prader-Willi syndrome and Smith-Magenis syndrome (Smith-Magenis syndrome can be particularly hard to distinguish from a neuromuscular disorder as it can often be associated with hyporeflexia or areflexia),[41] multiple minor congenital anomaly syndromes, and metabolic multisystem disorders.

Spinal Muscular Atrophies

The SMAs are predominantly autosomal recessive disorders characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. The most frequent and best known is infantile SMA, also called Werdnig-Hoffmann disease (SMA type I).[51] Approximately 95% of individuals with SMA are homozygous for a deletion of exon 7 of the survival motor neuron (SMN) gene (*SMN1*) on chromosome 5q13.[73] Although the phenotype varies in severity and age of onset, the acute infantile subtype is well defined and often presents during the neonatal period. This phenotype tends to "run true" in families. Clinically, infants exhibit a severe symmetric flaccid paralysis, which is characteristically greater in the lower limbs than in the upper limbs and greater proximally than distally.

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• BOX 56.1 Neonatal Neuromuscular Disorders

Anterior Horn Cell

- Traumatic myelopathy
- Hypoxic-ischemic myelopathy
- Acute infantile spinal muscular atrophy
- Infantile neuronal degeneration
- Neurogenic arthrogryposis

Congenital Motor and Sensory Neuropathy

- Congenital hypomyelinating neuropathy
- Charcot-Marie-Tooth disease
- Dejerine-Sottas disease
- Hereditary sensory and autonomic neuropathy

Neuromuscular Junction

- Acquired transient neonatal myasthenia
- Congenital myasthenia
- Infantile botulism
- Magnesium toxicity
- Aminoglycoside toxicity

Congenital Myopathy

- Nemaline myopathy
- Central core disease
- Myotubular myopathy
- Multi-minicore myopathy

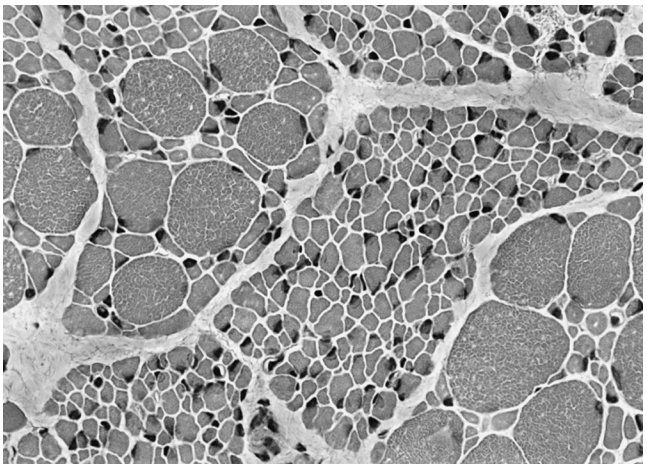
Muscular Dystrophy

- Congenital muscular dystrophy with merosin deficiency
- Congenital muscular dystrophy without merosin deficiency
- Walker-Warburg syndrome
- Muscle-eye-brain disease
- Fukuyama-type congenital muscular dystrophy
- Congenital myotonic dystrophy
- Duchenne dystrophy (Xp21-linked dystrophinopathy)
- Early infantile facioscapulohumeral dystrophy

Metabolic and Multisystem Disease

- Mitochondrial disorder
- Peroxisomal disorder
- Neonatal adrenoleukodystrophy
- Cerebrohepatorenal syndrome (Zellweger syndrome)
- Pompe disease (acid maltase deficiency)
- Severe neonatal phosphofructokinase deficiency
- Severe neonatal phosphorylase deficiency
- Debrancher deficiency
- Carnitine deficiency

The onset of this weakness may be identified by the mother, who experiences a decrease or loss of fetal movement during late pregnancy. Although decreased fetal movements may be reported in SMA I (Werdnig-Hoffman disease), this is more commonly reported in patients diagnosed with the prenatal-onset forms of SMA. Respiratory muscle function is poor in the infant. However, it is the intercostal muscles that are weak, because there is relative sparing of the diaphragm. This gives rise to abdominal breathing and a later characteristic bell-shaped deformity of the chest. Deep tendon reflexes are absent or difficult to elicit. The upper cranial nerves are spared, giving rise to an infant with an alert expression, a furrowed brow,



• **Fig. 56.1** Histologic section of muscle showing spinal muscular atrophy. Groups of circular atrophic fibers are interspersed among fascicles of hypertrophied type 1 fibers. Low magnification. (Courtesy of Hannes Vogel, MD, Baylor College of Medicine, Houston.)

and normal eye movements. The bulbar muscles are weak, which is reflected by a weak cry, poor suck and swallow reflexes, pooling of secretions, aspiration, and tongue fasciculations. Cardiac muscle is not affected, and classic arthrogryposis is usually not a feature although rarely it can be. Nerve conduction testing demonstrates normal or slightly decreased motor nerve conduction velocities and normal sensory nerve action potentials. Electromyography shows abnormal spontaneous activity with fibrillations and positive sharp waves as well as an increased mean duration and amplitude of motor unit action potentials, some of which are polyphasic. Serum creatine kinase activity is normal or only slightly elevated. Muscle biopsy reveals large groups of circular atrophic type 1 and 2 muscle fibers (Fig. 56.1). These fibers are interspersed among fascicles of hypertrophied type 1 fibers, which are three or four times normal size and represent fibers reinnervated by sprouting of surviving nerves.[51] This pattern might not be seen during the neonatal period, when there is often only widespread atrophy of type 1 and 2 muscle fibers, making histologic diagnosis difficult. With the advances made in the genetic diagnosis of this disorder, biopsies are rarely needed; however, a later biopsy should show evidence of reinnervation with large hypertrophied fibers and group atrophy.

The infant who presents during the neonatal period with severe acute infantile SMA characterized by profound hypotonia and weakness rarely survives beyond 1 year of age. It is the severity of weakness at the onset that determines outcome in SMA rather than the age of onset, although in most cases the earlier the onset, the greater the weakness. Artificial ventilation of an infant with severe early-onset SMA leads to an alert but completely paralyzed infant who is totally ventilator dependent.[51]

With the identification of the *SMN* gene in 1995, the diagnosis of SMA has been greatly facilitated, limiting the need for more invasive investigations. Additional understanding of the molecular genetics and protein function

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may provide insight into potential therapies for this otherwise fatal condition. The SMN coding region on chromosome 5q11.2-13.3 contains a telomeric and centromeric copy of the *SMN* gene, designated *SMN1* and *SMN2*, respectively. These genes are nearly identical in their coding sequence. A single nucleotide polymorphism (840C>T) in SMN2 causes disruption of normal translation.[62] The resultant protein produced by the centromeric copy is often truncated and nonfunctional. SMN2 can produce a small amount of full-length protein, providing partial compensation for mutations in SMN1, but the majority must be produced by SMN1. A direct relationship exists between the number of copies of the *SMN2* gene and the age of disease onset, with the SMA type I phenotype correlating with the lowest number of *SMN2* gene copies. Although continued progress has been made recently in defining the exact function of SMN protein, it still remains to be further defined. It is known to play a role in critical housekeeping function: so-called spliceosomal small nuclear ribonucleoprotein assembly, which is important for all cells.[33] How this translates into loss of the specific motor neuron cell RNA has yet to be elucidated.[8]

In December 2017, nusinersen became the first FDA-approved drug for the treatment of 5q SMA. It is an antisense oligonucleotide and acts to modify pre-mRNA splicing of SMN2 to promote increased production of full-length SMN protein.[47] Results of a randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial showed that a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]). These patients also had a statistically significant likelihood of event-free survival.[36] Additional therapy with single-dose gene replacement is currently in clinical trials.[58] Preliminary results are promising. With these emerging therapies, SMA is now a treatable disorder. This opens the door for consideration of this disorder to be included in newborn screening.

There are a number of genetically heterogeneous SMA variants, but most of these do not present during the newborn period. The variants most important in neonatal or prenatal presentations of SMA include SMA with pontocerebellar hypoplasia, X-linked SMA with arthrogryposis owing to mutations in the *UBE1* gene, and SMARD1 (spinal muscular atrophy with respiratory distress or distal infantile SMA with diaphragm paralysis) that is caused by mutations in the *IGHMBP2* gene, the gene encoding the immunoglobulin μ-binding protein.[39,40]

Arthrogryposis multiplex congenita is a heterogeneous group of disorders characterized by congenital contractures of multiple joints. It is typically the result of decreased fetal movement and can have multiple etiologies from neurogenic, muscular, and genetic syndromes, as well as connective tissue disorders. Many times, the specific etiology cannot be found.[52] The neurogenic arthrogryposes are genetically heterogeneous, and both autosomal recessive and X-linked inheritance have been reported.[17,55] A subgroup of neurogenic arthrogryposis is allelic with SMA type I, and deletions of *SMN* gene have been reported.[17] These disorders are of variable severity. Some show no progression, and muscle strength can even improve. In other cases, bulbar and respiratory function is severely affected, and the prognosis is poor. In the X-linked form, there is disease progression and early death.[55]

As noted above, infants with SMARD1 can present as neonates with congenital contractures along with their severe SMA presentation. Traumatic high cervical spinal cord injury (see Chapter 29) is a rare cause of myelopathy that can be misdiagnosed as SMA. In the absence of an asphyxial brain injury, the infant is alert with no cranial nerve signs. The myelopathy is manifested as a flaccid areflexic paralysis, which might be asymmetric. Clues to the diagnosis include evidence of trauma such as bruising or fractures and normal results on cranial nerve examination. After a few days, evidence of the myelopathy becomes more apparent with the appearance of bladder distention, priapism, and an absence of sweating below the level of the spinal lesion. Sensory testing is difficult but can be assessed by demonstrating facial grimacing to a prick on the face but no response below the neck (see Chapter 29).

In severe hypoxic–ischemic injury, there can be an areflexic flaccid paralysis resulting from death of spinal motor neurons.[21] However, there are also signs of an encephalopathy and multiorgan system damage.

Hereditary Motor and Sensory Neuropathies

The hereditary motor and sensory neuropathies are a genetically heterogeneous group of disorders with a spectrum of phenotypes that includes Charcot-Marie-Tooth disease types 1 and 2, hereditary neuropathy with liability to pressure palsies, Dejerine-Sottas syndrome, and congenital hypomyelinating neuropathy. These diseases may demonstrate an autosomal dominant, autosomal recessive, or X-linked mode of inheritance. Charcot-Marie-Tooth disease type 1 and hereditary neuropathy with liability to pressure palsies are demyelinating neuropathies, whereas Charcot-Marie-Tooth disease type 2 is an axonal disorder. Congenital onset is unusual, and these three forms of hereditary motor and sensory neuropathy most often present in the older child or young adult.[75] The two types that may present in the neonate include congenital hypomyelinating neuropathy and, less commonly, Dejerine-Sottas syndrome.[51,74]

Clinical manifestations vary. Affected infants are weak, hypotonic, and areflexic. The weakness is generalized, but a greater distal weakness might be detected. Arthrogryposis may be present in more severe forms. There are usually swallowing and respiratory difficulties. Sometimes facial weakness is present, but extraocular movements are usually normal. Any associated sensory loss is difficult to detect clinically. Prognosis depends on the initial degree of weakness. In some cases, there is an improvement in strength.[37]

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The disorders are characterized by markedly decreased motor nerve conduction velocities (typically less than 10 m/s) and elevated cerebrospinal fluid protein. Sural nerve biopsy in relatively mild cases shows varying degrees of hypomyelination with atypical onion-bulb formation. (Nerve biopsy in the neonatal period would be less likely to show the onion bulb formation.) More severe cases may show complete lack of myelin.[51] These disorders result from mutations in different genes. Moreover, different mutations in the same gene cause different phenotypes (Charcot-Marie-Tooth disease type 1, Dejerine-Sottas syndrome, congenital hypomyelinating neuropathy) and, at present, the clinical phenotype cannot always be predicted on the basis of the gene mutation. Identified alleles include Schwann cell genes involved in the formation, structure, and maintenance of peripheral myelin (*EGR2*, *PMP22*, *MPZ*, *CX32*, *6JB1*, *PRX*), neuronal genes involved in axonal transport (*NEFL*), and genes affecting both Schwann cell and neuronal structure (*MTMR2*).[72,73] Testing for these mutations is available on a clinical basis.

Hereditary Sensory and Autonomic Neuropathies

The hereditary sensory and autonomic neuropathies are characterized by selective involvement of peripheral sensory and autonomic neurons (Box 56.2). These disorders are autosomal recessive with the exception of hereditary sensory and autonomic neuropathy type I, which is autosomal dominant. All present with varying degrees of autonomic dysfunction or insensitivity to pain and temperature.[51] In some, there is absence of the normal axonal flare response to intradermal injection of histamine. In the older child, there is striking self-mutilation.

The best known of the hereditary sensory neuropathies is familial dysautonomia (Riley-Day syndrome; hereditary sensory and autonomic neuropathy type III). This disorder has a high carrier rate in individuals of Ashkenazi Jewish descent and has been mapped to chromosome 9q31-q33. Mutations in the gene for IkB kinase-associated protein (*IKBKAP*) account for 99% of affected individuals.[9] The clinical diagnosis of familial dysautonomia is based on five cardinal criteria: (1) absence of overflow tears, (2) absence of lingual fungiform papillae, (3) depressed patellar reflexes, (4) lack of axonal flare reaction after intradermal injection of histamine, and (5) Ashkenazi Jewish extraction. Additional clinical features typically include hypotonia, labile temperature and blood pressure, breath holding, pallor, poor feeding, failure to thrive, vomiting, loose stools, and irritability.

Treatment of these disorders is mainly supportive, and survival has improved with modern medical therapies. Patients who reach adulthood continue to demonstrate slow progression of their disease. Cognition may be impaired in some forms of the disease.[10]

Clinical testing is available for familial dysautonomia. Until more molecular genetic information is available, differentiation between the other various hereditary sensory neuropathies will continue to be made by distinct characteristics of the history and examination, sensory nerve conduction and action potential size, and changes on sural nerve biopsy.[10]

Congenital central hypoventilation syndrome should be considered in the differential diagnosis of a neonate presenting with an autonomic neuropathy. The classic neonatal form of this disease presents with an infant with hypotonia, decreased or absent deep tendon reflexes, hypoventilation with absence of response to hypercarbia, and autonomic dysfunction.[11,13] These infants typically have a mutation in the *PHOX2B* gene and are at risk for Hirschsprung disease and tumors of neural crest origin.[5,79,86]

• BOX 56.2 Hereditary Sensory and Autonomic Neuropathies

HSAN type I (hereditary sensory radicular neuropathy, autosomal dominant)
HSAN type II (congenital sensory neuropathy)
HSAN type III (Riley-Day syndrome, or familial dysautonomia)
HSAN type IV (congenital insensitivity to pain with anhidrosis)
HSAN type V (congenital insensitivity to pain with partial anhidrosis)
Progressive pan-neuropathy and hypotonia
Congenital autonomic dysfunction with universal pain loss
Familial amyloid neuropathy (autosomal dominant)

Neuromuscular Junction Disorders

Neuromuscular junction disorders are infrequent causes of weakness during the neonatal period. The principal conditions include transient acquired neonatal myasthenia, congenital myasthenia, infantile botulism, and toxic amounts of magnesium or aminoglycosides. These disorders are characterized by abnormal neuromuscular transmission, which is manifested by abnormal muscle fatigability and weakness that is sometimes permanent, particularly in the congenital forms.

Autoimmune myasthenia gravis in children and adults is caused by autoantibodies directed against neuromuscular junction proteins. In 80% of patients, acetylcholine receptor antibodies are detected in the serum. In the remaining patients, other pathologic antibodies, including those directed against muscle-specific kinase, interfere with the normal function of the acetylcholine receptor, resulting in disease.[82]

In acquired neonatal myasthenia gravis, the disease is more often active in the mother. However, she may have less obvious disease, be in remission, or not show clinical manifestations until after the pregnancy.[82] Transfer of immunoglobulin G antibodies occurs readily across the placenta. However, typical features develop in only 20% of infants born to mothers with myasthenia.[46,84] The proportion of

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maternal immunoglobulin G antibodies directed against the fetal type versus the adult type of acetylcholine receptor appears to have a strong influence on neonatal manifestations. Although there is no correlation between maternal antibody titers or disease severity and the development of neonatal myasthenia, there is an inverse relationship between maternal disease duration and the incidence of neonatal myasthenia. Maternal thymectomy may be protective against neonatal disease.[28]

The disorder usually presents within a few hours of birth, and onset after the third day has not been reported.[66,67] The most common presentation is generalized weakness and hypotonia.[63] Bulbar weakness is usually present, with feeding difficulties from poor sucking and swallowing, and a weak cry. Facial diplegia can be prominent, but ptosis and ophthalmoplegia are seen less frequently. Pooling of secretions and respiratory difficulties occasionally necessitate artificial ventilation. Deep tendon reflexes are normal. Assuming a correct diagnosis and management, most infants recover within a few weeks.[67] Some infants are severely affected with a history of polyhydramnios and the presence of arthrogryposis multiplex at birth.[27] Treatment is more difficult, and recovery is slower in these infants.

The diagnosis of transient neonatal myasthenia should always be suspected in the infant of a mother with active generalized acetylcholine receptor antibody-positive myasthenia gravis. When signs appear, a cholinesterase inhibitor is administered and the response gauged. To be sure of the diagnosis, an unequivocal and objective response should be chosen, such as an improvement in ventilation and oxygenation or sucking ability. Neostigmine methylsulfate, IM or SC, in a dose of 0.15 mg/kg is the preferred diagnostic anticholinesterase agent. The drug takes effect within 15 minutes of injection and lasts 1-3 hours. Muscarinic side effects (diarrhea, increased tracheal secretions) might require the use of atropine in appropriate doses. Although edrophonium chloride has a more rapid onset and less intense muscarinic side effects, there is a risk of respiratory arrest.[67] When necessary, the diagnosis can be confirmed with repetitive nerve stimulation,[44] which should be performed before and after the administration of a cholinesterase inhibitor. A diagnostically positive response occurs when the amplitude of the fifth evoked compound muscle action potential is reduced by 10% or more of the amplitude of the first response, and this decrement is corrected by a cholinesterase inhibitor.[67]

The management of transient neonatal myasthenia gravis must be early and vigorous, because these infants can deteriorate rapidly. Small, frequent tube feedings should be given and early ventilatory support considered. Neostigmine methylsulfate is given in a dose of 0.05-0.1 mg/kg, IM or SC, 30 minutes before feeding. The oral dose of neostigmine is approximately 10 times the intramuscular dose and is given approximately 45 minutes before feeding. Excessive doses can cause diarrhea, increased secretions, muscle fasciculations, and cholinergic weakness. Disappearance of disease activity is monitored clinically by assessing responses to gradual decreases in the anticholinesterase dose. In addition, repetitive nerve stimulation tests can be performed as well as measurement of acetylcholine receptor antibodies. Tube feeding and artificial ventilation are usually not required for longer than 1-2 weeks, and the average duration of treatment is 4 weeks, with recovery in 90% of infants in less than 2 months.[67]

The congenital myasthenic syndromes are infrequent causes of neuromuscular junction failure during the neonatal period but have become increasingly recognized. They are a group of genetic disorders that are acetylcholine receptor antibody negative and are caused by either presynaptic or postsynaptic inherited defects of the neuromuscular junction. Their precise characterization requires sophisticated laboratory techniques, which are not widely available.[32] Those manifested during the neonatal period are shown in Box 56.3. Postsynaptic disorders of the acetylcholine receptor are the most common. The subunit defect form is associated with significant ptosis and variable ophthalmoplegia. The rapsyn mutation involves a mutation of the receptor-associated protein at the synapse.[48] Typically, this is a more severe presentation than the subunit deficiency. In general, unlike acquired transient neonatal myasthenia gravis, ptosis is usually present in addition to varying degrees of ophthalmoplegia, bulbar palsy, and respiratory weakness. Fluctuating, generalized hypotonia and weakness are seen, and episodes of life-threatening apnea can occur. Exacerbations can be induced by activity, febrile illness, or other stress. These disorders often improve with age, but spontaneous exacerbations occur with a risk of sudden infant death. Arthrogryposis has been reported in one form of the disease.[32] A diagnostic response to cholinesterase inhibitors is variable but useful when positive. Some forms of the disorder, such as congenital endplate cholinesterase deficiency, are refractory to or worsened by cholinesterase inhibitors. The diagnosis is supported by a decremental response to repetitive nerve stimulation at low frequency (2 Hz). However, the low-frequency decremental response

• BOX 56.3 Congenital Myasthenic Syndromes Presenting During the Neonatal Period

Presynaptic Defects (8%)

- Choline acetyltransferase deficiency
- Paucity of synaptic vesicles and reduced quantal release
- Similar to Eaton-Lambert syndrome

Synaptic Basal Lamina-Associated Defects (16%)

- Endplate acetylcholine esterase deficiency

Postsynaptic Defects (76%)

- Kinetic abnormality of acetylcholine receptor (slow- and fast-channel syndromes)
- Acetylcholine receptor deficiency (subunit defect)
- Acetylcholine receptor deficiency (rapsyn mutation)

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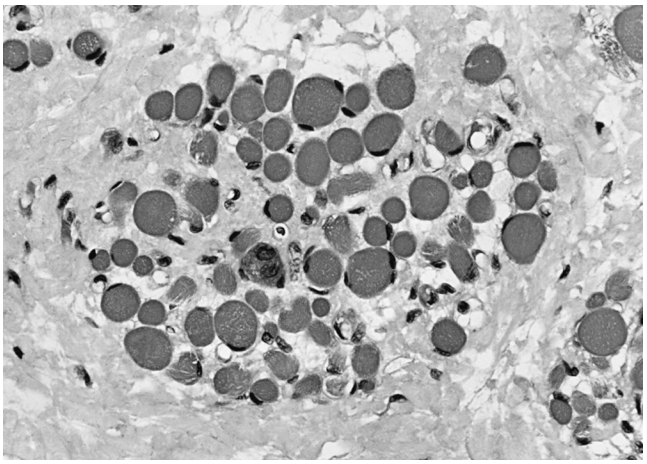
can be absent in infants with a defect in acetylcholine resynthesis or packaging but can be induced by prolonged 10-Hz stimulation.

A number of toxic agents disturb neuromuscular transmission in the newborn. Hypermagnesemia, usually secondary to IV administration of magnesium sulfate to the mother, causes a presynaptic failure of acetylcholine release by blocking calcium release.[70] The infant shows profound generalized weakness, areflexia, and respiratory dysfunction. In addition, the CNS and smooth muscle are affected, giving rise to stupor and an ileus. Exposure to excessive amounts of aminoglycosides, particularly in conjunction with neuromuscular blockers, can be followed by prolonged weakness from a presynaptic block. Bladder, bowel, and pupillary function are affected.[84,88] Both hypermagnesemia and the neurotoxic effects of aminoglycosides are worsened by hypocalcemia.

Infantile botulism affects infants between 2 weeks and 6 months of age (see Chapter 48).[23,38,84] Unlike botulism in children and adults, which is caused by ingesting the exotoxin of *Clostridium botulinum*, infantile botulism occurs when the intestine is colonized by the clostridia bacteria, where they produce their toxin. This toxin causes a presynaptic cholinergic blockage that affects autonomic as well as skeletal and smooth muscle function. The disorder has a clinical spectrum. Presentation varies from mild constipation and hypotonia to unexpected death. The classic form of the disorder presents with constipation and poor feeding followed by progressive hypotonic weakness and loss of deep tendon reflexes. There is usually marked cranial nerve dysfunction, which includes pupillary paralysis and ptosis. The weakness often progresses in a descending fashion. The illness usually lasts 1-2 months but relapses in a small number of patients.[38] Diagnosis is made by demonstrating an incremental response to repetitive nerve stimulation at high rates (20-50 Hz) and by the appearance of short-duration, low-amplitude motor unit potentials on electromyography.[50] Confirmation of the diagnosis is made on isolation of the organism from the stool. Prompt treatment with human-derived botulism immunoglobulin may significantly reduce the length of time needed for clinical recovery.[69] Management is otherwise supportive.

Congenital Muscular Dystrophy

The CMDs are a variable group of autosomal recessive disorders that share the common presentation of weakness and hypotonia at birth in conjunction with a dystrophic muscle biopsy. The muscle biopsy typically shows endomysial and perimysial connective tissue proliferation, replacement of muscle by fat, and variations in muscle fiber size (Fig. 56.2). There is little evidence of necrosis or regeneration. Immunocytochemical studies help distinguish between different types.[20,64] Clinically, muscular weakness is generalized and usually involves the face. Bulbar and respiratory muscle involvement is variable but can be severe. The creatine kinase level is elevated in some types but is normal or only moderately elevated in others.[51] Arthrogryposis is a common feature.



• **Fig. 56.2** Histologic section of muscle showing congenital muscular dystrophy. The biopsy shows connective tissue proliferation, replacement of muscle by fat, and variations in fiber size. Low magnification. (Courtesy of Hannes Vogel, MD, Baylor College of Medicine, Houston.)

• BOX 56.4 Congenital Muscular Dystrophies

Classic CMD

- Merosin-deficient CMD
- Primary merosin deficiency
- Secondary merosin deficiency
- Merosin-positive CMD
- Classic CMD without distinguishing features
- Rigid spine syndrome
- CMD with distal hyperextensibility (Ullrich type)

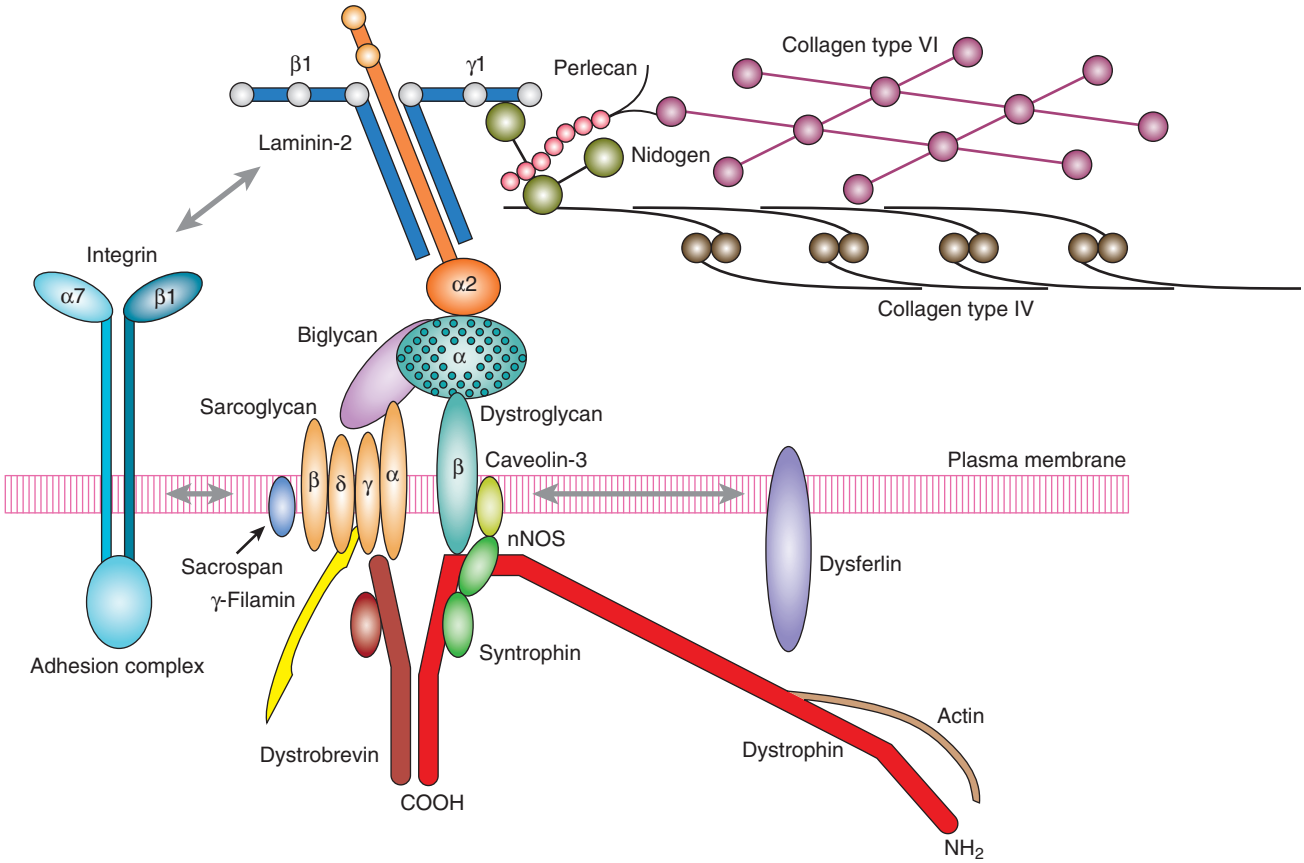
Syndromic Forms of CMD

- Fukuyama CMD
- Muscle-eye-brain disease
- Walker-Warburg syndrome

The CMDs have historically been divided into the nonsyndromic ("classic") forms, typified by normal cognition, and the syndromic forms, associated with brain malformations and mental retardation (Box 56.4). This distinction between the classic and syndromic forms has been blurred by advances in molecular genetics showing similarities between the groups and reports of classic CMD presenting with posterior pachygyria in association with cognitive defects.[54]

The classic forms are subdivided into merosin-positive and merosin-deficient subtypes. The merosin-negative form accounts for nearly 50% of all CMDs. Merosin is the heavy α2 chain of the heterotrimeric protein laminin 2 (Fig. 56.3). By linking the extracellular matrix with transmuscle-membrane, dystrophin-associated glycoproteins, the protein plays a critical role in myogenesis and myotubule membrane stability. It is also expressed in Schwann cells, trophoblasts, skin, and cerebral blood vessels. Mutations in the α2-laminin gene (*LAMA2*) on chromosome 6q are responsible for the disease. Sequence analysis of the

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• **Fig. 56.3** Schematic representation of the dystrophin-associated proteins and other sarcolemmal and extracellular proteins associated with congenital muscular dystrophy. nNOS, Neuronal nitric oxide synthase. (From Kirschner J, Bonnemann CG. The congenital and limb-girdle muscular dystrophies: sharpening the focus, blurring the boundaries. *Arch Neurol.* 2004;61:189; adapted from Jones HR, et al. *Neuromuscular disorders of infancy, childhood, and adolescence: a clinician's approach.* Philadelphia: Elsevier Science; 2003, with permission.)

LAMA2 gene is available. Diagnosis can also be achieved with muscle biopsy showing complete absence of merosin with immunocytochemical staining.[20] The CMDs can be classified according to the protein defect and, in many cases, this can be identified by immunocytochemistry or DNA analysis.[64] Abnormalities of extracellular matrix protein defects include laminin α2-deficient CMD (MDC1A) and collagen 6A deficiencies as in Ullrich CMD (UCMD 1, 2, and 3); integrin α7 deficiency (ITGA7); abnormalities of glycosyltransferases, which lead to abnormal O-glycosylation of α-dystroglycan and include O-mannosyltransferase 1 (POMT1), O-mannosyltransferase 2 (POMT2), o-linked mannose β1,2-N-acetyl glucosaminyl transferase (POMGnT1), fukutin, fukutin-related protein (FKRP), and acetylglucosaminyltransferase-like protein (LARGE); and endoplasmic reticulum proteins such as selenoprotein N, which causes rigid spine syndrome.

The clinical presentation of merosin deficiency typifies the classic form of the CMDs. There is marked neonatal hypotonia with generalized weakness and atrophy. Although facial weakness may be present, the eye muscles are spared. Contractures occur early and affect multiple joints. Involvement of chest wall muscles results in respiratory difficulties. Cognition is usually not affected. A peripheral neuropathy reflecting absence of merosin expression in Schwann cells can be seen as well. In addition, neuroimaging shows white matter changes, most appreciable after 6 months of age. The abnormality is best characterized by diffuse increased signal intensity on T2-weighted MRI sequences. These findings are thought to correlate with lack of merosin in the cerebral vessel walls.[81] A small minority of patients show structural dysgenesis with occipital pachygyria or agyria. Epilepsy is encountered in one-third of patients.[53]

Although similar in presentation, the other forms of classic CMD can be differentiated based on distinct clinical features and underlying molecular genetics. Ullrich CMD is associated with mutations in the protein subunits of type VI collagen and presents with rigidity of the spine and distal joint hyperextensibility.[25,45] Distinct from Ullrich CMD, CMD with rigid spine is associated with early rigidity of the spine and restrictive lung disease. A considerable number of these patients have been found to have mutations of the selenoprotein N gene on chromosome 1p36-p35.[61] Selenoprotein N mutations have also been described in patients with multi-minicore disease, a type of congenital myopathy. The function of the protein is unknown. Mutations

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of the gene for fukutin-related protein on chromosome 19q13 may result in either a severe CMD (CMD type 1C, or MDC1C) or childhood-onset limb-girdle muscular dystrophy.[53] Fukutin-related protein is a putative glycosyltransferase and, similar to the syndromic CMDs (discussed later), this form is associated with defective glycosylation of α-dystroglycan protein in the muscle membrane (see Fig. 56.3). A secondary merosin deficiency is also present on histochemical staining.[20] CMD with a partial merosin deficiency has been defined in a number of patients by biochemical studies. The partial deficiency is thought to be secondary to an underlying α-dystroglycan abnormality with abnormal binding of associated proteins. Linkage to chromosome 1q42 has been made in some of these cases.[15]

The syndromic forms of CMD are associated with brain malformations and ocular findings. The three main types are Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama CMD. All three forms result from mutations in genes encoding distinct glycosyltransferases and related proteins involved in post-translational modification of α-dystroglycan, a pathogenetic mechanism shared by the more classic phenotype MDC1C, as previously discussed.[53] Muscle membrane integrity is compromised by the defective α-dystroglycan, which is unable to bind effectively with either extracellular laminin or transmembranous β-dystroglycan (see Fig. 56.3). Muscle biopsy immunocytochemical techniques demonstrate the abnormal α-dystroglycan expression.[20,64] In the brain, abnormal alpha dystroglycan on glial scaffolds, neurons, and their processes are associated with neuronal migrational defects that include disarray of cerebral cortical layering, fusion of the cerebral hemispheres and cerebellar folia, and aberrant migration of granule cells. Disruption of the glial limitans results in cobblestone lissencephaly.[64,65]

Walker-Warburg syndrome is the most severe of the syndromic CMDs. Few infants survive for more than a few months, although prolonged survival is possible with modern medical techniques. Along with muscular dystrophy, typical features of the syndrome include cobblestone lissencephaly with agenesis of the corpus callosum, cerebellar hypoplasia, hydrocephalus, and encephalocele.[65] In contrast with other forms of lissencephaly, there is dysmyelination, with the white matter appearing dark on computed tomography scan and abnormally bright on T2-weighted magnetic resonance images. Ocular findings can include cataracts, microphthalmia, buphthalmos, persistent hyperplastic primary vitreous, and Peter anomaly.[22] Some patients with Walker-Warburg syndrome have been found to have mutations in the protein O-mannosyltransferase (*POMT1*) gene. The gene encodes an enzyme potentially involved in the biosynthesis of specific glycans associated with dystroglycan. The lack of *POMT1* mutations in many patients with Walker-Warburg syndrome suggests genetic heterogeneity.[65]

Muscle-eye-brain disease has many features in common with Walker-Warburg syndrome but is less severe.[22] Brain malformations can include cobblestone lissencephaly, absent septum pellucidum, dysgenesis of the corpus callosum, hydrocephalus, and white matter changes similar to Walker-Warburg syndrome. Eye findings include myopia, choroidal hypoplasia, optic nerve pallor, glaucoma, iris hypoplasia, cataracts, and colobomas. Newborns present with hypotonia, weakness, feeding difficulties, poor vision, and apathy. Distal contractures can be present. All infants ultimately exhibit mental retardation and seizures. In contrast to Walker-Warburg syndrome, most infants have a prolonged survival. However, independent ambulation is unusual. The development of high-amplitude visual evoked potentials by 2 years is a particular feature, and the electroencephalogram is always abnormal by 1 year of age.[31] A significant number of patients with muscle-eye-brain disease have mutations in the gene coding for the glycosyltransferase POMGnT1.[89]

Fukuyama CMD is almost entirely confined to Japan. Overall, the brain and ocular manifestations are less severe than in Walker-Warburg syndrome and muscle-eye-brain disease. A large proportion of patients have mutations of the fukutin gene on chromosome 9q31. The protein function is unknown. Muscle biopsy staining reveals absence of fukutin as well as abnormal glycosylation of α-dystroglycan.[20] In the brain, the cerebral cortex has a cobblestone appearance with pachygyria and polymicrogyria, but there are also areas with normal gyral patterns.[78] Other abnormalities, which differentiate the condition from Walker-Warburg syndrome, include white matter changes, which improve with age, and only mild ventriculomegaly and cerebellar polymicrogyria. Cerebellar and pyramidal tract hypoplasia are probably not features. Eye anomalies are minor and typical of Fukuyama-type CMD. Affected infants present with generalized weakness, hypotonia, and varying degrees of muscle contractures. Facial and bulbar involvement is usually present. Seizures are frequent, and mental retardation is moderate or severe. Survival into adolescence is typical.

Congenital Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant multisystem disorder of variable expression that is characterized by muscular dystrophy and myotonia in adults. In addition to involvement of muscle, many other systems are affected, including the gastrointestinal, endocrine, and skeletal systems, as well as the heart, brain, and eyes.[43,57] Two loci for the disease have been found and are characterized as DM1 and DM2. The genetic basis for DM1 is an expansion of CTG repeats in the myotonic dystrophy protein kinase (*DMPK*) gene on chromosome 19q13.3.[18] An amplification of greater than 45 repeats is usually associated with disease expression. DM2 is associated with a CCTG tetranucleotide expansion in the zinc finger 9 (*ZNF9*) gene on chromosome 3q21.[56] DM1 has a more severe clinical phenotype, with a progressively earlier onset in successive generations (genetic anticipation). Congenital myotonic dystrophy is the earliest presenting form of DM1, and it is an important cause of neonatal neuromuscular dysfunction, with an incidence of at least 1 in 3500 live births. These

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infants usually have greater than 1000 CTG repeats at the DMPK locus. Nuclear accumulation of the abnormal messenger RNA generated by this large repeat size is thought to cause a delay in the differentiation and maturation of skeletal muscle.[2] With rare exceptions, the disease is inherited from the mother.[90] This is related to oligospermia in male patients as well as a greater propensity for larger repeat expansions (more than 1000) during oogenesis than during spermatogenesis.[49,57] The earlier the onset of the disease in the mother and the more severe the clinical expression, the greater the risk for congenital myotonic dystrophy.[43,71] However, the disease can still be seen in offspring of only mildly affected mothers. The phenotypic variation in tissue expression is probably the result of somatic instability of the CTG repeat.[87]

At birth, affected infants frequently require resuscitation and are subject to the mortality and morbidity associated with neonatal encephalopathy (see Chapter 54). A history of polyhydramnios (from failure of fetal swallowing) and decreased fetal movements is frequent, and premature birth can complicate the diagnosis. Furthermore, delivery can be complicated by prolonged labor and postpartum hemorrhage because of poor uterine contractions.[43,71] Generalized weakness and hypotonia in the infant are profound, with facial diplegia and a characteristically tent-shaped triangular upper lip. Deep tendon reflexes are absent or difficult to elicit, and congenital talipes (clubfoot) is often present. Occasionally, joint contractures are more widespread.[43] There is often respiratory distress, and poor suck and swallow reflexes present the danger of aspiration. Eye movements are full, although the infant might not readily fix and follow. Poor respiratory function is due not only to muscle weakness but also to pulmonary immaturity and poor central respiratory control.[43] An elevated diaphragm on the right can be seen on radiographic examination and is probably caused by the presence of the liver on that side and weak diaphragmatic muscles. Hydrops fetalis can occur in infants with cardiac failure. Cardiac conduction defects are commonly seen later and typically are not a presenting finding in the newborn. Poor feeding is commonly seen in infants with this disorder. This is most likely multifactorial, including weakness of the facial muscles and most likely delayed gastric motility in these babies.[14,42] Laboratory investigations in general are not helpful, and the creatine kinase level is normal.

The pathologic appearance of muscle differs from that in adults. The fibers are small and round with central nucleation and display poor fiber type differentiation or relatively small type 1 fibers, giving an immature appearance.[2] The typical adult features appear later. Electromyography is often noncontributory because of poor movement, although myopathic potentials can be demonstrated. Clinical and electrical myotonia are not present but appear later, during early childhood. Neuroimaging reveals ventriculomegaly, intraventricular hemorrhage, subarachnoid hemorrhage, or early periventricular leukomalacia in premature infants. The ventriculomegaly is probably of prenatal origin.[26]

Diagnosis of myotonic dystrophy is supported by clinical and electromyographic examination of the mother and confirmed by molecular genetic analysis. If the infant survives, the hypotonia and severe weakness gradually improve and are no longer evident by later childhood, although motor development is delayed. The facial diplegia with ptosis, open jaw, and triangular mouth persist, giving rise to a characteristic appearance.[43,59] Many affected infants die early, even with intensive care. There is increased mortality among infants requiring greater than 30 days of ventilation, although eventual maturation of diaphragmatic musculature allows for independent ventilation in most.[19] In most patients, mental retardation or significant learning difficulties develop.[43] Unless there is a superimposed cerebral palsy syndrome from a complication of prematurity or perinatal asphyxia, most children walk by age 3 years.[59] All patients with congenital myotonic dystrophy eventually manifest the complete spectrum of features typical of adult-onset disease.

Other Muscular Dystrophies

Severe Xp21-linked dystrophin-deficient muscular dystrophy (Duchenne type) is a degenerative muscle disorder that rarely presents during the neonatal period.[68] Information is scarce on a typical phenotype during the neonatal period. Distinguishing features are an absence of arthrogryposis, high serum creatine kinase, and regeneration or degeneration on muscle biopsy. Diagnosis is made by DNA analysis and immunoelectrophoresis or immunocytochemistry.[51]

Facioscapulohumeral muscular dystrophy is an autosomal dominant disorder that usually presents during early adolescence. Although usually a fairly benign disorder, there is intrafamilial variability, and the disease can present in early infancy.[16] The responsible abnormal gene has been assigned to the subtelomeric region of chromosome 4.[51] Affected patients have a reduction in the normal number of repeats in the DNA sequence termed *D4Z4*. In normal individuals, the EcoR1-digested DNA fragment is usually larger than 28 kilobases (kb), whereas a shorter fragment of 14-28 kb is detected in cases of facioscapulohumeral muscular dystrophy, correlating with the smaller number of repeats.[51] In the early infantile form of the disease, facial weakness is characteristic, and the only manifestation might be partially open eyes during sleep. Progression is variable. In some cases, weakness is relatively mild, with later development of facial and shoulder girdle weakness. In other cases, there is early progressive weakness of the face, shoulder girdle, and ankle dorsiflexion, with loss of independent ambulation by late childhood. Bilateral sensorineural hearing loss is present in many cases. Retinal vascular abnormalities can also be found, which sometimes progress with exudation and retinal detachment. Creatine kinase levels are only moderately elevated. Biopsy of a proximal shoulder girdle muscle shows mild myopathic changes. Other pathologic findings include small, angular fibers; "moth-eaten" fibers; and cellular infiltrates that can be extensive and appear

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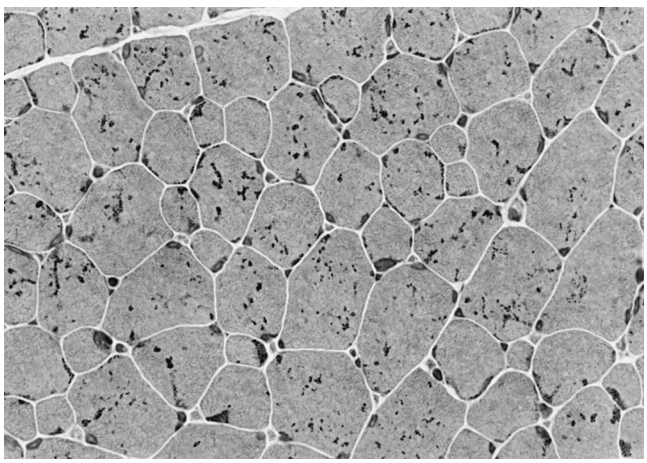
inflammatory. Although steroids in general are not beneficial in this disorder, albuterol has shown some modest benefit.[54] Electromyography of an affected muscle reveals a myopathic pattern with short-duration, low-amplitude polyphasic potentials.

Congenital Myopathies

The congenital myopathies are primary muscle disorders that are present at birth. Although their expression might not be apparent during the neonatal period, infancy, or childhood, these myopathies are probably all genetically determined. Muscular dystrophies, inflammatory myopathies, muscle diseases caused by metabolic disorders, and inborn errors of metabolism are not included in this group. Congenital myopathies are usually characterized on the basis of their histologic and histochemical features. Although more than 30 different types of congenital myopathies have been described, most of these are rare and unlikely to represent clinically distinct entities. The four myopathies discussed here are relatively common and represent distinct clinical entities with unique histochemical findings.

Nemaline Myopathy

Nemaline myopathy is so called because of the characteristic rod bodies in muscle, which in longitudinal section appear threadlike (Fig. 56.4). They are best seen after modified Gomori trichrome staining of frozen sections, in which they appear red against a blue-green myofibrillar background.[20] The rod bodies are usually subsarcolemmal, and their numbers in muscle are variable and not correlated with the severity of the disease. However, intranuclear rods can be seen in the severe neonatal form of the disease. On electron microscopy, the rods appear to originate from the Z-discs in conjunction with Z-disc thickening and streaming and are composed of thin filament proteins, α-actinin, and actin. In addition to nemaline rods, muscle biopsy shows variations in fiber size with a predominance of type 1 fibers, which are smaller than the type 2 fibers.



• **Fig. 56.4** Histologic section of muscle showing nemaline myopathy. Shown are variations in fiber size. Characteristic rod bodies are seen in the muscle fibers. Low magnification. (Courtesy of Hannes Vogel, MD, Baylor College of Medicine, Houston.)

The disorder has a wide clinical spectrum. A severe congenital form presents with generalized weakness and hypotonia involving the face, bulbar, and respiratory muscles but clinically sparing the eye muscles.[71] Milder forms present during the neonatal period or early childhood. It is relatively nonprogressive and has a facioscapuloperoneal pattern of weakness. The face is long and thin, the palate is arched, and muscle bulk is poor. A relatively mild adult-onset form also exists. All variants can show preferential diaphragmatic weakness with a significant percentage requiring prolonged assisted ventilation. The severity of respiratory involvement at delivery predicts survival. Motor outcome parallels respiratory involvement in the neonatal form.[72] Cardiac involvement is rare and secondary to respiratory disease and pulmonary hypertension. Likewise, a neonatal encephalopathy is related to respiratory failure with hypoxic-ischemic injury.[72] The creatine kinase is usually normal or only slightly elevated. Electromyography in the older child usually shows myopathy, but in the newborn infant it is typically not helpful. Most cases are sporadic, although both autosomal dominant and autosomal recessive inheritance can occur.

Mutations in seven genes encoding for muscle thin filaments have been identified. These include: alpha-tropomyosin (*TPM3*), beta-tropomyosin (*TPM2*), alpha-actin (*ACTA1*), nebulin (*NEB*), troponin T1 (*TNNT1*),[72,85] *CFL2* (muscle specific cofilin), and *KBTBD13 13*. Sequence analysis of these genes is available on a clinical basis.[1]

Mutations in the *TNNT1* gene on chromosome 19q13.4 cause a severe autosomal recessive form of the disease in the Amish population that usually has a fatal outcome in the second year of life.[64] There is otherwise no correlation between mutations in the same gene, mode of inheritance, and clinical severity. In addition, there is considerable intrafamilial variation in course and outcome.[1]

Central Core Disease

Central core disease is an autosomal dominant disorder. Muscle biopsy reveals characteristic central cores of degenerated myofibrils in type 1 fibers, which predominate.[20] The disorder is usually mild when it presents during the neonatal period. Muscle weakness and hypotonia are usually more prominent proximally, and congenital hip dislocation is a frequent associated finding.[51] Mild delay in motor maturation occurs, and scoliosis and contractures can develop later. The gene locus responsible for almost 80% of cases has been mapped to chromosome 19q12-13.2, which is closely linked to the gene for malignant hyperthermia and the ryanodine receptor (*RYR1*).[64] All affected patients are at risk for malignant hyperthermia.

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Multi-Minicore Myopathy

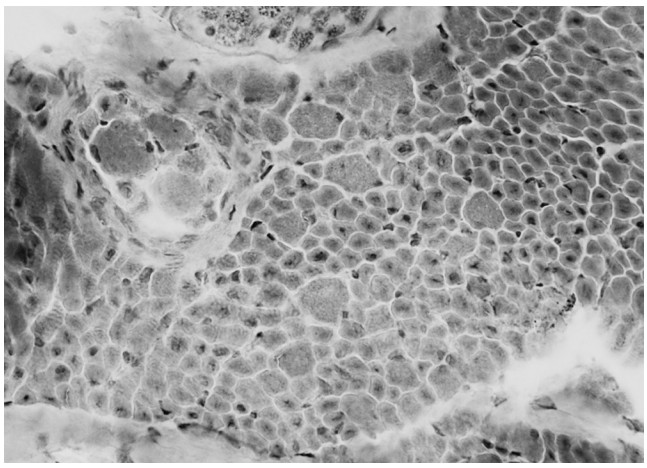
Multi-minicore disease is characterized by multiple small areas of sarcomeric disorganization that lack oxidative activity.[35] There is a predominance of small type 1 fibers. Four homogeneous phenotypes have been defined. The classic form presents with mild proximal weakness, joint laxity, scoliosis, and respiratory insufficiency with a rigid spine. An ophthalmoplegic form is associated with facial and generalized weakness. An early onset form may result in arthrogryposis. A slowly progressive form presents with hand amyotrophy. Cardiomyopathy may occur. Both autosomal recessive and sporadic inheritance may occur.[35] Diagnosis is by muscle biopsy, and mutations in the *SEPN1* or *RYR1* gene account for many of the cases.

Myotubular Myopathy

Myotubular myopathy presenting in the neonatal period is an X-linked recessive condition and one of the most severe congenital myopathies. It is caused by mutations in the myotubularin gene (*MTM1*) on chromosome Xq28. The protein tyrosine phosphorylase encoded by this gene is thought to have a vital role in normal myogenesis. The myopathy is characterized pathologically by muscle fibers that contain large central nuclei and resemble fetal myotubes (Fig. 56.5).[20] This central area also lacks myofibrils and appears as a clear area with adenosine triphosphatase staining. There is a predominance of small type 1 fibers. The appearance of the muscle is not caused by a general arrest in muscle development but rather is related to a persistence of fetal cytoskeletal proteins, vimentin, and desmin, which preserve the immature central portions of the nuclei.[20]

With onset during the fetal period, there is often history of polyhydramnios. Death may occur soon after birth or within the first year of life from respiratory failure, although long-term survival is possible. Typical clinical features include generalized hypotonia with facial weakness and ophthalmoplegia. Congenital contractures may be present. Although the disease is nonprogressive in survivors, these patients remain extremely weak, wasted, and unable to sit unsupported. Female heterozygotes may exhibit early onset of limb-girdle weakness but are usually asymptomatic.[76]

Diagnosis of the neonatal variants is initially made by muscle biopsy. Genetic analysis of the myotubularin gene is available and allows for prenatal diagnosis. The creatine kinase level is usually normal, and electromyography is not helpful.



• **Fig. 56.5** Histologic section of muscle showing myotubular myopathy. Shown are large muscle fibers with central nuclei seen primarily in small, predominantly type 1 fibers. Low magnification. (Courtesy of Hannes Vogel, MD, Baylor College of Medicine, Houston.)

Metabolic and Multisystem Disorders

A large number of metabolic disorders directly involve the neuromuscular system and are broadly divided into primary abnormalities of glycogen, lipid, mitochondrial, and peroxisomal metabolism.[84] Some are responsible for well-defined clinical syndromes, such as acid maltase deficiency, which causes Pompe disease, whereas others are protean in their manifestations (see Chapter 90).

Mitochondrial Myopathies

Mitochondrial myopathies are categorized according to the involved area of abnormal metabolism, as follows: (1) defects of substrate transport, (2) defects of substrate utilization and the citric acid cycle, and (3) defects of the electron transport chain and oxidative phosphorylation coupling.[71] In the newborn, defects in electron transport (respiratory chain) are those most likely to lead to prominent muscle disease. Other abnormalities of mitochondrial metabolism, such as pyruvate carboxylase and pyruvate dehydrogenase complex deficiency, are more likely to present with features of a progressive encephalopathy. The most common of the respiratory chain disorders presenting as a myopathy during the neonatal period is cytochrome-*c* oxidase deficiency.[51] Typically, the infant presents with profound generalized weakness, hypotonia, hyporeflexia, poor feeding reflex, respiratory difficulty, and lactic acidosis. Other features may include hepatomegaly, cardiomyopathy, renal tubular defects (de Toni-Fanconi syndrome), and macroglossia. Death occurs within a few months. A reversible form of cytochrome-*c* oxidase deficiency also occurs.[51] The disorder presents in a fashion similar to the severe form, but improves biochemically and clinically over the next 1-2 years. Early diagnosis is vital to provide continuing support while improvement takes place. Cytochrome-*c* oxidase deficiency should be suspected in any weak infant with lactic acidosis, particularly in conjunction with multisystem involvement. The creatine kinase level can be slightly elevated, but electromyography is usually not helpful. Muscle biopsy shows nonspecific myopathic changes, ragged red fibers on Gomori trichrome staining, and an absence of histochemical staining for cytochrome-*c* oxidase. Electron microscopy of muscle fibers demonstrates lipid and glycogen

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accumulations and an increased number of large, abnormal-looking mitochondria. The benign and severe forms are differentiated by immunohistochemical techniques, using antibodies directed against different subunits of cytochrome-*c* oxidase. In the fatal form, there is an absence of DNA-encoded subunit VIIa, b. In the benign form, however, both this subunit and the mitochondrial DNA-encoded subunit II are absent.[51] Cytochrome-*c* oxidase deficiency in Leigh syndrome (encephalopathy and magnetic resonance imaging changes) has been recently associated with mutations of *SURF1*, a gene located on chromosome 9q34. However, mutations have not been found in patients with cytochrome-*c* oxidase without Leigh syndrome.

Disorders of Glycogen Metabolism

Apart from acid maltase (alpha-glucosidase) deficiency (Pompe disease), the autosomal recessive disorders of glycogen metabolism (see Chapter 90) present only rarely during the neonatal period.[84] These rare presentations occur with debrancher enzyme deficiency, phosphorylase deficiency, and phosphofructokinase deficiency.

Pompe Disease (Type II Glycogen Storage Disease)

The infantile form of Pompe disease is caused by a deficiency of acid maltase (alpha-glucosidase). The disorder can present during the neonatal period, although clinical onset during the second month of life is more usual.[51,80] The enzyme deficiency causes glycogen accumulation in anterior horn cells of the spinal cord and in the muscles, heart, liver, and brain. Infants present with profound generalized weakness, hypotonia, hyporeflexia, impaired awareness, heart failure, and hepatomegaly. Tongue fasciculations, a large tongue, and severe bulbar weakness are often present. The chest radiograph and electrocardiogram demonstrate cardiomegaly, short PR intervals, and giant QRS complexes. The serum creatine kinase and liver enzymes are elevated, and electromyography shows combinations of denervation and myopathy, including fibrillations and small polyphasic potentials. Muscle biopsy reveals vacuoles containing glycogen, which stain with periodic acid-Schiff. The gene for the alpha-glucosidase enzyme protein is located on chromosome 17q23-25. Diagnosis typically is made by demonstrating the enzyme deficiency in leukocytes, lymphocytes, fibroblasts, or muscle or by demonstrating mutations in both alleles. Glucosidase alpha, acid (GAA), is the only gene known to be associated with Pompe disease. However, there is extensive genetic heterogeneity, and common mutations are found only in ethnic groups such as Ashkenazi Jews or the Amish in Pennsylvania. Prenatal diagnosis has been successful by demonstrating enzyme deficiency in cultured amniotic cells, linkage analysis, and mutation analysis. Prognosis is usually poor, with most infants dying within the first 6 months of life. Enzyme replacement therapy can in some cases delay the need for ventilator support and cardiac morbidity, but response is highly variable.[3,4,80]

Debrancher Enzyme Deficiency (Type III Glycogen Storage Disease)

Rarely, debrancher enzyme deficiency can present during the neonatal period with hypotonia, weakness, hypoglycemia, hepatomegaly, and liver dysfunction. Muscle biopsy shows abnormal glycogen storage, and diagnosis is established by demonstration of the debrancher enzyme deficiency.[51]

McArdle Disease (Type V Glycogen Storage Disease)

There are three different isozymes of phosphorylase (liver, brain, muscle), genes of which have been cloned and localized to different chromosomes.[77] Deficiency of the muscle enzyme on chromosome 11p13 causes McArdle disease.[51] Clinical presentation occurs typically during adolescence, with exercise intolerance, cramps, and myoglobinuria. However, the disorder shows clinical variability and rarely presents during the neonatal period.[24] Infantile McArdle disease presents as a weak, hypotonic infant typically with feeding difficulties. In some infants, the weakness is extreme, contractures are present, and the outcome fatal.[60] Even in the less severe neonatal form, the weakness is slowly progressive but without significant cranial nerve dysfunction. Muscle biopsy shows variations in fiber size, absence of phosphorylase staining, and subsarcolemmal glycogen-containing vacuoles. Unlike Pompe disease, the accumulated glycogen is not membrane bound.[20] Definitive diagnosis is made by demonstrating deficiency of the muscle isozyme or by demonstrating mutations in the phosphorylase gene. Treatment for this condition remains limited. There has been some success with high-protein diets or ingestion of sucrose before exercise.[83]

Phosphofructokinase Deficiency (Type VII Glycogen Storage Disease)

Phosphofructokinase deficiency usually presents with cramps on exercise and myoglobinuria. A severe infantile form presents during the neonatal period.[7] Affected infants exhibit hypotonia, progressive weakness, and contracture formation. Some infants have seizures, cortical blindness, and mental retardation.[84] The muscle biopsy findings are similar to those of McArdle disease, with non-membrane-bound subsarcolemmal glycogen deposits. Diagnosis is established by demonstrating a reduction of phosphofructokinase activity biochemically and histochemically.[20]

Primary Carnitine Deficiency

Primary carnitine deficiency is caused by a deficiency in the transport of carnitine from plasma into the cells of affected tissues.[51] The disorder usually presents in early childhood with a cardiomyopathy, proximal muscle weakness, or recurrent encephalopathy. Rarely, it presents during the neonatal period with weakness, hypotonia, and cardiomyopathy. Hypoketotic hypoglycemia is a clue to diagnosis.[84] Muscle biopsy shows lipid-containing vacuoles, and serum

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and muscle carnitine levels are low. The carnitine transporter defect can be demonstrated in cultured fibroblasts.[51]

Peroxisomal Disorders

Peroxisomal disorders can present during the neonatal period with profound hypotonia, weakness, and, at times, hyporeflexia or areflexia. Signs include CNS dysfunction; facial dysmorphism, as in Zellweger syndrome; hepatomegaly; cataracts; retinopathy; calcific stippling of epiphyses; and rhizomelia.[12] These disorders are discussed in Chapter 90.

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Key Points

- Infants with a neonatal neuromuscular disorder typically have severe muscle weakness in addition to hypotonia that is more commonly seen without weakness if secondary to a central cause.
- Infantile spinal muscular atrophy, a previously untreatable and frequently fatal disorder, now has an FDA-approved medication for treatment with additional emerging therapies on the horizon.
- Neuromuscular junction disorders are infrequent causes of weakness in the neonate but illustrate the importance of a good maternal history to be aware of the acquired types such as acquired neonatal myasthenia gravis.
- Congenital muscular dystrophies are a group of disorders typically presenting with severe weakness and hypotonia with central (leukoencephalopathy and brain migrational abnormalities) as well as peripheral causes (dystrophic muscle).
- Congenital myotonic dystrophy is a trinucleotide repeat disorder that presents with severe hypotonia, generalized weakness, and a tent-shaped triangular upper lip, typically from maternal inheritance.
- Nemaline myopathy is one of the congenital myopathies that can present in the neonatal period with severe weakness involving the face, bulbar, and respiratory muscles.

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57

Intracranial and Calvarial Disorders

KRYSTAL TOMEI AND MICKEY SMITH

Summary

This chapter explores those conditions that cause abnormal head shape or head size in the newborn infant. The underlying causes, clinical presentation, diagnosis, and available interventions will be presented.

Examination of the Head

Abnormalities are first identified by observation of the general shape and texture of the head and scalp. Palpation of neurocutaneous lesions are noted. The anterior fontanelle, demarking the junction of the frontal and parietal bones at the intersection of the metopic, coronal, and sagittal sutures, should always be palpated. It is usually soft, flat, and pulsatile with the heartbeat. The anterior fontanelle may be tense or full when a child is crying, but sustained bulging of the fontanelle may be indicative of a pathologic process associated with elevated intracranial pressure. It usually closes by 18 months of age, although some recent studies have shown that it can take up to 24 months to fully close (mean 16.3 months for boys and 18.8 months for girls).[2,17] The posterior fontanelle is smaller and denotes the junction of the parietal and occipital bones at the intersection of the sagittal and lambdoid sutures. It usually closes by 3 months. Palpation for abnormal splaying or overlap of the cranial sutures, measured in millimeters, should also be recorded.

Head circumference measurement should be recorded with each examination, as it is a gauge of intracranial volume. The occipitofrontal circumference (OFC) is obtained with a tape measure firmly pressed against the scalp to include the occiput at or just above the external occipital protuberance (inion) and the forehead just above the glabella. Gestation age-adjusted measurements should be made on growth charts for preterm infants.[4,22] Normal head growth occurs at approximately 2 cm per month in the first 3 months, 1 cm per month the next 3 months, and then 0.5 cm per month for the next 6 months.

The Neonate

Neurulation and Cleavage

An in-depth review of craniofacial development is beyond the scope of this chapter; however, there are well-studied defects in embryogenesis that lead to abnormally shaped heads in the neonate. Microcephaly, or a small head, is a primary manifestation of embryologic and congenital abnormalities resulting in a small brain[18] (Fig. 57.1). Briefly, the embryologic process begins with primary neurulation between days 17 and 27 of gestation. Errors in neurulation and neural tube closure lead to dysraphic malformations. The most devastating of all neural tube defects is anencephaly (Fig. 57.2). This fatal condition results from failure of the anterior neuropore to close, and leads to an absent cranial vault.

Abnormal cleavage, which is the normal separation of the embryonic forebrain to form paired telencephalic hemispheres by day 33 of gestation, can lead to conditions such as holoprosencephaly.[6,7,28] Varying degrees of holoprosencephaly exist, with the most complete form being alobar holoprosencephaly and lesser forms termed semilobar and lobar (Fig. 57.3). Associated median facial defects can range from a single midline eye to orbital hypotelorism, nose flattening, cleft lip and palate, or trigonocephaly.

Migration

Neuronal migration is the radial and tangential process by which the cerebrum is formed.[1] Progenitor cells migrate from the ventricular zone and basal forebrain to create the cortex. There is cortical disruption when this migration does not occur normally, and conditions like schizencephaly (cleft in the hemisphere) (Fig. 57.4), lissencephaly ("smooth brain") (Fig. 57.5), or polymicrogyria occur (Fig. 57.6). The hallmark features include gyral anomalies.[13] Midline structures are also often involved, such as failure of the corpus callosum to form completely or agenesis of the corpus callosum (Fig. 57.7). The septum pellucidum can also be absent.

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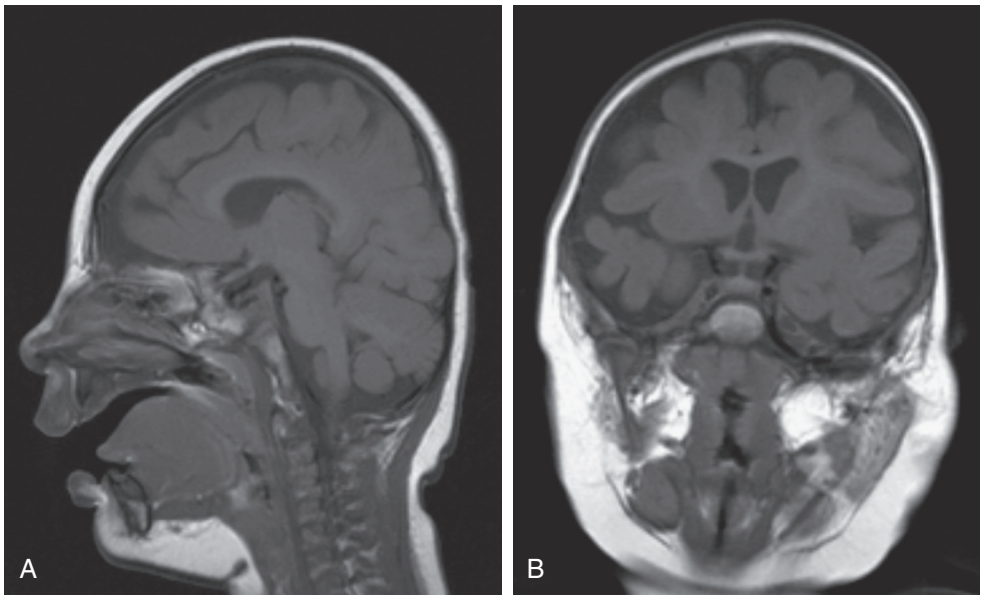
Abstract

Examination of the infant head shape and size is critical to evaluate for underlying pathologies that may impair neurologic development. Embryologic errors such as abnormal neurulation, cleavage, or migration can lead to congenital defects that inhibit normal formation of the central nervous system and then, in turn, external craniofacial development. Other factors, like in utero infections, can alter brain development and ultimately head size. Hydrocephalus is a common comorbidity in the infant with macrocephaly. Post-hemorrhagic hydrocephalus is frequently diagnosed in premature neonates. Congenital brain malformations like Dandy-Walker and Chiari II are other frequent comorbid conditions with hydrocephalus. Finally, craniosynostosis is a primary cause of misshapen heads in infants, but practitioners should be able to delineate true craniosynostosis from positional plagiocephaly, which is more common.

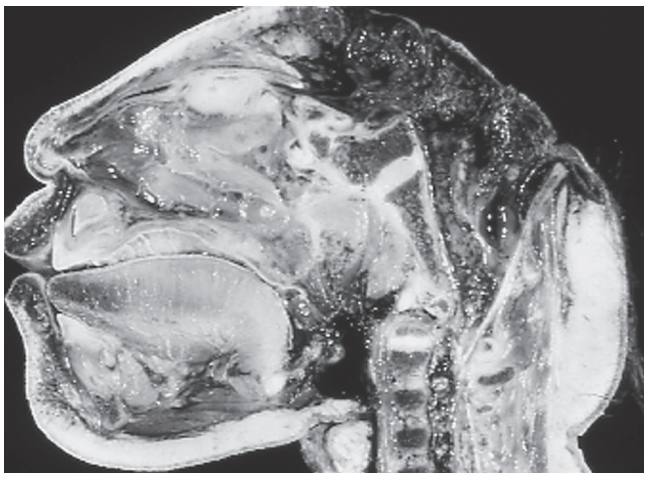
Keywords

hydrocephalus
craniosynostosis
congenital brain malformations

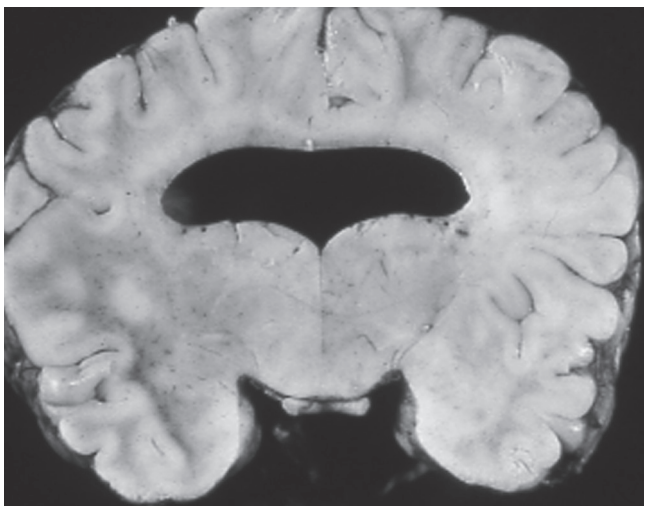
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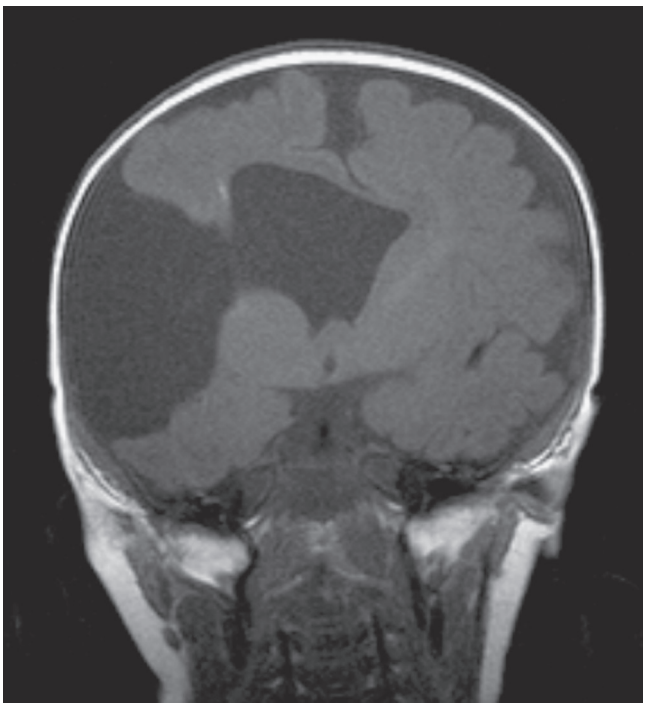
• **Fig. 57.1** Primary microcephaly. **A**, T1-weighted sagittal MRI. **B**, T1-weighted coronal MRI.



• **Fig. 57.2** Anencephaly.



• **Fig. 57.3** Semilobar holoprosencephaly, coronal specimen.

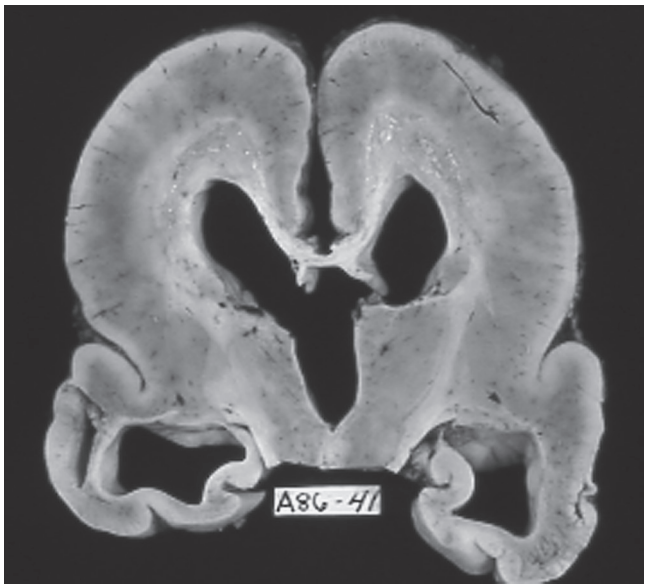


• **Fig. 57.4** Open-lipped schizencephaly. T1-weighted coronal MRI shows a large open cleft communicating with the right lateral ventricle and absence of the septum pellucidum.

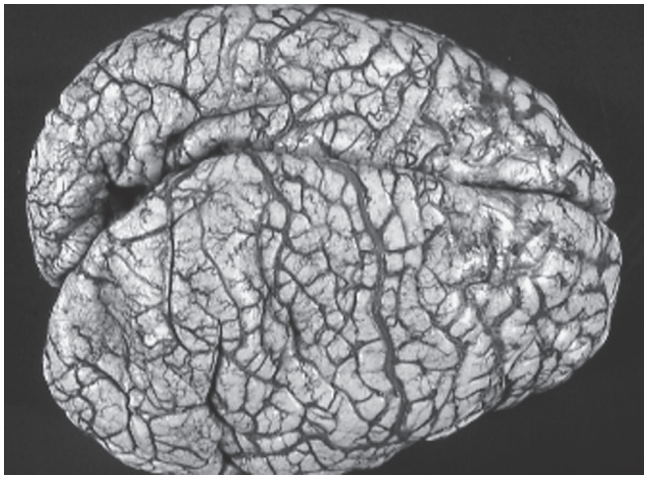
External features can lead to abnormally shaped heads (Fig. 57.8). Abnormal migration can also lead to syndromes of neuronal heterotopias, such as Aicardi syndrome characterized by microcephaly.[1]

Neural crest cells, first formed in a zone between the neural plate and the ectoderm, also play a major role in the formation of the fetal skull and face. Errors in that process, including in the migration of neural crest cells, lead to improperly formed face and heads.[1] Examples include Waardenburg syndrome and craniofrontal dysplasia.

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• **Fig. 57.5** Lissencephaly, coronal specimen.



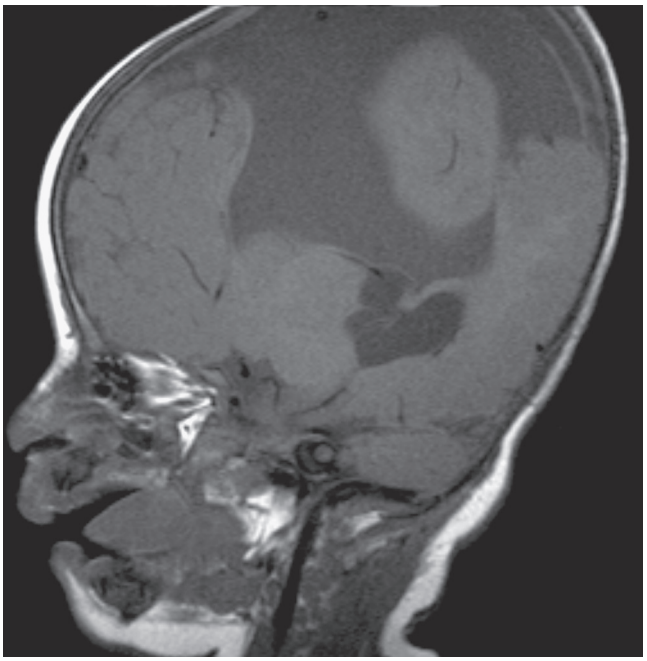
• **Fig. 57.6** Polymicrogyria.

Congenital Infections

In utero infections, collectively known as TORCH infections, also produce insults in the development of the craniofacial system. Implicated infections of the TORCH syndrome include toxoplasmosis, other agents (syphilis, varicella-zoster, parvovirus), rubella, cytomegalovirus, and herpes simplex virus. Microcephaly, seen even with hydrocephalus in the case of a toxoplasmosis infection, can be observed[14] (Fig. 57.9).

Hydrocephalus

Macrocephaly, conventionally defined as an orbitofrontal circumference more than two standard deviations above the mean, can be attributed to three possible processes. Macrencephaly, enlargement of the brain itself, can lead to large



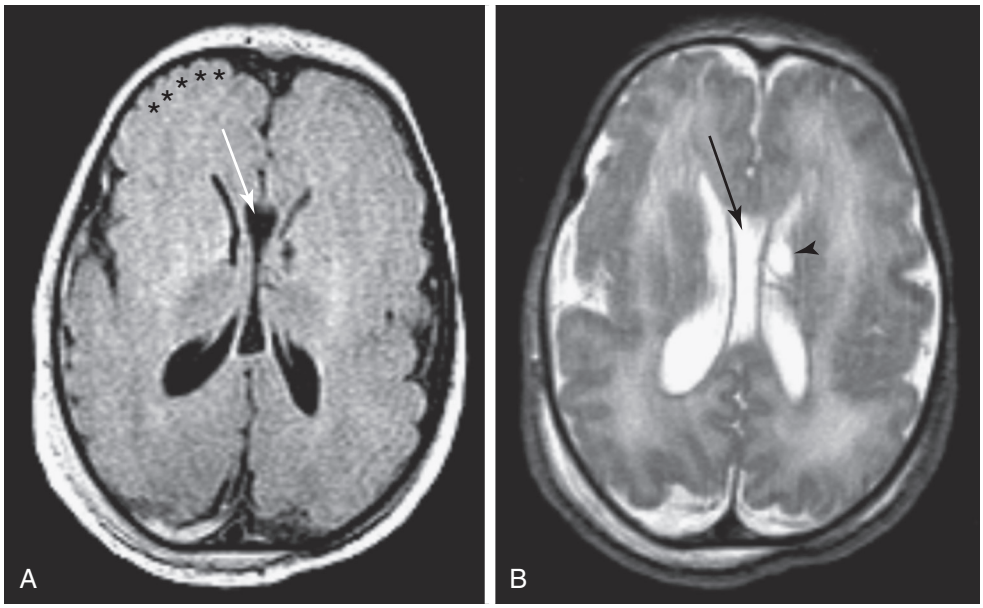
• **Fig. 57.7** Agenesis of the corpus callosum. T1-weighted MRI also demonstrates absence of septum pellucidum and a large midline cerebrospinal fluid collection.

heads and is seen in certain genetic, neurocutaneous, or metabolic syndromes.[20] Another cause of a large cranium includes neoplastic or enlargement of other structures, including vascular lesions like vein of Galen malformations. Here, we will focus on hydrocephalus and its macrocephalic and neurologic manifestations.

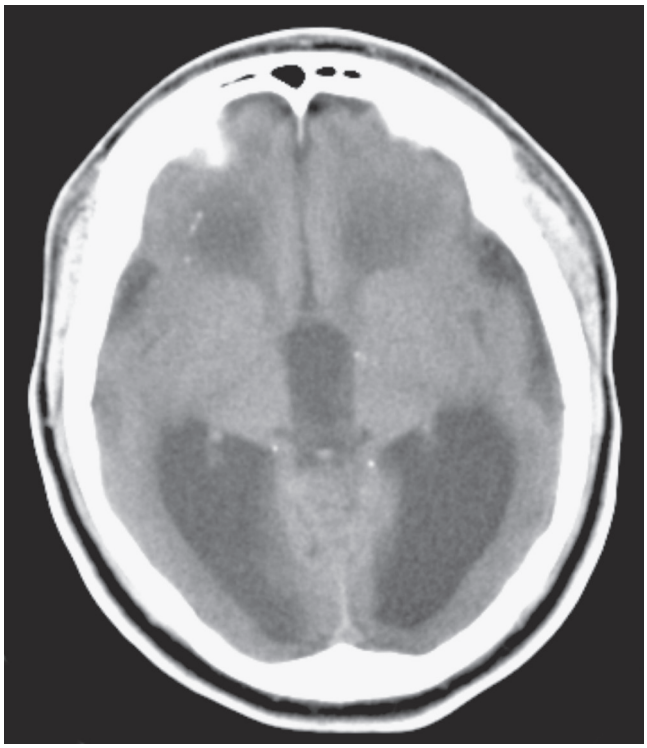
The normal rate of cerebrospinal fluid (CSF) production is about 0.3 mL/min, or 20 mL/hr.[5,19] In premature infants, the rate of CSF formation is lower. The newborn has a total volume of about 50 mL, and the majority is produced in the choroid plexus. Normal reabsorption into the venous system occurs via arachnoid villi granulations in the venous sinuses. An impaired balance between production and absorption leads to enlargement of the CSF fluid spaces. Failure from any reason, including structural or metabolic, to absorb CSF at a rate concomitant to its production leads to this imbalance. The clinical manifestation of hydrocephalus, including symptoms related to increased intracranial pressure, depends on the status of the cranial sutures. In a newborn with open sutures, macrocephaly may be a presenting sign, but a child over 2 years can present without macrocephaly but with elevated intracranial pressure signs such as headache, irritability, vomiting, lethargy, or sunsetting eyes. In the infant, external features include tense and bulging fontanelles and split sutures.

Hydrocephalus may be categorized as either acquired or congenital. Acquired causes include post-hemorrhagic hydrocephalus and post-meningitic hydrocephalus. Congenital causes include Dandy-Walker, Chiari malformations, or even aqueductal stenosis.[3]

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• **Fig. 57.8** Imaging of a patient with Zellweger syndrome, a peroxisomal disorder affecting the brain, kidneys, and liver. **A**, Fluid-attenuated inversion recovery (FLAIR) MRI. **B**, T2-weighted MRI. Note the multiple migrational abnormalities in this syndrome, including polymicrogyria (*asterisks* in **A**), subependymal cysts (*arrowhead* in **B**), cortical dysplasia, and ventricular anomalies, including a cavum septi pellucidi and cavum vergae (*arrow* in **A** and **B**).



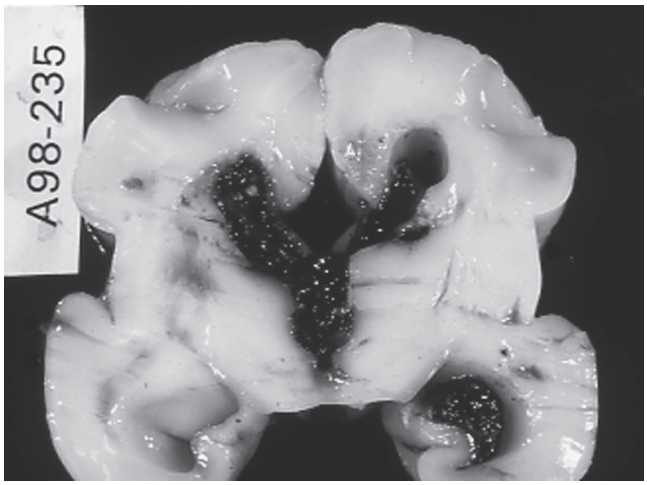
• **Fig. 57.9** Congenital toxoplasmosis. Noncontrast CT scan shows ex vacuo hydrocephalus and periventricular calcifications.

Intraventricular Hemorrhage

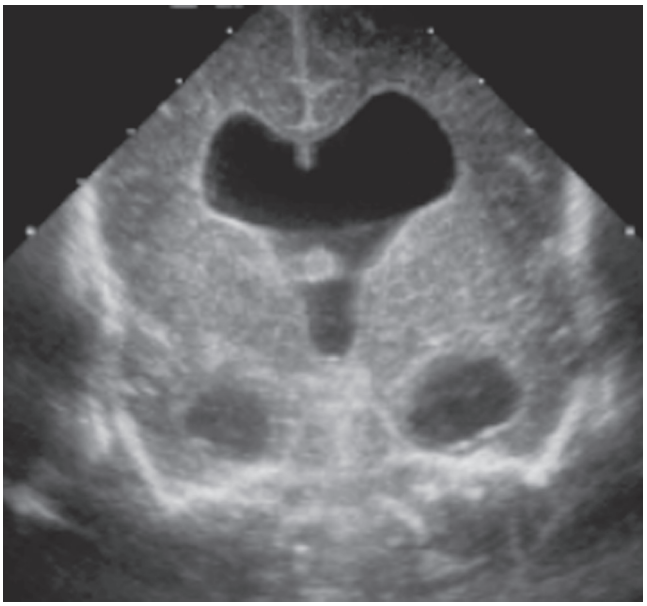
Post-hemorrhagic hydrocephalus can occur as a consequence of trauma resulting in intraventricular hemorrhage (IVH), but it is most often seen in premature infants with germinal matrix hemorrhage. The germinal matrix is a rich vascular network found in the periventricular subependyma, which normally involutes by 36 weeks' gestation.[21,25] However, in premature neonates this involution does not occur completely. In this context of lack of vascular support tissue, intraventricular hemorrhage, therefore, is most common in prematurity, with some studies showing up to 27% of preterm infants under 1500 grams being affected.[24] Nonetheless, term infants with coagulopathies can also develop IVH and as many as half developing delayed symptomatic IVH.[24]

Intraventricular hemorrhage by itself may result in ventriculomegaly without clinical hydrocephalus. A grading system of IVH based on the site of hemorrhage and with or without ventriculomegaly or intracerebral hemorrhage is often used when describing IVH and applying prognostication. Grade 1 is isolated to blood within the germinal matrix; in grade 2 IVH, there is bleeding within the ventricles without enlargement; in grade 3 IVH there is bleeding within ventricles with enlargement; and in grade 4 IVH the hemorrhage includes the surrounding brain parenchyma (Fig. 57.10). Close observation in those neonates with IVH and ventriculomegaly is recommended with weekly head ultrasounds and daily OFC measurements to monitor for the development of hydrocephalus.[21] The progression to clinical post-hemorrhagic hydrocephalus is defined as ventriculomegaly, signs of elevated intracranial pressure, and increasing OFC. The post-hemorrhagic hydrocephalus is typically an obstructive form, secondary to malfunctioning arachnoid villi due to the arachnoiditis from the blood (Figs. 57.11 and 57.12). Efforts to halt progression can include serial lumbar taps, ventricular taps through the fontanelle, medications to reduce CSF production, and

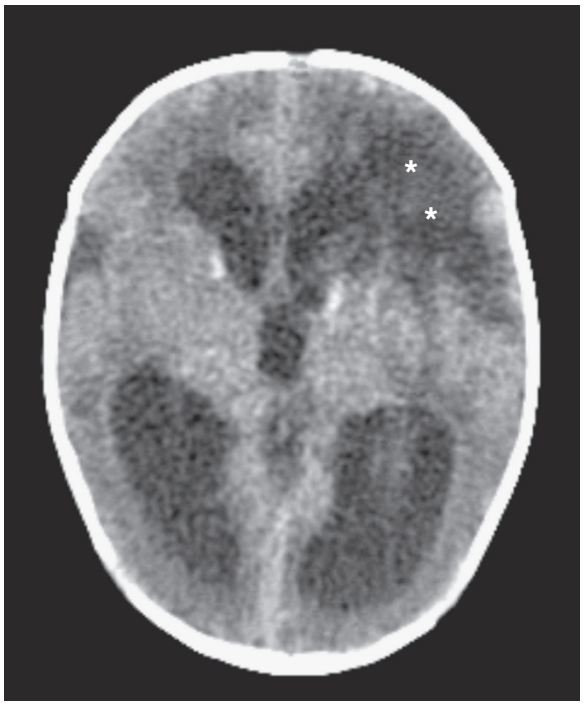
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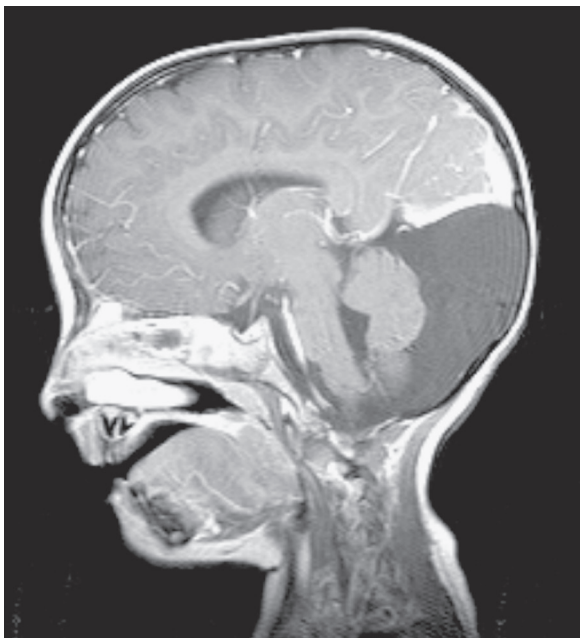
• **Fig. 57.10** Posthemorrhagic hydrocephalus. Diffuse intraventricular hemorrhage secondary to germinal matrix bleed (grade IV) is seen in this coronal specimen.



• **Fig. 57.12** Posthemorrhagic hydrocephalus. Coronal ultrasound scan shows enlarged lateral ventricles and intraventricular blood.



• **Fig. 57.11** Posthemorrhagic hydrocephalus after grade IV intraventricular hemorrhage of prematurity. CT scan demonstrates lateral ventricle enlargement and left frontal encephalomalacia (*asterisks*) at the site of parenchymal hemorrhage.



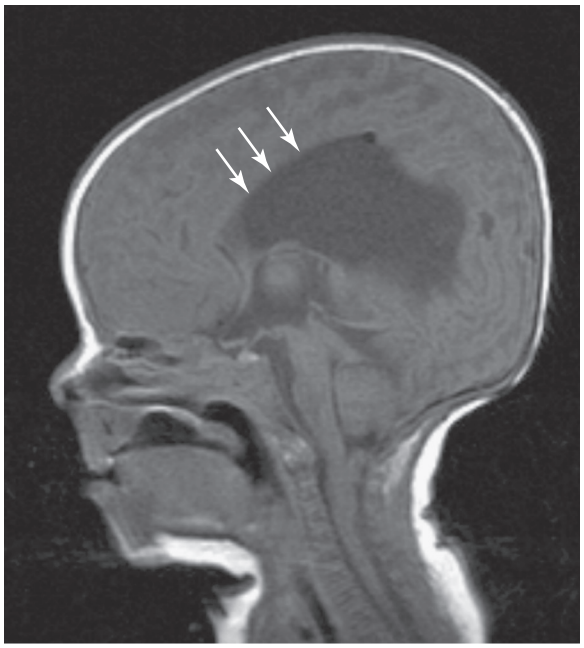
• **Fig. 57.13** Dandy-Walker malformation. T1-weighted sagittal MRI demonstrates cystic transformation of the fourth ventricle with posterior fossa enlargement, elevation of the torcular herophili, and dysgenesis of the inferior cerebellar vermis.

temporary methods of temperization including ventricular reservoir placement with serial reservoir taps or a subgaleal shunt.[11,15,16] Permanent diversion with CSF shunting may ultimately be required.

Congenital Brain Malformations

Congenital malformations, which typically produce macrocephaly and hydrocephalus, include those of the Dandy-Walker and Chiari variety. The Dandy-Walker malformation is characterized by fourth ventricular cystic transformation, partial or complete agenesis of the cerebellar vermis, and posterior cranial fossa enlargement with upward displacement of the torcula heterophili, transverse sinuses, and tentorium (Fig. 57.13). The resultant obstructive hydrocephalus leads to supratentorial ventriculomegaly present at birth or progressive over time. The previously described errors in neuronal migration such as agenesis of the corpus callosum and septum pellucidum or polymicrogyria may be appreciated on imaging. Externally, patients may have a high riding

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• **Fig. 57.14** Chiari II malformation. T1-weighted sagittal MRI shows partial agenesis of the corpus callosum (*arrows*) and multiple anomalies, including enlargement of the massa intermedia, beaking of the tectum, herniation of the cerebellum below the foramen magnum, and kinking of the medulla.



• **Fig. 57.15** Aqueductal stenosis. T1-weighted sagittal MRI shows noncommunicating hydrocephalus secondary to stenosis of the aqueduct of Sylvius (*arrow*). The lateral and third ventricles are enlarged, with a normal-sized fourth ventricle. An arachnoid cyst is present inferior to the cerebellum.

external occipital protuberance. Occipital encephaloceles or meningoceles, cleft lip and palate, or other craniofacial malformations are frequently observed.[23] The malformation is more frequent in girls than boys, and it occurs in approximately 1 in 25,000 live births.[23]

The Chiari II malformation is another congenital anomaly resulting in hydrocephalus and possibly macrocephaly. The malformation is characterized by an abnormal hindbrain, owing to a small posterior fossa, low-lying transverse sinuses, low-lying tentorium, and herniation of the cerebellar vermis below the foramen magnum. The tectum is beaked, and there may be supratentorial ventriculomegaly (Fig. 57.14). This malformation is uniformly associated with a lumbosacral myelomeningocele.[12] Externally, the head may not be enlarged at birth, with even a possibility of the OFC being small due to decompression of the CSF into the myelomeningocele sac. However, after closure of the myelomeningocele, it is important to continue to trend the OFC, as it may begin to rapidly expand. The clinical hydrocephalus is of the obstructive type, with other manifestations including cranial neuropathies or brainstem dysfunction due to exacerbation of the Chiari II malformation from downward pressure of untreated hydrocephalus.

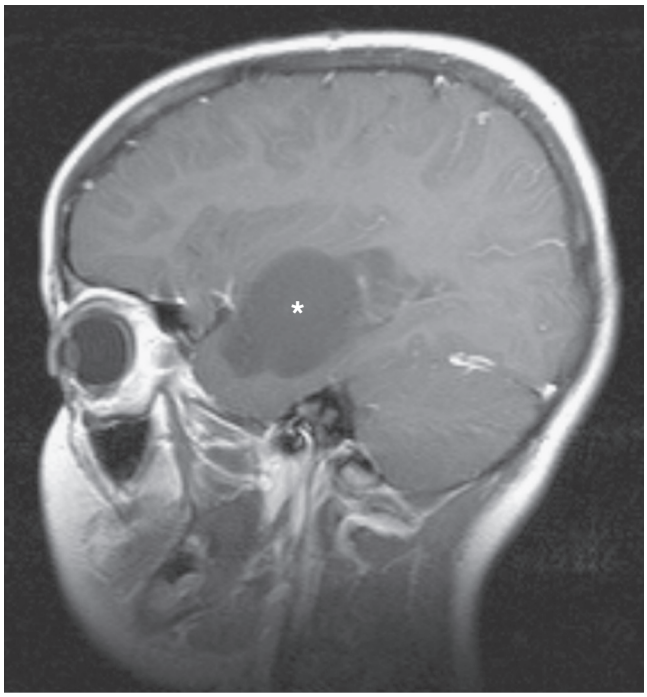
Other Causes

Other causes of hydrocephalus and concomitant macrocephaly include aqueductal stenosis, neoplasms, and vascular malformations. Each of these entities cause noncommunicating, or obstructive, hydrocephalus and are not always evident at birth.

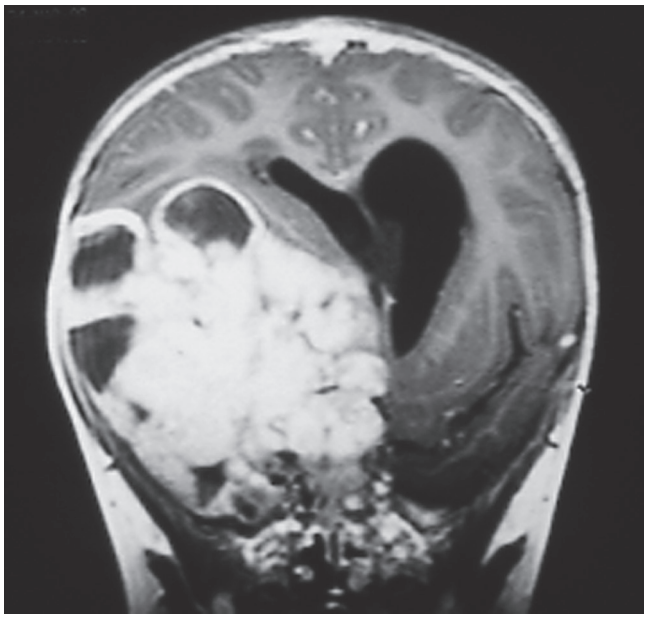
Stenosis of the cerebral aqueduct can be congenital or acquired, and it accounts for up to 10% of pediatric hydrocephalus. Radiographically, there is enlargement of the lateral and third ventricles and a normal fourth ventricle size (Fig. 57.15). A narrowed aqueduct, which normally measures about 0.5 mm in diameter and 3 mm in length at birth, alters dynamic flow and reabsorption of CSF.[8] Macrocephaly again may not be evident at birth but may progress prior to suture closure if the stenosis is severe. Acquired aqueductal stenosis can occur as the consequence of a neoplasm. However, changes in head shape or size may not be evident unless the neoplasm was present at birth or at an early age prior to suture closure. Examples include slow-growing tumors such as choroid plexus papilloma, low-grade astrocytoma, and ganglioglioma (Fig. 57.16), or rapidly growing ones such as primitive neuroectodermal tumor and teratoma (Fig. 57.17).

Vascular lesions are a rare cause of macrocephaly with possible hydrocephalus in the newborn. The vein of Galen malformation often presents with macrocephaly and clinical hydrocephalus. This malformation arises in the third trimester of pregnancy because of a persistent embryonic promesencephalic vein of Markowski. Patients present with refractory, high-output congestive heart failure. Treatment of the malformation is the mainstay of intervention; however, hydrocephalus may require intervention in symptomatic children in whom endovascular intervention is not possible or must be staged. Options for treatment include endoscopic third ventriculostomy or ventricular shunting.

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• **Fig. 57.16** T1-weighted, contrast-enhanced MRI demonstrating dysembryoplastic neuroepithelial tumor (DNET), a low-grade primary neoplasm of the right temporal lobe (*asterisk*).



• **Fig. 57.17** T1-weighted, contrast-enhanced MRI demonstrating a large primitive neuroectodermal tumor of the right temporal lobe deforming the brain.

Hydranencephaly

Hydranencephaly is a rare congenital anomaly marked by almost complete absence of the cerebral hemispheres. It is thought to occur as the result of a major in utero vascular insult during the second trimester, particularly bilateral occlusion of the carotid arteries. The brain undergoes intrauterine liquefaction and is essentially reduced to a bag of water, a meningeal sac containing CSF with high protein content. The diencephalon, brainstem, and posterior fossa structures are spared, and a thin occipital cortical rim may permit some visual function.

The newborn with hydranencephaly may appear neurologically normal at birth because of the normally functioning thalami and brainstem. Difficulty with visual fixing and following may be appreciated. The head size may be normal or even small at birth but can enlarge rapidly owing to malabsorption of the proteinaceous CSF. On occasion, the diagnosis of hydranencephaly is made after several months because of failure to achieve developmental milestones.

Significant macrocephaly may be treated with a ventriculoperitoneal shunt. The decision to shunt can be difficult because shunting is primarily done to make it easier to care for the infants and does not lead to an improved level of neurologic function. The long-term outcome for infants with hydranencephaly is poor, and most do not live for more than 1 or 2 years.

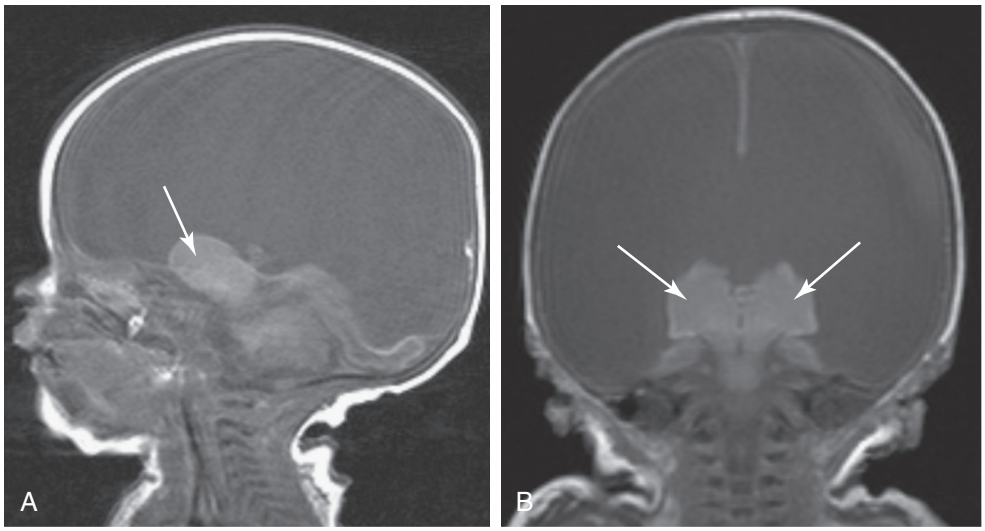
Hydranencephaly can be diagnosed by ultrasound, although magnetic resonance imaging (MRI) is much more accurate (Fig. 57.18). Hydranencephaly is distinguished from anencephaly by the presence of intact meninges and skull. It is important to distinguish between hydranencephaly and advanced hydrocephalus, which may have a similar clinical and radiographic presentation. The compressed cerebral mantle in hydrocephalus can expand, sometimes dramatically, after ventricular shunt placement.

Craniosynostosis

Abnormally shaped heads of infancy go beyond micro- or macrocephaly. In this instance of misshapen heads, craniosynostosis and deformational plagiocephaly are the two most common causes. The hallmark of craniosynostosis is the premature fusion of cranial sutures. The pathologic fusion of sutures places infants at risk for head shape abnormalities as well as elevated intracranial pressure secondary to craniocephalic disproportion if left untreated. Although the incidence of elevated intracranial pressure varies highly in the literature, it is estimated to be between 4.5%-44% of untreated children with craniosynostosis.[26] Most often, only a single suture is involved, causing characteristic head shapes that will be described further. Other times, multiple suture fusions combine as part of a greater craniofacial syndrome. Thus, craniosynostosis can be subdivided to either nonsyndromic or syndromic (Box 57.1). It should also be noted that while the majority of craniosynostosis is caused by primary closure of sutures, secondary causes can include metabolic or hematologic disorders, such as rickets, hyperthyroidism, polycythemia vera, and thalassemia.

The characteristic head shapes seen in craniosynostosis occur as a result of failure of perpendicular growth of the bones of the skull vault relative to the suture.[9] Compensatory growth at perimeter nonfused sutures can also contribute to the odd-shaped head. Molecularly, defects in fibroblast growth factor receptors (FGFRs) have been implicated in

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• **Fig. 57.18** Hydranencephaly. T1-weighted sagittal (**A**) and coronal (**B**) magnetic resonance images show almost complete absence of the cerebral hemispheres, with preservation of the thalami (*arrows*) and hindbrain.

• BOX 57.1 Causes of Abnormal Head Shape

Craniosynostosis
Nonsyndromic
- Sagittal synostosis
- Metopic synostosis
- Unilateral coronal synostosis
- Bilateral coronal synostosis
- Metopic synostosis

Syndromic
- Muenke syndrome
- Apert syndrome
- Crouzon syndrome
- Pfeiffer syndrome
- Saethre-Chotzen syndrome

Deformational Plagiocephaly

the etiology of craniosynostosis.[9,10] Normally, signals from the dura promote patent sutures until completion of brain growth. However, those signals are altered in the case of craniosynostosis.

The physical exam is the first step in diagnosing premature suture closure, as craniosynostosis is diagnosed clinically. Knowledge of the general types of misshapen heads can lead one to identify the typical fused suture (Table 57.1). In neonates, sutures are relatively mobile, and fusion of the suture can be diagnosed on physical exam by the absence of mobility along the suture of concern in combination with the shape of the infant's head. Plain skull x-rays can confirm the diagnosis, which demonstrate sclerosis along all or part of the fused suture. A CT scan increases sensitivity for diagnosis and may be useful in children who are older, where suture mobility is not as easily palpable and can be useful for operative planning should a reconstruction be warranted.

TABLE 57.1 Abnormal Head Shapes

Term	Definition	Fused Suture
Scaphocephaly	Boat head	Sagittal
Dolichocephaly	Long head	Sagittal
Clinocephaly	Saddle head	Sagittal
Brachycephaly	Short head	Bilateral coronal or lambdoid
Plagiocephaly	Oblique head	Unilateral coronal, lambdoid, deformational
Trigonocephaly	Triangular head	Metopic
Turricephaly	Towering head	Multiple
Acrocephaly	Peaked head	Multiple
Oxycephaly	Pointed head	Multiple
Hypsicephaly	High head	Multiple
Kleeblattschädel	Cloverleaf head	Multiple

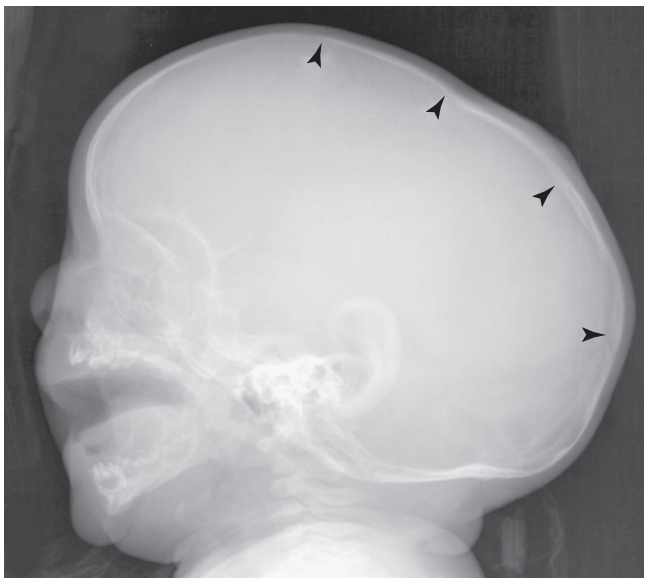
Nonsyndromic Craniosynostosis

Sagittal craniosynostosis is the most common type of nonsyndromic craniosynostosis. Premature sagittal suture fusion occurs in approximately 1:1000 live births with a 4:1 male to female preponderance.[9] A typical presentation will be an infant with scaphocephaly, or "boat-shaped head" (Figs. 57.19 and 57.20). In addition, there is often a narrow biparietal diameter, compensatory frontal bossing, temporal hollowing, and a prominent occipital protuberance. Neurologically, scaphocephalic infants are most often normal. Numerous surgical procedures exist to remodel the head, with most successful outcomes achieved when surgery

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is performed before 6 months of age.[9] This allows the brain growth, which triples in weight within a year, to help guide the remodeled head to a more normal shape.

Metopic craniosynostosis presents with trigonocephaly. A triangular-shaped forehead with a vertical keel over the forehead is noted clinically when the metopic suture prematurely fuses (Fig. 57.21). The anterior cranial vault is small, and there is usually associated hypotelorism, lateral canthi elevation, and temporal hollowing. Infants with severe craniofacial deformities can be treated surgically with endoscopic procedures or bifrontal craniotomy with orbital bar advancements.



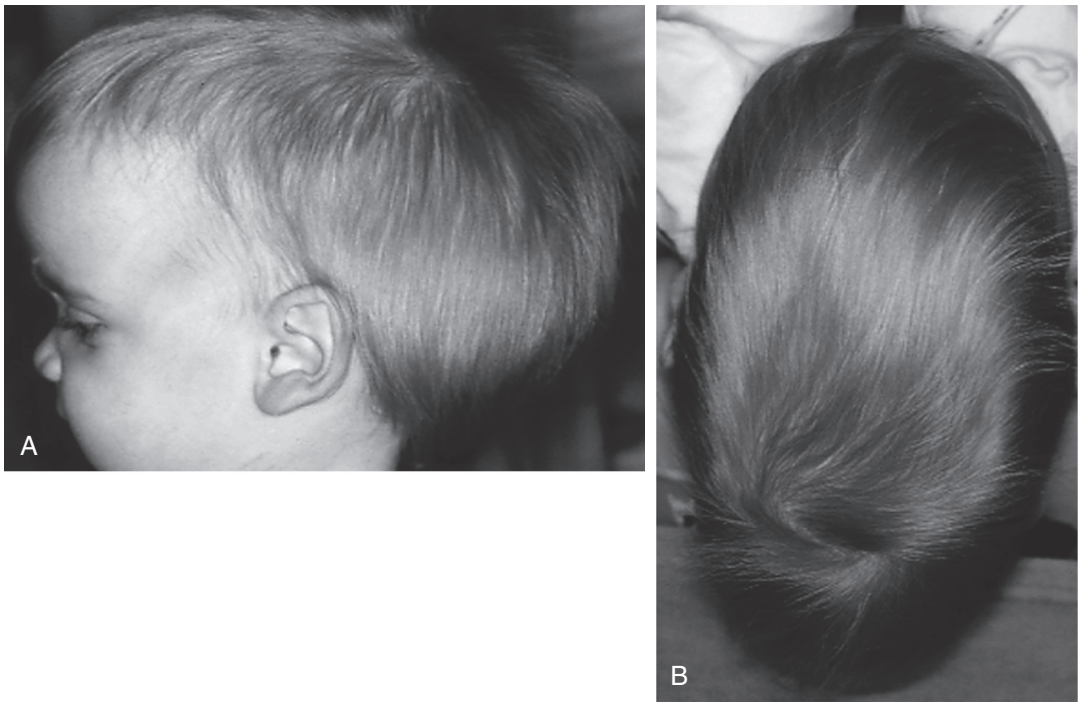
• **Fig. 57.19** Sagittal synostosis. Skull radiograph shows fusion of the sagittal suture (*arrowheads*) with scaphocephaly and frontal bossing.

Premature fusion of the coronal suture produces either plagiocephaly or brachycephaly, depending on whether one or bilateral coronal sutures are fused. Unilateral coronal synostosis is characterized by the "oblique" shaped head of anterior plagiocephaly. There is flattening of the ipsilateral forehead and compensatory bossing of the contralateral forehead (Fig. 57.22). The ipsilateral orbit is shallow with the superolateral margin drawn upward and backward, giving rise to the "harlequin eye" deformity seen radiographically (Fig. 57.23). Cranial vault reconstruction also includes craniotomy with orbital bar advancement.

Bicoronal craniosynostosis presents with brachycephaly, or "short" head. There are palpable ridges over both coronal sutures with the head foreshortened in the anterior–posterior plane. Sometimes, there is widening of the head and compensatory increased height, termed turricephaly (Fig. 57.24). Surgical correction is similar to that for unicoronal synostosis. Although most commonly nonsyndromic, all children with bicoronal synostosis should be evaluated to rule out underlying malformations, because premature bicoronal suture fusion is a hallmark pattern of syndromic craniosynostosis.[27]

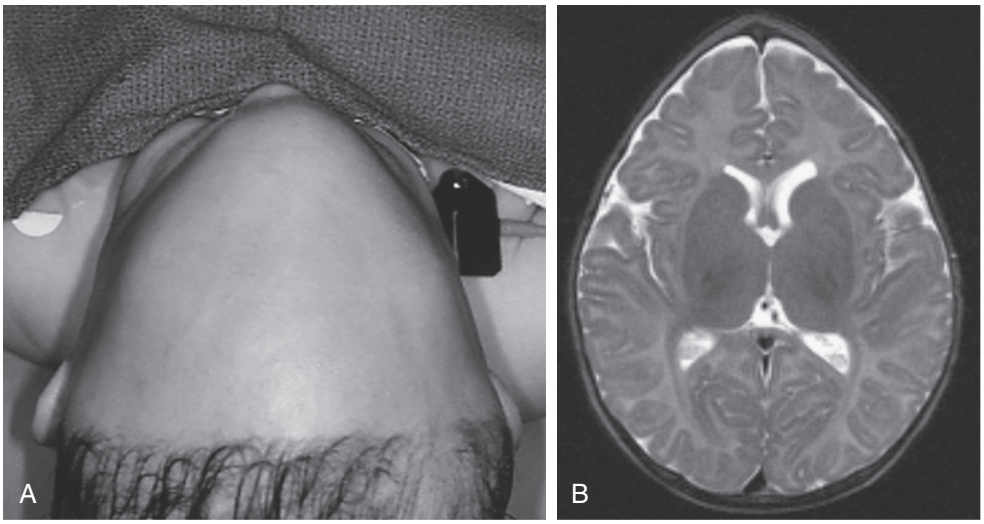
Positional Plagiocephaly

Also known as deformational posterior plagiocephaly, cranial asymmetry caused by flattening of the occiput is a common neurosurgical referral to rule out true craniosynostosis.

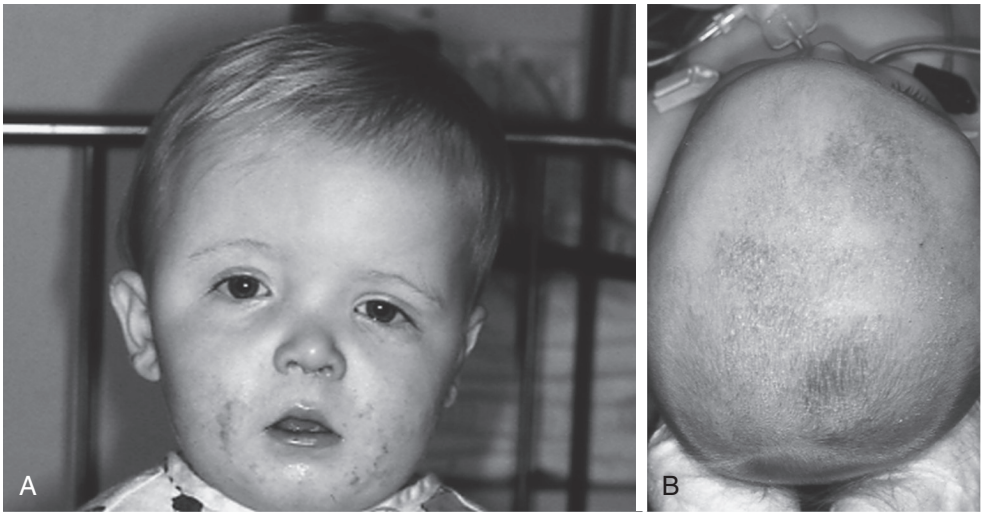


• **Fig. 57.20** Sagittal synostosis, with scaphocephaly, frontal bossing, and protuberance at the occiput. **A**, Side view. **B**, Top view.

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• **Fig. 57.21** Trigonocephaly secondary to premature fusion of the metopic suture. **A**, Top view. **B**, T1-weighted MRI.



• **Fig. 57.22** Unilateral right coronal synostosis. There is facial asymmetry, ipsilateral frontal flattening, and vertical orbital dystopia with inferior displacement of the contralateral orbit. **A**, Front view. **B**, Top view.

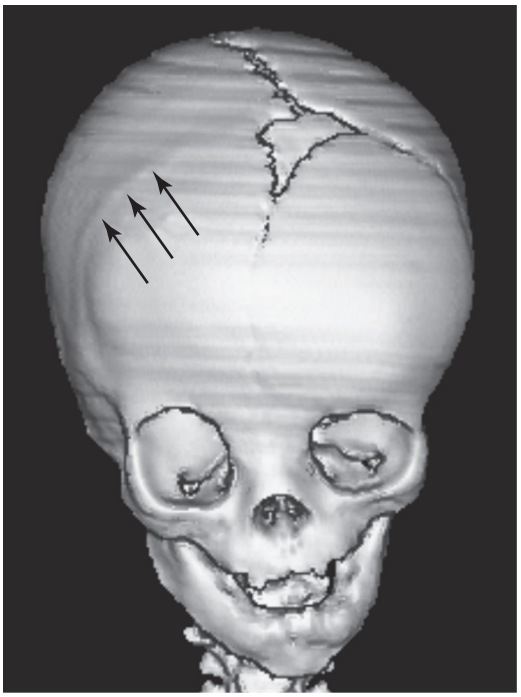
Often, a child will be referred with posterior plagiocephaly with concern for lambdoid craniosynostosis. Premature closure of the lambdoid suture is quite rare, estimated to account for approximately 3% of all craniosynostosis cases.[9] However, a thorough physical exam can quickly help decipher deformational from true plagiocephaly. In positional plagiocephaly, the head is typically described in shape of a parallelogram when viewed from above. There is unilateral occiput flattening, with ipsilateral frontal prominence. A major hallmark distinguishing positional plagiocephaly from plagiocephaly associated with lambdoid craniosynostosis is the position of the ipsilateral ear. It is displaced forward with both ears in the same horizontal plane in positional plagiocephaly from positional shifting of the ipsilateral skull, whereas it is displaced posteriorly in lambdoid synostosis from restriction of growth perpendicular to the ipsilateral lambdoid suture (Fig. 57.25).

Syndromic Craniosynostosis

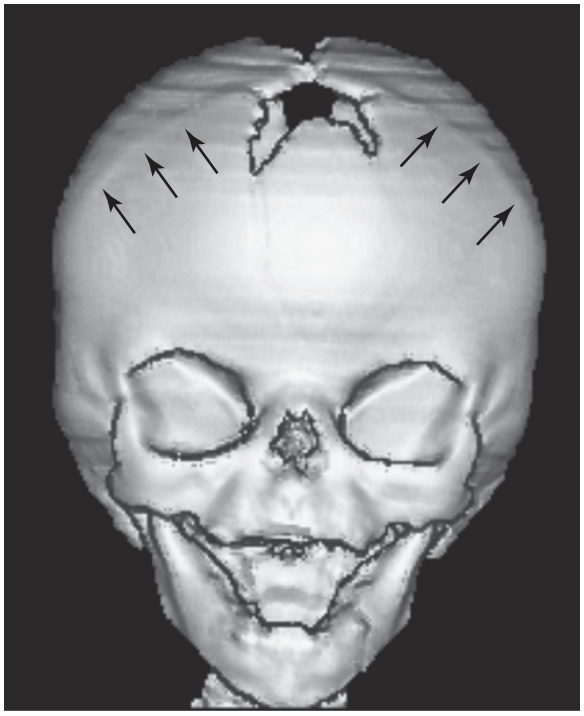
Craniofacial syndromes with craniosynostosis are often inherited in an autosomal dominant fashion. The most frequent syndromes have been localized to mutations encoding fibroblast growth receptor genes.[27] Clinically, there are a few associations common to craniofacial syndromes. Hearing loss, usually conductive, is shared by many of the syndromes. Respiratory difficulties, including obstructive sleep apnea, are common and are thought to be related to midface hypoplasia.[27] Various cognitive deficits are also often apparent, with or without the development of hydrocephalus.

Muenke syndrome is the most common of the syndromic craniosynostoses, afflicting as many as 1 in 30,000 live births.[27] It is inherited in an autosomal dominant fashion, with the *FGFR3* gene implicated. Most often, the coronal suture is involved in these patients, with bilateral

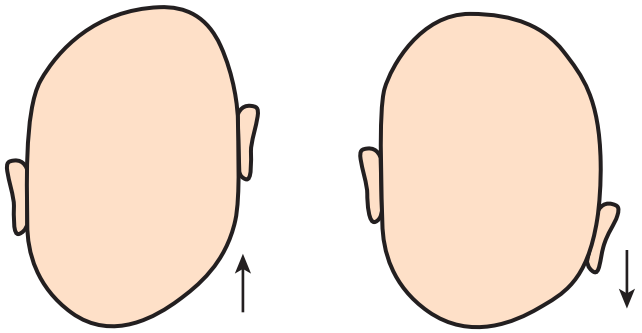
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• **Fig. 57.23** Unilateral right coronal synostosis (*arrows*) on three-dimensional CT scan. The ipsilateral orbit is drawn upward and backward (harlequin eye).



• **Fig. 57.24** Bicoronal synostosis (*arrows*). Three-dimensional CT scan shows brachyturricephaly.



• **Fig. 57.25** Deformational plagiocephaly (*left*) with right occipital flattening and anterior displacement of the ipsilateral ear. Right lambdoid synostosis (*right*) with right occipital flattening and posterior and inferior displacement of the ipsilateral ear.



• **Fig. 57.26** Apert syndrome. There is brachyturricephaly, maxillary hypoplasia, hypertelorism with downsloping of the palpebral fissures, and a depressed nasal bridge. The child also has symmetric syndactyly of the hands and feet.

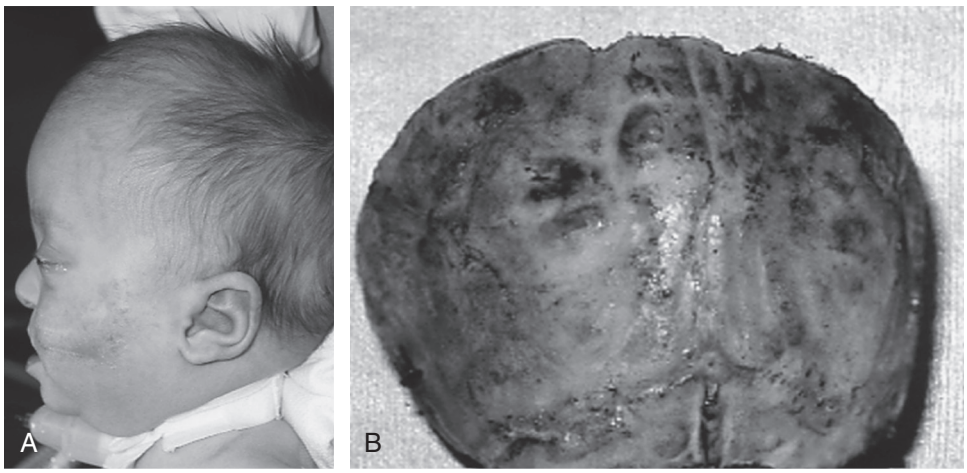
synostosis more common than unilateral. However, there is variability in presentation, because the spectrum of premature suture closure ranges from a single suture to pansynostosis. Sensorineural, rather than conductive, hearing loss is also more common in this syndrome compared to others. Genetic testing confirms the diagnosis. In addition to the calvarial shape predicated by which suture closes, there is also often mild midface hypoplasia with hypertelorism.

Apert syndrome can affect up to 1 in 65,000 births. Most mutations causing this syndrome are sporadic, although there are reports of autosomal dominant transmission.[27] The *FGFR2* gene is most often implicated. Clinically, the external head shape depends again on which suture(s) closes, but most often patients present at birth with brachyturricephaly with a flattened occiput (Fig. 57.26). Most often, the coronal sutures are fused with a widely open anterior fontanelle and metopic suture. Other hallmark features

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• **Fig. 57.27** Crouzon syndrome (craniofacial dysostosis) with brachyturricephaly, exophthalmos, and maxillary hypoplasia. **A**, Frontal view. **B**, Side view.



• **Fig. 57.28** Pfeiffer syndrome. **A**, Side view. There is brachyturricephaly, maxillary hypoplasia, and choanal atresia (note indwelling tracheostomy). **B,** Undersurface of the skull at craniofacial reconstruction demonstrates convolutional markings from increased intracranial pressure.

include maxillary hypoplasia, symmetric hand syndactyly, and cognitive delay.

Crouzon syndrome patients present similar in appearance to Apert syndrome; however, the craniofacial anomalies are not present at birth. Frequently, the coronal sutures are involved, and brachycephaly is most often observed. Other typical features include exophthalmos and maxillary hypoplasia (Fig. 57.27). Unlike Apert syndrome, cognitive delay is infrequent.

Other syndromes include Pfeiffer syndrome and Saethre-Chotzen syndromes. In Pfeiffer syndrome, there is usually involvement of the coronal sutures, although sagittal and lambdoid sutures are commonly involved as well. There is brachyturricephaly, maxillary hypoplasia, and choanal atresia (Fig. 57.28). Noncranial hallmark features of Pfeiffer syndrome include broad thumbs and great toes. Patients with Saethre-Chotzen syndrome present with brachycephaly, low-lying hairlines, ptosis, and hypertelorism.

Conclusion

Examination of the infant head shape and size is critical to evaluate for underlying pathologies that may impair neurologic development. Macrocephaly or accelerated head growth in the neonate should prompt evaluation for hydrocephalus or mass lesions. Premature infants remain at risk for germinal matrix hemorrhage which may predispose infants to post-hemorrhagic hydrocephalus. Finally, abnormalities in head shape should prompt evaluation for craniosynostosis, although positional plagiocephaly remains a much more common etiology for an abnormal head shape in an infant.

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Key Points

- An abnormally large head is a common sequela of hydrocephalus in infants; however, there are a range of causes of hydrocephalus in these patients.
- Early identification, surveillance, and intervention are critical to successful outcomes in hydrocephalus.
- A thorough physical exam will most often provide the diagnosis in the setting of an abnormal head shape.

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58

Spinal Dysraphisms

BYRON HILLS AND KRYSTAL TOMEI

Summary

This chapter reviews open and closed neural tube defects. We discuss imaging evaluation as well as physical exam findings. Finally, we discuss current trends in treatment and perinatal care.

Introduction

Neural tube defects (NTD) are the second-most common birth defect after congenital heart defects, affecting 1-2 in 1000 pregnancies worldwide. Spinal dysraphisms are a subset of neural tube defects and are classified as open or closed. The most common open spinal dysraphisms are meningocele and myelomeningocele. Closed spinal dysraphisms include a wider range of conditions, including spina bifida occulta, tethered cord, lipomyelomeningocele, split cord malformations, neuroenteric cyst, and several other conditions.[19] Although open spinal dysraphisms are usually compatible with postnatal survival, they can result in severe neurologic impairment correlating with the level of the lesion: inability to ambulate, urinary incontinence, hydrocephalus, scoliosis, and gastrointestinal (GI) disorders. Closed spinal dysraphisms are often less severe and sometimes asymptomatic but can cause severe neurologic impairment secondary to spinal cord tethering.[25] Given both the neurologic complexity and severity of these conditions, it is paramount to understanding the embryology, screening, management, and treatment to offer the best neurologic outcome for these patients.

Embryology

Understanding the embryology of spinal dysraphisms has helped in making advancements to improve the technology used when treating patients with spinal dysraphisms. Spinal dysraphisms result from a failure of one of the following processes: gastrulation, primary neurulation, disjunction, or secondary neurulation. Gastrulation is the process by which the bilaminar embryonic disc becomes trilaminar: consisting of mesoderm, endoderm, and ectoderm. When gastrulation occurs, a neuroenteric canal forms, creating a temporary connection between the dorsal and ventral surface of the trilaminar disc. Conditions such as split cord malformations and neuroenteric cysts are thought to arise from a persistent neuroenteric canal. Neurulation begins with the notochord-inducing formation of the central nervous system by signaling the ectodermal tissue to differentiate into the neuroectoderm and form the neural plate. The neural plate then folds inward until the edges of the plate contact one another, a process referred to as primary neurulation. Primary neurulation is thought to be initiated at multiple closure sites and proceeds in a zipperlike fashion, bidirectionally. At the end of primary neurulation, the neural tube separates from the surface ectoderm in a process called disjunction. During disjunction, the mesoderm migrates between the surface ectoderm and neural tube, forming the meninges, vertebrae, skull, and paraspinal muscles. Premature or incomplete disjunction can lead to lipomyelomeningocele and dermal sinus, respectively. Secondary neurulation represents the formation of spinal cord caudal to the midsacral region. During this process, multipotent cells come together to form a tail bud, which undergoes canalization to form the secondary neural tube.[9] Open spinal dysraphisms result from a severe delay or cessation of the progression of primary neurulation along the body axis. When the neural fold does not close properly the sclerotome is unable to cover the neuroepithelium, and a bifid vertebral canal results, leading to an open spinal dysraphism. Although unclear, it is believed that some closed spinal dysraphisms are a result of abnormalities of secondary neurulation, causing malformation of the lower sacral and coccygeal regions. This is thought to be the case, because these dysraphisms do not open to the external environment, resulting in tethering of the spinal cord because of faulty tissue separation, and the cell types contained within these dysraphisms usually have multiple germ layers, owing to the multipotential nature of the tail bud formed in secondary neurulation.[19]

Several signaling pathways and cellular functions are involved in the development of neural tube defects; these include planar cell polarity signaling (PCP), sonic hedgehog signaling (SHH), bone morphogenic signaling (BMP), grainyhead-like genes (GHRL), retinoid signaling (RA), and many cellular functions such as apoptosis and cellular proliferation. Several factors are responsible that can increase

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Abstract

Neural tube defects are one of the most common congenital anomalies encountered by neonatologists, occurring in 1-2 of 1000 pregnancies worldwide. Spinal dysraphisms are a small subset of neural tube defects ranging from severe conditions such as myelomeningocele to less severe conditions such as spina bifida occulta and are classified as open or closed. This book chapter highlights the embryology, pathology, and physical examination findings of various spinal dysraphisms. Finally, it offers insight into both the management and treatment of these conditions in hopes to provide the best care for these patients in the neonatal ICU.

Keywords

myelomeningocele
spina bifida
tethered cord
spinal dysraphism

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TABLE 58.1 Classification of Spinal Dysraphisms

Open Spinal Dysraphisms	Closed Spinal Dysraphism *With Subcutaneous Mass*	Closed Spinal Dysraphism *Without Subcutaneous Mass*
• Meningocele • Myelomeningocele	• Lipomyelomeningocele • Lipomyelocystocele • Terminal myelocystocele • Nonterminal myelocystocele	• Diastematomyelia • Neuroenteric cysts • Dermal Sinus • Caudal agenesis • Segmental spinal dysgenesis • Abnormal filum terminale • Intradural lipoma • Filar lipoma

the risk of developing neural tube defects and include both environmental and genetic factors. Environmental factors that affect the embryology of the central nervous system (CNS) and lead to an increased risk of development of NTDs include valproic acid, fumonisin (a fungal product), carbamazepine, trimethoprim, folate or vitamin B12 deficiency, inositol, and maternal diabetes mellitus. Genetic factors include the C67TT and a1298C polymorphisms of the gene methylenetetrahydrofolate reductase, which result in a 1.8-fold increased risk of NTDs and several modifier genes.[19]

Pathology

Understanding the pathology of spinal dysraphisms is important in diagnosis and management, including both surgical and nonsurgical treatments. Spinal dysraphisms are typically divided into open and closed dysraphisms. Open dysraphisms include meningocele and myelomeningocele (Table 58.1).

Open Spinal Dysraphisms

Meningoceles are usually classified by location as either posterior lumbar, sacral, or thoracic; posterior cervical and limited dorsal myeloschisis; and anterior sacral. These lesions vary in size, are pedunculated, transilluminate well, and may be covered by cutaneous elements (Fig. 58.1). In meningoceles, the meninges herniate through a defect in the posterior vertebral arches, but the spinal cord remains in the spinal canal. Thus, the spinal cord and nerve roots are normal in their structure and position in the spinal canal.[27] Myelomeningocele represents 50% of all neural tube defects. It is often subdivided into spinal bifida cystica and spina bifida aperta. In spina bifida cystica, there is an open spinal cord covered by a meningeal sac. In spina bifida aperta, the spinal cord is exposed (Fig. 58.2). Myelomeningocele-affected infants typically show neurologic deficits below the level of the lesion and may be associated with other conditions such as hydrocephalus, skeletal, renal, and GI disorders.[19,25]



• **Fig. 58.1** Meningocele—note the large fluid-filled sac protruding from the lumbar region. The skin edges terminate at the junction to the meninges.

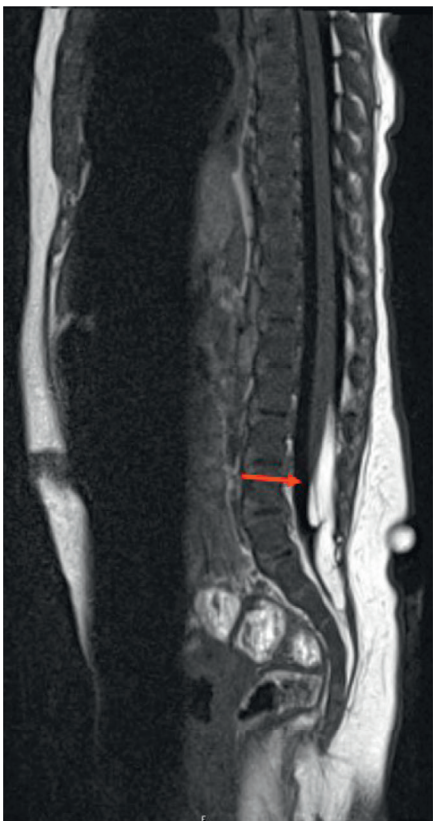


• **Fig. 58.2** Myelomeningocele—note the large central placode and open defect without an overlying meningeal sac.

Closed Spinal Dysraphisms

Closed spinal dysraphisms are subdivided into categories based on whether a subcutaneous mass is present. Closed spinal dysraphisms consist of spina bifida occulta, lipomyelomeningocele, dorsal dermal sinus, split cord malformation,

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• **Fig. 58.3** Lipomyelomeningocele—the red arrow denotes the area of tethering of the subcutaneous lipoma to the neural placode.



• **Fig. 58.4** Dermal sinus tract—similar to a lipomyelomeningocele but with an additional fibrous tract (red arrow) extending from a superficial skin dimple to the placode.

neuroenteric cyst, and several other conditions. They are often grouped into a generic term "tethered cord syndrome" that more appropriately describes the constellation of symptoms that can be associated with these disorders.

Spina bifida occulta is the mildest form of spina bifida and occurs when one or more vertebrae are split at the level of the spinous processes, but the spinal cord and corresponding nerve roots remain intact and in place. In this entity, the vertebral defect is covered by skin and can be associated with several cutaneous stigmata, including midline dimple, tuft of hair, change in skin coloration, sinus tract, and hemangiomatic lesion. Spina bifida occulta may be asymptomatic for years but can present later in life with varying degrees of neurologic compromise if associated with other closed dysraphisms.[19]

Lipomyelomeningocele is a complex closed spinal dysraphism that usually occurs in the lumbar or sacral region. It is characterized by a subcutaneous lipoma that extends through the lumbosacral fascia, vertebral arches, and dura to attach to the spinal cord as a tethering mass (Fig. 58.3). Given its association with spinal cord tethering, severe neurologic deterioration can result if left untreated. Nevertheless, because the subcutaneous fatty mass is usually evident at birth, patients are often diagnosed prior to neurologic symptoms developing, with as many as 48% of patients being neurologically intact at the time of initial diagnosis. Spinal lipomas differ in that the lipoma does not extend through the lumbar fascia and typically remains encased within the spinal canal. The various forms of lipomas are categorized into three types that are defined by their anatomic attachment to the spinal cord: dorsal, transitional, and caudal (or chaotic). In the dorsal type, there is an attachment of the lipoma with the dorsal spinal cord at the level of myeloschisis, or neural placode. The transitional type has a lipomatous attachment that extends beyond the level of myeloschisis down to the conus medullaris and may involve the nerve roots. The caudal type has a lipomatous attachment, which arises from the caudal end of the conus medullaris, often encasing the nerve roots. Patients with lipomyelomeningocele have both a congenital malformation of their spinal cord as well as a risk of retethering their spinal cord after release due to scarring. These patients may develop neurogenic bladder or bowel, orthopedic deformities, scoliosis, and spasticity as a result of their tethered cord.[24]

Dorsal dermal sinus is a rare spinal dysraphism that involves a tract lined by epithelium that traverses a variable depth usually terminating in or on the thecal sac (Fig. 58.4). This type of closed dysraphism is usually seen at the extremes of the neuraxis and may be associated with life-threatening

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infections, such as meningitis from bacteria tracking into the cerebrospinal fluid space. It can be associated with symptoms of a tethered cord, diastematomyelia, and inclusion cysts. Thus, despite the benign external appearance of this dysraphism, it can result in neurologic deficit and harbor great risks for patients if not addressed in a timely manner.[9,27]

Diastematomyelia is commonly referred to as split cord malformation and describes a phenomenon in which the spinal cord is split into two hemicords with each hemicord having its own set of ventral and dorsal nerve roots. They may be encased in a single dural sac, or the dural sac may be split at the level of the dysraphism. In addition, a fibrous or bony septum may be present between the hemicords. Frequently, the conus medullaris is low lying and tethered by a thickened filum terminale. This dysraphism can be associated with other dysraphisms such as myelomeningoceles and neuroenteric cyst. There is also a high instance of bony vertebral column abnormalities with split cord malformations, including butterfly vertebra, a widened spinal canal, fusion of pedicles, or failure of vertebral body segmentation. Neuroenteric cysts are closely associated with split cord malformation, and they often occur together because they both occur due to errors in gastrulation. Neuroenteric cysts occur most frequently at the lower cervical or upper thoracic regions and at the conus medullaris. These cysts can be extra- or intradural and, if intradural, can be anterior, posterior, or within the spinal cord.[12,28]

An abnormal filum terminale is the mildest form of a closed dysraphism, which can result in a tethered spinal cord. A filum is considered thickened when it is greater than 2 mm in diameter and contains an increased amount of connective tissue or fat with a low-lying conus medullaris. Similar to the other forms of closed spinal dysraphisms, these patients may be at risk of developing tethered cord syndrome and, if untreated, developing neurogenic bladder or lower extremity issues.[27]

Prenatal Screening and Prevention

In the early 1970s, maternal serum screening for fetal congenital malformations began with the advent of alpha fetoprotein (AFP) screening for neural tube defects. Today, screening has evolved with highly complex protocols utilizing cell-free DNA markers. However, AFP levels still represent the mainstay of screening for open neural tube defects. Maternal serum AFP screening is conducted between 15 and 21 weeks of gestation. Median maternal serum AFP levels increase steadily from 15-21 weeks' gestation. To account for the upward trend in maternal AFP that occurs in pregnancy, values are converted into multiples of the gestational age-specific median (MoMs). The typical cutoff for maternal serum AFP screening is 2.0-2.5 MoM, but using a cutoff of 2.0 MoM increases detection of open spina bifida by 10%. This cutoff brings the specificity for open spina bifida cases to 90%, and the sensitivity for anencephaly to 100% for the maternal serum AFP assay. Patients with elevated maternal serum AFP can opt to have amniocentesis to increase the likelihood of detection.[17] The amniotic fluid AFP level is then tested, and elevations along with a positive acetylcholinesterase confirmation test can detect 96% of open spina bifida cases. Ultrasound can also be used as a screening tool to detect open neural tube defects, with a sensitivity of 97% and specificity of 100% in the hands of an experienced sonographer.[18]

Risk of neural tube defects in humans is increased with folic acid deficiency and exposure of the embryo to excessive retinoic acid or vitamin A. Several studies have shown that 70% of neural tube defects can be prevented by preconception folic acid supplementation of 0.4 mg/day.[17,18] Mothers with one affected infant are at a higher rate than the general population for a second affected infant and should take 4 mg/day of folic acid before and during subsequent pregnancies.

Cutaneous Stigmata

Cutaneous stigmata are commonly found in closed spinal dysraphisms, because the skin and nervous system share an intimate embryologic origin. Recognition of cutaneous stigmata commonly associated with closed spinal dysraphisms is important, because early identification and intervention may prevent irreversible neurologic damage associated with tethered cord syndrome. Cutaneous stigmata are found in 4.2%-7.2% of all neonates with closed spina bifida, and the presence of two or more cutaneous stigmata has a high predictive value of a closed spinal dysraphism. Additionally, there should also be a high suspicion for closed spinal dysraphism when cutaneous stigmata occur in combination with anogenital or urogenital malformations. When assessing patients with cutaneous lumbosacral stigmata, it is important to recognize concerning features, thus these stigmata are typically separated into high-, intermediate-, and low-risk categories. High-risk cutaneous findings include two or more cutaneous lumbosacral stigmata, infantile hemangioma greater than 2.5 cm, dermoid cyst or sinus, lipoma, acrochordon, pseudotail, true tail, aplasia cutis, and congenital scars. Intermediate-risk cutaneous findings include atypical dimple (>5 mm diameter or >2.5 cm from anal verge), infantile hemangioma <2.5 cm, and hypertrichosis. Low-risk cutaneous findings include simple dimple, hyper- or hypopigmentation, melanocytic nevi, teratomas, port-wine stain, or telangiectases (Table 58.2). Based on the risk category, certain imaging modalities are recommended. MRI is recommended for all high-risk cutaneous findings. For intermediate-risk cutaneous finding, ultrasound is recommended for those <6 months and MRI for those >6 months. Lastly, most cases of low-risk cutaneous stigmata do not require imaging; if overly concerned, ultrasound can be performed.[26]

Imaging

The two major imaging modalities used to confirm and characterize spinal dysraphisms are spinal ultrasonography

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TABLE 58.2 Common Neurocutaneous Stigmata Separated Into Risk Category

High Risk	Intermediate Risk	Low Risk
• Lipoma • Acrochordon • Pseudotail • Aplasia cutis • Dermoid cyst or dermal sinus • Infantile hemangioma • >2.5 cm • >2 Cutaneous stigmata	• Atypical dimple • Infantile hemangioma <2.5 cm • Hypertrichosis	• Simple dimple • Hyper-or hypopigmentation • Melanocytic nevi • Teratomas • Port-wine stain or telangiectases

and MRI. Ultrasound is possible in newborns and in early infancy prior to 6 months of age because of the lack of ossification of the predominantly cartilaginous posterior elements of the spine. Spinal ultrasound can sometimes be performed after 6 months if a persistent posterior spinal defect is present. However, as the posterior elements ossify, the quality of ultrasound images decrease. MRI is extremely useful in the evaluation of pediatric spinal anomalies. Given the resolution provided by MRI of the soft tissues, it allows for improved diagnosis of spinal dysraphisms and has enhanced the possibility of earlier and case-tailored treatment, especially in the case of complex dysraphisms where there may be rotation of the neural elements. Thus, MRI is the gold standard for imaging spinal dysraphisms.[13]

Ultrasonography is widely used today for prenatal screening for spinal dysraphism. It represents a cost-effective imaging modality for diagnosing and treating spinal anomalies in utero. High-resolution ultrasonography offered today can accurately localize the site of osseous and soft tissue defects. This has made it possible to accurately diagnose conditions such as myelomeningocele, lipomyelomeningocele, and diastematomyelia in utero. During the second trimester fetal anatomic survey, it is important to visualize the longitudinal, sagittal, coronal, and axial images of the spine. This allows for a complete view of the spine to analyze for spinal anomalies. If the transabdominal scan is not optimal, transvaginal scans are done to evaluate the spine. In addition to localization of the conus medullaris and spinal defects, it is important to measure any visualized sacs, especially if in utero repair is planned, as larger defects may require tissue matrix for closure.[21] The components of any visualized sac are analyzed to determine the presence of neural elements, which appear as linear echogenic areas surrounded by anechoic cerebrospinal fluid. The neural placode of the myelomeningocele can also be visualized and appears as a hypoechoic, ovoid region within the sac.[4] The wall of the myelomeningocele is also assessed on the ultrasound and characterized as thin or thick. The accuracy of ultrasonography varies greatly and depends on operator experience, maternal obesity, fetal movement, and fetal positioning. Nevertheless, correct identification of spinal anomalies and associated CNS and non-CNS abnormalities has been reported to have a sensitivity rate of 97% and specificity rate of 100%.[6,9]

MRI is a useful adjunct imaging modality in the fetus, infants, and children for detecting and further characterizing spinal anomalies. The high resolution of the soft tissues offered by this imaging modality can provide better visualization and more understanding of patient-specific pathology prior to surgical intervention. It is useful in detecting the degree of hindbrain herniation prior to repair and evaluating both brain and spinal cord anatomy when ultrasound is limited. Fetal MRI is important to obtain when in utero repair of spinal dysraphism is being considered. If good-quality images are able to be obtained prenatally, it may eliminate the need for postnatal images, which often require sedation to obtain a quality image.[2,14,22]

Overall Management

Spinal neural tube defects can cause a wide variety of presentations and neurologic deficits. Thus it is of the utmost importance to properly manage these patients to improve their neurologic outcome and prevent infection in open spinal defects. The urgency and timing of intervention differs greatly between open and closed spinal dysraphism. Open spinal dysraphism requires more urgent management and intervention, because the neural tissue and cerebrospinal fluid are directly exposed to the outside environment, predisposing these children to infections such as meningitis. Myelomeningocele is one of the most morbid and debilitating of the open spinal neural tube defects. It can cause severe neurologic deficit, hydrocephalus, and meningitis in the postnatal period. Although some centers repair myelomeningoceles in utero during the prenatal period, postnatal repair of myelomeningoceles remains the standard of care. Nevertheless, no specific guidelines exist regarding the management of these conditions. Although each institution may differ in how they manage myelomeningoceles, the overall premise of management remains the same.[7] (See also Chapter 13.)

When myelomeningocele is diagnosed in utero, the first issue that arises is mode of delivery. Many institutions advocate for cesarean section prior to labor when compared to

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TABLE 58.3 Corresponding Motor and Sensory Levels for Assessment of the Functional Level of a Patient With Myelomeningocele

Level	Motor Function	Sensory Level
T10	Rectus	Umbilicus
L1	Hip flexion	Anterolateral thigh
L2	Hip adduction	Anteromedial thigh
L3	Knee extension	Knee and shin
L4	Dorsiflexion	Dorsum of foot
L5	Extensor Hallucis Longus	1st-2nd toe interspace
S1	Plantar Flexion	Plantar foot

Note: In general, hip flexion indicates higher lumbar, knee extension indicates mid-lumbar, and isolated club feet indicate a low-lumbar lesion.

TABLE 58.4 Signs and Symptoms of Hydrocephalus and Symptomatic Chiari II Malformation

Hydrocephalus	Chiari II Malformation
• Bulging anterior fontanelle • Increasing head circumference • Sunsetting eyes • Dilated scalp veins • Weakness • Irritability, vomiting • Hemodynamic instability (Cushing's triad)	• Nystagmus • Apnea • Gagging • Swallowing difficulties • Syncope • Weakness • Hemodynamic instability (lower brainstem)

vaginal delivery or cesarean section after labor. Some studies have shown improved motor function at 2 years of age in patients delivered via cesarean section prior to labor when compared to any mode of delivery after labor. Other studies have shown that once labor commences, there is no change in outcome based on mode of delivery. Given the impact upon the mother, if a cesarean section is recommended, this is often a discussion between the obstetrician and the neurosurgeon in the prenatal period that takes into consideration the presence or absence of hydrocephalus, which may preclude a vaginal delivery if the head size is too large. After the fetus is delivered, focus turns to prevention of infection, including prophylactic antibiotics, maintaining the sterility of the open dysraphism with sterile coverings, and timing of intervention.[3,15]

After delivery of the fetus, the size and location of the lesion should be noted. The lesion should also be assessed for leaking of cerebrospinal fluid. When assessing the lesion, sterile, nonlatex gloves are recommended to minimize the risk of latex sensitization.[11,23] The defect should be covered with a sterile, saline-soaked dressing. Larger defects should be covered by a plastic wrap to prevent heat loss. The infant should also be placed in a prone or lateral position to avoid prolonged pressure on the lesion.[20] A thorough neurologic examination should also be performed with the objective of defining the baseline neuropathology of the patient, paying attention to the observation of spontaneous activity, extent of muscle weakness, leg posture and paralysis, response to sensation, deep tendon reflexes, and anocutaneous reflex for assessment of spinal cord function. The functional level of the lesion is as important as the anatomic level, as there may not be an exact correlation depending on the functionality of the exposed neural tissue (Table 58.3). The newborn should also be evaluated for club feet, flexion, or extension of the hips, knees, or ankles, as this helps to define the level of the lesion. In addition, one should evaluate for signs of hydrocephalus, including a measurement of head circumference, assessment of the fontanelle and sutures for signs of splaying or fullness, and signs of brain stem compression from a Chiari II malformation. Concerning signs of apnea or bradycardia, lower brainstem dysfunction may be an indication to treat the hydrocephalus, and persistence of symptoms after treatment is a poor prognostic sign (Table 58.4). The spinal column may demonstrate kyphosis, and assessment should include evaluation for other congenital anomalies involving the heart, airway, kidneys, or GI tract.

Although there is no consensus for the specific type of prophylactic antibiotic used in these patients, the agents often used are ampicillin in addition to either gentamycin or cefotaxime. This provides coverage for group B streptococcus and gram-negative bacteria. Antibiotics should be started within 1 hour of birth and continued until at least 48 hours after repair. Prophylactic antibiotics and wound sterility greatly reduce the risk of early CNS infection, but timely repair of the defect also significantly reduces the risk of CNS infection.[8] Postnatal repair should be performed within 48-72 hours after birth.[5,7,10] However, most would advocate closure within 24-48 hours. Postoperatively, patients should remain in the prone or lateral position to avoid pressure on the incision and allow for wound healing. Close attention should also be placed to preventing urine or feces from entering the wound, and bumpers with drapes are often used between the wound and diaper to prevent diaper contents from affecting the wound and causing an infection. Given the high risk of hydrocephalus in this patient population, the infant should be monitored for signs and symptoms of hydrocephalus, and at the very least get daily head circumference measurements and weekly head ultrasounds.[7]

Closed spinal dysraphism management is less urgent than open spinal dysraphisms. This is because the defect is covered by skin and not directly exposed to the outside environment. Thus, prophylactic antibiotics are not needed for these conditions, with the potential exception being dermal sinus tracts that have direct extension into the thecal sac and an opening at the skin. Nevertheless, thorough neurologic examination should be performed in these patients to

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assess for any neurologic deficit given the close association with tethered spinal cord. Thorough cutaneous examination should also be performed to look for cutaneous stigmata for a subcutaneous fatty mass as in the case of lipomyelomeningocele. MRI of the entire spine is recommended for patients who have two or more cutaneous lumbosacral spine lesions, a subcutaneous back mass, or neurologic symptoms concerning for tethered cord syndrome. MRI or ultrasound is also recommended for patients with isolated midline cutaneous lumbosacral spine lesion. Patients with radiographically confirmed closed spinal dysraphism should be referred to neurosurgery for an evaluation. Surgery in these cases is nonurgent and is usually performed more urgently in patients with neurologic deficits in the setting of tethered cord. Conservative management with observation is reasonable for patients who are asymptomatic from a closed spinal dysraphism, although surgery may be considered as a prophylactic means of treatment because of the high risk of neurologic deterioration and potential for irreversible neurologic injury.[10,24]

Surgical Treatment

Open spinal dysraphisms require timely surgical intervention to reduce the risk of early CNS infection and further neurologic decline. Myelomeningocele, the most common open spinal dysraphism, can be treated either pre- or postnatally, although postnatal treatment still represents the standard of care. The Management of Myelomeningocele Study (MOMS) was a randomized study of 183 patients at several pediatric centers across the United States comparing prenatal to postnatal repair of myelomeningocele and published in 2011. Patients were randomly assigned to undergo either prenatal repair of the myelomeningocele before 26 weeks' gestation or standard postnatal repair. The primary endpoints of the study included fetal or neonatal death, need for shunt at 12 months, as well as mental development and motor function at 30 months. Of the 183 patients enrolled, 158 patients were evaluated at 12 months and results showed that only 40% of patients required shunt after prenatal repair compared to 82% in the postnatal group. The study also showed that the prenatal group had improved mental and motor development at 30 months when compared to the postnatal group. Secondary outcomes such as hindbrain herniation and ambulation at 30 months were also improved in the prenatal group. Although the study offered promising results, enrollment was stopped due to efficacy secondary to increased risk of preterm delivery and uterine dehiscence at delivery. In addition, the population of mothers who were able to enroll in the study due to the location restrictions associated with fetal repair narrowed the applicable population of both appropriate maternal candidates and size and location of lesion. The MOMS II trial is ongoing to look at delayed results and will hopefully provide more insight on the risks and benefits for prenatal repair.[1,16] Since the MOMS trial, other centers have started performing fetoscopic repair; however, these results are not widespread yet. Given the risks of prenatal repair as well as that these interventions are occurring at limited centers, postnatal repair still represents the standard of care for treatment. Repair is usually performed in a timely manner, between 24-48 hours, and involves approximation of the lateral edges of the open neural plate in the midline to form a neural tube, closure of a meningeal sac, and closure of the skin over the open defect. Although there is no specific data to support neural tube closure, it is believed that reforming the neural tube decreases the incidence of tethered spinal cord by decreasing the raw edge at risk of scarring. The most common condition to develop after repair is hydrocephalus, and infants must be monitored closely with head circumferences and head ultrasounds. Upwards of 60%-80% of infants with myelomeningocele develop hydrocephalus and require placement of shunt.[29] Other conditions that require monitoring and possible treatment in this patient population include Chiari II malformation, tethered cord, shunt malfunction, neurogenic bladder and bowel, and several orthopedic deformities.[10]

Closed spinal dysraphism is amenable to a delay in surgical intervention when compared to the open dysraphism, as the defect is not exposed to the external environment. Surgical treatment is often required for infants with tethered cord syndrome with a neurologic deficit, as some patients can be asymptomatic from their closed spinal dysraphism. Surgical treatment involves removal of the subcutaneous mass (if any), identification of the defect and release of the tethered, possible release of the filum terminale, preservation of neural elements, and prevention of retethering of the spinal cord. Given the complexity of the surgery for neural tube defects, surgery is not without significant risks. Common risks of surgical intervention include neurologic decline from tethered cord or secondary to nerve injury during the surgery, incomplete wound healing or wound dehiscence, infection, and meningitis. Patients with lipomyelomeningocele have a complication rate between 10% and 30%, a 5.8% risk of worse neurologic function after surgery, and between a 10% and 20% risk of retethering postoperatively.[24]

Conclusion

Spinal neural tube defects are a diverse group of congenital spinal anomalies and can result in severe neurologic outcomes. These conditions range from open spinal dysraphisms, which require prompt delivery, ICU management, and surgical intervention, to closed spinal dysraphism which may initially be asymptomatic, and can be treated in a delayed fashion. These infants may have other severe conditions that can require complex management in the neonatal ICU. Thus, it is paramount for clinicians to understand the embryology, pathogenesis, physical examination findings, management, and treatment to provide the optimal care for these patients in the ICU.

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Key Points

- Spinal dysraphisms include both open and closed defects with varying degrees of neurologic impairment.
- Open defects include meningocele and myelomeningocele, which may be repaired prenatally but more commonly are repaired postnatally and warrant urgent surgical repair and perinatal antibiotic prophylaxis to prevent meningitis.
- Monitoring for signs of infection, hydrocephalus, and symptoms of a Chiari II malformation are critical in the perinatal period.
- Closed spinal dysraphisms may be amenable to delayed treatment to prevent neurologic decline from a tethered spinal cord.

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Hearing Loss in the Newborn Infant

BETTY VOHR

Background

Tremendous progress has been made during the past 25 years in the identification of hearing loss (HL) in newborns. The National Institutes of Health issued a "Consensus Statement on Early Identification of Hearing Impairment in Infants and Young Children" in 1993 that concluded that all infants admitted to the neonatal intensive care unit (NICU) should be screened for HL before hospital discharge and that universal hearing screening should be implemented for all infants within the first 3 months of life.[47] The percentage of infants screened for HL in the United States has increased from 46% in 1999 to 98.4% in 2014 (https://www.cdc.gov/ncbddd/hearingloss/2014-data/2014_ehdi_hsfs_summary_h.pdf). The percentage of infants who fail the screening process is about 1.6%, and rates of permanent HL subsequently diagnosed by comprehensive audiology testing range from 1-3 per 1000, making congenital HL the most common birth defect diagnosed as a result of the newborn screening process. However, a report to assess the impact of universal hearing screening in a large cohort of infants identified a prevalence of deafness by school age of 3.65/1000 compared to a neonatal rate of 1.79/1000.[69] It is important to recognize that the neonatal screen does not identify all HL and is least sensitive to mild impairments. Undetected, HL in young infants and children negatively affects communication development, academic achievement, literacy, and social and emotional development,[73,77] whereas early identification and intervention, particularly within the first 6 months of life, clearly provide benefit for communication development in infants.[41,46,63-66,73] There is accumulating evidence that the brain may be optimally responsive to language input early in life.[13,14,29,59]

Based on these findings, the Joint Committee on Infant Hearing 2007 Position Statement published the 1-3-6 recommendation to maximize the outcomes of infants with all degrees of HL[3]: 1) All infants in the NICU and well-baby nursery should be screened for HL no later than 1 month of age. 2) Infants who do not pass the screen should have a comprehensive evaluation by an audiologist skilled in assessing infants and children, no later than 3 months of age for confirmation of hearing status. 3) Infants with confirmed HL should receive appropriate intervention no later than 6 months of age from professionals with expertise in HL and deafness in infants and young children.[75]

Normal Hearing and Hearing Loss

The ear consists of outer, middle, and inner components. The external ear includes the pinna and the outer ear canal. Sound waves travel through the air and are conducted through the outer ear canal to the tympanic membrane, where vibrations enter the middle ear and are amplified and transmitted through the ossicles to the fluid within the cochlea (inner ear). Sound waves in the inner ear are transmitted through the fluid and stimulate both the outer and inner hair cells of the cochlea. The outer hair cells respond to sound energy by producing an echo of sounds called otoacoustic emissions, and the inner hair cells act by converting mechanical energy into electrical energy transmitted to the cochlear branch of the eighth cranial nerve, the brainstem, and finally the auditory cortex for perception of the meaning of sounds. In normal hearing individuals, all components of the pathway are intact and functioning. Blockage of sound conduction in the outer or middle ear may result in either a transient (fluid or debris) or permanent (anatomic abnormality such as atresia or microtia) conductive HL. Failure of sound transmission within the cochlea, outer and inner hair cells, and eighth cranial nerve are a manifestation of sensorineural HL, whereas pathology of the inner hair cells and eighth cranial nerve with intact outer hair cells is characteristic of neural HL, also referred to as *auditory neuropathy* or *auditory dyssynchrony*.[11,57,60]

Hearing loss can be classified as bilateral or unilateral and as slight, mild, moderate, severe, or profound. Hearing loss severity is defined by measuring the hearing threshold in decibels (dB) across frequencies (Box 59.1). Normal hearing has a threshold of 10-15 dB. It is important to recognize that the presence of even slight and mild HL can impact on language development in young children and may be progressive. For children with bilateral HL, the severity of loss is based on the better-functioning ear.[6]

The types of transient and permanent HL that can be identified at birth with newborn screening include sensorineural, neural, and conductive (Table 59.1). Transient conductive HL may also be present, especially in infants who

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Abstract

Rates of permanent hearing loss subsequently diagnosed by comprehensive audiology testing range from 1 to 3 per 1000, making congenital hearing loss the most common birth defect diagnosed as a result of the newborn screening process. Permanent hearing loss is found in association with genetic mutations, over 400 congenital syndromes, and medical risk factors such as extreme prematurity and CMV infection. Undetected hearing loss in infants and children negatively affects communication development, academic achievement, literacy, and social-emotional development. There is substantial evidence that early diagnosis and intervention for infants and young children with permanent hearing loss is associated with improved outcomes. The current EHDI 1-3-6 recommendation for success is to screen by 1 month, diagnose by 3 months, and provide appropriate intervention services consistent with family choice by 6 months. Successful care coordination of the child with hearing loss requires the partnering of the primary care provider, audiologist, otolaryngologist, early intervention provider, developmental pediatrician, geneticist, and family.

Keywords

hearing loss
risk factors
diagnosis
early intervention
language
outcomes

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• BOX 59.1 Definitions of Degrees of Hearing Loss

• No hearing loss	10-15 dB
• Slight	16-25 dB
• Mild	26-40 dB
• Moderate	41-55 dB
• Moderately severe	56-70 dB
• Severe	71-90 dB
• Profound	≥ 91 dB

TABLE 59.1 Types of Hearing Loss

Type	Characteristics
Sensorineural	Pathology involving cranial nerve VIII and outer hair cells and inner hair cells of the cochlea that impairs neuroconduction of sound energy to the brainstem
Permanent conductive	Anatomic obstruction of the outer ear (atresia) or middle ear (fusion of ossicles) that blocks transmission of sound
Neural or auditory neuropathy or auditory dyssynchrony	Pathology of the myelinated fibers of cranial nerve VIII or the inner hair cells that impairs neuroconduction of sound energy to the brainstem. The function of the outer hair cells remains intact.
Transient conductive	Debris in the ear canal or fluid in the middle ear that blocks the passage of sound waves to the inner ear
Mixed hearing loss	A combination of sensorineural or neural HL with transient or permanent conductive HL

have been hospitalized in a NICU. Mixed HL is a combination of permanent HL and transient conductive HL.

Neonatal hearing screening programs in the United States are conducted under the guidance of an audiologist. An audiologist, experienced in assessing infants and young children, is responsible for completing the comprehensive diagnostic assessment needed to confirm the diagnosis of HL. Increasing numbers of NICUs are completing the diagnostic assessment prior to discharge to avoid a delay in the diagnosis for the most medically high-risk infants.

Tests for Hearing Loss

Screening and diagnostic hearing tests are shown in Table 59.2. Physiologic tests include those that measure electrical activity or reflexes and include otoacoustic emissions (OAEs) and auditory brainstem response (ABR) testing. These tests do not require an active response from the infant and can be performed when the infant is asleep or quiet awake. Otoacoustic emission screen measurements are obtained using a sensitive microphone within a probe inserted into the ear canal that records the sound produced by the outer hair cells of a normal cochlea in response to a sound stimulus. Abnormal outer and middle ear function caused by blockage or background noise may interfere with recording OAEs. Automated auditory brainstem response (AABR) for screening and ABR for diagnostic testing are obtained from surface electrodes that record neural activity in the cochlea, outer and inner hair cells, auditory nerve, and brainstem in response to a click stimulus. In AABR, a predetermined algorithm provides an automated pass-or-fail response to the presence or absence of wave 5 on the ABR. Both OAE and ABR detect sensorineural and conductive HL. A false-positive fail screen for permanent HL may result from outer or middle ear dysfunction, including the presence of a transient conductive HL (fluid or debris) or noise interference. Otoacoustic emissions cannot be used to screen for neural HL, because pathology in this disorder involves the inner hair cells, eighth cranial nerve, and brainstem with intact outer hair cells. Infants with neural HL will, therefore, fail ABR but pass OAE. The Joint Committee on Infant Hearing 2007 states that infants cared for in the NICU for greater than 5 days are at highest risk for neural HL and, therefore, should be screened only with AABR.[3,48] Some hospitals use a two-step screen with both AABR and OAE. Screen time with OAE is quicker and more cost effective, and OAE is, therefore, considered an acceptable screen in the well-baby nursery. OAE will not identify auditory neuropathy and, therefore, is not recommended for screening in the NICU.

Tympanometry (immittance) testing is used to assess the peripheral auditory system, including the function, intactness, and mobility of the tympanic membrane, the pressure in the middle ear, and the mobility of the middle ear ossicles. A probe is placed in the inner ear, and air pressure is changed to assess the movement of the tympanic membrane. The tympanogram shows the response of the tympanic membrane in response to the pressure stimulus: A type A curve is considered a normal response. A completely flat response may be reflective of fluid in the middle ear or perforation of the tympanic membrane. Tympanometry is not used for screening.

Behavioral tests include vision reinforcement audiometry (VRA), which is appropriate for rested alert infants with a developmental age of at least 6 months. The infant must have the functional capability of turning to sounds. For administration of VRA, the infant sits on the mother's lap in a sound booth, earphones are inserted, and the infant is conditioned to turn to sounds that are paired to animated toys that appear either to the right or left side. Traditional behavioral testing is used for toddlers at least 2.5 years of age. Children respond by placing a block in a box each time they hear a sound.

For confirmation of an infant's hearing status, a test battery is required to cross-check results of both the

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TABLE 59.2 Tests for Hearing Screening and Diagnosis

Test	Mechanism	Type of Hearing Loss
Otoacoustic emissions (OAE) screen	OAE tests represent a response of the outer hair cells in the cochlea to a sound stimulus; the hair cells produce echolike responses that can be detected and recorded with a high-sensitivity microphone. Automated equipment is available.	Sensorineural Conductive
Automated auditory brainstem response screen (AABR)	Automated auditory brainstem response screen tests based on threshold algorithms have become standard for screening.	Sensorineural Conductive Neural
The Following Physiologic and Behavioral Tests Are Used As Part of a Diagnostic Battery		
Auditory brainstem response (ABR) diagnostic	Auditory brainstem response potentials are a reflection of electrical activity in cranial nerve VIII and auditory brainstem pathway that can be detected with scalp electrodes to produce an auditory brainstem response.	Sensorineural Conductive Neural
Tympanometry battery	This measure of middle ear function is part of the battery for all children. For infants younger than 6 months, a high-frequency probe tone of 1000 Hz is indicated.	Conductive
Vision reinforcement audiometry (>6 months of age) Conditioned audiometry response (>2.5 years of age)	Observations of the infant's behavioral responses to sounds	Sensorineural Conductive Neural
Standard audiometry (>4.5 years of age)	Observation of the child's behavioral responses to a task in response to sounds	Sensorineural Conductive Neural

physiologic measures and the behavioral measures.[70] The purposes of the audiologic test battery are to assess the integrity of the auditory system, estimate hearing sensitivity across the frequency range, and determine the type of loss. Infants who fail a newborn screen should have a diagnostic assessment as soon as possible after the newborn screen and not later than 3 months of age.

Primary care physicians and health centers are beginning to implement routine surveillance and hearing screening of children with OAE and tympanometry during well-child visits.[4,5,31,56] This would appear to be an important adjunct to newborn screening because of the known rate of late onset by school age, which is equivalent to the rate identified in newborn screening. However, NICU infants who fail the newborn screen should never be screened in the medical home but should be referred to an audiologist. In addition, children who do not pass the OAE screen in the medical home need to be referred to audiology for further diagnostic testing.

Early Intervention Services

There is a body of evidence supporting the importance of early enrollment in early intervention services to improve the outcomes of children with HL. Before universal hearing screening, children with severe to profound HL were identified at 24-30 months of age and subsequently demonstrated significant delays in communication, language, and literacy. The Colorado study first reported that children with HL who received intervention services before 6 months of age had speaking, sign, or total communication language scores comparable with hearing children at 3 years of age.[73,74] A second report demonstrated that at 12-16 months, children with HL who were enrolled in early intervention at 3 months or younger had significantly higher scores for number of words understood, words produced, early gestures, later gestures, and total gestures compared with children enrolled after 3 months of age.[64] The Joint Committee on Infant Hearing 2007 recommends that infants with all degrees of unilateral or bilateral HL need to be referred to early intervention services at the time of diagnosis and receive services no later than 6 months of age. These services should be provided by professionals who have expertise in HL, including educators of the deaf, speech-language pathologists, and audiologists. The 2013 Supplement to JCIH 2007 Position statement provides comprehensive guidelines for early intervention after confirmation that the child is deaf or hard of hearing.[33] The 12 best practice goals and guidelines recommended provide an evidence-based framework for family-centered culturally competent, individualized early intervention services to meet the diverse needs of children and families regardless of type and degree of HL and modality of communication (Table 59.3).

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TABLE 59.3 Best Practice Guidelines for Early Intervention Services for Children who are Deaf or Hard of Hearing

Goal 1	Access to timely and coordinated entry into EI programs supported by a data management system capable of tracking
Goal 2	Timely access to coordinators with specialized knowledge and skills related to working with children and adults who are deaf or hard of hearing
Goal 3	• EI providers who have the professional qualifications and core knowledge and skills to optimize the child's development and child/family well-being • EI services to teach American Sign Language provided by professionals who have native or fluent skills and are trained to teach parents/families and young children • EI services to develop listening and spoken language provided by professionals who have specialized skills and knowledge
Goal 4	Children with additional disabilities have access to specialists with the qualifications and specialized skills to support optimal outcomes.
Goal 5	Children from culturally diverse backgrounds and/or non-English-speaking homes have access to culturally competent services of the same quality and quantity as provided to majority culture families.
Goal 6	All children have progress monitored every 6 months to 36 months, with standardized, norm-referenced developmental assessments for language (spoken and/or signed), the modality of communication (auditory, visual, and/or augmentative), and social–emotional, cognitive, and motor skills.
Goal 7	Children with all degrees of hearing loss, including unilateral or slight hearing loss, auditory neuropathy, and progressive or fluctuating hearing loss, receive appropriate monitoring and immediate referral to EI services as needed.
Goal 8	Families are participants in the development and implementation of EHDI systems at the state/territory and local level.
Goal 9	Families have access to other families who have children who are D/HH and are trained to provide culturally and linguistically sensitive support and guidance.
Goal 10	Individuals who are D/HH are active participants in the development and implementation of EHDI systems at the national, state/territory, and local levels.
Goal 11	Children who are D/HH and their families have access to support, mentorship, and guidance from individuals who are D/HH.
Goal 12	All children who are D/HH and their families are ensured of fidelity in the implementation of EI.

D/HH, Deaf or hard of hearing; EHDI, early hearing detection and intervention; EI, early intervention.

Etiology of Hearing Loss

It is estimated that at least 50% of congenital HL is hereditary. Nearly 400 syndromes and hundreds of genes associated with HL have been identified.[15,45,72] Genetic HL is about 30% syndromic and 70% nonsyndromic. Among children with nonsyndromic HL, 75%-85% of cases are autosomal recessive (*DFNB, deafness*, *neurosensory*, *autosomal recessive*), 15%-24% are autosomal dominant (*DFNA*, *deafness*, *neurosensory*, *autosomal dominant*), and 1%-2% are X-linked (*DFN*). Therefore, most infants with HL have nonsyndromic autosomal recessive HL and are born to hearing parents. A single gene, *GJB2*, which encodes Connexin 26, a gap-junction protein expressed in the connective tissues of the cochlea, accounts for up to 50% of all cases of profound nonsyndromic HL. More than 100 mutations of *GJB2* have been identified. A single *GJB2* mutation, 35delG, accounts for up to 70% of the mutations. The etiology of HL will be reviewed relative to the risk factors for HL published by the Joint Committee on Infant Hearing 2007 (Box 59.2).

Several mitochondrial DNA mutations of the 12S rRNA gene are associated with aminoglycoside-induced nonsyndromic HL. This is potentially important for NICU infants, because aminoglycosides are one of the most common medications administered in the NICU.[16] Two studies have examined the frequency of these genes in NICU populations and identified a rate of ≈1%-1.8%.[24,32] Neither study, however, identified an association in neonates between the presence of the genetic marker in conjunction with aminoglycoside administration and HL. Neonatal genetic screening with rapid turnaround is not available. A concern with the current reports, however, is that mitochondrial HL has variable age of onset and may not be identified in the newborn period. In addition, it has been suggested that there may be a modifier gene effect that is protective.[32]

Risk Factors

The first two risk factors in Box 59.2 are obtained by parent report. Parents may not be aware of a family history of HL (risk factor 2) or of syndromes associated with HL until

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• BOX 59.2 Risk Factors Associated with Permanent Congenital, Delayed Onset, or Progressive Hearing Loss

1. Caregiver concerns* regarding hearing, speech, language, or developmental delay
2. Family history of permanent HL*
3. Neonatal intensive care for greater than 5 days, and hyperbilirubinemia requiring exchange transfusion regardless of length of stay
4. In utero infections, such as cytomegalovirus,* Zika virus, herpes virus, rubella, syphilis, and toxoplasmosis
5. Craniofacial anomalies, including atresia, microtia, and temporal bone anomalies
6. Physical findings, such as white forelock, that are associated with syndromes known to include a sensorineural or permanent conductive HL
7. Syndromes associated with HL or progressive or late-onset HL,* such as neurofibromatosis, osteopetrosis, and Usher syndrome. Other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen.
8. Neurodegenerative disorders* such as Hunter syndrome or sensory motor neuropathies such as Friedreich ataxia or Charcot-Marie-Tooth disease
9. Culture-positive postnatal infections* associated with sensorineural HL, including confirmed bacterial and viral (especially herpesviruses and varicella) meningitis
10. Head trauma, especially basal skull or temporal bone fracture that requires hospitalization
11. Chemotherapy*

*Risk factors that are of greater risk for delayed onset or progressive hearing loss. HL, Hearing loss.

discussing the possibility with relatives. If a family history of HL is reported for an infant who passes the screen, ongoing surveillance is indicated with at least one follow-up audiologic assessment by 24-30 months of age. All families with an infant with HL, regardless of family history of HL, will benefit from a genetics consultation. Risk factor 1, caregiver concern regarding hearing, speech, language, or developmental delay in the first 2-3 years of life,[21] has also been shown to be associated with an increased risk for late-onset or progressive HL not detected in a newborn screen. It is important to remember that the rate of HL doubles between birth and school age from 1-3 per 1000 in newborns to about 3-4 per 1000 at school age[70]; therefore, caregiver concern should prompt a referral for further evaluation.

Medical complications are associated with 40% of childhood permanent HL. Risk factor 3 includes infants requiring NICU care for greater than 5 days *and any of the following exposures regardless of length of stay*: extracorporeal membrane oxygenation, assisted ventilation, exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide or lasix), and hyperbilirubinemia requiring exchange transfusion.[27,53,71] Risk factor 4 includes in utero infections such as cytomegalovirus, herpes, rubella, syphilis, toxoplasmosis, and Zika virus.[23] Cytomegalovirus remains the most common medical cause of both early- and delayed-onset HL in infants and children.[9,28] Most infants with congenital cytomegalovirus infection have no clinical findings at birth, and the diagnosis goes unrecognized. Treatment of children with positive CMV, but without clinical findings or HL, with valgancyclovir remains controversial because of an increased risk of side effects.[12,34] Zika virus is also a neurotropic virus that has emerged and is associated with early and possibly delayed onset HL. It may occur in association with abnormalities of the central nervous system, and the type of HL is either sensorineural or auditory neuropathy.[20,35] Because of the association with CNS abnormalities, these infants should be screened with AABR.

Risk factors 5-8 are all associated with congenital abnormalities or syndromes. Risk factor 5 includes craniofacial anomalies, such as those involving the pinna or ear canal, ear pits, and temporal bone anomalies.[62] These defects are common in both the well-baby nursery and the NICU. Many of these findings reflect abnormalities in the embryologic development of the ear. The external ear, middle ear, and Eustachian tube develop from the branchial apparatus beginning at the fourth week of gestation. The pinna arises from the coalescence of the first and second arch tissues of the first branchial cleft, which will become the external auditory canal. The Eustachian tube and middle ear space develop from the first pharyngeal pouch, and the ossicles from the mesoderm of the first and second arches. The inner ear develops from surface ectoderm and neuroectoderm beginning in the third week of gestation, with the cochlea, semicircular canals, utricle, and saccule formed by 15 weeks. The inner ear reaches adult size by 23 weeks. Risk factor 6 includes visible physical findings such as white forelock, which is associated with Waardenburg syndrome.

Risk factor 7 includes syndromes associated with neonatal, progressive, or late-onset HL such as neurofibromatosis, osteopetrosis, and Usher syndrome. Usher syndrome is the most common cause of autosomal recessive syndromic HL (4%-6% of children with HL). Affected individuals develop vestibular problems secondary to progressive retinitis pigmentosa and become blind with increasing age. Subtypes are associated with either mild to severe or severe to profound HL. Early diagnosis is critical, because a visual means of communication is not an option for a child who will become blind with increasing age. Other frequently identified syndromes include Waardenburg, Pendred, Jervell and Lange-Nielsen, and Alport syndromes.[2,15,44] The most common autosomal dominant syndrome is Waardenburg syndrome. It occurs in 1%-4% of children with HL. Children have sensorineural or permanent conductive HL and associated heterochromia iridis. Pendred syndrome is the second most common autosomal recessive cause of syndromic HL. It is characterized by severe to profound HL and euthyroid goiter, which presents during adolescence or later. An abnormality called Mondini dysplasia or dilated vestibular aqueduct, which is diagnosed by computed tomography examination of the temporal

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bones, is associated with Pendred syndrome. Jervell and Lange-Nielsen syndrome is characterized by prolongation of the QT segment on electrocardiogram and is associated with sudden infant death and syncope. Children with QT prolongation should be seen in consultation by cardiology for management. Branchio-otorenal syndrome is autosomal dominant and occurs in 2% of HL. It is characterized by preauricular pits, malformed pinnae, branchial fistulas, and renal anomalies. Alport syndrome is X-linked or autosomal recessive, occurs in 1% of children with HL, and is associated with progressive HL.

Risk factor 8 consists of neurodegenerative disorders such as Hunter syndrome or sensory motor neuropathies such as Friedreich ataxia and Charcot-Marie-Tooth syndrome.[44]

Risk factor 9 is culture-positive postnatal infections and includes confirmed bacterial and viral (especially herpesviruses and varicella virus) meningitis. Meningitis is associated with an increased incidence of sensorineural HL.[1,17] Children with cochlear implants may be at increased risk of meningitis.[8,51]

Risk factors 10 and 11 are risk factors encountered after discharge. Serious head trauma, especially basal skull or temporal bone fractures requiring hospitalization, is a risk factor for HL in childhood.[7,37] Although rare in children, chemotherapy for leukemia or cancer remains a risk factor, which in some cases is reversible.[30] Box 59.2 specifically identifies the risk factors associated with delayed-onset HL. Although all children with a risk factor should have ongoing surveillance in the medical home and at least one follow-up visit with an audiologist, children with increased risk for delayed-onset HL may benefit from more frequent assessments.

Medical Workup for Hearing Loss and Care Coordination

An initial physician visit is beneficial after a newborn hearing screen is failed. At that time, parents are informed of the risk of HL and the importance of follow-up with an audiologist. A second physician visit should be scheduled with the family as soon as a diagnosis of HL is made to discuss the audiologist's report, provide information on community resources, and support for the family during a stressful time. During the postdiagnosis appointment, the physician reviews the pregnancy, neonatal, and family history for HL, re-examines the child for evidence of any craniofacial abnormalities or a syndrome associated with HL, and discusses the benefits of early intervention services and amplification. The primary care physician, therefore, needs to be aware of community resources and to support the family choice of early intervention program and mode of communication. Ongoing communication of the primary provider with the family is necessary to answer questions and provide support. Sharing evidence of significantly improved outcomes as a result of early diagnosis and early intervention provides some reassurance and comfort to the family. During this time of transition, some families derive benefit from meeting other families with young children with HL who are farther along in the process. Successful care coordination of the child with HL requires the partnering of the primary care provider, audiologist, otolaryngologist, early intervention provider, developmental pediatrician, geneticist and, most important, the family.

Every infant with confirmed HL should be evaluated by an otolaryngologist with knowledge of pediatric HL. The otolaryngologist conducts a comprehensive assessment to determine the etiology of HL and provides recommendations and information to the family, audiologist, and primary care provider on candidacy for amplification, assistive devices, and surgical intervention, including reconstruction, bone-anchored hearing aids, and cochlear implantation.

Because of the prevalence of hereditary HL, all families of children with confirmed HL should be offered a genetics evaluation and counseling. This evaluation can provide families with information on etiology, prognosis, associated disorders, and the likelihood of HL in future offspring. The geneticist will review the family history for specific genetic disorders or syndromes, examine the child, and complete genetic testing for syndromes or gene mutations for nonsyndromic HL such as *GJB2* (Connexin 26).[15,58]

Additional referrals may be made at that time for a developmental assessment or other indicated specialty evaluation. Because 30%-40% of children with confirmed HL have comorbidities or other disabilities, the primary care physician should closely monitor developmental milestones and initiate referrals related to suspected disabilities as needed.[31,42] Because of the association of HL with vision impairments and the importance of vision for children with HL, it is recommended that each child with a permanent HL have at least one examination to assess visual acuity by an ophthalmologist experienced in evaluating infants.

Middle Ear Disease

Otitis media with effusion (OME) is highly prevalent among young children, and about 90% of children have an episode of OME before starting school.[38] Middle ear status should be monitored closely in children with permanent HL, because the presence of middle ear effusion can further compromise hearing. Recommendations related to diagnosis of OME include examination with a pneumatic otoscope and documentation of laterality, duration of effusion, and severity of symptoms. Although about 40%-50% of children with OME do not have symptoms,[54,55] some children may have associated balance problems.[25] Medical management of OME in children with permanent HL may include hearing testing, amplification adjustment, and tympanostomy tubes.[38,55] Most OME is self-limited, and 75%-90% of cases spontaneously resolve in 3 months.[54] Therefore, a 3-month period of observation is recommended. Evidence suggests that no benefit is derived from the use of antihistamines or decongestants in children. Children with

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persistent OME (≥4 months' duration) with associated persistent HL or structural injury to the tympanic membrane or middle ear become candidates for surgical intervention with tympanostomy, which has been shown to be associated with decreases in middle ear effusion and improved hearing.

Communication Options

One of the important decisions that the family needs to make for the child is the communication mode that will work optimally for the child and family. There are five options. Auditory oral communication encourages the use of residual hearing and amplification with visual support (speech reading), and the goal is spoken language. Auditory verbal communication is based on listening skills alone, and the goal is spoken language. Cued speech uses a visual communication system that combines listening with eight hand shapes in four placements near the face and supports spoken language. Total communication combines all means of communication and encourages simultaneous use of speech and sign. Deaf children learn American Sign Language, and English is learned as a second language once American Sign Language is mastered. The choice of communication option for the family may change over time depending on the progress of the child and the degree of HL. For example, for an infant born with a profound HL, the family may initially choose total communication, but after a cochlear implant at 12 months of age, may use predominantly auditory verbal or auditory oral communication.

Audiologic Devices

Hearing Aids

Hearing aids are compact and worn either in-the-ear (ITE) or behind-the-ear (BTE), and can be fitted on an infant in the first month of life. The main components are the microphone that picks up sounds and the amplifier. The audiologist uses computer programming to adjust the sound for an individual child's needs. If the child has different degrees of HL at different frequencies, the audiologist adjusts the gain (loudness) by frequency. Normal speech range is from 500-2000 Hz. Ear molds are made from an impression of the child's ear. As a young infant grows, the ear molds may need to be replaced every 6-8 weeks.

Frequency-Modulated Systems

Frequency-modulated (FM) systems were developed for individuals with HL to hear better in noisy environments. An FM system consists of a microphone and a receiver. A small radio transmitter is attached to a microphone and a small radio receiver. A parent or teacher wears the FM transmitter and microphone while the child wears the FM receiver. The FM transmitter sends a low-power radio signal to the FM receiver that needs to be within 50 feet of the transmitter. The FM receiver gets the signal from the microphone and sends it to a personal hearing aid or cochlear implant. Listening to the FM signal is similar to listening to speech only inches away. Frequency-modulated systems can be used in a variety of situations, including in the home, while shopping, or at school.

Cochlear Implants

Children and adults who are deaf or severely hard of hearing can be fitted for cochlear implants. According to the US Food and Drug Administration (FDA), as of December 2012, approximately 324,000 people worldwide have received implants. In the United States, roughly 58,000 adults and 38,00 children have received them.[22] Candidacy criteria for pediatric cochlear implantation currently is 18 months or older for children with severe to profound bilateral sensorineural HL and 12-18 months for children with profound HL. There are increasing reports demonstrating the beneficial effects on speech and language for infants with bilateral profound HL implanted before 12 months of age.[36,40,76] In cases of deafness caused by meningitis, implants may be placed early in the first year of life. A lack of benefit in the development of auditory skills with amplification needs to be demonstrated for eligibility for an implant. Children up to 7 years of age appear to derive the greatest benefit from a cochlear implant for the development of speech.[29,59] Because of an increased risk for bacterial meningitis, it is recommended that physicians monitor all patients with cochlear implants, particularly children whose implants have a positioner,[8,51] for middle ear and other infections. *Streptococcus pneumoniae* is the most common pathogen causing meningitis in cochlear implant recipients.[51] All children with cochlear implants should be vaccinated according to the American Academy of Pediatrics high-risk schedule.

Continued Surveillance

The Joint Committee on Infant Hearing 2007 has recommendations for ongoing surveillance in the medical home for all infants with and without risk factors for HL.[3] Regular surveillance of developmental milestones, auditory skills, parental concerns, and middle ear status should be performed in the medical home, consistent with the American Academy of Pediatrics periodicity schedule.[3] All infants should have an objective standardized screen of global development with a validated screening tool at 9, 18, and 24-30 months of age or at any time if the health care professional or family has concern.[3] Language screens that can be used in the primary care setting include the Early Language Milestone Scale,[18] the MacArthur Communicative Development Inventory,[26] the Language Development Survey,[52] and Ages and Stages.[10]

Infants who do not pass the speech-language portion of a global screening or for whom there is a concern regarding hearing or language should be referred for speech-language evaluation and audiology assessment. This recommendation

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was implemented because of the known increase in the number of children identified with HL between the newborn screen and school age. This is related to three factors: (1) mild HL is missed with newborn screening tools, (2) some children experience delayed-onset or progressive HL such as that associated with cytomegalovirus, and (3) some children experience late-onset HL secondary to trauma or chemotherapy. Infants with OME may have transient HL and associated language delays.

Further management and evaluation of hearing skills and HL have been outlined by Cunningham et al. in an AAP Clinical Report. In addition to risk factors for hearing loss, it specifically addresses the need for continued surveillance of speech and language milestones in the first 36 months of life.[19]

Stress and Impact on the Family

Parents perceive varying degrees of stress when they are informed that their infant has failed a newborn hearing screen. Although the screen result may be either a false-positive or a true fail, most parents will have some increase in worry until their infant is rescreened. Neonatal intensive care infants have higher false-positive rates and higher fail rates than well-baby nursery infants. In one study of well-baby nursery infants, parents reported increased "worry" at 2-8 weeks of age when they returned for the rescreen.[68] Mothers who were more informed about hearing screening experienced decreased worry. Physicians who understand the screening process can support the family whose infant fails the screen, encourage the family to return for the rescreen, and follow up with the family about the rescreen results. A second study reported that mothers of infants with a false-positive screen did not report increased levels of stress or impact at 12-16 months or at 18-24 months.[67] In addition, greater family resources were protective against persistent stress, whereas NICU stay contributed to prolonged stress.[67]

There is a continuum of increasing stress for families whose infants are identified with HL that increases as they progress through the hearing screen fail, rescreen fail, diagnostic fail, and intervention process.[61] Perception of stress at the time of diagnosis varies significantly among parents. Parents who are culturally deaf may have anticipated the diagnosis and be totally comfortable with it. Hearing parents of children diagnosed with an HL perceive greater stress, which is, in part, related to the fear of disability.[49,50,67] About 95% of children with congenital HL are born to hearing parents. Prompt sharing of diagnostic test results with the family and physician and referral to early intervention services by the audiologist on the day of diagnosis may provide needed information and support to parents to mediate stress.

If the physicians become aware of financial difficulties experienced by the family, the case manager from Part C Early Intervention should be alerted to assist the family to identify resources such as a hearing aid loaner program, Social Security benefit, Katie Beckett Program, or eligibility for Medicaid. The physician may also facilitate referrals to parent support groups such as Hands and Voices and Family Voices. Because half of the children identified with congenital HL had been in a NICU and because about 40% of children with permanent HL have other disabilities, these children may require the resources of a number of different medical and educational disciplines, adding to both the financial and emotional burden.[39,43]

In summary, infants born in 2017 with congenital HL who have early identification, amplification, and intervention have enhanced opportunities for successful communication and academic achievement.

Key Points

- Neonates requiring care in the NICU are at increased risk of auditory neuropathy and should always be screened with AABR.
- Hearing loss is found in association with genetic mutations, over 400 congenital syndromes, and medical risk factors such as extreme prematurity and CMV infection.
- Undetected hearing loss in infants and children negatively affects communication development, academic achievement, literacy, and social–emotional development.
- Early amplification and increased daily use of hearing aids are associated with improved speech and developmental outcomes.
- Provision of early intervention services no later than 6 months of age is associated with improved speech and American Sign Language communication skills.
- Newborn hearing screening does not identify all hearing loss, and ongoing surveillance of hearing skills and language skills in the medical home to identify progressive and late onset hearing loss is indicated.

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Early Childhood Neurodevelopmental Outcomes of High-Risk Neonates

DEANNE E. WILSON-COSTELLO AND ALLISON H. PAYNE

Advances in obstetric and neonatal care, which have been responsible for the improved survival of high-risk neonates, have not resulted in decreased morbidity. Since perinatal interventions can alter later growth and development, long-term follow-up is essential to ensure therapies such as oxygen administration and postnatal steroids, which demonstrate dramatic and immediate positive effects, are not associated with adverse long-term outcomes. The earliest follow-up studies of preterm infants after the introduction of modern methods of neonatal intensive care in the 1960s described a decrease in adverse neurodevelopmental sequelae compared with that of the preceding era. During the 1980s and 1990s, there was a continued decrease in mortality, and thus the absolute number of both healthy and neurologically impaired survivors increased.[29] Furthermore, the survival of increasing numbers of extremely immature infants with low birth weight resulted in a relatively high disability rate in the subpopulation of infants born weighing less than 750 g or born at less than 26 weeks' gestation.[121] Since 2000, mortality rates for infants with very low birth weight have leveled off. Several studies suggest declining rates of major neurodevelopmental impairment, including cerebral palsy.[113] As the initial survivors of neonatal intensive care have reached young adulthood, a myriad of more subtle neurodevelopmental issues such as visuomotor problems, learning disabilities, autism, or developmental coordination disability have flooded the literature. Additionally, the survival of increasingly immature infants along with improvements in managed care systems have resulted in early discharge of infants with unresolved medical or surgical issues such as oxygen dependence, need for assisted ventilation, maintenance of external medical devices, or dependence on gastrostomy feeds.

Infants at highest risk for later neurodevelopmental problems resulting from perinatal sequelae include those who had severe asphyxia, severe intracranial hemorrhage, infarction or periventricular leukomalacia, meningitis, seizures, respiratory failure resulting from pneumonia, persistent fetal circulation, or bronchopulmonary dysplasia, and multisystem congenital malformations, as well as children born with extremely low birth weight or at extremely early gestational age (Boxes 60.1 and 60.2). The rates of health problems and neurodevelopmental sequelae are inversely proportional to both birth weight and gestational age (Fig. 60.1 and Table 60.1).

Although most survivors of prematurity are not significantly impaired, there are a variety of medical and neurodevelopmental sequelae that necessitate scrutiny. Therefore, follow-up programs should be an integral extension of every neonatal intensive care unit. The goals of effective follow-up programs include early identification of neurosensory or developmental disability, parental counseling, identification and treatment of medical complications, identification of risk factors for impairment, evaluation of the impact of therapeutic interventions, and provision of feedback for perinatal and pediatric caregivers. In particular, specialized follow-up care must consider problems of growth, development, behavior, and chronic disease. If possible, follow-up care should initially involve the coordinated and complementary effort of the neonatologist and the primary care pediatrician. If there are concerns for developmental or neurologic problems, the child should also be referred to a subspecialist or a child development center.

The initial continuity of care by the neonatologist is important to reassure the family that the same personnel responsible for the life-saving decisions are continuing to assume responsibility for the child's adaptation into home life. Neonatal care providers also benefit from involvement in follow-up care by maintaining contact with infants leaving the nursery and observing the long-term consequences of prematurity and neonatal morbidities. Growth (weight, height, and head circumference), neurologic development, psychomotor and cognitive development, vision, and hearing all should be longitudinally assessed within follow-up. Transitioning care of these infants to the general pediatrician gradually may greatly benefit the patient, the family, and the pediatrician as trust and familiarity are developed.

In planning neonatal follow-up programs, various models of care are possible but may be constrained by

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Abstract

Improved survival of extremely preterm infants has not resulted in decreased morbidity. As the total number of survivors at risk for neurodevelopmental problems increases, the need for better understanding of the long-term medical and neurodevelopmental issues that confront these children also grows. Medical complications, including chronic lung disease, poor growth, neurologic sequelae, feeding issues, and sensory deficits, require ongoing interventions, such as home oxygen administration, apnea monitoring, high-caloric-density formulas, and physical and occupational therapy. These survivors are at risk for a variety of cognitive, motor, psychiatric and behavioral problems. High-risk neonates have increased likelihood of school-age learning disability, special education, lower IQ, and decreased productivity in adulthood. This chapter will evaluate risk factors, medical complications, neurodevelopmental assessments, neurodevelopmental problems, and long-term outcomes of high-risk neonates.

Keywords

neurodevelopmental follow-up
cerebral palsy
long-term outcomes
neurodevelopmental assessments

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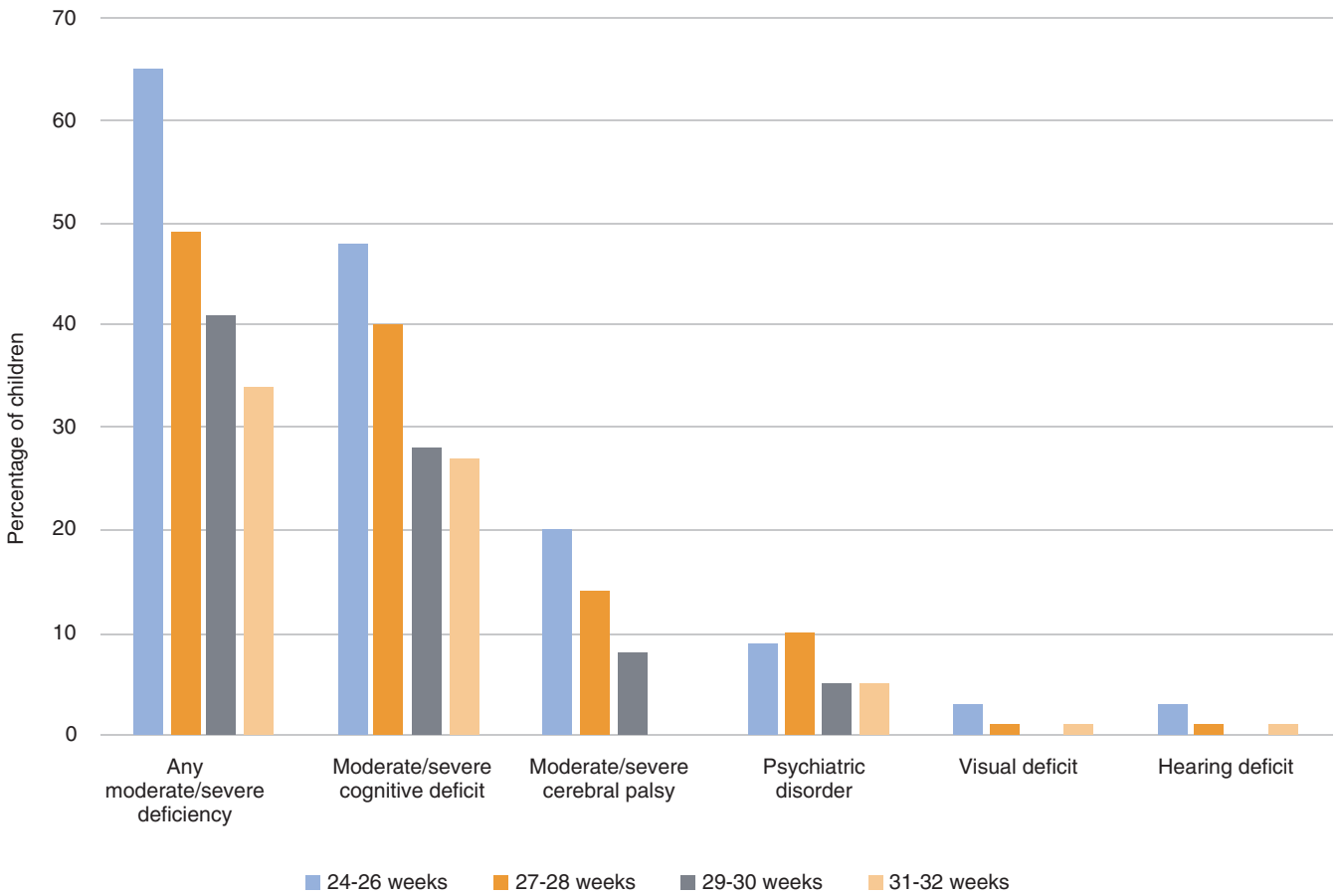
available resources.[59] A minimal requirement for the clinical monitoring of outcomes is a periodic assessment of growth and neurosensory development during the first 2 years of life. The ideal is a comprehensive program involving all aspects of care, including well-baby care, evaluation of outcome, social and educational intervention, and therapy when needed. A home nurse visiting program, especially during the early postdischarge period, and parent support groups for selected high-risk conditions (e.g., children with chronic lung disease) also should be considered. There is evidence that educational enrichment during infancy and early childhood might improve the early childhood outcome of high-risk and preterm infants, especially those from socioeconomically deprived groups. The lack of hypothesis-driven

• BOX 60.1 Factors Affecting Outcome of the Infant With Very Low Birth Weight

- Birth weight less than 750 g or less than 25 weeks' gestation
- Periventricular hemorrhage (grades III and IV) or infarction
- Periventricular leukomalacia
- Persistent ventricular dilation
- Neonatal seizures
- Chronic lung disease
- Neonatal meningitis
- Subnormal head circumference at discharge
- Parental drug abuse
- Poverty and parental deprivation
- Coexisting congenital malformation

• BOX 60.2 Factors Affecting Outcome of the Term Infant

- Birth depression or asphyxia
- Persistent pulmonary hypertension
- Meningitis
- Intrauterine growth failure
- Intrauterine infection
- Symmetric growth restriction (microcephaly)
- Major congenital malformations
- Neonatal seizures
- Extracorporeal membrane oxygenation (ECMO) and nitric oxide therapy
- Persistent hypoglycemia
- Severe hyperbilirubinemia



• **Fig. 60.1** Percentage of 8-year-old children born very preterm between 24 and 32 weeks' gestation from 1997-1998 with major impairments. (Data from Marret S, et al. Brain injury in very preterm children and neurosensory and cognitive disabilities during childhood: the EPIPAGE cohort study. *PLoS ONE* 8 (5): e62683. doi:10.1371/journal.pone.0062683.)

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trials of early developmental intervention has resulted in little evidence of sustained improvement in school-age neurodevelopmental outcomes.[81]

Outcomes from different centers are heavily influenced by the demographic and socioeconomic profile of the parents, the regional incidence of extreme prematurity, the percentage of inborn patients at a given center, a selective treatment or admission policy, site-specific practice patterns, and the rate of follow-up. Intercenter differences in neonatal sequelae and outcome are well described.[116] Regional results, rather than national or international cohort data, may therefore reflect a more accurate picture of outcome, because they include all infants born in an area. This is the ideal situation, but such studies are rarely available in the United States. Individual centers should be aware of their own patients' social risk factors and rates of neonatal morbidity and, if possible, maintain their own follow-up outcome data.

TABLE 60.1 Health Outcomes by Birth Weight at 8 Years

	Birth Weight (kg)			
	<1	1-1.49	1.5-2.49	≥2.5
Asthma (%)	17	18	12	11
Rehospitalization, previous year (%)	7	7	5	2
Limitation of >1 activity of daily living because of health (%)	46	34	27	17

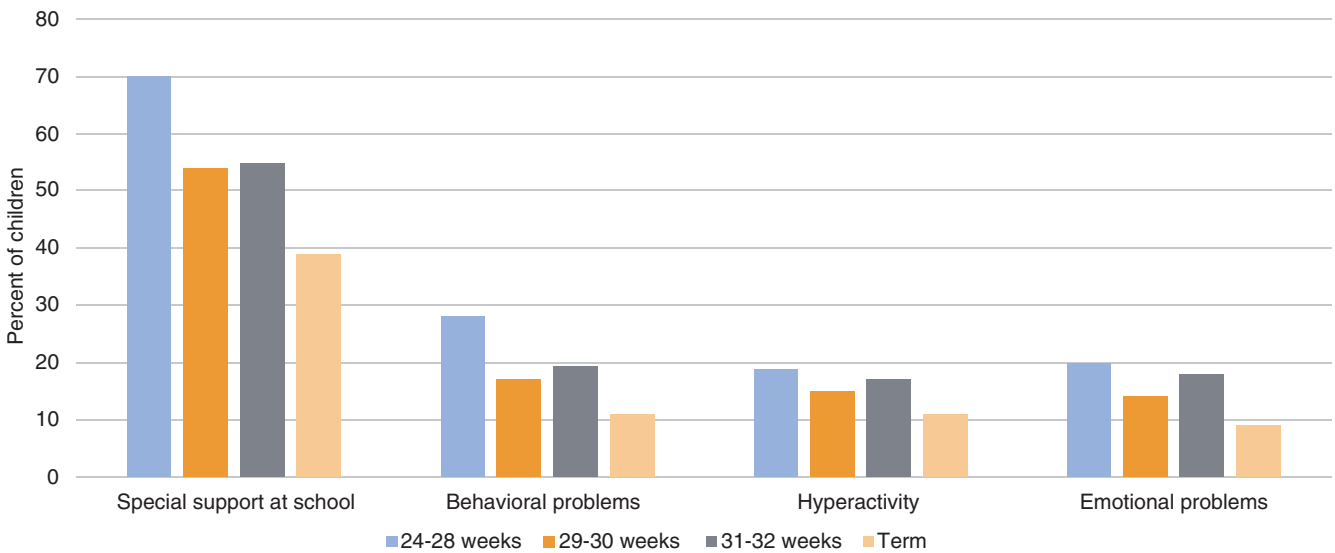
Data from Hack M, et al. Long-term developmental outcomes of low birth weight infants. *Future Child.* 1995;5:176.

Any evaluation of the outcome studies of high-risk infants must include the population status (inborn, outborn, or regional) and the choice of a comparison group that includes either a normal birth weight group or infants within a similar birth weight or gestational age range who do not have the condition or therapy under study. It also is essential to control for sociodemographic factors, such as maternal marital status, ethnicity, and education, and to consider possible genetic factors when evaluating cognitive outcome or school performance.[67]

Consideration of neonatal mortality is important for judging the aggressiveness and level of neonatal care, which might influence the quality of outcome of the survivors. Other factors to be considered are the rate of loss of infants to follow-up, the neonatal and postdischarge death rate, the age at follow-up, and the method of follow-up. Two years is the earliest age to get a fairly reliable assessment of neurodevelopmental outcome. At age 4-5 years, cognitive function and language can be better measured, and follow-up at age 7-9 years allows an assessment of subtle neurologic and behavioral dysfunction and school academic performance (Fig. 60.2).[44,89,109]

Because it is impossible to provide ongoing high-risk follow-up care for all infants treated in the neonatal intensive care unit, specific criteria have been proposed to identify children at greatest risk for sequelae.[72] Traditionally, follow-up programs primarily targeted children with birth weight of less than 1500 g or gestational age of less than 32 weeks. However, therapies such as inhaled nitric oxide and extracorporeal membrane oxygenation have increased the demand for highly specialized follow-up clinics for term infants with persistent pulmonary hypertension, meconium aspiration, and sepsis.

In addition, a growing number of infants with major congenital malformations such as congenital diaphragmatic



• **Fig. 60.2** Rates of school problems among 8-year-old very preterm versus term-born children. (Data from Larroque B, et al. Special care and school difficulties in 8-year-old very preterm children: the EPIPAGE cohort study. *PLoS One.* 2011;6(7):e21361.)

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• BOX 60.3 Suggested Criteria for Severe Disability at Age 2 Years

Malformation
- Impairs the performance of daily activities

Neuromotor Function
- Unable to sit
- Unable to use hands to feed
- Unable to control head movement (or no head control)

Seizures
- More than 1 per month despite treatment

Auditory Function
- Hearing impaired despite aids

Communication
- Unable to comprehend
- Unable to produce more than five recognizable sounds

Visual Function
- Blind or sees light only

Cognitive Function
- About 12 months behind at 2 years

Other Physical Disability

Respiratory
- Requires continual oxygen therapy
- Requires mechanical ventilation

Gastrointestinal Function
- Requires tube feeding
- Requires parenteral nutrition

Renal Function
- Requires dialysis

Growth
- Height or weight more than 3 standard deviations below mean for age

From Johnson A. Follow up studies: a case for a standard minimum data set. *Arch Dis Child.* 1997;76:F61.

hernia now survive the neonatal period to require intensive ongoing follow-up support. Centers with active research components could select additional candidates for follow-up in the high-risk clinic on the basis of participation in specific research studies. Because of the significant costs associated with evaluating all eligible follow-up patients in the clinic setting, parent and teacher questionnaires have been suggested. These questionnaires typically provide a checklist of various individual measures of health status and disability (Box 60.3).[53]

Medical Problems

A variety of common problems of prematurity often continue after NICU discharge. Following birth, hemoglobin concentrations decrease more severely among premature infants, necessitating the subsequent monitoring of hemoglobin levels and reticulocyte counts, which typically rise by 3-6 months age. One hospital-based study suggests that the liberal use of blood transfusions may improve neurologic outcomes and decrease apnea.[11,125] Apnea of prematurity, resulting from immature regulation of breathing, obstruction due to immature airway reflexes, or delayed coordination of sucking, swallowing, and breathing, may recur in preterm infants who develop upper respiratory infection or receive general anesthesia for surgical procedures such as inguinal hernia repair. In these cases, the use of caffeine in conjunction with cardiorespiratory monitoring may be considered.[46,125] For infants discharged on caffeine and home monitoring, the medication may be either weaned or discontinued abruptly; however, monitoring should continue for at least 1-2 weeks following the withdrawal of medication. The AAP suggests that home monitoring for apnea of prematurity may be stopped by 43 weeks' postmenstrual age; however, others have recommended discontinuation at 45 weeks for the most immature infants.[1,108]

Neonatal medical complications include chronic lung disease, intraventricular hemorrhage, retinopathy of prematurity, hearing loss, increased susceptibility to infections, and sequelae of necrotizing enterocolitis. These in turn can contribute to multiple rehospitalizations after discharge, poor physical growth, and an increase in postneonatal deaths. Children with neurologic sequelae such as cerebral palsy and hydrocephalus have a higher rate of rehospitalization for conditions such as shunt complications, orthopedic correction of spasticity, and eye surgery. Furthermore, a high percentage of children with chronic lung disease, extreme prematurity, or both, require rehospitalization during their first year. Comprehensive reviews on the prevention and treatment of bronchopulmonary dysplasia emphasize changing epidemiology and risk factors for bronchopulmonary dysplasia.[8,123] The survival of extremely immature infants has resulted in a large number of infants requiring oxygen past 28 days of life with the preferred definition of bronchopulmonary dysplasia being oxygen requirement at 36 weeks' postconceptual age. These children may require home oxygen and other medications such as diuretics or bronchodilators after discharge. Infants on home oxygen require intermittent pulse oximetry monitoring, as they are at risk for cardiopulmonary complications such as cor pulmonale. Those receiving diuretics require periodic evaluation of their electrolyte status. Drugs such as furosemide, which increase urinary calcium excretion, may need to be discontinued or replaced with diuretics such as aldactone or chlorothiazide if nephrocalcinosis develops. With increased work of breathing, infants with chronic lung disease may require fortification to more than 120-150 kcal/kg/day for weight gain, as well as fluid restriction. Immunoglobulin therapy to prevent respiratory syncytial virus infection is recommended for infants less than 32 weeks with bronchopulmonary dysplasia. Since they are prone to recurrent respiratory infections, poor nutrition, and growth failure

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related to chronic lung disease, they require multispecialty follow-up, including neonatal, developmental, nutrition, and pulmonary specialists. The medical complications of bronchopulmonary dysplasia tend to become less prominent after the second year of life, although airway reactivity and asthma may persist.

Central nervous system complications such as posthemorrhagic hydrocephalus, periventricular leukomalacia (PVL), and porencephaly, which typically appear prior to discharge, place affected infants at greatest risk for ongoing neurodevelopmental problems.[18] Although infants with grades III and IV periventricular hemorrhage are at greatest risk for these complications, ELBW infants with grade I subependymal or grade II intraventricular hemorrhage may also have neurodevelopmental problems.[85,117] Infants with ventriculoperitoneal shunts are at risk for shunt malfunction due to occlusion of the cannula, with subsequent increase in intracranial pressure or shunt infection, which may present as lethargy, irritability, apnea, vomiting, seizures, or increasing head circumference. Infants with intracranial shunts require ongoing surveillance of head circumference for rapid or slow growth. Improved detection of cerebellar hemorrhage in extremely premature infants has demonstrated its significant association with cognitive and motor impairment.[126] MRI evaluations of very preterm infants at term have detected more subtle periventricular leukomalacia caused by ischemic white matter damage or abnormalities of the corpus callosum, increasing the risk of cerebral palsy.[4] Because of the improved predictability of neurodevelopmental outcomes with MRI, many centers use MRI scans at term to assist in parental counseling and follow-up of very preterm infants.[96]

Physical Growth

Intrauterine or neonatal growth restriction, or both, occurs commonly in preterm infants. The poor neonatal growth is related to inadequate nutrition during the acute phase of neonatal disease, feeding intolerance, and chronic medical sequelae that result in increased calorie requirements. These include chronic lung disease, recurrent infections, and malabsorption secondary to necrotizing enterocolitis. The use of postnatal steroids may also contribute to growth failure. A multicenter prospective study of ELBW infants suggests that neonatal growth influences subsequent neurodevelopment and growth outcomes.[30] Prolonged intubation and repetitive insertion of nasogastric tubes can lead to aversions in oral feeding. Additionally, incoordination in suck, swallow, and breathing patterns accompanied by a hyperactive gag reflex may cause apnea and aspiration in preterm infants and parental anxiety. Since most preterm infants require 110-130 kcal/kg/day, fortification or supplementation of feeds is essential. Catch-up growth may occur later in infancy and childhood until ages 2-3 years. While some SGA infants show a rapid increase in weight gain after discharge, many continue to have poor catch-up growth. Poor feeding in chronically ill or neurologically impaired children may also affect neonatal growth. The parents' size contributes to the eventual growth outcome.

Assessment of head growth is an essential element of preterm follow-up. The largest frontal-to-occipital diameter is used to determine head circumference, which typically increases by 0.7 cm/week. Increases of more than 1.2 cm/week may suggest ventricular dilatation. By 12-18 months, the rate of head growth decreases significantly. Intrauterine and neonatal brain growth failure and lack of later brain catch-up growth can affect cognitive functioning and correlates with MRI imaging findings.[9,21] Any infants with very low birth weight who are small for gestational age also have subnormal head growth, and brain growth failure can occur during the neonatal period. Catch-up brain growth can occur during infancy in infants with very low birth weight who are either appropriate or small for gestational age; however, as many as 10% of infants with very low birth weight who are appropriate for gestational age and 25% who are small for gestational age still have a subnormal head size at 2-3 years of age that persists at school age. Poor growth attainment is especially apparent in the child with an extremely low birth weight or gestational age and typically begins in the NICU.

Growth after discharge is a good measure of physical, neurologic, and environmental well-being. Premature infants typically require 110-130 kcal/kg/day to maintain growth. However, infants at high risk for postnatal growth failure, including those with severe bronchopulmonary dysplasia and increased work of breathing, infants with short bowel syndrome predisposed to dumping or receiving home parenteral nutrition, those with congenital heart disease on diuretics, and others with major malformations or inborn errors of metabolism may require more calories to sustain growth. To promote optimal catch-up growth of high-risk infants, neonatal nutrition must be maximized. This is especially important because catch-up of head circumference occurs only during the first 6-12 months after the expected date of delivery. Increased-calorie postdischarge formulas have been introduced to support higher caloric and mineral delivery. These formulas have been associated with improved growth to 9 months. Reports of osteopenia or rickets of prematurity associated with breast milk have increased with the improved survival of extremely premature infants whose birth precedes the period of greatest in utero mineral accretion. Despite the increased risk of osteopenia, early childhood neurodevelopmental outcomes are improved by breastmilk.[114] Although rickets of prematurity appears to be a self-resolving disease, postdischarge formulas with higher calcium and phosphorus content have enhanced growth and bone mineral accretion among preterm infants. However, it is important to balance appropriate catch-up growth and mineral supplementation with an avoidance of excessive rates of growth, which are concerning for promotion of later metabolic syndrome and obesity. Emerging data raises questions about the relationship between early catch-up growth and increased risk of obesity, cardiac disease, and hypertension in adulthood.[27,66]

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Neurodevelopmental Outcome

Transient Neurologic Problems

A high incidence of transient neurologic abnormalities, ranging from 20%-40%, occurs in high-risk infants, with a peak incidence of transient dystonia occurring at 7 months' corrected age.[16] Transient abnormalities of muscle tone such as hypertonia or hypotonia (occurring as poor head control at 40 weeks' postconceptional age), poor back support at 4-8 months, or a slight increase in muscle tone of the upper extremities are associated with increased risk of later cognitive and motor problems. Because some degree of physiologic hypertonia normally exists during the first 3 months, it may be difficult to diagnose the early developing spasticity related to cerebral palsy.

Children who will later develop cerebral palsy often initially have hypotonia (poor head control and back support) and only later develop spasticity of the extremities. Spasticity during the first 3-4 months is, however, a poor prognostic sign. Persistence of primitive reflexes also might be a sign of early cerebral palsy. Although mild hypotonia or hypertonia persisting at 8 months usually resolves by the second year, it might indicate later subtle neurologic dysfunction.[45]

Major Neurologic Sequelae

Major neurologic sequelae can usually be diagnosed during the latter part of the first year of life or even earlier if they are very severe. Major neurologic disability is usually classified as cerebral palsy (spastic diplegia, spastic quadriplegia, or spastic hemiplegia or paresis), hydrocephalus (with or without accompanying cerebral palsy or sensory deficits), blindness (usually caused by retinopathy of prematurity), seizures, or deafness (Box 60.4). The intellectual outcome can differ greatly according to neurologic diagnosis. For example, children with spastic quadriplegia usually have severe developmental delay, whereas children with spastic diplegia or hemiplegia may have better mental functioning. Cognitive function is not easily measurable until after 2-3 years of age, especially among neurologically impaired children.

• BOX 60.4 Types of Neurologic Dysfunction in Children Who Were High-Risk Neonates

- Motor deficits
- Spastic diplegia
- Spastic quadriplegia
- Spastic hemiplegia
- Mental retardation
- Seizures
- Hearing deficits
- Visual abnormalities
- Eye motility dysfunction
- Posthemorrhagic hydrocephalus
- Visuomotor deficits
- Learning deficits
- Subtle neurologic dysfunction
- Hyperactivity
- Poor attention

Most neurologic problems either resolve or become permanent during the second year of life. During the second year, the environmental effects of maternal education and social class begin to play a major role in the various cognitive outcome measures. Further problems could emerge during the school-age years. These include subtle motor, visual, and behavioral difficulties even among children with normal intelligence. These are best diagnosed and treated in a psychological and educational, rather than a medical, follow-up setting.

Cerebral palsy, an umbrella term that refers to "a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions of the developing brain," occurs about 70 times more frequently among infants with extremely low birth weight than among controls with normal birth weight. Risk factors include periventricular echolucencies noted on cranial ultrasound, intrauterine and neonatal infection, hypotension, severe respiratory distress, hypothyroxinemia, postnatal corticosteroid exposure, and multiple gestation.[39,98,102] Despite these identified factors, most cerebral palsy cases, especially among term infants, do not have a readily identifiable cause. Protective factors could include maternal antenatal corticosteroid therapy, preeclampsia, and antenatal magnesium sulfate.[24,69] Although birth asphyxia has been identified as a frequent cause of cerebral palsy among term infants, low Apgar scores have correlated poorly with cerebral palsy for preterm infants.

Epidemiologic studies of cerebral palsy rates have been hampered by disagreement over both the specific diagnostic criteria used and the age at which a diagnosis should be made. Furthermore, studies differ on their estimates of the prevalence of cerebral palsy depending on the denominator used for calculation. For example, assessments may be reported relative to the number of live births, the number of NICU admissions, or the number of survivors evaluated. The risk of developing CP is higher in infants of lower gestational age. Typically, term infants have a risk of 1 per 1000 births, versus rates of 10 per 1000 for infants between 32 and 36 weeks' gestation and 100 per 1000 for those born at extremely low gestational ages.[82]

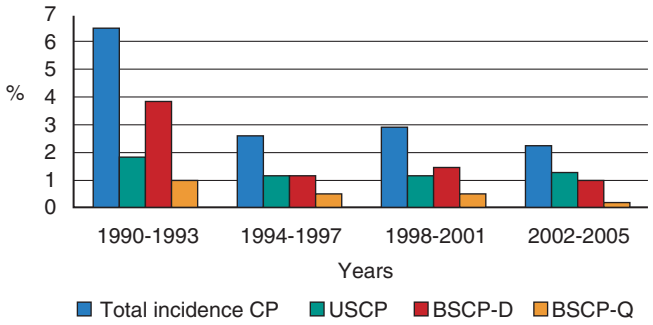
Most of the cases of cerebral palsy among preterm children pertain to children with spasticity rather than to the athetotic or dyskinetic types of cerebral palsy. These include the subtypes with bilateral (diplegia, quadriplegia) or unilateral (hemiplegia) spasticity. Diplegia and hemiplegia are the most common types of cerebral palsy seen in preterm children. Spastic cerebral palsy accounts for approximately 85% of all cases and greater than 90% of preterm CP cases. The neurologic symptoms of spastic CP include increased tone with velocity-dependent increased resistance to passive movement; pathologic reflexes such as hyperreflexia or pyramidal signs like the Babinski response; and abnormal

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patterns of movement and posture characterized in the lower limbs by equines foot, crouch gait, internal rotation, and hip adduction. In the upper limbs, the typical posture is arm flexion with fisted hands, adducted thumbs, and poorly coordinated finger movements. Symptoms of bilateral spastic cerebral palsy include motor deficit with contractures impairing normal gait, cognitive problems (which are seen less often in preterm than term children), visual problems such as blindness or strabismus, and epilepsy in the most severe cases.

Children with global hypotonia are usually not included in the diagnosis of cerebral palsy. Cerebral palsy was previously defined as mild, with no loss of function and independent walking; moderate, with functional disabilities requiring assistance for walking with aids or walkers; and severe, nonambulatory, requiring a wheelchair. Cerebral palsy was alternatively labeled *disabling* or *nondisabling* to incorporate a crude measure of functional impairment. With the exception of these descriptive terms, there was no reliable measure of the severity of motor disability or consideration of other cognitive or neurosensory problems associated with cerebral palsy. In 2004, an international workshop on the definition and classification of cerebral palsy proposed inclusion not only of motor disorders but also of other associated deficits that may coexist, including seizures and cognitive, perceptual, sensory (visual and hearing), and behavioral impairments.[10] The 2004 classification also includes anatomic and radiologic findings and causation and timing of the lesion. This new system has enhanced the evaluation of functional outcomes for children with cerebral palsy.[60] In the future, its use should also improve studies of trends in the rates of cerebral palsy and its correlates.

The diagnosis of cerebral palsy is usually delayed until motor development has been established. The minimal age before a definitive diagnosis can be made should be at least 3 years and preferably 5 years of age. This is because in some cases the neurologic findings may decrease or disappear by 5 years of age, and in other mild cases, the findings may only become apparent later.[7,84,102] The longest study of trends in the rates of cerebral palsy has been that of Hagberg and colleagues. They monitored the rates in western Sweden in a series of nine reports from 1954 until 1998.[47] During the 1950s, very few of the children with cerebral palsy in the western Swedish register were born before 28 weeks' gestation, whereas by 1995-1998, 20%-25% of these children were born at this extremely low gestation, evidence of the increase in survival of these infants. Survival increased progressively during the periods of study. Overall, the prevalence of cerebral palsy among preterm infants decreased between the periods 1954-1958 and 1967-1970, partly owing to discontinuation of various iatrogenic therapies such as prolonged starvation and discontinuation of limitation of oxygen thought to cause retinopathy of prematurity. After the introduction of methods of neonatal intensive care and the increase in survival of infants of extremely low birth weight and gestation, the rates of cerebral palsy increased



• **Fig. 60.3** Cerebral palsy (CP) incidence and type from 1990-2005. BSCP-D, Bilateral spastic CP-D (diplegia); BSCP-Q, bilateral spastic CP-Q (quadriplegia); USCP, unilateral spastic CP. (Data from van Haastert IC, Groenendaal F, Uiterwaal CS, et al. Decreasing incidence and severity of cerebral palsy in prematurely born children. *J Pediatr.* 2011;159(1):86-91.e1.)

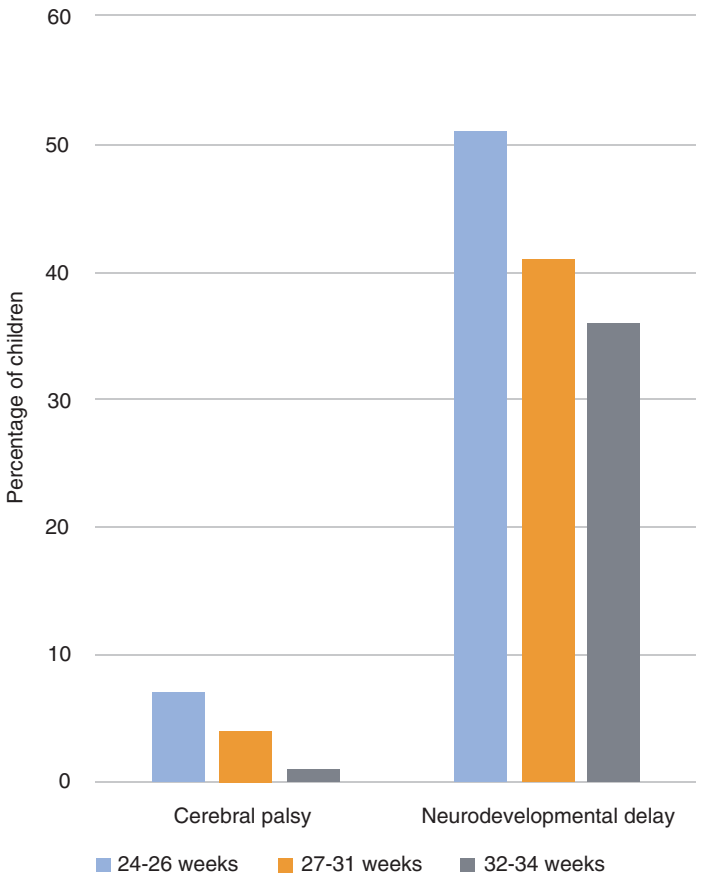
from 1987-1990, with an increase in cases with severe multiple handicaps. Similar trends were noted by others. The prevalence then decreased significantly from 1995-1998. Data continue to show encouraging trends with decreasing incidence and severity of cerebral palsy in prematurely born children (Fig. 60.3).[113]

In contrast to these optimistic reports, population-based studies from France (EPIPAGE and EPIPAGE-2) showed that survival without moderate to severe disability increased for infants born at 25-26 weeks' gestation (46% vs 62%) and for those born at 27-31 weeks' gestation (82% vs 90%); however, there was no difference in survival without major disability for infants born earlier than 24 weeks' gestation (29% vs 26%).[3] The EPIPAGE follow-up studies continue to demonstrate declining rates of cerebral palsy and neurodevelopmental delays with advancing gestational age (Fig. 60.4).[86] In a population-based study from the United Kingdom (EPICure study) of infants born less than 26 weeks, survival improved from 39% in the 1990s to 52% in 2006. At 3 years, there was a higher proportion of survivors without disability (6%-16%); however, there was no change in the proportion of survivors with severe disability (18% vs 19%).[74]

The advent of modern neuroimaging techniques such as magnetic resonance imaging (MRI) offers improved potential to comprehensively visualize brain lesions associated with cerebral palsy. Cranial ultrasound was judged as normal in 35% of children with cerebral palsy in the entire EPIPAGE study of all preterm children born below 33 weeks' gestation. In systematic review of MRI studies in children with cerebral palsy, roughly 90% of preterm-born children had cerebral abnormalities, most commonly periventricular white matter lesions (see Chapter 52).[112]

Isolated motor disorders, such as developmental coordination disorder (DCD), which affect approximately one-third of preterm children, are more common than cerebral palsy. By definition, these children have no neurosensory impairment and demonstrate intact cognitive function. They display a variety of fine and gross motor delays

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• **Fig. 60.4** Rates of cerebral palsy and neurodevelopmental delay at 2 years by gestation. (Data from Pierrat V, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22-34 weeks gestation in France in 2011: EPIPAGE-2 cohort study. *BMJ.* 2017;358:j3448.)

resulting in difficulties with common motor tasks, such as manipulating pencils or silverware, pedaling a bicycle, or performing routine motor tasks of daily living.[118] Associations have been made between these "minor" motor disorders and cognition, behavior, and overall decreased function at school age.[33]

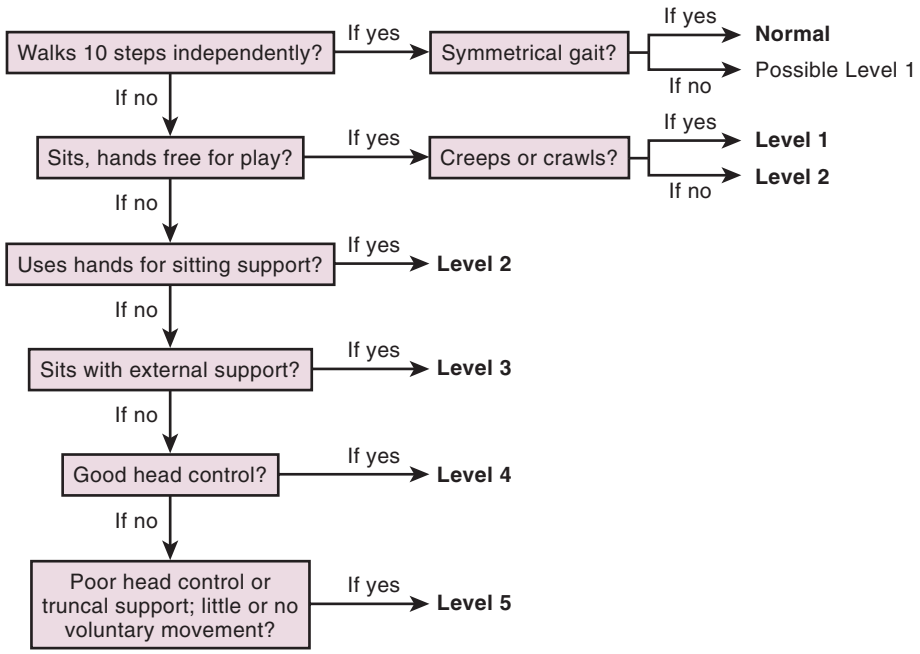
Assessment of Functional Outcomes

One of the most widely used tools to classify gross motor function for children with cerebral palsy is the Gross Motor Function Classification System (GMFCS) introduced by Palisano.[83] This tool defines motor function according to self-initiated movement with emphasis on sitting, walking, and mobility using a five-level classification system in which criteria meaningful to daily living distinguish the levels. Distinctions are based on functional limitations; the need for hand-held mobility devices such as walkers, crutches, or wheeled mobility; and, to a much lesser extent, quality of movement. Because classification of motor function is dependent on age, separate descriptions are applied over a variety of age ranges. The focus of GMFCS is on determining which level best represents the child's present abilities and limitations. Emphasis is placed on usual performance in home, school, and community settings rather than on what the children can do as their best capability. An example of the classification system used for toddlers is presented in Fig. 60.5.

Other measures used in examining functional outcomes include limitations in activities of daily living, such as difficulty feeding, dressing, and toileting, as well as the inability to play or communicate with other children. Instruments for measuring functional status include the Functional Independence Measure for Children,[77] the Vineland Adaptive Behavior Scale,[99] and the Battelle.[78] Most of these functional assessments are applicable only after 2 years of age.

The functional measures of outcome that focus on the consequences of the various diverse medical, behavioral, and cognitive disorders resulting from prematurity are more suited for planning services for children with special health care needs. Additional measures that can be used include the assessment of the overall health status of the child, the Child Health and Illness Profile, and the QUICCC (Questionnaire for Identifying Children with Chronic Conditions), and measures of the quality of life of the child.[61,91,103,104] Children with a birth weight of less than 750 g or gestational age younger than 26 weeks have higher rates of functional limitations, greater compensatory dependence, and an increased need for services compared with those with a birth weight of greater than 750 g.[43] Data

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• **Fig. 60.5** Gross motor function classification system for toddlers. (Data from Palisano RJ, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol.* 1997;39:214.)

from Europe indicate that increased survival of infants with a birth weight of less than or equal to 750 g coincided with slightly greater impaired neurodevelopmental outcome at 2 years of age. Small-for-gestational-age infants are especially at risk. With the exception of a few children (3%-5%) with severe disability, the major needs for services are those related to special education for the various academic learning and behavioral problems in school. Although reports by Saigal and associates and others note an acceptable quality of life for most adolescents and young adults who were born preterm, even for those with disability, educational and behavioral problems persist into adolescence and young adulthood.[14,91]

Timing of Follow-Up Visits

The initial follow-up visit should occur shortly after discharge from the neonatal nursery. This visit is important for evaluating how the child is adapting to the home environment. During the visit, accuracy of home medication and oxygen administration, formula preparation, and parental concerns are particularly important to address. The frequency of subsequent follow-up visits is determined by the severity of specific active medical and neurodevelopmental issues of the individual child, the intensity of follow-up, and the optimal age for developmental assessment. Multidisciplinary follow-up clinics have merged primary pediatric care with neurodevelopmental follow-up, creating a "medical home" for children with sequelae of prematurity. Such comprehensive clinics have been suggested to improve outcomes at reduced cost. A clinic visit at about 4-6 months of corrected age is important for documenting problems of inadequate catch-up growth and severe neurologic abnormality that might require intervention or occupational and physical therapy. Since many of the active medical issues have resolved, this visit offers the opportunity to direct families toward emerging developmental and behavioral issues. Eight to twelve months of corrected age is a good time to identify the suspicion or presence of cerebral palsy or other neurologic abnormality. It also is an excellent time for the first developmental assessment to be performed, usually the Bayley Scales of Infant Development, because the children show little stranger anxiety at this age and most are cooperative. Although behavioral patterns are becoming established, early cognitive skills are still very dependent on motor function.

By 18-24 months of age, most transient neurologic findings will have resolved, and the neurologically abnormal child will be showing some adaptation, with improving functional ability. Environmental factors exert increasing influences on functional assessment. Most potential catch-up growth will have occurred. At the same time, the cognitive and language scales of the Bayley Scales of Infant Development provide some assessment of the child's cognitive functioning independent of motor development. Evaluating performance at 2 years on the basis of corrected age rather than chronologic age is controversial but conventionally accepted. Since formal testing of development rather than intelligence is conducted, an underestimate of subtle problems may occur. Results of individual developmental testing may be readily compared with multicenter network data.

At 3 years, other measures of cognitive function can be performed that better validate the child's mental abilities.

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Expressive and receptive language is well measurable at this age. Verbal and nonverbal skills can be readily differentiated. Measures of pre-academic readiness, visual-motor integration, executive function, and attention may be compared by standardized methods. The predictability of later intelligent quotient (IQ) scores on the basis of scores at this age is acceptable. From 4 years of age, more subtle neurologic, visuomotor, and behavioral difficulties are measurable. Neuropsychologic evaluation may identify problems with attention, learning, behavior, and socialization, which may affect school performance, even in children who have normal intelligence.[50]

Developmental and Neurologic Testing

The neurologic examination during infancy is largely based on changes in muscle tone that occur during the first year of life. The examination developed by Amiel-Tison measures the progressive increase in active muscle tone (head control, back support, sitting, standing, and walking) together with the concomitant decrease in passive muscle tone. This also documents visual and auditory responses and some primitive reflexes. This method gives a qualitative assessment of neurologic integrity, which is defined as normal, suspect, or abnormal. A conventional neurologic examination should be performed thereafter, together with the Amiel-Tison method for early childhood.[2] Under normal conditions, general movements triggered by the neonatal nervous system and generated by the central pattern generators located in the neonatal brainstem lend variability to motor output. Reduced modulation of the central pattern generators results in less variable movements and may indicate fetal or neonatal compromise. The Prechtl General Movement Assessment has demonstrated merit for identification of infants at risk for neuromotor deficits.[101] A systematic review suggests that General Movement Assessment of Infancy is the most sensitive and specific test available for early prediction of spastic cerebral palsy in high-risk infants.[15]

The Bayley Scales of Infant Development is the most commonly used tool for monitoring early cognitive and motor development for high-risk infants. During the past 25 years, longitudinal follow-up programs have used this assessment tool to evaluate early outcomes. It is also used clinically to identify infants who might benefit from interventional services. The scales were developed for children 1 month to 3 1/2 years of age. The first and second editions of the Bayley Scales were divided into three subtests or scales (mental, motor, and behavior) and provided a Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) with a mean of 100 and a standard deviation of 15. The Mental Development Index and Psychomotor Development Index scores have long served as useful tools for neonatal outcomes research. The 1992 revision yielded lower scores than those described for children born during the 1980s and early 1990s and tested with the original Bayley Scales.

In 2006, the third edition of the Bayley Scales was introduced. A primary goal was to add additional scales that meet federal and state mandates requiring assessment of five development domains from birth through 3 years of age. As a result, the newest version contains five scales: cognitive, language, motor, social-emotional, and adaptive behavior, the latter two in the form of parent questionnaires. Thus, the third edition of the Bayley Scales does not generate a "mental developmental index" but rather separate cognitive and language scores. The adoption of Bayley III has resulted in controversy as scores are higher compared to prior editions.[6] Preliminary evaluations have suggested improved early cognitive outcomes for preterm infants using the third edition of the Bayley Scales. However, there is concern that this apparent "improvement" in early cognitive outcomes from the Bayley II and Bayley III era may reflect an underestimation of impairment on the Bayley III rather than a true improvement in outcome.[115] Bayley III includes at-risk toddlers in 10% of its normative sample. Furthermore, score differences between Bayley III and the previous editions are greatest at the lower end of the neurodevelopmental function scales, increasing concern for under-identification of neurodevelopmental impairment. As the subscales differ between the two versions and direct comparisons of Bayley II MDI and Bayley III cognitive or language scores are not feasible, conversion methods suggest the new cognitive score is 6-10 points higher than the MDI and the motor score is 8-14 points higher.[75] Similar trends have been reported with Bayley III use in full-term children, suggesting the need for term control groups in the evaluation of outcomes of NICU therapies.

It is not clear that infant tests measure the same constructs as intelligence tests that are administered to older children and adults. Infant tests are seen as a description of current functioning and thus are not predictive. Generally, infant tests have not been shown to have long-term validity, especially for some clinical subgroups. The poor prediction is considered to result from difficulties in infant testing, measurement error, changes in function of the child, and environmental influences that become more evident after 2 years of age. Several studies of children with extremely low birth weight have reported significantly lower rates of intellectual impairment at school age than during early childhood.[88]

The Ages and Stages Questionnaire may be used as a screening tool for children aged 3 months to 5 years to identify developmental delays.[17] The tool uses parents as the source of information about child development and has been successful in identifying cognitive and motor delays in the follow-up of premature infants and those with hypoxic ischemic encephalopathy.[63] However, it does not give a quantitative assessment and thus cannot be used to quantify outcome in specific high-risk populations. The Wechsler Scales may be used with prekindergarten and school-age children. The Wechsler Intelligence Scale for Children, third edition, is probably the most commonly used instrument for school-age assessment. The Kaufman Test was standardized

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on a 2 1/2- to 10-year-old population and is less heavily weighted by verbal items than other tests. Other useful early school-age evaluations include the Behavior Rating Inventory of Executive Function (BRIEF), the Developmental Neuropsychological Assessment (NEPSY-II), the Attention Deficit Hyperactivity Rating Scales, and the Woodcock-Johnson III. Neurodevelopmental follow-up assessments used for surveillance, research, or both require serial evaluations because of rapid developmental changes and test-taking behavioral issues among young children.

Ophthalmologic testing should be performed in all high-risk children. AAP has published guidelines for screening of retinopathy of prematurity.[35] If the results are abnormal, repeat examinations should be done at the discretion of the ophthalmologist. Complete vascularization typically occurs by 44-48 weeks' corrected age. Serial examinations should continue until the neonatal retina is fully vascularized. Preterm children with a history of retinopathy should be screened for refractive abnormalities and amblyopia at 6 months' corrected age, 12 months' corrected age, 2-3 years, prior to beginning school, during grade school, and during adolescence when rapid ocular growth occurs (see Chapter 96 for specific examination timetables).

Hearing loss is more prevalent among NICU graduates than in the general population. Hearing should be screened before discharge from the neonatal intensive care nursery. Most hearing screening programs use the otoacoustic emissions test, in which a small earphone and microphone are inserted into the infant's ears. When sounds are played, a normally functioning ear will create an echo that can be picked up by the microphone. In a baby with hearing loss, no echo can be detected. Otoacoustic emissions can reliably detect hearing losses greater than 1500 Hz but only in the presence of outer hair cell dysfunction. Auditory brainstem response testing may be used for infants who fail the initial hearing screen. The auditory brainstem response test uses electrodes to detect brain waves. As sounds are played, the test measures the brain's response. The test can detect improper functioning in the inner ear, acoustic nerve, and auditory brainstem pathways associated with hearing. It can detect hearing sensitivity from 1000-8000 Hz (see Chapter 59). Hearing should be re-examined at 12-24 months, because hearing loss can appear later as a sequela of ototoxic drugs such as diuretics. In addition, late-onset hearing loss can occur secondary to cytomegalovirus infection in the newborn period. Hearing loss related to middle ear infections can also occur after the neonatal period and during the first 2 years of life.

Methodologic Considerations in Neurodevelopmental Outcome Studies

Many biologic and environmental factors affect the outcomes of preterm infants. In addition to gestational age, birth weight, gender, and the severity of medical complications, socioeconomic factors such as social support and exposure to positive or negative life experiences all affect outcome. In general, the evidence suggests that biologic risk factors play a greater role in determining early outcome than social factors. Neurodevelopmental outcome has been increasingly used as the benchmark to determine the efficacy of medical interventions. Unfortunately, long-term follow-up studies are expensive, relatively slow to yield results, subject to human factors that are difficult to control such as subject dropout, and often deemed not as precise as bench research. Nevertheless, long-term follow-up is critical to identify possible negative effects of interventions that are not obvious in the nursery. For example, the use of postnatal steroids for the treatment of chronic lung disease enhanced extubation success but only later revealed severe neurodevelopmental sequelae. Because the results of long-term follow-up are being used to guide future interventions, it is imperative that outcome studies be rigorous and hypothesis driven. The following methodologic flaws that may compromise outcome studies have been described: inadequate description of the study population, lack of consideration to perinatal course, single-hospital samples, lack of appropriate comparison groups, excessively high dropout rates, no assessment of environment, too short follow-up duration, vague outcome measures, variability in diagnostic criteria, inclusion of severely handicapped children in the computation of mean scores, lack of consensus on correction for prematurity, change in testing instruments, changes in medical therapies during the study period, and intrinsic problems unique to birth weight or gestational age cohorts. Cause-and-effect inferences must be tempered by alternative explanations of observed events that could be produced by confounders. Both mediating and moderating variables can alter the attributable influence of any particular variable on outcome. Regional or geographically based data derived from nationwide, collaborative networks are most generalizable. Established multicenter networks enable assessment of low-incidence issues and allow for adequate sample sizes. Several large multicenter networks include the NICHD Neonatal Research Network (15 centers), the Vermont Oxford Network (>400 centers), and the Canadian Neonatal Network (17 centers).

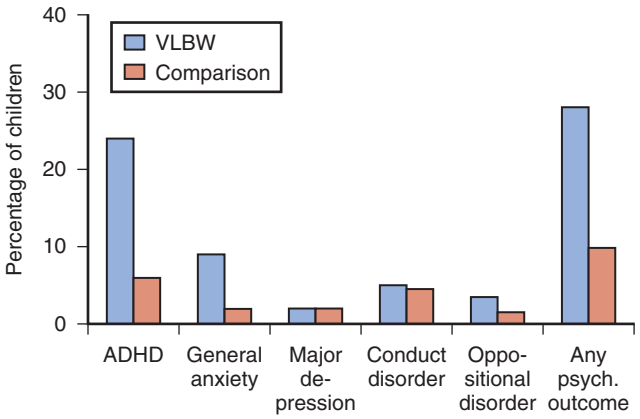
Subject loss can bias the rates of impairment as risk for dropout increases in larger, less sick babies from lower socioeconomic backgrounds. Recommended retention rates of 90% for early childhood, 80% for school age, and 70% for young adulthood have been suggested. Comparison of children who drop out and those who continue in follow-up is essential to prevent data bias. Illness severity scores such as the SNAP (Score for Neonatal Acute Physiology) or Neurobiologic Risk Score may be used to weigh the impact of individual but competing biologic factors on outcome. Early evaluations, below 1 year of age, may be more affected by recovery from medical issues and place more weight on motor outcomes. These early assessments are limited in their ability to evaluate behavior or language. By 18-24 months, environmental factors become more influential, language becomes more elaborate, and cognitive processes

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show improved prediction of later function. A trend toward worsening outcomes of preterm children at school age is a significant concern.[68] Demand for higher-level skills may cause frustration and loss of motivation, resulting in refusal to test or behavioral disorders such as attention deficit hyperactivity disorder. Although the incidence of major disability, such as moderate to severe cognitive disability, sensorineural deficits, cerebral palsy, or neurodevelopmental impairment, has decreased to 6%-8% of low birth weight infants (<2500 grams), 14%-17% of very low birth weight infants (<1500 grams), and 20%-34% of extremely low birth weight infants (<1000 grams), more subtle problems with motor coordination, executive function, and behavior occur frequently with decreasing gestational age.[19,87]

School-Age Outcome

Measuring school-age outcomes is an important landmark in longitudinal follow-up. Most of the school-age outcome studies of very premature children have been descriptive rather than hypothesis driven and have included measurements of growth, health, school performance, behavior, quality of life, self-esteem, cognition, motor function, and various neuropsychologic assessments. They have compared these premature survivors with children of normal birth weight, documenting significantly more major and subtle neurologic dysfunction, lower intelligence, poorer performance on tests of language and academic achievement, and more behavioral difficulties than control groups of children with normal birth weight who have similar race, gender, and sociodemographic backgrounds.[57] When only those children free of major neurologic impairment are considered, some of these differences disappear. However, significant differences in tests of visuomotor function and mathematics continue.[110] There are also behavioral differences that interfere with the child's attention and ability to complete a task (Fig. 60.6).[44] In a multicenter ELGAN (Extremely Low Gestational Age Newborns) study of survivors born less than 28 weeks' gestation, one-quarter of children had moderate to severe cognitive impairment at 10 years of age, with boys having greater risk than girls.[57]

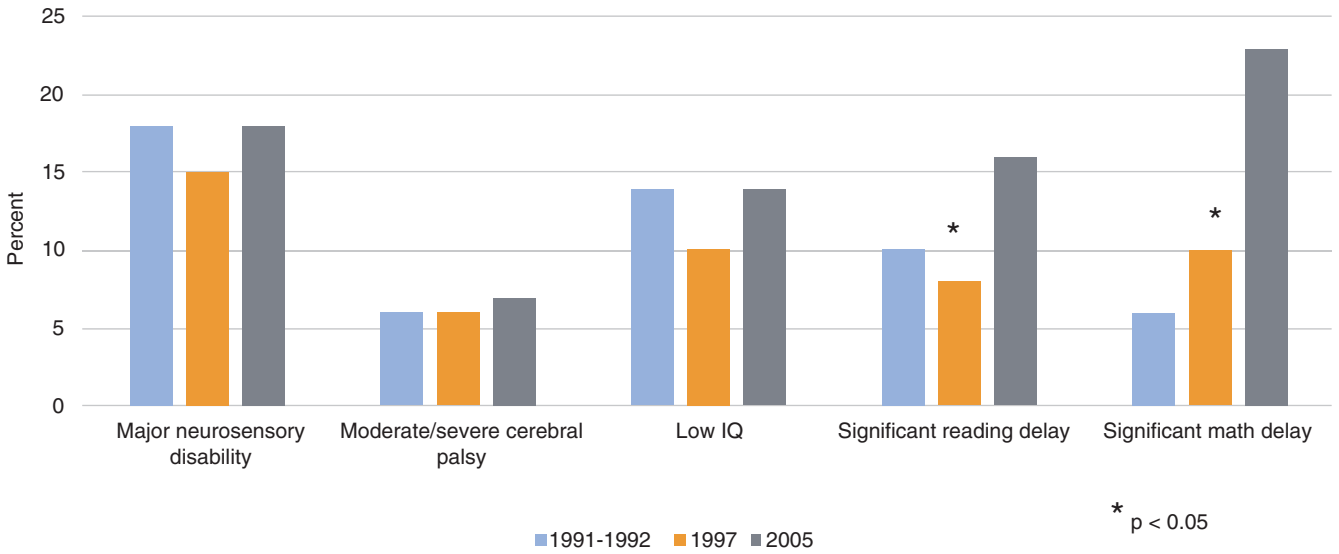


• **Fig. 60.6** Psychiatric (psych.) outcomes in adolescent children who had very low birth weight (VLBW). ADHD, Attention deficit hyperactivity disorder. (Data from Botting N, et al. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birth weight children at 12 years. *J Child Psychol Psychiatry.* 1997;38:931.)

Few studies have compared school-age outcomes among premature infants over time. Cheong et al. compared 8-year outcomes of infants less than 28 weeks' gestation within Australia's Victorian Infant Collaborative Study between birth cohorts of 1991-1992, 1997, and 2005. Survival rates to age 8 improved from 53%-70% between eras and moderate-severe disability rates were stable. However, the improvement in survival was not an improvement in survival without disability, attributed largely to an increase in mild intellectual disabilities. Although mean intelligence scores did not differ, academic achievement scores for reading and mathematics were lower in 2005 than in 1997, accompanied by increased rates of academic problems in the later period. These outcomes were not explained by differences in perinatal care or sociodemographic variables between eras[22] (Fig. 60.7).

Longitudinal follow-up of preterm-born cohorts from birth to school age suggests that although rates of impairment decline with advancing age, significant neurodevelopmental disabilities persist for many preterm survivors. In the EPICure study of infants born less than 26 weeks' gestation from Great Britain and Ireland, disability was evaluated at 30 months, 6 years, and 11 years of age. Although rates of severe disability decreased from 30% at 30 months of age to 22% at 6 years, at 11 years of age 45% had serious functional disability compared with 1 percent of term-born classmates. In addition, more than half of the extremely preterm survivors had special education needs.[54,55] In terms of their overall health status, extremely preterm children have many more functional limitations and compensatory dependency needs and require many more services above routine than term-born children.[43] These differences persist even when children with neurosensory impairments are excluded. Although most children with very low birth weight remain in the regular school system, many have difficulty coping with the demands of school learning and require more special education and remedial resources.[70] The problems that appear to be most related to academic success, in addition to cognition, fall within the neuropsychologic and psychiatric domains and include deficits in attention, memory, and behavior.[37] Most preterm children who are free from major disability are functioning within the low-normal range on intelligence quotient tests. Sociodemographic and environmental factors may contribute more to the differences in cognitive outcomes than biologic risk factors, with social risks becoming more pronounced as the children age. Structural brain abnormalities detected by magnetic resonance imaging and involving the lateral ventricles, corpus callosum, and white matter are more common among preterm survivors than among controls. These findings provide an anatomic basis for neurodevelopmental problems.

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• **Fig. 60.7** Comparison of rates of school age neurodevelopmental problems among infants born extremely preterm at <28 weeks' gestation over the past two decades. (Data from Cheong J, et al. Changing neurodevelopment at 8 years in children born extremely preterm since the 1990s. *Pediatrics.* 2017;139.)

School-Age Behavioral Problems

The most commonly reported childhood behavioral problems of prematurity are disorders of attention and hyperactivity, emotional difficulties, and socialization issues. Rates of attention deficit hyperactivity disorder (ADHD) range from 20%-30% for preterm children versus 5%-10% for term-born children. In a meta-analysis of six behavioral studies of preterm infants, Bhutta et al. reported a relative risk for ADHD of 2.64 (95% confidence intervals [CI] 1.85-3.78).[13] Poor cognition may contribute to attention deficits in preterm children or vice versa. In the EPICure study evaluating the outcomes of children born before 26 completed weeks of gestation in the United Kingdom and Ireland, Wolke reported no difference in the prevalence of ADHD between preterm and term controls after adjusting for IQ.[119] Reports based on screening assessments have suggested that autism may be more prevalent among preterm children.[34,62] The EPICure 2 study reported a positive screening result on the Modified Checklist for Autism in Infants and Toddlers (M-CHAT) in 41% of children born at 26 weeks of which 62% had coexisting disabilities, suggesting that the screen must be viewed in light of other neurodevelopmental problems.[58] In a young adult study of more than 900,000 subjects from a Norwegian national registry, autism spectrum disorder occurred nearly three times more frequently among preterm survivors and nearly 9 times more frequently among those born at extremely low birth weight.[76] Although no single perinatal or neonatal factor has been identified in the etiology of autism spectrum disorder, the increasing trend emphasizes the importance of early screening. Internalizing problems such as depression, anxiety, and poor adaptive skills have all been associated with prematurity, resulting in socialization and peer relationship difficulties. Furthermore, motor delays due to extreme prematurity may compromise playground skills, causing peer victimization and rejection. Immature behavioral patterns leading to parental overprotection may yield additionally poor socioemotional adjustment.

Young Adult Outcomes

Information on the young adult outcomes of the initial survivors of neonatal intensive care has been reported from around the developed world.[43,92,128] The studies have differed with regard to whether they were regional or hospital-based and the birth weight group, rate of survival, sociodemographic status, and types of outcome studied. Despite these differences, the overall results suggest that neurodevelopmental and growth sequelae of prematurity persist into young adulthood. Traditionally, educational attainment, employment, independent living, marriage, and parenthood have been considered as markers of successful transition to adulthood. When compared with controls with normal birth weight, young adults with very low birth weight have poorer educational achievement, more chronic illnesses such as asthma or cerebral palsy, and less physical activity. Higher rates of obesity among females have also been reported. In terms of brain structure, diffuse abnormalities including reduction in gray and white matter volume, increased ventricular volume, thinning of the corpus callosum, and periventricular gliosis have all been reported among young adults born prematurely.[32,97] The impact of these structural differences on brain function is uncertain; however, cognitive and behavioral differences have been reported. In general, young adults with very low birth weight report less risk taking. Fewer females born at very low birth weight have ever dated or been involved

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in an intimate relationship. In addition, pregnancy and childbirth rates are lower for young women with very low birth weight. Alcohol and marijuana use also tend to be less prevalent among the former preterm adults.[41] Although the information varies, there is currently no clear evidence of an increase in attention deficit hyperactivity disorder or psychosis among adult preterm survivors. However, there is some evidence for an increase in anxious, withdrawn, and depressed symptoms, predominantly among women. This may affect both the development of adult social interactions and the formation of permanent relationships and predispose to further psychopathology later in life.[40]

The adult outcomes described to date pertain mainly to preterm infants born in the 1970s and early 1980s, a time when neonatal mortality was high and few extremely immature infants survived. In one such Canadian study of adults in the third decade of life, those born at extremely low birth weight had lower levels of employment, income, and self-esteem. In addition, fewer were married or had children.[90] Despite statistically significant differences in most outcomes measured, including educational achievement, health status, and socialization, most preterm survivors born during the early years of neonatal intensive care do well and live fairly normal lives. In fact, studies have demonstrated similar self-esteem, overall health satisfaction, and quality of life compared with adults with normal birth weight.[92,128]

Researchers in Sweden and Norway have used national longitudinal databases to examine the adult outcomes over the complete spectrum of gestational age, ranging from 23 weeks to term gestation, thus allowing for the examination of the relative outcomes of extremely preterm, late preterm, and term-born children.[64,76,107] These national studies, which link birth data to later outcomes, also have the advantage of including all the subjects of interest with very little loss to follow-up. Data reported from these national databases pertain to health, functional, educational, and developmental outcomes of importance to society but provide very little in-depth analysis of the correlates and predictors of specific outcomes. The two major predictors of adult outcomes are lower gestational age, which reflects perinatal injury, and family sociodemographic status, which reflects both genetic and environmental effects. Preliminary long-term follow-up data suggest that preterm and low birth weight children have a higher incidence of hypertension, visceral obesity, asthma, neurodevelopmental problems, and perturbations in glucose-insulin homeostasis. Speculation exists regarding the relationship between these noncommunicable disorders and possible alterations in genetic programming caused by events such as intrauterine growth restriction, premature interruption of pregnancy with change in redox state, nutritional and pharmacologic protocols used in the nursery, and postdischarge maximization of catch-up growth. The association among insulin sensitivity, altered glucose metabolism, and premature birth has been reported in a number of studies from many parts of the world. Additionally, a prevalence of type 2 diabetes in subjects born prematurely has also been reported. Unfortunately, there is a limited understanding of the mechanisms underlying these possible programming effects.

Children Born at the Threshold of Viability

Infants born at less than 24 weeks' gestation are often considered to be born at the threshold of viability. With advanced perinatal care, survival of this subpopulation has improved from 32%-46% in the early 1990s[105] to 45%-70% in the 2000s.[28,49-51,74,94,95,106,111] Evaluating the outcomes of these infants born at the threshold of viability is one of the most difficult dilemmas facing obstetricians and pediatricians. Outcome data are variably reported by birth weight or gestational age classifications and are exquisitely dependent on many covariates. Data may also suffer bias related to varying medical and societal approaches to intervention for this subpopulation.[25,31,93] Published outcome reports derive from a range of cohorts, including those from single tertiary centers with selected patients and others based on geographically defined areas. Furthermore, survival and morbidity show wide variation between cohorts, which may be partly attributed to differences in definitions or denominators. Additionally, even within this narrow subpopulation, variation in survival and outcomes can be seen from the lower to the higher end of the gestational age range.[28,36,51,74,94,95]

As the mortality rate of extremely premature infants declines, the natural next questions concern the outcomes of the survivors. The increase in survival reported by several cohorts between eras has been associated largely with a stable but broad range of rates (7%-67%) of moderate-severe impairment.[23,28,48,74,94] However, there is some evidence that the incidence of mild disability and/or developmental delay may be increasing.[28]

In the largest cohort of infants less than 27 weeks' gestation (EPICure 2 birth cohort 2006) compared to EPICure 1 (birth cohort 1995), there was an observed improvement in survival without disability of NICU-admitted infants from 23%-34%. Improvements in developmental testing scores and reduction in neurologic morbidity, but no change in the rates of severe impairment, were also reported. Of note, these outcome gains were significant only in infants born at 24-25 weeks, whereas the differences between cohorts for 22- to 23-week infants did not change.[74] In a similar comparison of less than 25-week outcomes between two epochs (1999-2001 versus 2002-2004) from the Neonatal Research Network, Hintz et al. found no statistically significant differences in survival or 18- to 22-month outcomes between the epochs with moderate-severe cerebral palsy in 11%-15%, cognitive impairment in 45%-51%, and composite neurodevelopmental impairment in 50%-59%.[48]

Factors influencing outcomes at the threshold of viability are similar to those in the larger very preterm population. In multivariate analyses, exposure to antenatal corticosteroids, female sex, singleton birth, higher birth weight, and greater gestational age have been associated with reductions in the risk for death or profound impairment. Maternal chorioamnionitis, neonatal sepsis, transient hypothyroxinemia,

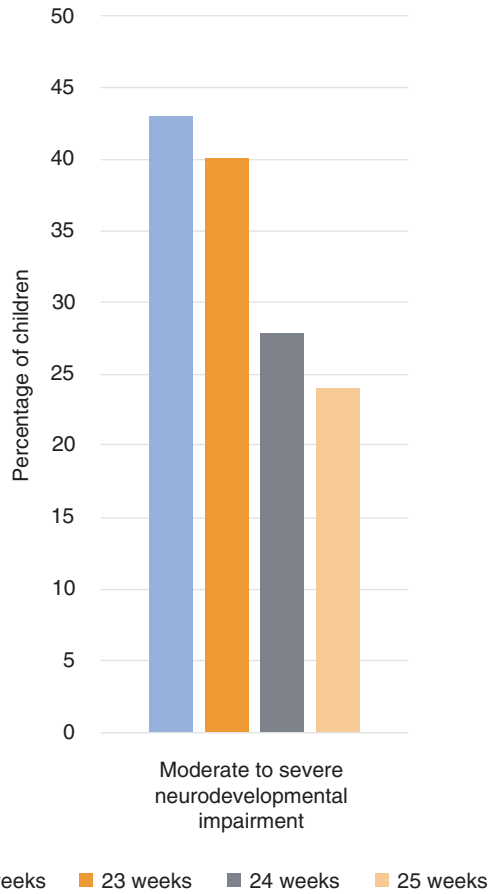
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jaundice, postnatal steroid exposure, and the major neonatal morbidities of chronic lung disease, severe brain injury, and severe retinopathy of prematurity have all been associated with increased risk of poor neurodevelopmental outcomes.[5,38,110,122,124]

School-age follow-up of the EPICure 1 cohort at 6 years revealed cognitive impairment in 21% of the children, severe disability in 22%, and disabling cerebral palsy in 12%.[68] In terms of overall function, the EPICure children demonstrated school difficulties, language problems, poor respiratory health, and a variety of pervasive behavioral problems, including attention deficit, hyperactivity, and social-emotional problems.[120] At 11 years of age, the EPICure 1 survivors continued to demonstrate cognitive impairment with specific problems in reading and mathematics. Fifty-seven percent required special educational services.[54] Similar results have been reported at school age for regional cohort of children born weighing less than 1000 g or before 28 weeks' gestation in Australia.[26]

A review of the international literature on survivors of a birth weight of less than 750 g or before 26 weeks' gestation reveals that during early childhood, the rates of severe neurosensory disability range from 9%-37%, with cerebral palsy occurring in 5%-37%, blindness in 2%-25%, and deafness in 0%-7%. Subnormal cognitive function is noted in 15%-47% of survivors.[50] A meta-analysis of the early school age outcomes of extremely preterm survivors born between 22 and 25 weeks' gestation demonstrates a substantial likelihood of moderate to severe neurodevelopmental impairment among this entire group[73] (Fig. 60.8).

This population of children thus represents a subgroup of preterm children who are at the highest risk for poor school performance.



• **Fig. 60.8** Rates of moderate to severe neurodevelopmental impairment at 4-8 years for children born 22-25 weeks' gestation. (Data from Moore G, et al. Neurodevelopmental outcomes at 4-8 years of children born at 22-25 weeks' gestational age. A meta-analysis. *JAMA Pediatr.* 2013;167(10):967-74.)

Early Intervention

Strategies to positively impact the neurodevelopmental outcomes of premature infants after the acute neonatal period have been actively sought as survival rates for the population have improved. Interventions in the neonatal or infant/toddler period have typically focused on parent education, parent–infant relationships, infant stimulation, infant development, and specific therapies such as physical therapy, occupational therapy, speech therapy, or infant special education.

The Infant Health and Development Program is the largest randomized trial using a comprehensive early intervention program and family support services. The study involved a 3-year birth cohort (1985-1988) of low birth weight infants (<2500 g) from eight US centers with program implementation from neonatal discharge to 36 months' corrected gestational age and extended longitudinal follow-up to 18 years of age. The program improved the intelligence quotient scores of the children at 3 years of age; however, children of the lowest birth weight (<1000 g) and thus at greater biologic risk were less responsive to the intervention. Subsequent follow-up of the cohort at age 8 years demonstrated improvement in growth status for the intervention cohort but only minimal effects of the intervention on cognitive status, school achievement, or behavior.[20] A study suggests that longer, more intensive community-based early intervention services may be associated with higher kindergarten skill levels.[65] Late adolescent outcomes of children enrolled in the Infant Health and Development Program have been reported, suggesting slight improvements in full-scale IQ, mathematics, vocabulary, and behavior among those who received early intervention; however, these improvements were noted only among the larger preterm children.[71]

A large meta-analysis of randomized trials of early developmental interventions with initiation at less than 1 year of age suggested that such interventions lead to significant positive differences in cognitive and behavioral outcomes at infant and preschool ages but that the effects do not persist to school age or into adulthood.[42,100] Small improvements in motor outcome at infant ages were found in the meta-analysis as well but were not sustained past infancy. Additional studies of the impact of early intervention on childhood outcomes have yielded mixed results.[52,56,79,80,127]

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Despite these findings, there continues to be optimism for the potential of early intervention programs. Most intervention outcome assessments include cognitive, behavioral, and motor components that are best suited to identify major disabilities. There is speculation that such measures may lack sufficient sensitivity to identify or monitor improvement in minor problems or disabilities that are believed to be related to long-term neurodevelopmental outcomes.[81] In addition, it has been suggested that early interventions may have meaningful impact on parent outcomes such as maternal anxiety, depression, and self-efficacy, which may, in turn, influence infant outcomes.[12] Childhood interaction with family members and other children is an important part of normal development. This process may be compromised among preterm children whose parents are recovering from the emotional stress of multiple medical problems in a vulnerable child. Intervention programs can help maximize the potential for developmentally normal interactions for these parents and children.

Key Points

- Preterm-born children are at increased risk for impaired neurodevelopmental outcome, which includes cognitive abnormalities, motor deficits, cerebral palsy, and vision and hearing losses, with the risk of impairment increasing with decreasing gestational age.
- Neonatal complications associated with increased risk of poor outcome include bronchopulmonary dysplasia, severe intraventricular hemorrhage, poor growth, severe retinopathy of prematurity, and congenital anomalies. Socioeconomic factors such as poor education, maternal drug abuse, and low income also increased risk.
- Former preterm infants are more likely to develop psychologic and behavioral problems, including attention deficit hyperactivity disorder, anxiety, depression, and autism spectrum disorder.
- School-age children born preterm are at increased risk for functional disabilities that impact daily activities.
- Many adults who were born preterm report a similar quality of life to those born at term.

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The Role of Neonatal Neuroimaging in Predicting Neurodevelopmental Outcomes of Preterm Neonates

SUSAN R. HINTZ AND NEHAL A. PARIKH

Cranial Ultrasound

Cranial ultrasound (CUS) is the most widely used neuroimaging method for preterm infants. Cranial ultrasound uses high-frequency sound waves, transmitted through open fontanelles, to detect differences in echogenicity between tissues and allow identification of anatomic structures, hemorrhage, and fluid collections. Early reports of CUS to image brain injury in preterm infants utilized anterior fontanelle views.[75,90] Since that time, the importance of mastoid (posterolateral) and posterior fontanelle views have been highlighted as critical to appropriately visualize other areas of the brain, including cerebellum, vermis, fourth ventricle, posterior fossa subarachnoid space, and trigone and occipital horns of the lateral ventricle.[30,61] CUS is an operator-dependent modality, imaging procedures and views may differ among institutions and studies, and there is no uniform approach to serial imaging protocols. Nevertheless, in skilled hands, with optimized technology and views, CUS can provide detailed information with improved accuracy compared with earlier studies.[26] Furthermore, CUS is a bedside, noninvasive neuroimaging modality and, therefore, is ideal for repeated imaging.

Brain Injury among Preterm Infants Diagnosed by CUS

A grading approach to categorize severity of intracranial hemorrhage (ICH) in preterm infants was published in the late 1970s.[76] In this system, hemorrhage confined to the germinal matrix is defined as grade I, into the ventricle without dilation as grade II, into the ventricle with dilation as grade III, and with parenchymal hemorrhage as grade IV, which in the original description was defined as accompanying intraventricular hemorrhage (IVH). This system remains broadly applied, both for research and for family counseling. Using these traditional definitions, severe ICH may be decreasing over time among extremely preterm infants. The *Eunice Kennedy Shriver* NICHD Neonatal Research Network (NRN) reviewed from 1993-2012 maternal and neonatal care, as well as morbidities and mortality among infants born at 22+0/7 weeks' to 28+6/7 weeks' gestational age in one of the participating academic US centers.[96] Among extremely preterm infants overall, the proportion with severe ICH (defined as grade III or IV IVH) decreased from 1993-2012 (19%-13%), with significant reductions for infants born at 26 weeks', 27 weeks', and 28 weeks' gestational age (GA) but not for those 22-25 weeks' GA. Cystic periventricular leukomalacia (cPVL) also decreased for infants 26, 27, and 28 weeks' GA, with 2012 rates 4%, 3%, and 2% respectively.

However, the complexity of the interpretation of CUS findings, evolving recognition of neuropathologic etiologies of intraparenchymal echogenicity or periventricular hemorrhagic infarction (PVHI), and limitations of outcomes prediction with any single neuroimaging or other finding, should give clinicians cause for prudence and careful consideration in using these classifications alone for prognostic guidance. The grading system does not include consideration for nonhemorrhagic periventricular echogenicity or echolucency such as cPVL, nor does it include ventricular dilation not associated with hemorrhage, or cerebellar hemorrhage, all of which have been associated with neurodevelopmental impairment.[13,55,57,77] In some studies, persistence of periventricular echodensity or "flaring" on CUS is assessed,[24] a finding that has been suggested to be predictive of neuromotor outcome. Since the initial description of these grades, periventricular hemorrhagic infarction (PVHI) has been proposed to be caused by impairment of venous drainage leading to venous infarction, with subsequent hemorrhagic evolution in periventricular white matter,[34,36] thus may exist as an isolated finding. Furthermore, the extent and severity of the injury associated with PVHI is not further quantified. Nevertheless, strong associations between major ICH

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Abstract

Neonatologists, neurologists, and other providers who care for high risk, very premature infants in the neonatal intensive care unit (NICU) have at times been frustrated by the inability to give families more accurate, informed answers to their questions about the neurodevelopmental outcomes of their children. Our ability to prognosticate about individual cognitive and developmental outcomes in early childhood is limited. Prediction of school age and later childhood endpoints at the time of NICU discharge, including complex academic, behavioral, and executive function outcomes, presents still greater challenges. With advances in development and utilization of cranial ultrasound (CUS) and magnetic resonance imaging (MRI), enhanced and detailed delineation of brain injury in the preterm infant has led to research to improve our understanding of links to developmental outcomes. But despite extensive and evolving experience with neonatal neuroimaging, substantial controversies exist as to when, how, and which neuroimaging studies should be performed for preterm infants and how these results should be interpreted and presented to families.

Keywords

preterm
cranial ultrasound
magnetic resonance imaging
white matter abnormality
neurodevelopmental outcome
cerebral palsy

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and adverse neurodevelopmental outcomes among preterm infants have been described in numerous single-center, multisite, and population-based analyses. Detailed evaluation of these associations, however, may point more to a mechanism via white matter (WM) injury rather than hemorrhage into a ventricle in and of itself.

CUS Findings and Neurodevelopmental Outcomes

The focus of many investigations has been on exploring the prognostic capabilities of major CUS findings with cerebral palsy (CP). The majority of studies have found significant associations of severe CUS abnormalities with neuromotor outcomes at 18-36 months. The EPIPAGE study followed a French regional cohort of 22-32 weeks' GA infants to 2 and 5 years of age.[3,12] Cerebral palsy (CP) was determined by questionnaires sent to pediatricians. At 2 years, among children with a history of white matter abnormalities (defined as PVL, ventricular dilation, or intraparenchymal hemorrhage or cyst), 24% were diagnosed with CP; 57% of those with cystic PVL were diagnosed with CP. The presence of cerebral lesions on neonatal CUS was independently associated with CP at 5 years. At 5 years, among those with cystic PVL, 61% had CP; among those with intraparenchymal hemorrhage, 50% had CP. At both 2 and 5 years, among those with no CUS abnormalities, CP was diagnosed in just over 4%. In EPICure 1, a population-based study of infants 20-25 6/7 weeks' GA born in the United Kingdom and Ireland from March 1995 to January 1996,[107] severe CUS abnormalities (defined as parenchymal hemorrhage, cystic changes, or ventricular dilatation on the last CUS) were associated with CP (OR 4.95, 95% CI 2.25–10.85) and with severe motor disability (OR 7.15, 95% CI 2.73–18.74). Of importance, when children with motor disability were excluded, severe CUS abnormality was not significantly correlated with Bayley Scales of Infant Development 2nd edition (BSID-II) mental developmental index (MDI) score. The NICHD Neonatal Research Network (NRN) reported the 18-22 months' corrected age outcomes of a cohort of extremely low birth weight (ELBW) infants born in the 1990s[56] and also found that after adjusting for numerous confounding variables, grade III or IV IVH (OR 2.4, 95% CI 1.8–3.1) and cPVL (OR 10.5, 95% CI 7.2–15.2) were associated with moderate to severe CP. Among extremely preterm infants <25 weeks' GA in the NRN, IVH grade III or IV, and cystic PVL were also independently associated with moderate to severe CP.[42] The Extremely Low Gestational Age Newborn (ELGAN) study was a multicenter study designed to identify characteristics and exposures that increase the risk of neurodevelopmental impairments at early childhood follow-up among children born before 28 weeks' gestation.[54,73,74] Three CUSs were required at specified age ranges during NICU hospitalization. At 2 years, intraparenchymal hemorrhage was strongly independently associated with moderate to severe CP (RR 4.2, 95% CI 2.1–8.1), but white matter injury on CUS as defined by echolucency (RR 16, 95% CI 7.6–32) and ventriculomegaly (RR 11, 95% CI 5.5–21) demonstrated even stronger associations.[54] In multivariable analyses adjusting for numerous confounders, isolated IVH without white matter injury did not appear to be associated with neurologic or developmental impairment at 2 years as defined by BSID II psychomotor developmental index (PDI) and MDI scores.[73,74] Only when accompanied by white matter lesions was IVH independently associated with significantly increased risk for CP and no more than a minimal increased risk for adverse developmental outcome.

These studies and others show that severe neonatal CUS abnormalities are associated with subsequent neuromotor impairment. Nevertheless, the risk for CP is not completely eliminated with the finding of a normal CUS, although it is reassuring. In the EPIPAGE study,[3,12] only 4.4% of those with normal CUS went on to be diagnosed with CP at 2 years. However, evaluating the data in a different way, of the 164 children diagnosed with CP, more than one-third had no abnormality on neonatal CUS. In the ELGAN study, almost half of the children with CP at 2 years had all normal CUSs, and the positive predictive value (PPV) of ventriculomegaly or echolucency for moderate or severe CP was poor.[54,73,74] Nevertheless, with meticulous technical attention and serial CUS imaging, impressive predictive capability for CP has been reported. In a single center, de Vries et al. reported 76% sensitivity and 95% specificity of CUS abnormalities for CP at 2 years for patients <32 weeks' GA.[25] Of importance, among those with major CUS abnormalities who developed CP, approximately 30% were noted only after 28 days of age on serial imaging, including some cystic changes that were found only on late scans or were observed to collapse or coalesce over time. In longer-term follow-up at 5 years of age in the EPIPAGE cohort, major CUS abnormalities remained strongly associated with motor challenges, with CP seen in 61% of those with cPVL and 50% in those with intraparenchymal hemorrhage, compared with 4% in infants with normal neonatal CUS.[12]

Although severe CUS findings are associated with subsequent adverse motor findings, CUS findings alone are poorly predictive of early developmental outcomes or later childhood cognitive and learning outcomes unless more detailed CUS and other factors are taken into account. Hack et al. found that severely abnormal CUS findings among ELBW infants was independently associated with abnormal neurologic outcome but not with BSID II MDI <70, at 20 months.[37] However, about 40% of ELBW infants with neurologic abnormality at 20 months did not have abnormal CUS, and about half of those with abnormal CUS did not go on to have neurologic abnormality. Similarly, among ELBW infants in the NICHD NRN with at least two neonatal CUSs during hospitalization and all CUSs reported as normal, either BSID II MDI <70 or CP was still present in 29% at 18-22 months.[56] Further analyses demonstrate that the presence of severe IVH on CUS accounts for a very small fraction of the variation in

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major handicap or low MDI score,[2] and models that include clinical variables predict neurodevelopmental outcomes significantly better than those with CUS variable alone.[16] Even with serial CUS and evaluation of detailed findings, major CUS abnormalities have not been found to be strongly associated with cognitive delay at 2 years.[25] In the 8-year follow-up of the EPIPAGE cohort, ~40% of those with major neonatal CUS abnormalities had no significant cognitive or learning challenges identified, whereas 30-40% of those with no neonatal CUS abnormalities had moderate to severe challenges.[65] This underscores the need for long-term surveillance through childhood for all born extremely preterm regardless of neuroimaging findings.

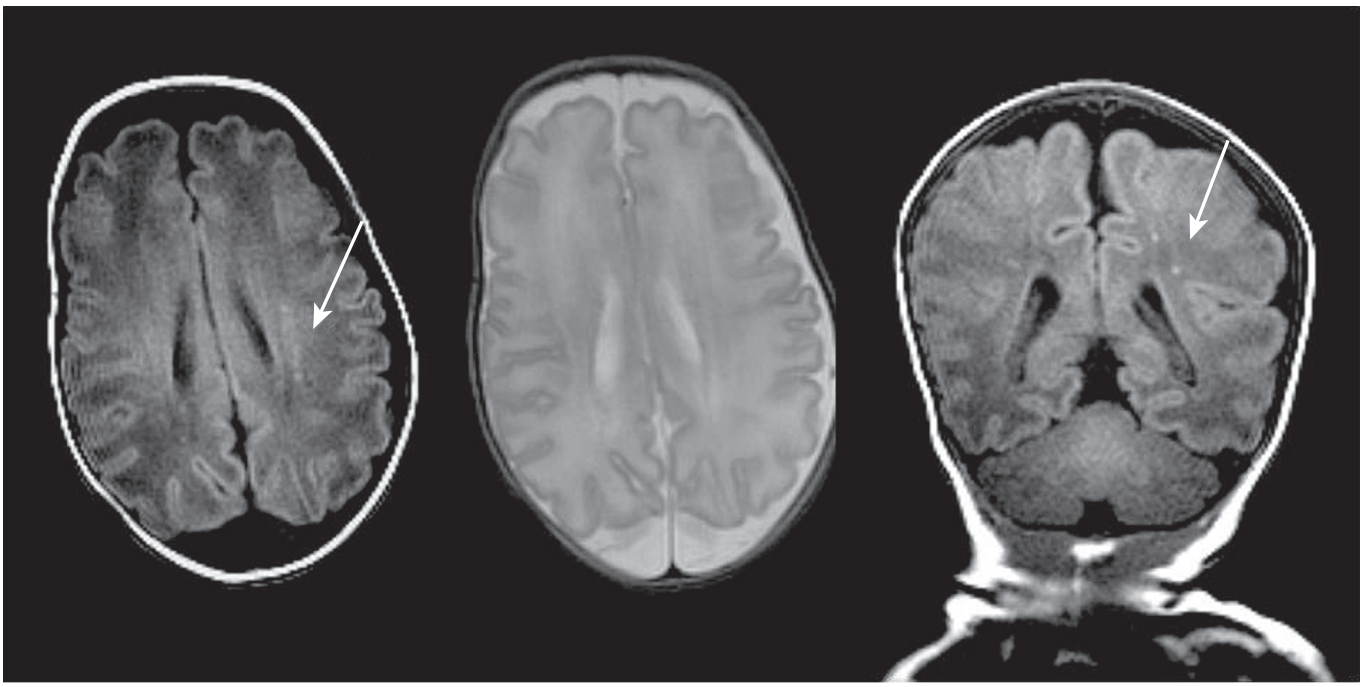
Potential Limitations to Interpretation

Details pertaining to severity of IVH and PVHI may be important to understanding implications for outcome, as can the presence or absence of other clinical findings and morbidities. Any grade III and IV ICH have often been combined into a single "severe" category both for the purposes of research and clinical counseling. However, Bassan and colleagues scored the severity of PVHI on CUS on the basis of extent, bilaterality, and midline shift.[11] Two-thirds of those with PVHI had significant neurodevelopmental impairments, but severity of outcome was correlated with CUS PVHI severity score. Merhar et al. found that the rate of neurodevelopmental impairment increased with unilateral to bilateral ICH, as well as with sepsis and postnatal steroid exposure.[67] Of note, the group also found that although infants with bilateral grade IV had substantially worse BSID-II MDI and PDI scores than those with unilateral, those with bilateral and unilateral grades I–III IVH had similar outcomes, and those with grade III had similar outcomes to those with grades I-II. Among preterm infants surviving after intraparenchymal hemorrhage in a single center spanning a more recent era when Bayley Scales 3rd edition (Bayley-III) was in use, Tsai and colleagues found significant predictors of CP, including ventriculomegaly, intraventricular echodensity, and ventricular shunt, but no clinical, imaging, or sociodemographic factors were significantly associated with low cognitive scores.[100] In a retrospective analysis of extremely preterm infants diagnosed with grade III or IV ICH in the NICHD NRN with 18-22 month follow-up including Bayley-III, bilaterality of the findings as well as the presence of PHVI were associated with death or impairment, although birth weight, presence of shunt, and exposure to postnatal steroids influenced prediction.[27] Conversely, "low-grade" (grades I and II) hemorrhage is often considered to confer no additional risk for adverse neuromotor or developmental outcomes. In a single-center study, ELBW infants with uncomplicated grade I or II IVH were reported to have poorer neurodevelopmental outcomes at 20 months than those with normal CUS, even after adjusting for confounding risk factors.[79] However, a multicenter study of infants <27 weeks' GA born 2006–2008 found that 18-22 month outcomes did not differ for those with grades I and II than for those without hemorrhage.[80] A large, single-center, case-control study of infants 24-32 weeks' GA found no difference in neurodevelopmental outcomes between those with grade I-II and those with normal CUS,[83] whereas grade I-II was found to be associated with adverse neurodevelopmental outcomes among 23-27 weeks' GA infants in a regional cohort in Australia.[15] In evaluating associations of neonatal CUS findings with later outcomes, the National Brain Hemorrhage Study cohort isolated germinal matrix, and IVH without ventricular enlargement was not associated with adverse outcomes at 6 and 9 years.[81] In even longer-term follow-up, utilizing data from the low birth weight sample of the Infant Health and Development Program study, grades I and II were also not independently associated with cognitive, behavioral, or academic outcomes at 3, 8, or 18 years of age.[7] These disparate findings with regard to low-grade hemorrhage may be reflective of differences in patient population, era, brain imaging and outcomes, ascertainment tools, and details of brain injury.

Interpretation of the applicability of studies relating severe or low-grade CUS findings with neurodevelopmental outcomes may also be challenged by the validity of findings. The NICHD NRN assessed interobserver reliability of CUS findings between two central readers and accuracy of local compared with central readers.[43] Agreement between central readers was high for major CUS findings such as grade III or IV IVH and degree of ventriculomegaly (kappa = 0.84 and 0.75, respectively) but much worse for lower-grade IVH (kappa = 0.4). The sensitivity of local reader interpretation was also excellent for severe IVH (88%-92%) but poor for grade I or II IVH (48%-68%). Also, in many studies, no specific CUS protocols were required, and the frequency of CUS was not specified. A primary guideline for CUS screening in the United States is the Practice Parameter for Neuroimaging of the Neonate in 2002,[66] which recommends screening with CUS for all infants with GA <30 weeks at 7-14 days, and "optimally" again at 36-40 weeks' postmenstrual age. However, more frequent and detailed surveillance protocols using high-resolution techniques may increase the sensitivity of CUS for identifying infants at high risk for adverse outcomes.[24,25,57]

It is clear that CUS alone can be a valuable tool to assist in prediction of neuromotor outcomes. But studies of neonatal CUS and later outcomes have implicated white matter injury as the important underlying etiology linking abnormal brain imaging findings with adverse neurodevelopmental outcomes among preterm infants. This has led to the suggestion that white matter injury can be better recognized and more comprehensively characterized; we may be better able to predict adverse motor and developmental outcomes and potentially anticipate specific needs for early evaluation and intervention. More importantly, a better understanding of the connection between perinatal events and brain injury may allow for prevention or amelioration of brain injury in the preterm. These broad hypotheses have formed the basis for investigation of magnetic resonance imaging (MRI) as

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• **Fig. 61.1** Noncystic punctate white matter injury on MRI. Selected brain MRI images (axial T1, axial T2, coronal T1) of an infant born at 24 5/7 weeks' GA at 35 2/7 weeks' PMA. Images show noncystic punctate white matter injury, as demonstrated by areas of hyperintensity on T1 (*arrows*) in the absence of marked hypointensity on T2. Qualitative cerebral volume loss is also appreciated.

a routine or adjuvant neuroimaging modality for preterm infants.

Conventional (Qualitative) Magnetic Resonance Imaging

Brain MRI has been increasingly utilized for research and clinical purposes since the 1980s. With optimization of MR methods for detecting neonatal brain injury, greater availability of MR scanners closer to and within the neonatal intensive care unit (NICU), and broader availability of MR-compatible monitoring, transport, and imaging equipment, MRI has become a more routine advanced neonatal neuroimaging approach.[40,68] An enhanced understanding that nonsedated scans can be obtained for premature infants with simple feeding and swaddling, or by using polystyrene bead-filled "huggers," has also led to greater utilization of MRI.[70,108]

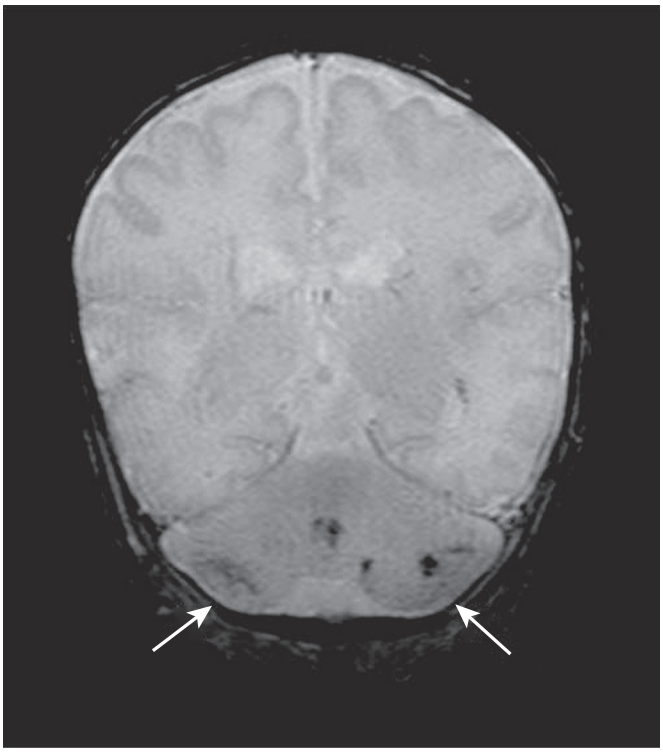
White Matter Abnormalities

A major focus of interest and study for preterm neuroimaging and outcomes has been on white matter injury. As described previously, CUS markers of white matter injury have been shown to be risk factors for adverse neuromotor outcomes. White matter injury, such as cystic PVL and ventriculomegaly due to periventricular white matter loss, should be easily detectable by CUS. However, CUS does not detect diffuse white matter injury or subtle white matter lesions as well as MRI[47,69] (Fig. 61.1). A relatively low sensitivity of CUS for detection of noncystic white matter abnormalities has been reported,[29,47,69] although many of these studies have not performed frequent sequential scans during the neonatal period. Existing and increasing evidence points to the fact that white matter injury in preterm infants is associated with broader brain maturational disturbances. White matter abnormality (WMA) on MRI in preterm infants is associated with reduced cortical and deep gray matter volume,[13,48] which in turn is associated with lower developmental scores and working memory in early childhood.[60,104] Pre-oligodendroglial cells of the developing white matter are known to be vulnerable to a number of perinatal and neonatal clinical factors, including hypoperfusion, systemic inflammation, and infection.[105,106] But perhaps more important than direct injury to developing white matter, subplate neurons, and axonal growth and elongation processes is the resulting reduced connectivity affecting the cerebral white matter, deep gray matter, cortex, and cerebellum.[103] Reduction of crucial connections during a period in rapid brain development may be associated with brain maturational disturbances, suggesting an overall link to impaired neural connectivity.[28,105] Classification systems have been used to "score" or "grade" white matter injury by MR imaging at term equivalent age,[48,69] and an updated classification system includes cerebellar injury and volumetric measures.[52]

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Areas of the Brain and Findings of Interest

Compared with CUS, MRI offers a more complete visualization of anatomic features and details of injury. However, to what extent this added detail can improve neurodevelopmental outcome prediction is an area of active research. For example, among preterm infants, CUS and MRI evidence of cerebellar injury has been associated with adverse developmental outcomes, including motor, cognitive, communication, and behavioral impairments.[41,59,60,104] Adverse neurodevelopmental outcomes appear, at least in part, to be linked to developmental disruption to the cerebral cortex associated with the cerebellar injury.[58,60] The cerebellum can be visualized by CUS, using mastoid fontanelle views, but MRI allows delineation of cerebellar lesion topography and identification of supratentorial injury, which may help predict severity of neuromotor delays[59] (Fig. 61.2). Limperopoulos and colleagues followed preterm infants with isolated cerebellar hemorrhagic injury, age-matched controls, and with cerebellar hemorrhagic injury in addition to parenchymal injury.[59] At a mean of 32 months, infants with isolated cerebellar hemorrhagic injury had high rates of severe motor disabilities (48%), expressive language (42%), delayed receptive language (37%), and cognitive deficits (40%), whereas the control group was reported to have none of these delays. Those with cerebellar hemorrhagic injury plus parenchymal injury were not at higher risk for these disabilities, although neuromotor impairment was more severe. In a different cohort with lower cerebellar injury rates, cerebellar injury was not found to be strongly related to 2-year developmental or motor outcomes.[52] However, cerebellar injury seen only on MRI, not on CUS, has been shown to be common among very preterm infants and associated with significantly increased odds of abnormal neuromotor exam at approximately 5 years,[97] although others have reported very small cerebellar hemorrhage to be less frequent and not associated with adverse neurodevelopmental outcomes at 2 years corrected age.[95]



• **Fig. 61.2** Cerebellar injury on MRI. Brain MRI image of an infant born at 24 3/7 weeks' GA at 36 1/7 weeks' PMA. Images show injury of the cerebellum (*arrows*), as demonstrated by bilateral areas of hypointensity on gradient echo (GRE) sequences (*dark areas in the cerebellum*), consistent with mineralization or hemorrhage.

Several classic studies demonstrated that MRI provides prognostic information that is complementary to that provided by CUS. Using an approach of sequential CUS and subsequent term-equivalent age MRI with assessment of myelination of the posterior limb of the internal capsule (PLIC), de Vries and colleagues demonstrated a positive predictive value of 96% for death or CP at 2 years, with a negative predictive value of 69%. Of note, the authors caution that performing MRI at an earlier time point (35-38 weeks' PMA) may not be reliable to assess myelination of the PLIC.[24] Among infants with CUS evidence of periventricular echodensities, Sie et al. reported that neonatal MRI identified additional punctate to extensive white matter lesions, accurately predicted the location and extent of brain injury on MRI at 18 months, and that neonatal MRI scores (based on severity and extent of lesions) predicted motor and visual outcomes at 18 months extremely well.[87] These researchers suggested that, particularly among infants with inhomogeneous periventricular echodensities on CUS, neonatal MRI provided additional valuable information for predicting later outcomes. Other investigators have demonstrated that neonatal MRI may be complementary to specific exam findings in predicting neuromotor outcomes among very and extremely preterm infants.[88,93]

Neonatal MRI to Predict Early Neurodevelopmental Outcomes

Early studies that compared predictive capability of MRI with CUS focused on neuromotor impairments as primary outcome, were primarily small single-center efforts, and were limited by size and different approaches to timing of imaging.[23,70,87] Subsequently, white matter abnormality scoring systems have been implemented, and larger cohort investigations have been published, among the first of which was a multicenter prospective study in Australia and New Zealand comparing serial CUS with near-term MRI findings and their association with 2-year outcomes in 167 infants <30 weeks' GA.[108] The authors demonstrated 1) that the presence of moderate-severe white matter abnormalities on MRI was significantly associated with severe motor delay and CP, independent of CUS abnormalities and other risk factors; 2) a significant correlation between white and gray matter abnormalities; 3) increasing severity of white matter injury was linearly related to worse BSID II

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MDI scores, but an independent association of "moderate-severe white matter injury" with "severe cognitive delay" was not found; 4) gray matter abnormality on neonatal MRI was not significantly associated with later neuromotor or cognitive impairments after adjusting for CUS findings. Although sensitivity of moderate-severe WMA to predict CP (65%), neurosensory impairment (82%), and severe cognitive delay (41%) was greater than that of CUS abnormalities (18%, 16%, and 15%, respectively), the total number of the cohort with moderate (n = 29) or severe (n = 6) white matter injury was small, approximately half of those with moderate-severe white matter injury by neonatal MRI did not have neurodevelopmental impairment at 2 years, and the sensitivity of CUS to predict outcome was much lower than in other studies. In a cohort of extremely preterm infants in Sweden, Skiold et al. found an overall lower rate of moderate to severe impairment at 30 months' corrected age than had previously been reported but utilized the Bayley-III.[89] The authors found that infants with moderate-severe WMA on MRI had lower cognitive and language BSID III scores compared with infants with none or mild white matter abnormalities, but there was no difference in motor scores. Furthermore, 35% of those with CP at 30 months had none or only mild white matter abnormalities on MRI. Of note, the authors had previously demonstrated that infants in this group with a normal CUS at term had normal or only mild white matter abnormalities on MRI.[45] The NICHD Neuroimaging and Neurodevelopmental Outcomes (NEURO) study was a prospective study of early and late CUS and near-term MRI, including 480 infants <28 weeks' gestation, with outcomes including BSID-III assessed at 18-22 months.[41] Late CUS and near-term MRI were performed within 2 weeks of each other, thus allowing for comparison of relatively contemporaneous neuroimaging findings. In multivariable models, both late CUS findings reflective of WM injury and MRI findings of significant cerebellar injury remained independently associated with adverse neurodevelopmental outcomes. In models that did not include late CUS, MRI findings of both moderate to severe WMA and significant cerebellar lesions were independently associated with adverse outcomes. Early CUS findings were not associated with adverse outcomes when any late neuroimaging was taken into account. These results demonstrate the need to understand the evolution of brain injury over time rather than to rely on early findings. In a recently published extremely preterm Dutch cohort follow-up study of term equivalent MRI among infants 24-28 weeks, the prognostic value of the expanded MRI scoring system[52] for 2-year outcomes utilizing Bayley-III was limited, with scores accounting for just a small amount of variance in neurodevelopmental outcome.[18]

In addition, many groups have now reported on outcomes relative to diffuse excessive high-signal intensities (DEHSI) on term equivalent MRI. This is a common finding, reported on term equivalent MRI in 50%-90% of preterm infants; due to links between this qualitative finding and quantitative measures, DEHSI was hypothesized to represent WMA.[21,55] However, follow-up studies have demonstrated that DEHSI is not associated with neurodevelopmental outcome among preterm infants in early childhood,[22,50,89] nor has it been shown to be associated with mild neurologic dysfunction, scores on MABC assessment, cognition, visual-motor integration, or behavior at 6-7 years.[17]

Later Childhood Outcomes and Need for Further Study

The incremental advantage of term equivalent age MRI over sequential, carefully performed CUS to predict very early childhood neurodevelopmental outcomes is not clear. But 18-30-month outcomes do not provide a complete picture of the subtle neurologic, functional, or cognitive future for these high-risk infants. Later childhood follow-up of neuroimaging cohorts is providing additional clues to what can be understood from injury detected on MRI. Woodward and colleagues reported that among children born very preterm, white matter injury on neonatal MRI was independently associated with neurocognitive delays at 4 and 6 years of age.[109] Furthermore, those with no white matter abnormalities on neonatal MRI showed no neurocognitive impairments compared with their full-term peers. The presence of any white matter abnormalities on neonatal MRI also appears to be independently correlated with expressive language scores among children born very preterm at 5 years of age.[46] Spittle and colleagues demonstrated that the presence of moderate to severe white matter abnormalities on neonatal MRI was associated with a nine-fold increase in the odds of motor impairment at 5 years as measured by the Movement ABC.[94] Nevertheless, the authors noted that nearly one-third of those with no white matter abnormality on neonatal MRI still had motor impairment at 5 years. Behavioral and psychiatric outcomes may be associated with injury detectable by neonatal MRI.[20,99] Recent studies have also shown term equivalent brain MRI scores to be associated with lower IQ, math and motor scores,[5] and poorer memory and learning performance[72] at 7 years among very preterm children.

Neurologic and particularly cognitive outcomes are influenced by a multitude of variables. Even in an era of advanced neuroimaging, it is naïve to consider that there is a single, perfect test to allow for individual prediction of later neurodevelopmental outcome; furthermore, presenting neuroimaging results to families without a clear context of the limitations of these findings is neither reasonable nor appropriate.[49] A recent publication has suggested avoidance of "routine" term equivalent conventional brain MRI for screening purposes due to "insufficient evidence that the practice improves long term outcomes."[44] Yet numerous studies in preterm infants have delineated the links between near-term conventional MRI findings and neurodevelopmental outcomes through early childhood, particularly highlighting the strengths of associations with neuromotor outcomes.[4] Although capability of conventional MRI or indeed any neonatal neuroimaging modality

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to predict complex early cognitive or behavioral outcomes is limited,[102] the number of potentially informative neonatal neuroimaging studies with school age and later childhood follow-up is restricted. Systematic reviews have highlighted numerous factors which influence cognitive development. There is still certainly much to be gained by optimization of current institutional CUS imaging protocols and continued rigorous research evaluation and comparison of neuroimaging methods. At the present time, brain MRI is likely to be used in most institutions as a complementary tool to CUS in the preterm infant, with this bedside imaging modality serving as the primary neuroimaging method[23,71] and with high-risk preterm patients identified that may benefit from further evaluation and identification of subtle injury based on CUS findings and clinical course.[24,32,33,86] There is great potential in continuing research to elucidate how clinical events and processes affect the preterm brain and how that injury is linked with outcome, with the ultimate goal of undertaking well-conceived studies of neuroprotective strategies and interventional programs to improve the outcomes of preterm infants. To that end, future studies can further focus on identifying specific high-risk groups of preterm infants for which MRI would improve our understanding of injury to the developing brain and the connections with neurodevelopmental outcomes, and, importantly, to allow for risk stratification for neuroprotective and interventional trials. Patient-oriented research to better delineate potential benefit of MRI findings to patients and to families will also be critical. Investigations using advanced MR techniques including diffusion MRI (dMRI), resting state functional connectivity MRI (fcMRI), volumetric methods, and surface morphometry hold enormous promise to help to explore these questions.[4]

Advanced MRI: Opening a New Window into the Preterm Developing Brain

Over the past two decades, scientists have built upon the solid foundation of conventional brain MRI and pushed the technologic envelope to develop more sensitive modes of MRI. Advanced MRI such as dMRI, volumetric MRI, magnetic resonance spectroscopy (MRS), and fcMRI is an umbrella term for any quantitative, more sensitive mode of MRI that can peer deeper into the brain to provide more objective measures of regional gray and white matter microstructure, macrostructure, metabolites, and function (Fig. 61.3). These advanced imaging modalities appear to offer the greatest potential to develop sensitive and accurate diagnosis of the encephalopathy of prematurity and prognostic biomarkers of neurodevelopmental impairment (NDI).[8,10,78,104] Early evidence suggests that such modalities are more sensitive than conventional MRI in detecting and can further improve our ability to understand perinatal brain injury, impaired brain development, and functional impact on NDI.[8,62,78]

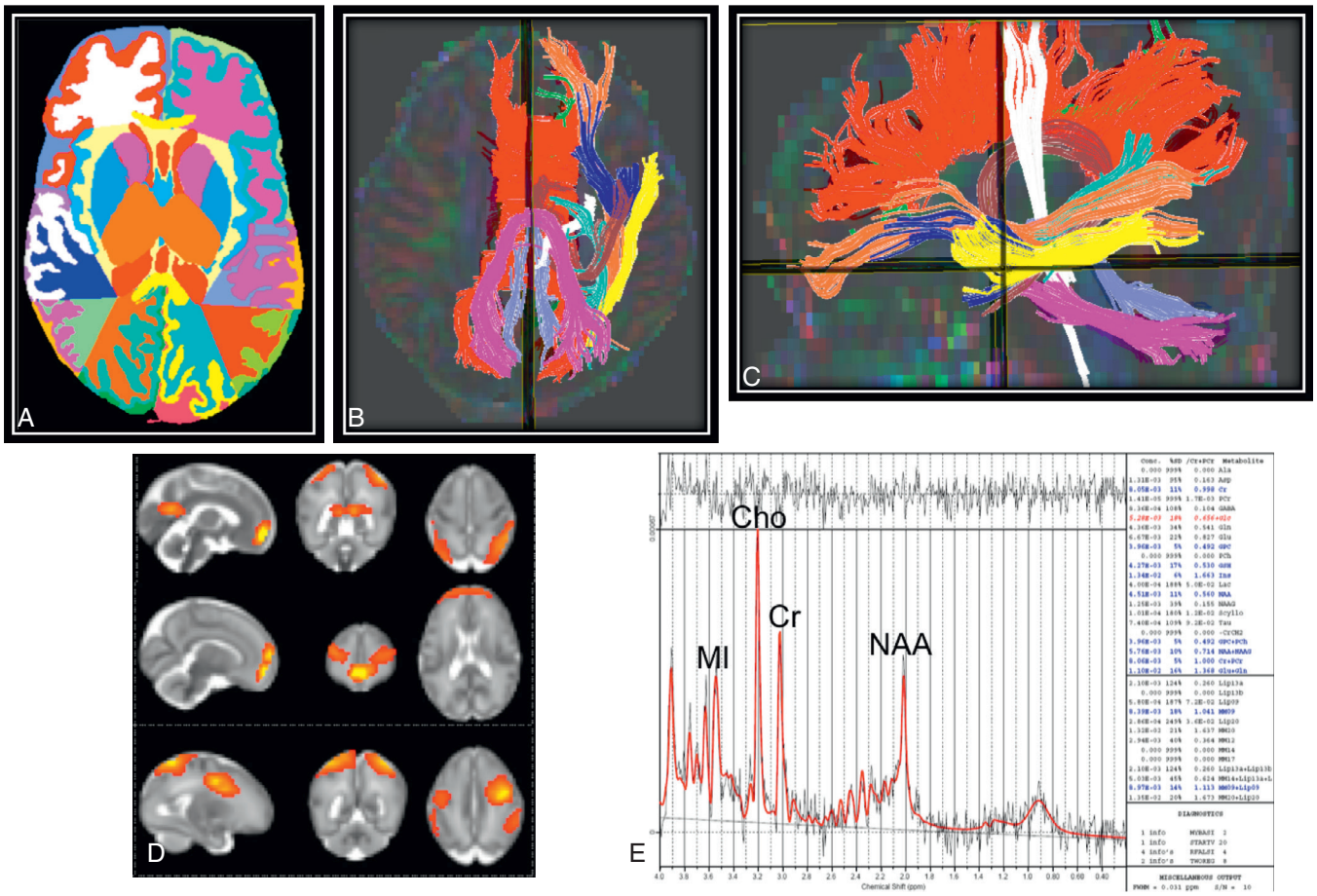
Numerous epidemiologic,[38] neuropathologic,[104] and advanced MRI studies[14,101,110] have now confirmed that overt perinatal brain injuries such as intraventricular/periventricular hemorrhage and periventricular leukomalacia are decreasing in prevalence due to improved care. These have been supplanted by highly prevalent and more subtle, diffuse brain abnormalities and brain maturational delays that are more readily detected using advanced MRI modalities.[104] The high prevalence of brain maturational delays/abnormalities and their association with NDI were largely unrecognized prior to the use of advanced brain MRI.[1,19,31,82] Some signal abnormalities that are visible on structural MRI can only be reliably quantified using dMRI and specialized image processing software.[39,53] Structural and functional connectivity studies using dMRI and fcMRI have demonstrated altered cortical–subcortical and short-range corticocortical connections, respectively, in very preterm infants as compared to healthy term controls by term-equivalent age.[6,9,35,85,91,98] These observations suggest that very premature birth and subsequent NICU care result in widespread decreased/altered neural connectivity. These connectivity abnormalities may be the neurobiologic antecedents of the cognitive and behavioral abnormalities that are commonly observed in this population of high-risk infants.

Predicting Motor, Cognitive, and Behavioral Abnormalities with Advanced MRI

Currently, it takes between 2 and 5 years to detect and accurately diagnose motor, cognitive, and behavioral/psychiatric abnormalities despite that many of these functional disabilities are the result of early injuries, abnormalities, or delays in brain development. Earlier identification could readily facilitate targeted early intervention therapies during the first 3 years after birth, when brain development is explosive and exhibits the greatest neuroplasticity.[51] Currently, advanced MRI applications offer the best opportunity for early, accurate identification of later functional disabilities in high-risk preterm infants. A recently completed systematic review examined the accuracy of advanced MRI measures in very preterm infants at term-equivalent age as prognostic biomarkers for NDI at 18 months' corrected age or later.[78] Of a total of 47 eligible studies that were identified, the two most common modalities studied were dMRI and morphometric studies such as volumetric MRI or two-dimensional brain measurements (Table 61.1). No fcMRI prognostic studies were found. More recent studies used 3.0 T scanners to take advantage of improved signal to noise and/or faster scanning times.

Several studies demonstrated an independent or incremental benefit of advanced MRI over cranial US or conventional MRI. This is despite the fact that most studies did not combine biomarkers; such an approach is sure to enhance outcome prediction. Almost all studies attempted to predict NDI only at 18-24 months' corrected age. While this is the current standard for most clinical trials in neonatology, it is now well recognized that testing at this young age using standardized tests such as the Bayley-III has suboptimal reliability and exhibits poor sensitivity in predicting

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• **Fig. 61.3** Examples of brain-advanced MRI measurements including morphometry (A), diffusion tractography (B and C), functional connectivity MRI (D), and magnetic resonance spectroscopy (E). Representative advanced MRI examples at term-equivalent age display an extremely low birth weight infant's brain that was segmented into tissue classes, subcortical structures, and lobes (A); 10 white matter tracts, displayed in axial and sagittal orientations (B and C); panel D shows blood-oxygen level dependent activations in the default mode (top panel), executive control (middle), and frontoparietal networks (bottom); and panel E is a processed proton MRS spectrum displaying the four main metabolites, including N-acetylaspartate (NAA), creatine (Cr), choline (Cho), and myo-inositol (MI). (With permission from Parikh NA. Advanced neuroimaging and its role in predicting neurodevelopmental outcomes in very preterm infants. *Semin Perinatol.* 2016;40(8):530-541.)

TABLE 61.1 Summary of Important Findings from Advanced MRI Prognostic Biomarkers Systematic Review

dMRI (N = 25); morphometric studies (N = 25); Magnetic Resonance Spectroscopy (MRS) (N = 5)	
Most common cerebral quantitative measurements	1) Regional brain diameter or volume on structural MRI; 2) fractional anisotropy and/or mean diffusivity on dMRI; 3) brain metabolites, most commonly N-acetylaspartate (NAA)/choline ratio on MRS
Brain regions most predictive of NDI (identified in three or more studies)	Corpus callosum; centrum semiovale; sensorimotor cortex; subcortical gray matter; posterior limb of the internal capsule; cerebellum
Predicted outcomes examined	Cerebral palsy; minor motor abnormalities; permanent hearing loss; cognitive deficits; working memory; executive function; psychological/behavioral abnormalities

NDI, Neurodevelopmental impairment.
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infants with intellectual impairments at school age.[63,64,92] Nevertheless, this limitation has also plagued most conventional MRI studies and likely contributes to decreased prediction accuracy. Ongoing studies are attempting to follow study cohorts to older ages to address this limitation.

In addition to the reliance on predicting shorter-term outcomes, additional limitations include the enrollment of small, single-center cohorts, no reporting of inter- or intrarater measurement reliability, lack of blinding to imaging and other prognostic variables, no reporting of systematic differences in infants lost to follow-up, and lack of reporting of prognostic test properties.[78] These limitations may, in part, explain the slow translation of advanced MRI research into clinical practice. Other explanations likely include the need for expensive advanced MRI hardware and software and robust post-processing software for acquired images. Such post-processing software is still being modified or developed specifically for neonates/infants, and there remains a lack of consensus on which software or methods to use. Despite the practical and technologic limitations, brain macrostructure, microstructure, and metabolite prognostic biomarkers appear very promising for early, accurate prediction of NDI in very preterm infants. Such an advance will improve parental counseling and provide early post-NICU discharge risk stratification. Further development is also needed to identify biomarkers that are predictive of treatment response and to develop advanced MRI as a surrogate endpoint.

Future Developments

Advanced MRI modalities possess several novel features that have contributed to their greater sensitivity in diagnosing abnormalities and predicting NDI. These features include:

- ability to query morphometric, microscopic, metabolic, and physiologic/functional derangements;
- quantitative nature, which lends greater study power than qualitative assessments for diagnostic and prognostic studies; and
- objective measurements that are increasingly being made using automated methods, which increases study power and validity by reducing measurement error.

Resting state fcMRI studies in very preterm infants have shown reduced or aberrant connectivity in the thalamocortical network and other rich club or important nodes as compared to healthy term controls.[9,85,91] While such widespread connectivity changes have yet to be correlated with NDI, other than in one recent study,[84] the likelihood that functional connectivity will be independently predictive of functional impairments is high. More studies are ongoing and will likely confirm the value of this new tool for accurate prognostication.

Advances in imaging hardware, software, computing power, and artificial intelligence have accelerated the development of these modalities and permitted increasingly objective, observer-independent automated tools designed to process big data, specifically for infant brains.[8] To be sure, many challenges remain due to infants' smaller brain size, paucity of myelination, and high risk of motion artifacts that reduce image resolution and necessitate development of infant-specific atlases and image processing methods. Nevertheless, the future is very bright for advanced MRI. If additional research can validate the sensitivity of advanced MRI measures, such as structural and functional connectivity, to identify most high-risk infants soon after birth, neonatologists will be able to facilitate targeted postdischarge early intervention or enrollment into neuroprotective trials. Such improvements could also provide prompt safety and/or efficacy assessment of NICU clinical practices and neonatal neuroprotective clinical trials and serve as a surrogate measure for later developmental and motor challenges.

Key Points

- Cranial US is the most widely used neonatal neuroimaging, and severe intracranial hemorrhage is associated with adverse neuromotor outcomes. However, limitations of outcome prediction with any single neuroimaging should give clinicians cause for prudence in prognostic guidance.
- Conventional brain MRI, which offers a more complete visualization of the brain and greater sensitivity to detect white matter injury than cranial US, has been increasingly utilized for research and clinical purposes. Existing and increasing evidence points to the fact that white matter injury in preterm infants is associated with broader brain maturational disturbances.
- Many studies in preterm infants have delineated the links between near-term conventional MRI findings and neurodevelopmental outcomes through early childhood, particularly highlighting the strengths of associations with neuromotor outcomes.
- Advanced MRI tools have opened a new window into preterm brain development and uncovered the high prevalence of diffuse white matter injuries and brain immaturity in very preterm infants.
- Despite extensive and evolving experience with neonatal neuroimaging, substantial controversies exist as to when, how, and which neuroimaging studies should be performed for preterm infants, and how these results should be interpreted and presented to families.

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62

Lung Development and Maturation

SUHAS G. KALLAPUR AND ALAN H. JOBE

A Brief History

An understanding of lung development and maturation is central to the care of preterm infants, because lung function is so critical to survival of the preterm. Pattle and Clements first noted surface-active substances in pulmonary edema foam and lung extracts. In 1959, Avery and Mead correlated respiratory failure with decreased surfactant levels in saline extracts from the lungs of infants with respiratory distress syndrome (RDS).[3] Once the association between atelectasis with hyaline membranes and surfactant levels was appreciated, a large international research effort was focused on the surfactant system. The first direct clinical benefit was the development in 1971 of the lecithin-sphingomyelin (L-S) ratio, using amniotic fluid to predict lung immaturity and the risk for RDS in preterm infants by Gluck and colleagues. Phosphatidylglycerol was identified for lung maturity testing in 1976 by Hallman and colleagues.[24] The induction by Gregory and colleagues of continuous positive airway pressure to maintain functional residual capacity (FRC) for infants with RDS was the first application of the respiratory physiology of RDS to improve outcomes.[22] Liggins and Howie first reported a decreased incidence in RDS with maternal corticosteroid treatments in 1972.[42] The feasibility of surfactant treatment for lung immaturity was demonstrated in animal models in the 1970s, primarily by Robertson and Enhörning,[57] and surfactant was successfully used in humans by Fujiwara and colleagues in 1980.[20] This research resulted in the development of perhaps the two most effective treatments for RDS in neonatology—antenatal corticosteroids and postnatal surfactant. This progress in the application of research to the pulmonary care of the infant is continuing as molecular and cell biologic observations improve the general understanding of lung development. The major challenge for the future is the prevention of bronchopulmonary dysplasia (BPD) in infants who are very preterm.

Lung Structural Development

Embryonic Period

The lung first appears as a ventral bud off the esophagus just caudal to the laryngotracheal sulcus.[10,61] The grooves between the lung bud and the esophagus deepen, and the bud elongates within the surrounding mesenchyme and divides to form the main stem bronchi (Fig. 62.1). Subsequent dichotomous branching forms to the conducting airways. The branching of the endodermal endothelium is controlled by the underlying mesenchyme, because removal of the mesenchyme stops branching. Transplantation of the mesenchyme from a branching airway to more proximal airway induces airway development in the new location.

The commitment of endodermal cells to epithelial cell lineages requires the expression of families of transcription factors that include thyroid transcription factor-1, forkhead gene family members, and others.[69] At least 15 homeobox domain-containing genes (*HOX* genes) also contribute to lung morphogenesis. Multiple other growth and differentiation factors, such as retinoic acid and the fibroblast growth factor family members (FGF)-7 and FGF-10 and their receptors, are temporally and spatially expressed and are critical to early lung morphogenesis and subsequent development. Genetic ablation of these transcription and growth factors causes lung developmental abnormalities that range from trachea-esophageal fistula and altered branching morphogenesis to severe lung hypoplasia and complete aplasia of the lungs. Lobar airways are formed by about 37 days, with progression to segmental airways by 42 days and subsegmental bronchi by 48 days in the human fetus. The pulmonary vasculature branches off the sixth aortic arch to form a vascular plexus in the mesenchyme of the lung bud. Major regulators of vascular development are vascular endothelial growth factor (VEGF) and its receptors in the mesenchyme. Vascular development additionally requires extracellular matrix (fibronectin, laminin, type IV collagen) and other growth factors such as platelet-derived growth factor. The pulmonary artery can be identified by about 37 days, and venous structures appear somewhat later. Abnormalities in early lung embryogenesis cause trachea-esophageal syndromes, branching morphogenesis abnormalities, and aplasia.

Pseudoglandular Stage

The 15-20 generations of airway branching occur in the pseudoglandular period of lung development from about the fifth to the eighteenth week, when airway branching

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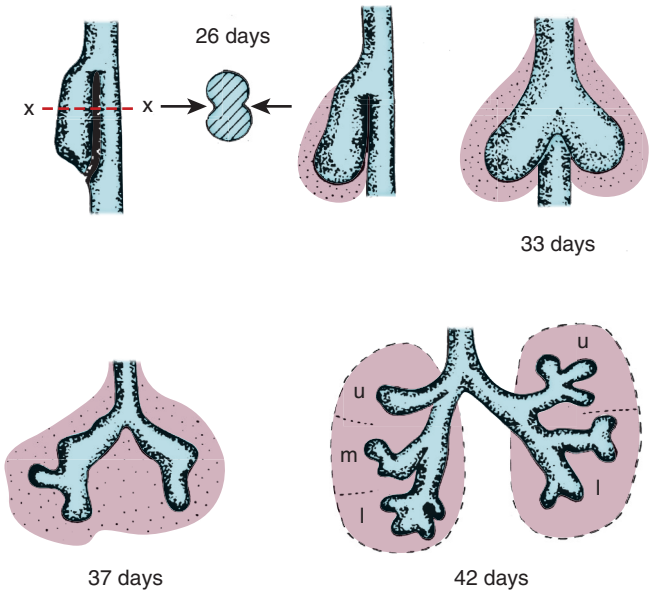
Abstract

Lung development and maturation are the critical organ developmental processes that are essential for early neonatal transition following birth. Abnormalities in early gestational lung development result in congenital anomalies such as tracheal-esophageal fistula, pulmonary hypoplasia, and lung atresia. The basic airway branching pattern is complete prior to very preterm viability. The saccular preterm lung alveolarizes after about 32 weeks with alveolarization continuing through adolescence. Early or induced lung maturation is frequent and contributes to the survival of extremely preterm infants. The clinical interventions with antenatal corticosteroid therapy and postnatal surfactant are major contributors to improved lung function and survival of preterm infants. Surfactant treatments improve multiple aspects of lung function. Chorioamnionitis will expose the fetal lung to inflammation, which will induce early lung maturation and enhance the effects of prenatal corticoid treatments. The remarkable survival of early gestation infants depends on early lung maturation.

Keywords

surfactant
antenatal corticosteroids
inflammation
surfactant treatment
induced lung development

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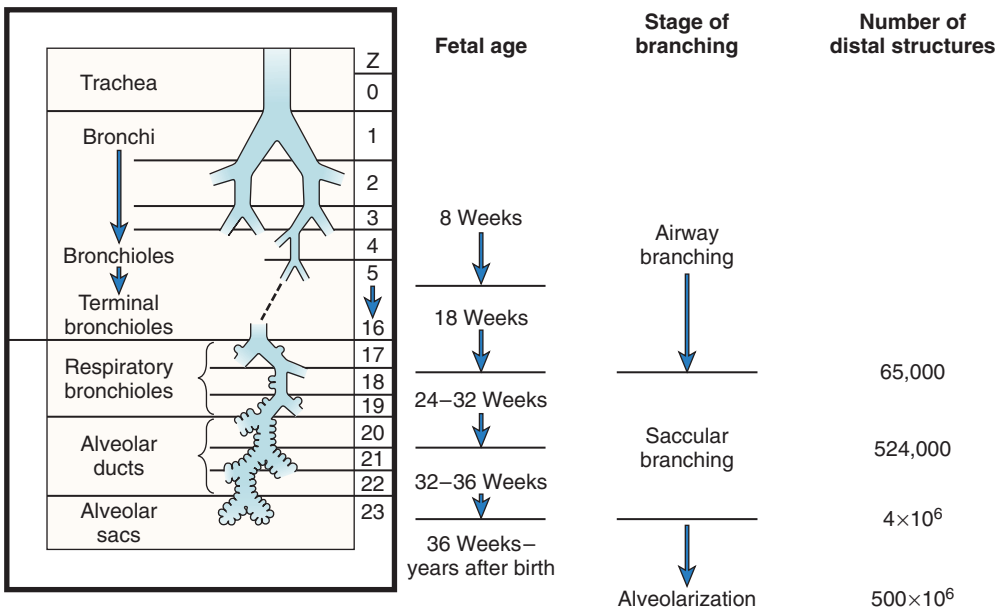


• **Fig. 62.1** Embryonic lung development. At 26 days, the lung first appears as a protrusion of the foregut. By 33 days, the lung bud has branched, and by 37 days the prospective main bronchi are penetrating the mesenchyme. Airways to the lobar and initial segmental bronchi have formed by 42 days. (Modified from Burri PW. Development and growth of the human lung. In: Fishman AP, Fisher AB, eds. *Handbook of physiology: the respiratory system.* Bethesda, MD: American Physiological Society; 1985:1, with permission.)

is complete (Fig. 62.2). The developing airways are lined with simple cuboidal cells that contain large amounts of glycogen. Neuroepithelial bodies and cartilage appear by 9-10 weeks. Ciliated cells, goblet cells, and basal cells are in the epithelium of proximal airways by 13 weeks. In general, epithelial differentiation is centrifugal in that the most distal tubules are lined with undifferentiated cells with progressive differentiation of the more proximal airways. There are multiple regulators of branching morphogenesis such as FGF-10, FGF-7, endothelial growth factor, transforming growth factor-α, and their receptors.[65] Upper lobar development occurs earlier than lower lobe development in animals, and a similar pattern of development probably occurs in humans. Early in the pseudoglandular stage, the airways are surrounded by a loose mesenchyme with the developing vasculature and capillaries. Pulmonary arteries grow in conjunction with the airways, with the principal arterial pathways being present by 14 weeks. Pulmonary venous development is in parallel but with a different pattern that demarcates lung segments and subsegments. By the end of the pseudoglandular stage, airways, arteries, and veins have developed in the pattern corresponding to that found in the adult.

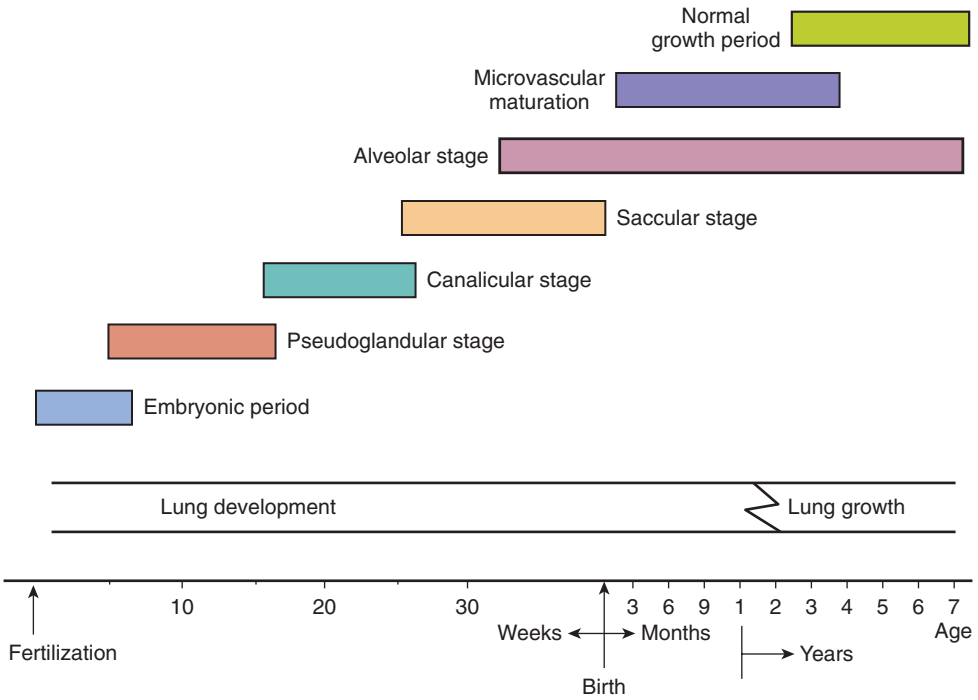
Canalicular Stage

The canalicular stage between 16 and 25 weeks' gestation represents the transformation of the previable lung to the



• **Fig. 62.2** Airway branching, fetal age, and number of branches during lung development. Airway branching results in about 16 generations of airways by about 18 weeks' gestation. Branching of distal saccular structures yields respiratory bronchioles and alveolar ducts in the saccular lung by about 32 weeks' gestation. Alveolarization continues from 32 weeks until maturity. (Modified from Burri PW. Development and growth of the human lung. In: Fishman AP, Fisher AB, eds. *Handbook of physiology: the respiratory system*. Bethesda, MD: American Physiological Society; 1985:1.)

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• **Fig. 62.3** Timetable for lung development. The timing of the saccular and alveolar stages and the period of microvascular maturation overlap with indeterminate initiation and endpoints. (Modified from Zolner TB, Burri PH. The postnatal development and growth of the human lung: II. Morphology. *Respir Physiol.* 1987;67:269, with permission from Elsevier Science.)

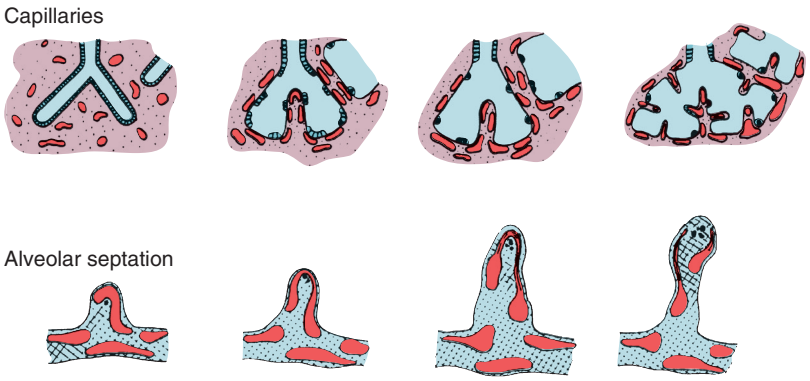
potentially viable lung that can exchange gas (Fig. 62.3).[73] The bronchial tree has completely branched, and respiratory bronchioles are forming. The three major events during this stage are the appearance of the acinus, epithelial differentiation with the development of the potential air-blood barrier, and the start of surfactant synthesis within recognizable type II cells.[10] The acinus in the mature lung is the tuft of about 6 branching generations of respiratory bronchioles, alveolar ducts, and alveoli originating from a terminal bronchiole (see Fig. 62.2). This saccular branching is the critical first step for the development of the future gas exchange surface of the lung. The mesenchyme surrounding the airways becomes more vascular and more closely approximated to the airway epithelial cells (Fig. 62.4). Capillaries initially form as a double capillary network between future airspaces and subsequently fuse to form a single capillary. With fusion of the vascular and epithelial basement membranes, a structure comparable to the adult air-blood barrier forms. If the double capillary network fails to fuse, the infant will have severe hypoxemia resulting from alveolar-capillary dysplasia. The total surface area occupied by the air-blood barrier begins to increase exponentially toward the end of the canalicular stage, with a resultant fall in the mean wall thickness and an increased potential for gas exchange.

Epithelial differentiation is characterized by proximal to distal thinning of the epithelium by transformation of cuboidal cells into thin cells that line tubes. The tubes grow both in length and in width with attenuation of the mesenchyme, which is simultaneously becoming vascularized. During the canalicular stage, many of the cells would best be characterized as intermediary cells, because they are neither mature type I nor type II epithelial cells.[71] These epithelial cells develop characteristics of mature type II cells such as lamellar bodies, supporting the concept that type I cells are derived from type II cells or intermediary cells that then further differentiate into type I cells. After about 20 weeks in the human fetus, cuboidal cells rich in glycogen begin to have lamellar bodies in their cytoplasm. The transcription factors TTF-1, FOXa1, FOXa2, and GATA 6 mediate type II cell differentiation.[71] The glycogen in type II cells provides substrate for surfactant synthesis as the lamellar body content increases. In the adult human lung, the thin type I cells occupy about 93% of the alveolar surface versus 7% for type II cells. About 8% of lung cells are type I cells, and about 16% of lung cells are type II cells.

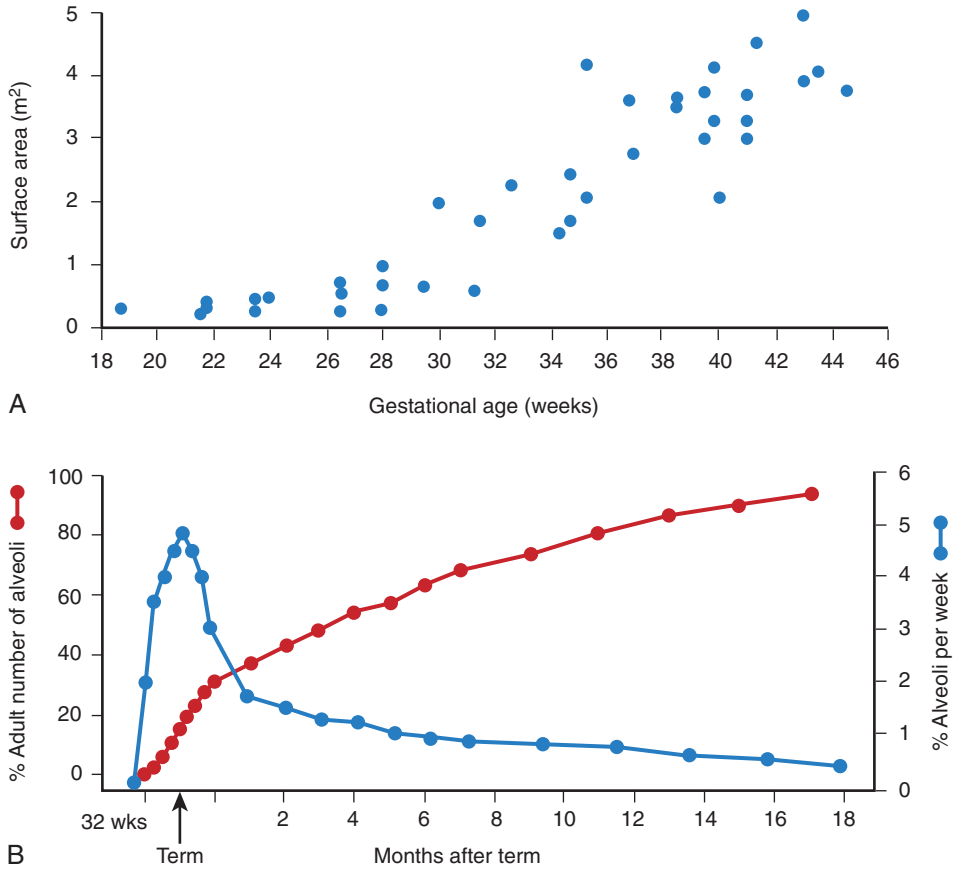
Saccular and Alveolar Stages

The saccular stage encompasses the period of lung development during the potentially viable stages of prematurity from about 24 weeks to term. The terminal sac or saccule is the developing respiratory bronchiole or alveolar duct that is elongating, branching, and widening prior to the initiation of alveolarization at about 32 weeks in the fetal human lung.[61] Alveolarization is initiated from these terminal saccules by the appearance of septa in association with capillaries, elastin fibers, and collagen fibers (see Fig. 62.4). Shallow alveolar structures with crests (or septa) with elastin at the free margin of the crests can be identified by 28 weeks' gestation in the human. Alveolar numbers increase

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• **Fig. 62.4** Development of alveolar septa and capillaries. An alveolar septum is identified by the epithelium folding over elastic fibers with subsequent elongation of the septum. Capillaries arrange themselves around epithelial tubes. The double-capillary network becomes progressively more closely associated with the epithelium of the developing airspace with subsequent loss of the double-capillary network. (Modified from Burri PW. Development and growth of the human lung. In: Fishman AP, Fisher AB, eds. *Handbook of physiology: the respiratory system*. Bethesda, MD: American Physiological Society; 1985:1, with permission.)



• **Fig. 62.5** Increases in surface area and alveoli with development. **A,** The large increase in lung surface area does not occur until after the saccular lung begins to alveolarize. **B,** Alveolar number and weekly rate of accumulation of alveoli are expressed as a percentage of the adult number of alveoli. The curves assume that the term infant has 30% of the adult number of alveoli. (**A,** Redrawn from Langston C, et al. Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis.* 1984;129:607. **B,** Idealized curves based on Langston C, et al. Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis.* 1984;129:607; and Hislop AA, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. *Early Hum Dev.* 1986;13:1.)

rapidly from about 32 weeks' gestation to term when the human lung contains between about 50 and 150 million alveoli.[41] For comparison, the adult human lung has about 500 million alveoli.[52] The most rapid rate of accumulation of alveoli occurs between 32 weeks' gestational age and the first months after term delivery (Fig. 62.5). The potential lung gas volume and surface area increases from about 25 weeks' gestation to term. This increase in lung volume, and the surface area of sacculi, establishes the anatomic potential for gas exchange and thus for fetal viability. There is a wide range of lung volumes and surface areas at a given gestational age. Therefore, the gas exchange potential of different fetuses at the same gestational age will be determined in part by the structural development of the lung. Human newborns born at 22 or 23 weeks' gestation can have a sufficiently mature lung structure to support gas exchange,

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indicating that structural lung maturation can be induced at very early gestational ages. Since antenatal corticosteroids increase survival at these early gestational ages, their use must support maturation of this early gestational potential for gas exchange.[11]

Alveolarization progresses rapidly from late fetal to early neonatal life. The traditional view was that alveolar development was completed by early childhood and that new alveoli do not develop in adults. Newer evidence in rats using 3-D visualization with high-resolution synchrotron radiation x-ray tomographic microscopy demonstrated that new alveoli continued to be formed well into adulthood.[62] Using hyperpolarized helium MRI, Narayanan et al. demonstrated that alveolar formation continues until at least 20 years of age.[48] This potential for continued alveolar growth explains why many preterm infants with interrupted lung development at birth can have relatively good lung function later in life.

A number of factors that can stimulate or interfere with alveolarization have been identified (Box 62.1).[39] Chronic mechanical ventilation of preterm animals using modest tidal volumes and low oxygen exposures interrupts both alveolarization and vascular development (Fig. 62.6).[13] Mechanical ventilation of the saccular lung disrupts elastin at the developing crests and induces an "arrest in development" characterized by lack of secondary crest formation and resulting in fewer and larger alveoli without much fibrosis or inflammation (Fig. 62.7).[6] Preterm infants who have died after long-term ventilation or after the development of bronchopulmonary dysplasia (BPD) also have decreased alveolar numbers and an attenuated microvasculature with less prominent airway injury and fibrosis than in the past.[5] Factors that likely contribute to this arrest of lung development include many of the components of care of preterm infants. Antenatal glucocorticoid treatments in monkeys and sheep cause thinning of the interstitium and an increased surface area for gas exchange with delayed alveolar septation. Postnatal glucocorticoid treatments of the saccular lung also interrupt alveolarization and capillary development. Hyperoxia or hypoxia and poor nutrition can interfere with alveolarization. In transgenic mice, overexpression of proinflammatory mediators in the pulmonary epithelium interferes with alveolar development. Antenatal lung inflammation associated with chorioamnionitis in sheep causes delayed alveolar and microvascular development.[72] Thus, multiple factors may contribute to delayed alveolarization in preterm infants. Because lung growth following the completion of alveolarization is by increase in airway and alveolar size, any event that decreases alveolar number could impact lung function as the individual ages. However, the growth potential of the human lung is remarkable, and infants with mild BPD had normal alveolar numbers at 10 to 14 years of age as estimated by hyperpolarized helium MRI.[47] The residual lung structural abnormalities in the lungs of infants who have survived severe BPD remain to be characterized.

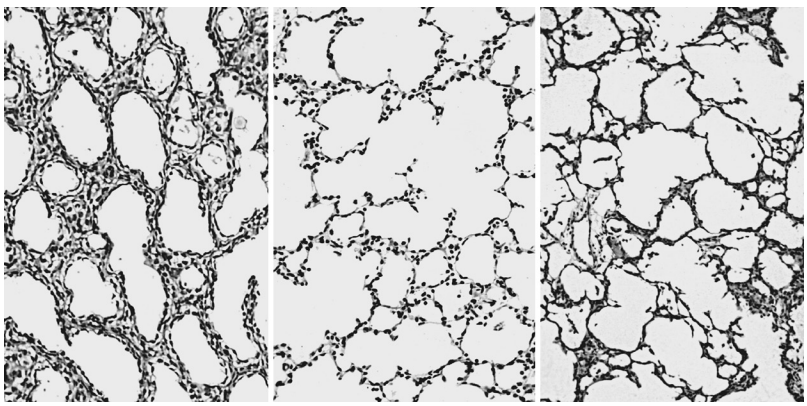
• BOX 62.1 Modulators of Alveolarization

Factors That Delay or Interfere With Alveolarization

- Mechanical ventilation
- Antenatal and postnatal glucocorticoids
- Pro-inflammatory mediators
- Chorioamnionitis
- Hyperoxia or hypoxia
- Poor nutrition

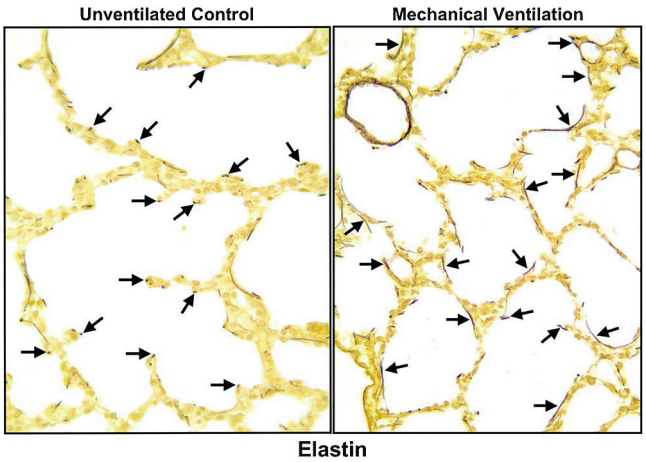
Factors That Stimulate Alveolarization

- Vitamin A (retinoids)
- Thyroxin



• Fig. 62.6 Tissue from lungs of ventilated preterm baboons. *Left,* The lung of a 125 days' gestation fetal baboon has rounded saccular structures with thick walls (×170). *Center,* Lung from a term baboon (186 days' gestation) with airspaces that are a mixture of saccular and alveolar structures (×170). *Right,* Lung tissue from a preterm baboon delivered at 125 days' gestation and ventilated for 30 days demonstrates enlarged airspaces with increased interstitial cellularity (×70). The ventilated lung has larger airspaces even though the photomicrograph is at a 2.4-fold lower magnification. (Modified from Coalson JJ, et al. Neonatal chronic lung disease in extremely immature baboons. *Am J Respir Crit Care Med.* 1999;160:1333, with permission. Copyright 1999 American Lung Association.)

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• **Fig. 62.7** Changes in elastin distribution in lungs of 5-day-old mice ventilated for 24 hours with 40% oxygen. Lung sections from controls (*left*) demonstrate elastin with Hart stain at the tips of developing septa. In contrast, the ventilated lungs (*right*) have more elastin without the focal distribution in the distal airspaces. (Reprinted with permission from Bland RD, et al. Mechanical ventilation uncouples synthesis and assembly of elastin and increases apoptosis in lungs of newborn mice. Prelude to defective alveolar septation during lung development? *Am J Physiol Lung Cell Mol Physiol.* 2008;294:L3.)

Fetal Lung Fluid

The fetal airways are filled with fluid until delivery and the initiation of ventilation. Most of the information concerning quantitative aspects of fetal lung fluid is from the fetal lamb with sonographic and pathologic correlates available for the human. The fetal lung close to term contains enough fluid to maintain the airway fluid volume at about 40 mL/kg of body weight, which is somewhat larger than the FRC once air breathing is established.[43] The composition of fetal lung fluid is unique relative to other fluids in the fetal sheep and most other mammalian species.[30] The chloride content is high (157 mEq/L), whereas the bicarbonate and protein contents are very low. In contrast, the bicarbonate and chloride concentrations in fetal lung fluid from the rhesus monkey are not different from plasma values, demonstrating species differences in ion composition of fetal lung fluid. The electrolyte composition is maintained by transepithelial chloride secretion with bicarbonate reabsorption. Fetal lung fluid contains little protein, because the fetal epithelium is quite impermeable to protein. Active transport of Cl^- from the interstitium to the lumen yields a production rate for fetal lung fluid of 4-5 mL/kg per hour. Assuming the fetus is 3-4 kg, the daily production of fetal lung fluid is about 400 mL per day. Fetal lung fluid flows intermittently into the pharynx with fetal breathing movements, and some of this fluid is swallowed while the rest mixes with the amniotic fluid. The pressure in the fetal trachea exceeds that in the amniotic fluid by about 2 mm Hg, maintaining an outflow resistance and the fetal lung fluid volume. The secretion of fetal lung fluid seems to be an intrinsic metabolic function of the developing lung epithelium, because changes in vascular hydrostatic pressures, tracheal pressures, and fetal breathing movements do not greatly alter fetal lung fluid production rates.

Although normal amounts of fetal lung fluid are essential for normal lung development, its clearance is equally essential for normal neonatal respiratory adaptation.[51] Fetal lung fluid production can be completely stopped at term by vascular infusions of epinephrine at concentrations that approximate the levels of epinephrine present during labor. The epinephrine-mediated reversal of fetal lung fluid flux from secretion to reabsorption does not occur in the preterm lung. However, epinephrine-mediated clearance can be induced by pretreatment of fetal sheep with the combination of corticosteroid and triiodothyronine. Inhibition of prostaglandin synthesis with indomethacin in the fetus reduces the production of fetal lung fluid and urine. Fetal lung fluid production and volumes are maintained in the fetal sheep until the onset of labor. During active labor and delivery, fetal lung fluid volumes decrease, leaving about 35% of the fetal lung fluid to be absorbed and cleared from the lungs with breathing. Most of the fluid moves rapidly into the interstitial spaces and subsequently into the pulmonary vasculature, with less than 20% of the fluid being cleared by pulmonary lymphatics. The clearance of the fluid from the interstitial spaces occurs over many hours. Fluid clearance after birth results from active sodium transport via the epithelial sodium channel (ENaC). Genetic ablation of subunits of ENaC causes death in newborn mice because fetal lung fluid is not cleared from the lungs. Glucocorticoids upregulate the messenger RNA (mRNA) for the ENaC subunits in the fetal human lung. Transient respiratory difficulties in many infants are caused by delayed clearance of fetal lung fluid.

Pulmonary Hypoplasia

Pulmonary hypoplasia is a relatively common abnormality of lung development, with a number of clinical associations and anatomic correlates.[15] Primary pulmonary hypoplasia is unusual and is likely caused by abnormalities of the transcription factors and growth factors that regulate early lung morphogenesis, such as thyroid transcription factor-1 and FGF family members.[71] Severe forms of acinar aplasia result from abnormal regulation of lung growth and development. Secondary pulmonary hypoplasia is associated with either a restriction of lung growth or the absence of fetal breathing (Box 62.2). Any reduction of the chest cavity by a mass, effusion, or external compression can impact lung growth. Lung hypoplasia can be minimal or severe. Severe pulmonary hypoplasia associated with renal agenesis and prolonged oligohydramnios is characterized by a decrease in lung size and cell number together with narrow airways, a delay of epithelial differentiation, and surfactant deficiency. Relatively short-term oligohydramnios caused by ruptured membranes in the sixteenth to twenty-eighth week of gestation also can result in pulmonary hypoplasia; the magnitude in general correlates with the severity and length of the oligohydramnios. Infants with congenital diaphragmatic

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• BOX 62.2 Clinical Associations of Pulmonary Hypoplasia

Thoracic Compression

- Renal agenesis (Potter syndrome)
- Urinary tract outflow obstruction
- Oligohydramnios before 28 weeks' gestational age
- Extra-amniotic fetal development

Decreased Intrathoracic Space

- Diaphragmatic hernia
- Pleural effusions
- Abdominal distension sufficient to limit chest volume
- Thoracic dystrophies
- Intrathoracic masses

Decreased Fetal Breathing

- Intrauterine central nervous system damage
- Fetal Werdnig-Hoffmann syndrome
- Other neuropathies and myopathies

Other Associations

- Primary pulmonary hypoplasia
- Trisomy 21
- Multiple congenital anomalies
- Erythroblastosis fetalis

hernia have more severe hypoplasia on the ipsilateral side than on the contralateral side, although the contralateral lung also may be hypoplastic. The lungs have fewer and smaller acinar units, delayed epithelial maturation, and an associated surfactant deficiency. In experimental models, tracheal occlusion in late gestation can reverse much of the pulmonary hypoplasia resulting from diaphragmatic hernia, but the occlusion induces a decrease in type II cells and surfactant deficiency. Fetal tracheal occlusion is being introduced as a therapy for very high-risk fetuses with some success.[1]

Other Disorders of Lung Development

Congenital malformations of the lung, including the distal parenchyma, trachea–bronchial tree, and vascular structures, are relatively rare but may present with severe respiratory compromise during the neonatal period. Congenital cystic adenomatoid malformations (CCAM) are characterized by multicystic areas of over-proliferation and dilatation of terminal respiratory bronchioles with lack of normal alveoli. CCAM are intrapulmonary lesions that contain various types of epithelial linings and maintain communication with the normal trachea–bronchial tree and retain a normal blood supply. They are usually unilobar and unilateral. Stocker's classification subdivides the cysts into five categories dependent upon the size and epithelial lining of the cyst.[17]

Bronchogenic cysts are usually single, unilocular cysts filled with fluid or mucous; however, when located in the lung parenchyma they may be multiple. They are lined by pseudostratified ciliated columnar respiratory epithelium and contain hyaline cartilage plates. Bronchogenic cysts most commonly occur in the mediastinum, although they may occur anywhere throughout the thoracic cavity or elsewhere. When located in lung parenchyma or alongside airways, there is no communication between the cysts and the trachea–bronchial tree.[17] Congenital lobar emphysema is identified as hyperinflation of one or more pulmonary lobes and leads compression of surrounding structures. This compression may lead to mediastinal shift. Most commonly, the left upper or right middle lobes are affected.[17] Pulmonary sequestrations are portions of the lung that are in isolation from neighboring lung tissues and with no communication to the bronchial tree. Pulmonary sequestrations receive blood supply from a systemic artery, and venous drainage may occur through either a pulmonary or systemic vein. Pulmonary sequestrations can be divided into two categories: intralobar (15%) and extralobar sequestrations (85%).

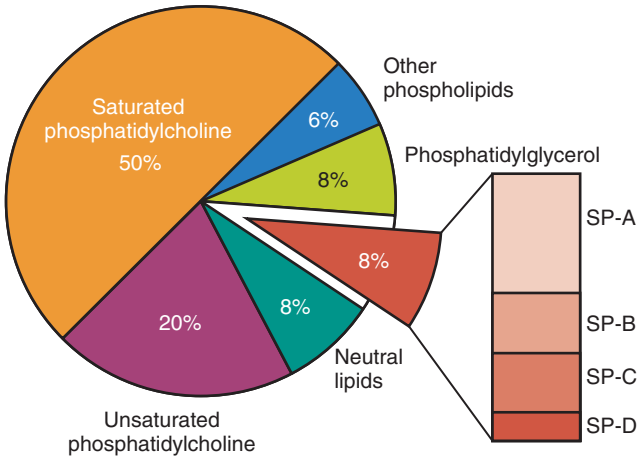
Alveolar capillary dysplasia with misaligned pulmonary veins is a rare and lethal congenital malformation of the lung that involves both acinar structure and intrinsic pulmonary vasculature. A majority of infants with this disorder have mutations in the *FOXF1* gene, with abnormal development of the capillary vascular system around the alveoli of the lungs. The characteristic pathologic finding is misaligned pulmonary veins located with the pulmonary artery with medial hypertrophy in the same adventitial sheath.[63] Although 60%-80% of the infants have extrapulmonary abnormalities, the characteristic presentation is severe persistent pulmonary hypertension unresponsive to therapy. Congenital acinar dysplasia (CAD) is a very rare form of primary interstitial lung disease characterized by diffuse bilateral impairment of pulmonary acini (the respiratory bronchioles, alveolar ducts, and alveoli). Most cases are fatal.[59]

Alveolar Macrophages

The sentinel immune cells of the lung are alveolar macrophages. In adult humans and animals these cells are located in the airspaces directly in contact with the alveolar hypophase. Alveolar macrophages derived from monocytes from the circulation take residence in the lung. Local cues and growth factors including GM-CSF and the transcription factor PU.1 differentiate these monocytes to alveolar macrophages.[46] Once differentiated, alveolar macrophages do not recycle and have a relatively long life span under normal conditions. Important functions of alveolar macrophages include immune surveillance, phagocytosis of invading microorganisms, antigen presentation, interactions with adaptive immune cells, and surfactant homeostasis.

Fetuses do not normally have alveolar macrophages. In nonhuman primates and sheep, very few macrophages are found in the fetal lung.[38] Alveolar macrophages begin to populate the lung in large numbers postnatally with the onset of air breathing. Exposure to chorioamnionitis—an

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• **Fig. 62.8** Composition of surfactant. The major component is saturated phosphatidylcholine. The surfactant proteins contribute about 8% to the mass of surfactant.

TABLE 62.1 Changes in Surfactant With Development

Variables	Immature Lung	Mature Lung
Type II Cells		
Glycogen lakes	High	Gone
Lamellar bodies	Few	Many
Microvilli	Few	Many
Surfactant Composition		
Sat PC/Total PC	0.6	0.7
Phosphatidylglycerol (%)	<1	10
Phosphatidylinositol (%)	10	2
Surfactant protein A (%)	Low	5
Surfactant function	Decreased	Normal

PC, Phosphatidylcholine; Sat, saturated.

infection in the amniotic fluid and fetal membranes—can mature the lung macrophages and stimulate their migration into the fetal alveolar spaces.

Surfactant Metabolism

Composition

Surfactant recovered from lungs of all mammalian species by alveolar wash procedures contains 70%-80% phospholipids, about 8% protein, and about 10% neutral lipids, primarily cholesterol (Fig. 62.8). The composition of the phospholipids in surfactant is unique relative to the lipid composition of lung tissue or other organs. About 60% of the phosphatidylcholine species are saturated, meaning that both fatty acids esterified to the glycerol phosphorylcholine backbone are predominantly the 16-carbon saturated fatty acid, palmitic acid. Most other phosphatidylcholine species in surfactant have a fatty acid with one double bond in the two position of the molecule. Saturated phosphatidylcholine is the principal surface-active component of surfactant and can be used as a relatively specific probe of surfactant metabolism. The acidic phospholipid phosphatidylglycerol is present in surfactant in small amounts that vary between 4% and 15% of the phospholipids in different species (Table 62.1). Surfactant phospholipids from the immature fetus or newborn contain relatively large amounts of phosphatidylinositol, which then decrease as phosphatidylglycerol appears with lung maturity.[24] Phosphatidylglycerol in amniotic fluid can be measured as a test for lung maturity. The surfactant from the preterm lung is qualitatively inferior relative to surfactant from the mature lung when tested for in vivo function than is surfactant from term newborns.[32]

There are four relatively surfactant-specific proteins.[70] SP-A is a water-soluble 24-kDa collectin that is heavily glycosylated in the carboxy-terminal region with blood group antigen as well as other carbohydrate moieties to yield a protein of about 36 kDa. SP-A monomers contain a collagen domain and form a collagen-like triple helix that then aggregates to form a multimeric protein with a molecular size of 650 kDa. SP-A contributes to the biophysical properties of surfactant primarily by decreasing protein-mediated inhibition of surfactant function. Mice that lack SP-A have no tubular myelin but have normal lung function and surfactant metabolism, indicating that SP-A is not critical to regulation of surfactant metabolism. The major function of SP-A is as an innate host defense protein and as a regulator of inflammation in the lung.[37] SP-A binds to multiple pathogens such as group B streptococcus, *Staphylococcus aureus*, and herpes simplex type 1. The protein facilitates phagocytosis of pathogens by macrophages and their clearance from the airspace. SP-A can prevent influenza virus infection and decrease the inflammation caused by adenovirus. Patients with a deficiency of SP-A have not been identified, although polymorphisms in SP-A are associated with increased risk for RDS, BPD, and viral bronchiolitis.[23] SP-A levels are low in surfactant from preterm lungs and increase with corticosteroid exposure. SP-A is not a component of surfactants used for treatment of RDS.

SP-B and SP-C are two small hydrophobic proteins that are extracted with the lipids from surfactant by organic solvents. These proteins contribute about 2%-4% to the surfactant mass.[70] The primary translation product of SP-B is 40 kDa, from which SP-B is clipped to become an 8-kDa protein before it enters lamellar bodies for co-secretion with the phospholipids from the type II cell. SP-B facilitates surface absorption of lipids and low surface tensions on surface area compression. Animals with antibodies to SP-B develop respiratory failure, and infants with a genetic absence of SP-B have lethal respiratory failure after term birth. The genetic absence of SP-B is most frequently caused by a two base-pair insertion (121 ins 2) resulting in a frameshift and premature termination signal resulting in a

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complete absence of SP-B. Multiple other mutations resulting in complete or partial SP-B deficiencies have been described.[50] The lack of SP-B causes a loss of normal lamellar bodies in type II cells, a lack of SP-C, and the appearance of incompletely processed SP-C in the airspaces. These pro-SP-C forms are diagnostic of SP-B deficiency. Respiratory failure develops in mice that have less than about 20% of the normal amount of SP-B.[28]

The primary translation product of SP-C is a 22-kDa protein that is processed to an extremely hydrophobic 4-kDa protein that is associated with lipids in lamellar bodies.[70] The mRNA for SP-C appears in cells lining the developing airways from early gestation. With advancing lung maturation, the mRNA for SP-C becomes localized only to type II cells. Although the sequence and cellular localization of the protein have been remarkably conserved across species, mice that lack SP-C have normal lung and surfactant function at birth. However, the mice develop progressive interstitial lung disease and emphysema as they age. Infants with a progressive interstitial lung disease can lack SP-C, as can large kindreds of patients with the onset of interstitial lung disease at variable ages.[50] These patients generally do not have genetic alterations in the coding region of the protein but have dominant negative mutations that disrupt the processing of SP-C. SP-B and SP-C probably work cooperatively to optimize rapid adsorption and spreading of phospholipids on a surface and to facilitate the development of low surface tensions on surface area compression. Surfactants prepared by organic solvent extraction of natural surfactants or from lung tissue contain variable amounts of SP-B and SP-C. Such surfactants are similar to natural surfactants when evaluated for in vitro surface properties or for function in vivo.[54] Surfactant recovered from preterm animals has low amounts of SP-B and SP-C, which may, in part, explain its poor function.[67]

SP-D is a hydrophilic protein of 43 kDa that is a collectin with structural similarities to SP-A.[70] It has a collagen-like domain as well as a glycosylated region that gives it lectin-like functions. This protein is synthesized by type II cells and Clara cells as well as in other epithelial sites in the body. Like the other SPs, its expression is developmentally regulated by glucocorticoids and inflammation. SP-D is a large multimer that functions as an innate host defense molecule by binding pathogens and facilitating their clearance. The absence of SP-D results in increased surfactant lipid pools in the airspaces and emphysema but no major deficits in surfactant function in mice. The addition of SP-D to a surfactant used to treat preterm lambs decreased the ventilator-mediated inflammation.[60] No humans with SP-D deficiency have been described.

The incidences of genetic abnormalities of the surfactant system are not well known. A report of more than 300 term infants with severe RDS found about 14% had SP-B deficiency. A deficiency of the ATP-binding cassette transporter gene *ABCA3* was more common.[7] This *ABCA3* gene product is localized to lamellar bodies and functions as a lipid transporter. The clinical presentation of ABCA3 deficiency is very much like SP-B deficiency. Some of the lethal RDS in term infants is explained by mutations in genes essential for surfactant metabolism. However, other infants with respiratory failure probably have yet-to-be-identified mutations in genes that disrupt other aspects of lung development.

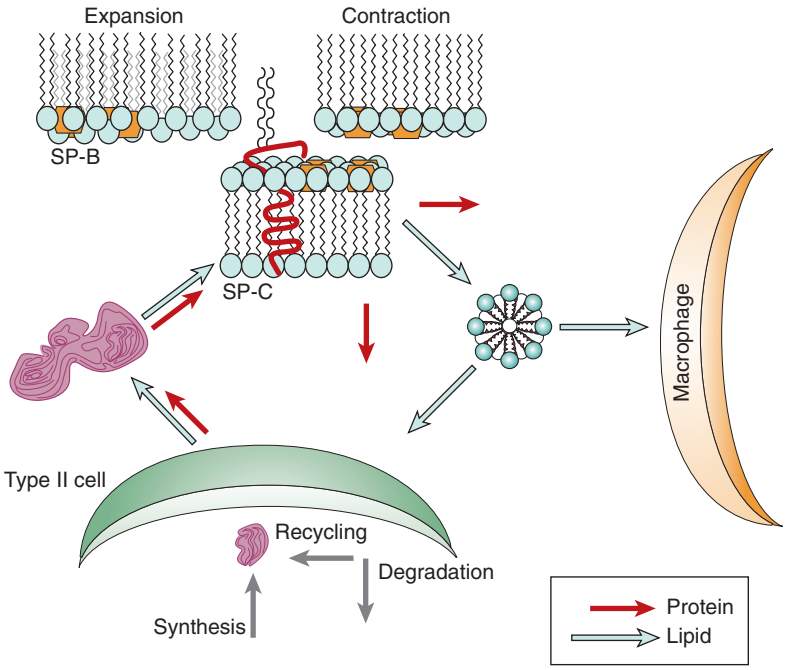
Synthesis and Secretion

The type II cell is responsible for the major pathways involved in surfactant metabolism (Fig. 62.9). The synthesis and secretion of surfactant is a complex sequence of biochemical synthetic events that results in the release by exocytosis of the lamellar bodies to the alveolus. The basic pathways for the synthesis of phospholipids are common to all mammalian cells. Specific enzymes within the endoplasmic reticulum use glucose, phosphate, and fatty acids as substrates for phospholipid synthesis. The uniqueness of a phospholipid is determined by the character of the fatty acid side chains esterified to the glycerol carbon backbone and by the head group (e.g., choline, glycerol, and inositol) linked to the phosphate. Although the overall synthetic pathways are known, the details of how the components of surfactant condense with SP-B and SP-C to form the surfactant lipoprotein complex within lamellar bodies remain obscure. Ultrastructural abnormalities of type II cells with SP-B deficiency and ABCA3 deficiency in term infants indicate that these gene products are critical to lamellar body formation.[70] If SP-B is absent, lamellar bodies are abnormal, and SP-C is not processed correctly. Normal surfactant secretion can be stimulated by a number of mechanisms. Beta-agonists and purines such as adenosine triphosphate are potent stimulators of surfactant secretion. Surfactant secretion also is stimulated by mechanical stretch such as with lung distention and hyperventilation. The surfactant secretion that occurs with the initiation of ventilation following birth probably results from the combined effects of elevated catecholamines and lung stretch.

Surfactant Pool Sizes

Following the observation of Avery and Mead that saline extracts of the lungs of infants with RDS had high minimum surface tensions,[3] decreased alveolar and tissue surfactant pools were demonstrated in preterm animals. Increasing surfactant pool sizes correlate with improving compliances during development, although other factors such as structural maturation also influence compliance. Infants with RDS have surfactant pool sizes on the order of about 5 mg/kg of body weight. Preterm lambs with RDS can be managed with continuous positive airway pressure if their surfactant pool sizes exceed about 4 mg/kg.[45] The quantity of surfactant recovered from the airspaces of infants with RDS is not much less than the amount of surfactant found in the alveoli of healthy adult animals or humans. However, much less surfactant is recovered from preterm than healthy term animals, who have surfactant pool sizes of about 100 mg/kg of body weight.[32] The large amount of

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• **Fig. 62.9** Surfactant metabolism in the type II cell in the alveolus. The lipid-associated surfactant proteins B (SP-B) and SP-C track with the lipid from synthesis to secretion and surface film formation. The small vesicular forms of surfactant do not contain SP-B or SP-C.

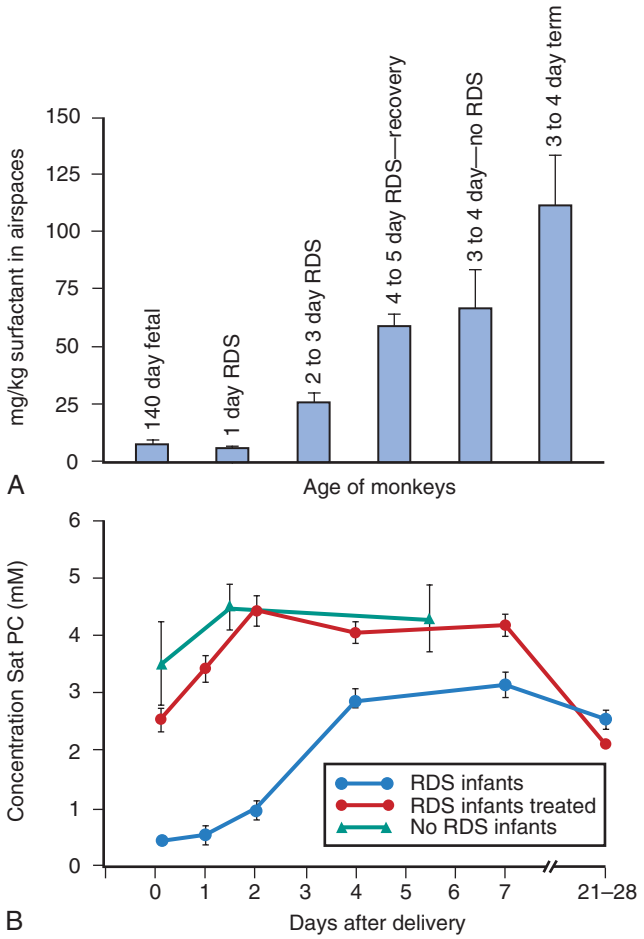
surfactant in amniotic fluid in the human at term indicates that the term human fetal lung also has large pool sizes. Both the quantity and the quality of the surfactant from the preterm together with inhibition of surfactant function contribute to the deficiency state. The clinical observation that many preterm infants and animals respond remarkably to surfactant treatment supports the conclusion that in many infants surfactant deficiency is the primary problem. The endogenous pool sizes of surfactant that are sufficient for good lung function are lower than for treatment doses of surfactant, probably because the endogenous surfactant is optimally distributed and treatment doses of surfactant are not distributed uniformly at the alveolar level.

The rate of increase in the pool size of alveolar surfactant after preterm birth was measured in ventilated preterm monkeys recovering from RDS (Fig. 62.10).[29] The surfactant pool size increased toward the 100 mg/kg value measured in term monkeys within 3-4 days. Hallman and colleagues measured the concentration of saturated phosphatidylcholine in airway samples from infants recovering from RDS and compared the results with values for infants without RDS and for surfactant-treated infants.[25] The concentration of saturated phosphatidylcholine increased over a 4- to 5-day period to become comparable with values for normal or surfactant-treated infants. This slow increase in pool size is consistent with a clinical course of RDS of 3-5 days without surfactant treatment. The explanation for why surfactant pool sizes increase slowly after preterm birth is apparent from measurements of the kinetics of surfactant secretion and clearance in the newborn (Fig. 62.11). Following the intravascular injection of radiolabeled precursors of surfactant phosphatidylcholine, incorporation into lung phosphatidylcholine is rapid. However, there are long time delays between synthesis and the movement of surfactant components from the endoplasmic reticulum through the Golgi apparatus to lamellar bodies for eventual secretion. Phosphatidylcholine secretion was measured in human infants with RDS using intravascular infusions of the glucose and palmitic acid precursors labeled with stable isotopes.[8,9] Glucose-labeled phosphatidylcholine was detected in the airway samples after about 20 hours, and peak enrichment of the stable isotope occurred at about 70 hours. Therefore, delays between synthesis and secretion and the interval to peak airway accumulation of endogenously synthesized surfactant lipid are long in the preterm human.[14]

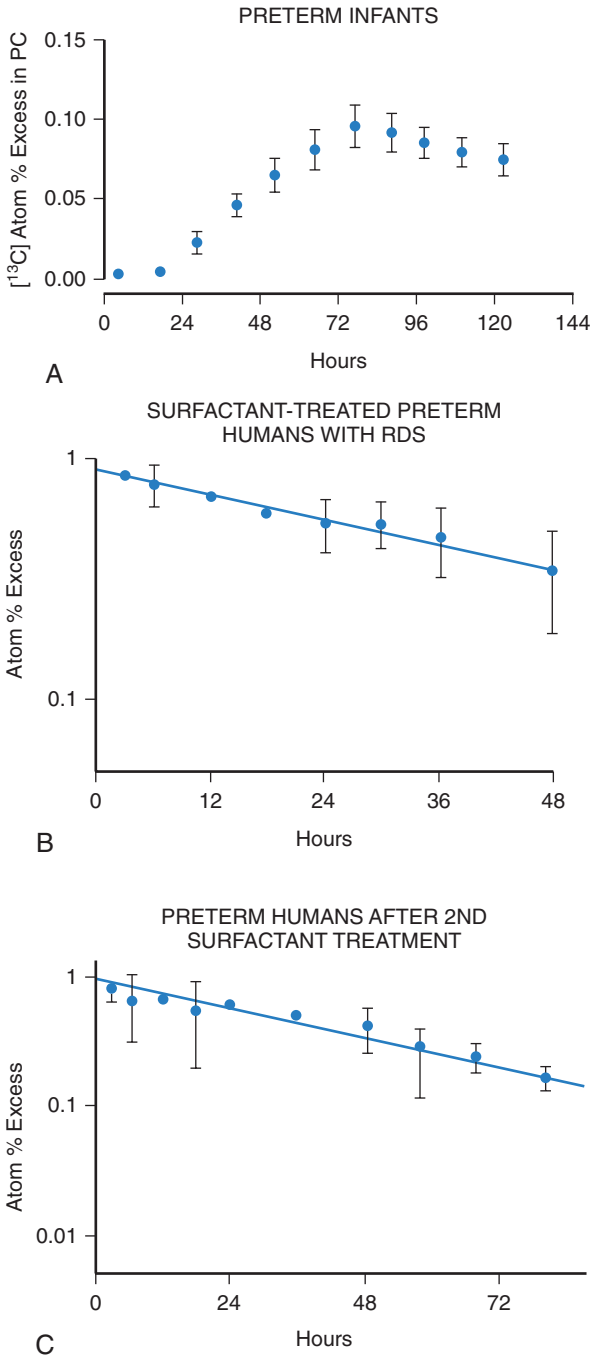
The slow secretion and alveolar accumulation of surfactant are balanced in the term and preterm lung by slow catabolism and clearance. Trace amounts of stable isotope labeled surfactant phospholipid given into the airspaces with treatment doses of surfactant to infants with RDS had half-life values of several days.[66] Trace or treatment doses of surfactant given into the airspaces do not remain static in the airspaces. The surfactant phospholipids move from the airspaces back to type II cells, where they are taken up by an endocytotic process into multivesicular bodies. In the term and preterm lung, about 90% of the phospholipids are recycled back to lamellar bodies and re-secreted to the airspace. The phospholipids are recycled as intact molecules without degradation and resynthesis. In the adult lung, this process is perhaps only 50% efficient.

The metabolic characteristics of surfactant phospholipids in the preterm are favorable for surfactant treatment strategies.[32] Alveolar and tissue pool sizes are small, and the rate of accumulation is slow. Treatment acutely increases both the alveolar and tissue pools, because the exogenously administered saturated phosphatidylcholine is taken up into type II cells and processed for re-secretion. The surfactants

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• **Fig. 62.10** Changes in surfactant pool sizes with resolution of respiratory distress syndrome (RDS). **A,** The amount of surfactant recovered by alveolar lavage from monkeys with RDS and cared for with mechanical ventilation is shown relative to age and stage of the disease. **B,** The concentrations of saturated phosphatidylcholine (Sat PC) in airway samples from infants with RDS, infants with RDS treated with surfactant, and infants without RDS are graphed relative to age from birth. The concentration of Sat PC approached values for healthy preterm infants by 4-7 days. (**A,** Data from Jackson JC, et al. Surfactant quantity and composition during recovery from hyaline membrane disease. *Pediatr Res.* 1986;20:1247. **B,** Data drawn from Hallman M, et al. Surfactant protein A, phosphatidylcholine, and surfactant inhibitors in epithelial lining fluid: correlation with surface activity, severity of respiratory distress syndrome, and outcome in small premature infants. *Am Rev Respir Dis.* 1991;144:1376.)



• **Fig. 62.11** Time course of appearance of de novo synthesized surfactant and clearance of treatment doses of surfactant from airway samples of ventilated infants with RDS. **A,** Labeling of PC in airway samples of preterm surfactant-treated mechanically ventilated infants with respiratory distress syndrome after intravascular infusion of [^{13}C] glucose for the first 24 hours of life. The label in the PC is expressed as atom percent excess. (Data redrawn from Bunt JE, et al. The effect in premature infants of prenatal corticosteroids on endogenous surfactant synthesis as measured with stable isotopes. *Am J Respir Crit Care Med.* 2000;162:844.) **B,** Curve for decrease in atom percent excess in airway samples for [^{13}C]dipalmitoylphosphatidylcholine-labeled surfactant used to treat preterm ventilated infants with respiratory distress syndrome. The atom percent excess in the initial surfactant dose given after delivery fell exponentially for 48 hours. **C,** A second dose given at about 2 days of age resulted in a similar clearance curve. (Data redrawn from Torresin M, et al. Exogenous surfactant kinetics in infant respiratory distress syndrome: a novel method with stable isotopes. *Am J Respir Crit Care Med.* 2000;161:1584.)

used clinically are not equivalent in function to native surfactant in the mature lung. However, within hours following surfactant treatment of preterm animals, the surfactant recovered by alveolar wash has improved function, indicating that the preterm lung, if uninjured, can transform the surfactant used for treatment with poor function into a good surfactant.[67] Also of benefit is the slow catabolic rate of the lipid components of surfactant. This characteristic of the system means that the surfactant used for treatment remains in the lungs and is not rapidly degraded. Infants treated with surfactant can be extubated earlier if they maintain higher surfactant pool sizes.[68] Treatment doses of surfactant do not feedback-inhibit the endogenous synthesis of

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saturated phosphatidylcholine or the surfactant proteins. No adverse metabolic consequences of surfactant treatment on the endogenous metabolism of surfactant or other lung functions have been identified.

There is less information about the metabolism of the surfactant proteins in the preterm lung. SP-A, SP-B, and SP-C all seem to be recycled to some degree from the airspace back into lamellar bodies for re-secretion with surfactant.[32] All three proteins have alveolar clearance kinetics that are similar to saturated phosphatidylcholine in the preterm lung. Therefore, the critical surfactant components are conserved by recycling. The presumed function of the recycling pathways is to reassemble the components to regenerate biophysically active surfactant. SP-B and SP-C enter the lamellar bodies during their biogenesis in parallel with the phospholipids. In contrast, de novo synthesized SP-A is secreted independently of the lamellar bodies. This protein then associates with the phospholipids to form tubular myelin in the airspace. Lung injury of the preterm results in abnormalities in surfactant metabolism and function.

Alveolar Life Cycle of Surfactant

After secretion as lamellar bodies, surfactant goes through a series of form transitions in the airspace.[32] The lamellar bodies "unravel" into an elegant structure called *tubular myelin.* This lipoprotein array has SP-A at the corners of the lattice and requires at least SP-A, SP-B, and the phospholipids for its unique structure. Tubular myelin and other surfactant lipoprotein arrays are the reserve pool in the fluid hypophase for the formation of the surface film within the alveolus and small airways. Area compression of this film then squeezes out unsaturated lipid and some protein components of surfactant with concentration of saturated phosphatidylcholine in the surface film. New surfactant enters the surface film and "used" surfactant leaves in the form of small vesicles, which then are cleared from the airspaces. The major difference in composition between the surface-active tubular myelin and loose lipid arrays and the small vesicular forms is that the small forms contain little SP-A, SP-B, or SP-C. Although a complete surfactant contains multiple lipid and protein components, all of the components are not essential for biophysical function. Surfactants for treatment work well despite lacking some components of native surfactant.

Just preceding and following birth, lamellar bodies are secreted to yield an alveolar pool that is primarily lamellar bodies and tubular myelin. This surfactant then begins to function with aeration of the lung. As the newborn goes through neonatal transition, the percentage of surface active forms falls as the small vesicular forms increase. At equilibrium, approximately 50% of the surfactant in the airspaces is in a surface-active form and 50% is in the inactive vesicular form.[67] The vesicular forms of surfactant are believed to be the pools used for recycling of the phospholipid components of surfactant. The total surfactant pool size is not equivalent to the amount of active surfactant. In the preterm, conversion from surface active to inactive surfactant forms occurs more rapidly. Pulmonary edema can further accelerate alveolar conversion, with the net result being a depletion of the surface-active fraction of surfactant despite normal or high total surfactant pool sizes.

Physiologic Effects of Surfactant in the Preterm Lung

Alveolar Stability

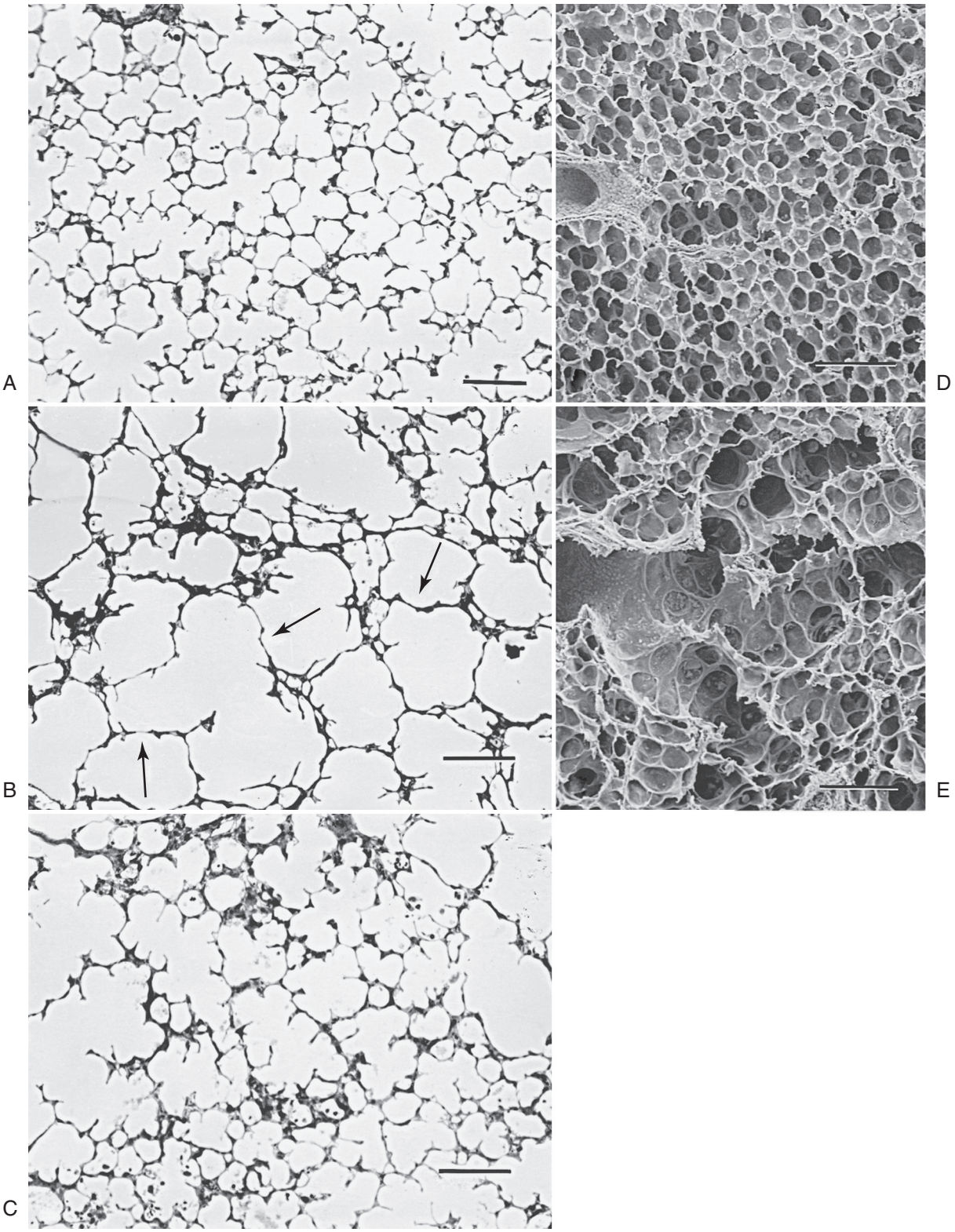
The air-exposed surfaces of alveoli are complex polygonal shapes that are interdependent in that their structures are determined by the shapes and elasticity of neighboring alveoli and airways. The forces acting on the pulmonary microstructure are chest wall elasticity, lung tissue elasticity, and surface tensions of the air-fluid interfaces in the small airways and alveoli. Although the surface tension of surfactant decreases with surface area compression and increases with surface area expansion, the surface area of an alveolus changes very little with tidal breathing. The low surface tensions resulting from surfactant help prevent alveolar collapse and keep interstitial fluid from entering the alveolus. Surfactant also keeps small airways from filling with fluid to cause luminal obstruction.[18] If alveoli collapse or fill with fluid, the shape of adjacent alveoli will change, which may result in regional distortion, overdistention, or collapse. When positive pressure is applied to a surfactant-deficient lung, the more normal alveoli tend to overexpand and the less normal (i.e., less surfactant) alveoli collapse, generating a nonhomogeneously inflated lung (Fig. 62.12).[53] Surfactant treatment can normalize alveolar size.

Pressure-Volume Curves

The effects of surfactant on the preterm surfactant-deficient lung are demonstrated by pressure-volume relationships during quasistatic inflation and deflation (Fig. 62.13).[55] The pressure needed to open a lung unit is related to the radius of curvature and surface tension of the meniscus of fluid in the airspace leading to the lung unit. In the collapsed or fluid-filled lung, there are different units with different radii. The units with larger radii and lower surface tensions "pop" open first because, with partial expansion, the radius increases and the forces needed to finish opening the unit decrease. The movement of fluid with high surface tensions in the airways causes very high sheer forces that can disrupt the airway epithelium.[33] Preterm surfactant-deficient rabbit lungs do not begin to inflate until pressures exceed 25 cm H_2O. With surfactant treatment, the fluid menisci in the airways have lower surface tensions that decrease the opening pressure from about 25 to 15 cm H_2O in this example with preterm rabbit lungs. The subsequent inflation is more uniform as more units open at lower pressures, resulting in less epithelial injury and overdistention of the open units.

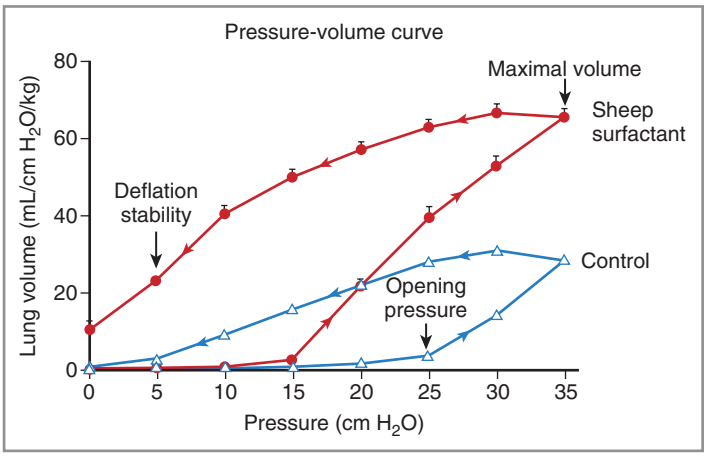
A particularly important effect of surfactant on the surfactant-deficient lung is the increase in maximal volume

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• **Fig. 62.12** Ventilation of the preterm lamb lungs for 24 hours results in nonuniform alveolar inflation and dilation of alveolar ducts. Light microscopy in frames on left demonstrates uniform alveolar sizes in fetal lungs that have not been ventilated **(A)**, dilated ducts and shallow alveoli (*arrows*) after 24 hours of ventilation **(B)**, and a more normal-appearing lung following surfactant treatment at birth and ventilation for 24 hours **(C)**. Scanning electron microscopy in the frames on the right taken at the same magnification demonstrates alveoli of uniform size in the unventilated lung **(D)** and dilated alveolar ducts with flattening of some alveoli and compression of others creating microatelectasis **(E)**. Bar is 160 m. (Modified from Pinkerton KE, et al. Lung parenchyma and type II cell morphometrics: effect of surfactant treatment on preterm ventilated lamb lungs. *J Appl Physiol.* 1994;77:1953, with permission.)

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• **Fig. 62.13** Pressure-volume relationships for the inflation and deflation of surfactant-deficient and surfactant-treated preterm rabbit lungs. The control lungs are from 27-day preterm rabbits. Surfactant deficiency is indicated by the high opening pressure, the low maximal volume at a distending pressure of 35 cm H_2O, and the lack of deflation stability at low pressures on deflation. In contrast, treatment of 27-day preterm rabbits with a natural surfactant alters the pressure-volume relationships. (From Creasy RK, et al., eds. *Creasy & Resnik's maternal-fetal medicine*. 6th ed. Philadelphia: Elsevier; 2009:201.)

at maximal pressure. In the example in Fig. 62.13, maximal volume at 35 cm H_2O is increased about 2.5-fold by surfactant treatment to a volume that is similar to that achieved in a term newborn rabbit lung. The opening pressures for many distal lung units in the surfactant-deficient lung exceed 35 cm H_2O and exceed the rupture pressure of the preterm lung. This volume difference resulting from surfactant treatment is lung volume that improves gas exchange, because it is primarily alveolar gas volume. Lung volume recruitment is achieved rapidly with surfactant treatment. Another important effect of surfactant is the stabilization of the lung on deflation. The surfactant-deficient lung collapses at low transpulmonary pressures, whereas the surfactant-treated lung retains about 40% of the lung volume on deflation to 5 cm H_2O, which is the static volume equivalent of functional residual capacity.

Dynamic lung mechanics also are altered by surfactant treatments. Time constants for deflation increase, resulting in less effective lung emptying. The clinical correlate is that a surfactant treatment may increase the FRC of infants with RDS by two mechanisms: the improved deflation stability and the longer expiratory time constant. The consistent initial response of infants with RDS to surfactant treatments is a rapid improvement in oxygenation, whereas improvements in P_{CO_2}, compliance, and, therefore, ventilatory support variables tend to change more gradually. Improved oxygenation without changes in ventilation results from the acute increase in lung volumes following surfactant treatments.

Lung Maturation

Surfactant Appearance With Development

Lamellar bodies first appear within type II cells by 20-24 weeks' gestation in the human fetus, and the amount of saturated phosphatidylcholine increases in lung tissue to term. This early presence of surfactant within human fetal lung tissue is consistent with the clinical experience that some infants born as early as 23 weeks' gestation have little lung disease. Lung maturity as defined by the absence of RDS in the human fetus is generally present after 35 weeks' normal gestation. Therefore a 12-week window of "early maturation" is possible for the human, at least in part because the surfactant synthetic and storage machinery is inducible in the human early in gestation.

The tests for fetal lung maturation depend on surfactant components in amniotic fluid reflecting the status of surfactant in the fetal lung. The lung secretes fetal lung fluid and any surfactant released into that lung fluid. The flow of fluid out of the lung is the episodic balance between fetal swallowing and loss of fetal lung fluid to the amniotic cavity. The amniotic fluid can be characterized as the fetal cesspool, containing all fetal excretions as well as desquamated cells and other biologic matter.[12] Tests of lung maturation depend on the flow of fetal lung fluid into the amniotic fluid being sufficient to change amniotic fluid composition in a timely manner relative to the fetal lung maturation. A remarkable aspect of the human fetus is the extraordinary inducibility of lung maturation at early gestational ages.

Tests of lung maturation with amniotic fluid have been developed to identify fetuses with early lung maturation. These tests include the L/S ratio of lecithin to sphingomyelin, measurements of phosphatidylglyceral as a relatively unique component of surfactant, assessments of surface activity by bubble stability test, measurements of lamellar body numbers, and several commercial tests. Obstetric practice seldom uses lung maturation tests currently, because decisions about delivery are based on clinical assessments of the mother and fetus. If preterm delivery is likely then antenatal corticosteroids are used routinely. However, amniotic fluid can in theory be used to assess the maturational status of multiple fetal organ systems using protein or mRNA analysis. New tests of fetal studies based on amniotic fluid may become of value clinically.[35,58]

Induced Lung Maturation

The incidence of RDS needs to be interpreted within the context of maturational phenomena that occur spontaneously in the preterm. Most infants destined to deliver at term do not have mature lungs until about 36 weeks'

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gestational age. Although the incidence of RDS in clinical practice increases as gestational age decreases, the incidence of RDS is not easily defined because of variable definitions and the effect of different clinical care strategies on the diagnosis of RDS. For example, from 1997-2002, the NICHD Neonatal Research Network defined RDS as the need for oxygen and some ventilatory support, plus a compatible chest roentgenogram. With this definition, the incidence of RDS for infants less than 1 kg was 63%.[19] For 2003-2007, the definition was changed to the use of supplemental oxygen for more than 6 hours, and 95% of similar infants now had a diagnosis of RDS.[64] In contrast, only about 50% of infants with birth gestations less than 28 weeks that are initially supported with CPAP have sufficient RDS to receive surfactant.[4] If the use of surfactant is a surrogate for significant RDS, then many very early gestation infants did not have severe RDS. Biologically, this indicates that induced lung maturation is frequent. This spontaneous early lung maturation in the human fetus is believed to result from stress-induced maturation events that can be maternal, placental, or fetal in origin. However, despite fetal stress, fetal growth restriction or preeclampsia do not induce lung maturation.

The changing epidemiology of RDS results in part from the more frequent use of antenatal glucocorticoids and a change in obstetric practices to delay preterm delivery as long as possible. Numerous clinical trials have documented that maternal corticosteroid treatments decrease the incidence of RDS by about 50%, and those infants with RDS tend to have less severe disease. Chronic infection and fetal exposure to inflammation and histologic chorioamnionitis are frequent in those pregnancies with preterm labor between 22 and 30 weeks' gestation[21] and are associated with a decreased incidence of RDS. In experimental models, bacterial endotoxin, the proinflammatory cytokine interleukin-1 (IL-1), or fetal exposure to live ureaplasma induce lung maturation when given by intra-amniotic injection.[39] Fetal proinflammatory exposures induce striking increases in surfactant and improvements in postnatal lung function after preterm delivery of lambs without increasing fetal cortisol levels.[40] Therefore fetal exposure to inflammation may have the short-term benefit of decreasing RDS. Prematurity cannot be considered a normal condition. It is useful to think of the infant with RDS as the normal unstressed preterm, whereas the preterm without RDS has experienced a stress sufficient to induce lung maturation.

Glucocorticoids and Lung Maturation

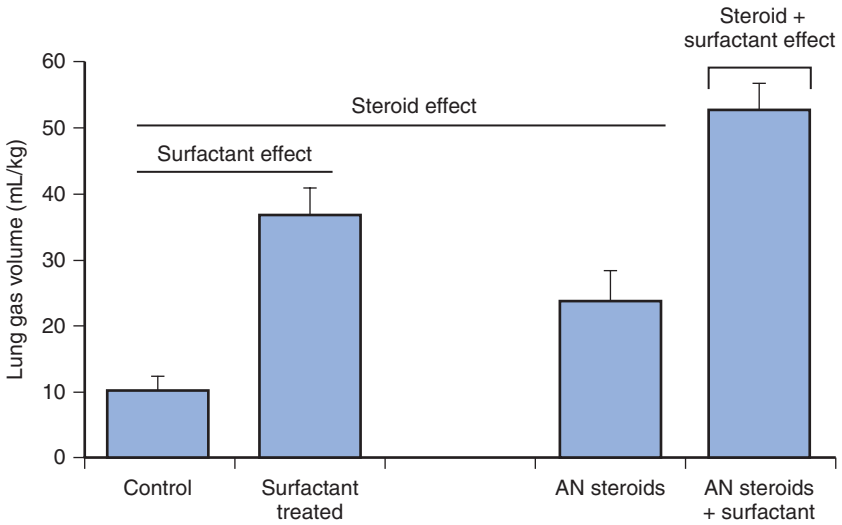
The events resulting in spontaneous early lung maturation in the human have not been well characterized. Explants of human lung at 14-20 weeks' gestational age differentiate in organ culture in the absence of hormonal stimuli, and agents such as corticosteroids and thyroid hormones accelerate maturation.[44] Several agents, such as insulin and transforming growth factor-β, tend to block lung maturation, and androgens delay maturation. Because about half of corticosteroid-treated fetuses do not seem to respond, it is reasonable to propose that fetal lung maturation normally is suppressed in favor of growth. If this suppression is released by stress-related signals, then the lung is susceptible to either endogenously mediated maturational signals or to exogenous effectors. Corticosteroids are one of the categories of agents that can influence lung maturation; however, other agents also can influence lung maturation. The inducing agents can act additively or synergistically in terms of both the timing and the magnitude of the response in experimental models.

The responses of the fetal lung to corticosteroids are multiple and impact many different systems that could influence the clinical outcome.[36] Corticosteroids induce lung structural maturation by increasing the surface area and lung volumes for gas exchange. Type II cell maturation has been noted primarily in vitro. Biochemical markers of maturation include glycogen loss from type II cells, increased fatty acid synthesis, increased β-receptors, and increased choline incorporation into surfactant phosphatidylcholine. In vivo, animals demonstrate improved lung function and survival. Corticosteroid treatment also decreases the tendency of the preterm lung to develop pulmonary edema. The primary effect of corticosteroids on the fetal lung is generally considered to be induction of surfactant synthesis. However, effects on enzymes in the synthetic pathway have not been consistently demonstrated, and surfactant pool sizes do not increase until more than 4 days after maternal glucocorticoid treatments in sheep.[31] Lung function can improve following corticosteroid treatments, even if surfactant is not increased, because of changes in lung structure. In preterm animal models, corticosteroid treatment changes the dose-response curve such that less surfactant is needed to cause larger clinical responses. Because of increased lung volume, corticosteroid-treated fetuses also have improved responses to postnatal surfactant (Fig. 62.14).[27] There are additive or synergistic effects between the corticosteroid-exposed lungs and surfactant treatments.

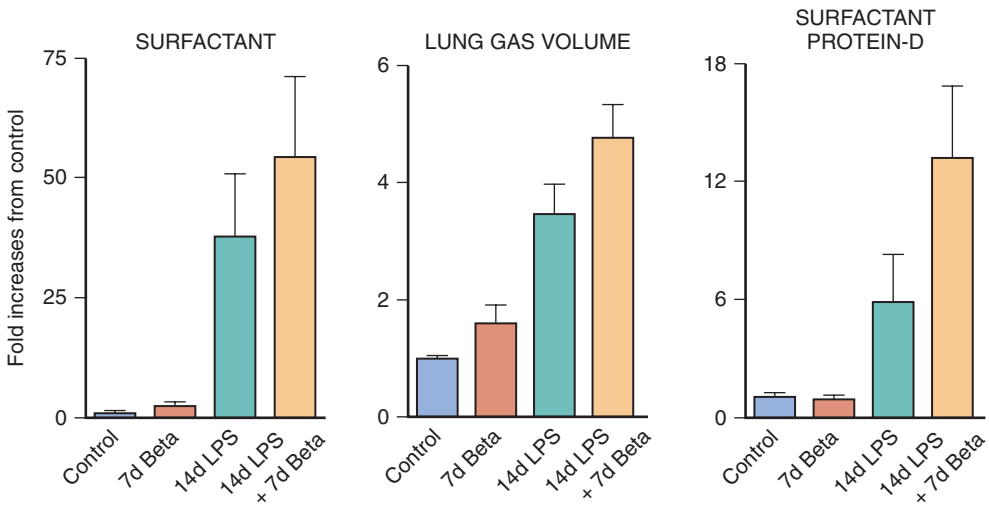
Antenatal corticosteroid treatment is now the standard of practice for pregnancies at risk of preterm delivery.[56] This therapy is effective and safe, although there is not long-term follow-up data for infants born before 28 weeks' gestation. Repetitive courses of antenatal glucocorticoids have been given at 7- to 10-day intervals, a practice based on the suggestion that the fetal benefit was lost after this interval.[31] Maternal glucocorticoid treatments at 7-day intervals in sheep cause fetal growth restriction but augment lung maturation. Randomized trials in women at risk for preterm delivery demonstrate modest benefit, but there is some concern about longer-term outcomes, especially for infants exposed to four or more antenatal doses of antenatal corticosteroids.[16]

The only other lung maturation strategy that has been extensively evaluated clinically is the combination of corticosteroids and thyrotropin-releasing hormone (TRH). Thyroid axis hormones induce lung maturation and can act synergistically with corticosteroids in vitro. Thyroid

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• **Fig. 62.14** Combined effects of corticosteroids and surfactant treatments on lung volumes of ventilated preterm lambs. Fetal sheep were exposed to saline or corticosteroids and then randomized to treatment with surfactant prior to a short period of ventilation. The gas volume of the lung at a static pressure of 40 cm H_2O is given as mL/kg. Both antenatal corticosteroids and surfactant increased the lung gas volumes, and both treatments had a larger effect. AN, Antenatal. (Modified from Ikegami, et al. Corticosteroid and thyrotropin-releasing hormone effects on preterm sheep lung function. *J Appl Physiol.* 1991;70:2268-2278.)



• **Fig. 62.15** Combined responses of the fetal sheep lung to antenatal corticosteroids and intra-amniotic *E. coli* lipopolysaccharide (LPS). Fetal sheep were exposed to maternal betamethasone treatments (Beta) or intra-amniotic LPS as an inflammatory mediator that causes chorioamnionitis at 7- or 14-day intervals before preterm delivery. All values are normalized to a value of 1 for the control. The changes in the amount of surfactant lipids, lung gas volume, and surfactant protein-D were larger with the LPS exposure, and both exposures further increased the markers of lung maturation. (Modified and redrawn from Kuypers, et al. Intra-amniotic LPS and antenatal betamethasone: inflammation and maturation in preterm lamb lungs. *Am J Physiol Lung Cell Mol Physiol.* 2011;302:L380.)

hormones do not cross the human placenta efficiently, but the tripeptide TRH crosses to the fetal circulation and increases fetal thyroid hormone levels. Unfortunately, when evaluated in large randomized controlled trials, TRH demonstrated no benefit and possible risks were identified.[2] Therefore, the use of TRH to supplement antenatal corticosteroid therapy is not recommended.

Intrauterine Infection and Lung Maturation

As noted earlier, fetal exposure to chorioamnionitis also can induce lung maturation. In experimental models, intra-amniotic endotoxin or IL-1 will induce more striking lung maturation than will maternal corticosteroid treatments (Fig. 62.15).[40] The inflammatory mediators trigger lung

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maturation by direct contact with the fetal lung and induce a modest lung inflammation/injury response that resolves with large improvements in lung mechanics and increased surfactant lipid and protein pool sizes.[34] Of clinical relevance, the maturational effects of maternal corticosteroids and chorioamnionitis seem to be additive for induced lung maturation.[49] The corticosteroids can suppress inflammation initially, but the inflammatory response is amplified in the fetal sheep at later times, perhaps because corticosteroids mature fetal innate immune responses. In clinical practice, ruptured membranes, a surrogate for chorioamnionitis, are not a contraindication to maternal corticosteroid treatment.[26]

This chapter focuses on the lung. However, maturation of other organs occurs in parallel in most fetuses. Other organs also are sensitive to corticosteroids and other agents. Maternal corticosteroid treatments not only decrease the incidence and severity of RDS but also decrease the incidence of patent ductus arteriosus, intraventricular hemorrhage, and necrotizing enterocolitis and increase kidney tubular function and postnatal blood pressure. Therefore, strategies to optimize maturation of the fetus at risk for preterm delivery target not only the lung but also other organs.

Key Points

- Adequate lung development is essential for survival of the premature infant.
- The surfactant system can have early maturation induced by antenatal corticosteroids.
- Surfactant treatments can improve lung function remarkably.
- The fetal lung responds to inflammation with induced maturation.

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63

Assessment of Neonatal Pulmonary Function

JULIANN M. DI FIORE AND WALDEMAR A. CARLO

Most neonates requiring intensive care present with respiratory symptoms. Although standard techniques for assessing pulmonary function can be applied in a healthy infant, special limitations and problems are encountered in very small or sick neonates. Methods have been developed to evaluate pulmonary function in neonates with suspected abnormalities of the cardiopulmonary system. This section presents a practical and clinical approach to disordered cardiopulmonary function and attempts to help distinguish between heart and lung disease.

Clinical Observations

Five common physical signs relay indirect information regarding pulmonary function: respiratory rate, retractions, nasal flaring, grunting, and cyanosis.

Respiratory Rate

Precise monitoring of respiratory rate is invaluable, as deviations from the normal respiratory patterns have been observed with mechanical pulmonary dysfunction, acid–base imbalances, and arterial blood gas abnormalities. During spontaneous breathing, infants can only achieve successful gas exchange within a limited range of respiratory rates. At low rates, decreased alveolar minute ventilation may occur, while at high rates and corresponding low tidal volumes (V_T), a large proportion of the minute ventilation is wasted in ventilating dead space.

Infants may also adjust the respiratory rate to minimize work of breathing. The total work of breathing consists of elastic and resistive components. The elastic component represents the work required to stretch the lungs and chest wall during a tidal inspiration, and the resistive component is the work required to overcome friction caused by lung tissue movement and gas flow through the airways. Healthy infants rely on tidal volumes of 6-7 mL/kg and approximate respiratory rates of 40-60 breaths per minute. However, during the first hour after birth respiratory rates may be higher, with approximately 50% of healthy newborns having respiratory rates greater than 60 breaths per minute.[40] Newborns with stiff lungs, such as those with respiratory distress syndrome (RDS), attempt to compensate for the increased workload with rapid shallow breathing, whereas patients with increased resistance (e.g., subglottic stenosis) usually exhibit slower and deeper breathing (Fig. 63.1).

Retractions

The neonatal chest wall is extremely compliant, and substernal, subcostal, and intercostal retractions are readily observable even with a relatively minor derangement in lung mechanics. Retractions are caused by negative intrapleural pressure generated by the contraction of the diaphragm and other respiratory muscles and the mechanical properties of the lungs and chest wall. In neonates with respiratory distress, retractions become more apparent as the lungs become stiffer.

Apart from their characteristic appearance in RDS and other pulmonary diseases, severe retractions can signal complications of respiratory disease such as airway obstruction, misplacement of an endotracheal tube, pneumothorax, or atelectasis (see Chapter 64). Decreased retractions in the presence of adequate inspiratory effort suggest that lung compliance and/or resistance is improving.

Nasal Flaring

Nasal flaring is another sign of respiratory distress often observed in infants. The dilation of nostrils produced by contraction of the alae nasi muscles results in a marked reduction in nasal resistance. Because newborns are preferential nose breathers and because nasal resistance contributes substantially to total lung resistance, nasal flaring markedly decreases the work of breathing. Nasal flaring is occasionally observed in the absence of other signs of respiratory distress, particularly during feeding and active sleep.

Activation of other respiratory muscles, such as the genioglossus (tongue) and laryngeal muscles, is also important for optimal function of the upper airway. The genioglossus

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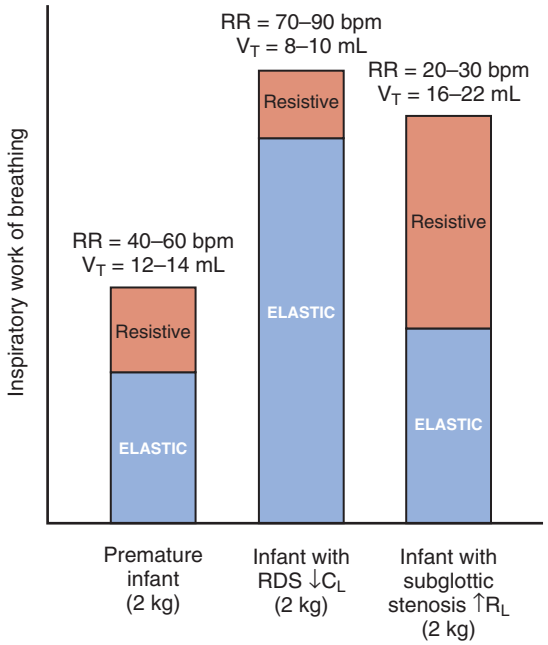
Abstract

Most neonates requiring intensive care present with respiratory symptoms. Although standard techniques for assessing pulmonary function can be applied in a healthy infant, special limitations and problems are encountered in very small or sick neonates. Methods have been developed to evaluate pulmonary function in neonates with suspected abnormalities of the cardiopulmonary system. These include physical signs that relay indirect information (i.e., respiratory rate, retractions, nasal flaring, grunting, and cyanosis), cardiovascular assessment (i.e., blood gas measurements, end tidal or transcutaneous CO_2, and pulse oximetry), and physiologic measurements (i.e., radiographic evaluation, lung volume, and respiratory mechanics). Used in combination, these methods can be valuable tools in optimizing oxygenation and CO_2 elimination while using the lowest possible level of respiratory support to minimize lung injury and improve long-term outcomes.

Keywords

oxygen
blood gas monitoring
resistance
compliance
carbon dioxide
lung volume
time constant

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• **Fig. 63.1** Relative contributions of the elastic and resistive components of the work of breathing in infants with normal pulmonary function, decreased lung compliance (C_L), and increased lung resistance (R_L). RDS, Respiratory distress syndrome; RR, respiratory rate; V_T, tidal volume.

muscle protrudes the tongue and, in part, maintains pharyngeal patency, whereas the laryngeal muscles move the vocal cords and regulate airflow, particularly during expiration.

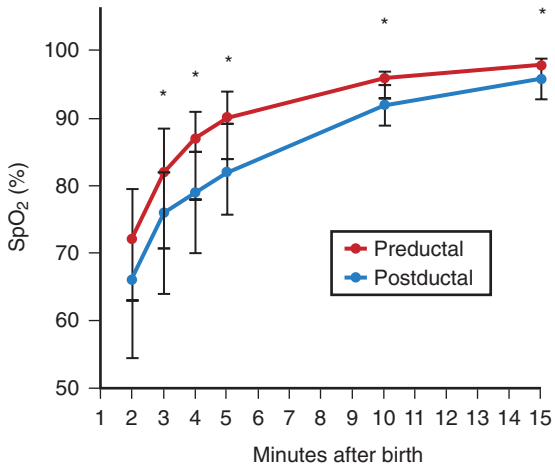
Grunting

With normal breathing, the vocal cords abduct to enhance inspiratory flow. In some respiratory disorders and with initiation of air breathing after birth, neonates attempt to close (adduct) their vocal cords during the initial phase of expiration, holding gas in the lungs and producing an elevated transpulmonary pressure in the absence of airflow. The elevated pressure and corresponding increased lung volume result in enhancement of the ventilation–perfusion ratio ($\dot{V}/\dot{Q}$). During the last part of the expiratory phase, gas is expelled from the lungs against partially closed vocal cords, causing an audible grunt.

Grunting may be either intermittent or continuous, depending on the severity of lung disease. Grunting can maintain functional residual capacity (FRC) and partial pressure of arterial oxygen (Pa_{O_2}) equivalent to the application of continuous distending pressure. Because endotracheal intubation abolishes grunting, maintenance of lung volume with positive end-expiratory pressure (PEEP) is important following intubation.

Cyanosis

Central cyanosis, best observed by examining the tongue and oral mucosa, is an important indicator of impaired gas exchange. Clinical detection of cyanosis depends on the



• **Fig. 63.2** A rapid postnatal rise in oxygenation occurs during the normal fetal to neonatal transition. Preductal and postductal levels measured by way of pulse oximetry showed significantly lower postductal than preductal levels at 3, 4, 5, 10, and 15 minutes. *$P < .05$. (Mariani G, et al. Pre-ductal and post-ductal O_2 saturation in healthy term neonates after birth. *J Pediatr.* 2007;150:418.)

total amount of desaturated hemoglobin. Thus, patients with anemia may have a low Pa_{O_2} without clinically detectable cyanosis, and patients with polycythemia may be clinically cyanotic despite a normal Pa_{O_2}. Peripheral cyanosis may be normal in neonates but also occurs in situations of decreased cardiac output. The clinical features of cyanosis and their significance are discussed in detail in Part 12, The Cardiovascular System.

Cardiovascular Assessment

Blood Gas Measurements

Maintaining optimal gas exchange is the primary function of the lung. Thus, pulmonary evaluations should include blood gas estimates in addition to measurements of pulmonary mechanics. Both invasive and noninvasive blood gas measurements are available in the neonatal population. Invasive blood gas measurements are the optimal mode for accurate measures of oxygen and carbon dioxide, whereas noninvasive measurements are ideal for continuous documentation of the rapid changes that occur in this population. These rapid changes in blood gas values begin with the initiation of the first breath after normal delivery, resulting in a rapid fall in Pa_{CO_2} within minutes of birth. During this time, Pa_{O_2} rises quickly to levels of 60-90 mm Hg, although some degree of mismatching of $\dot{V}/\dot{Q}$ is evident during the first day after birth. This is believed to be the result of intracardiac and pulmonary right-to-left shunting. Data in larger groups of infants have characterized the increase in oxygenation following birth by way of pulse oximetry, allowing for further differentiation between preductal and postductal levels (Fig. 63.2).[48] (See also Chapter 33.) The speed with which pulmonary ventilation and perfusion are uniformly distributed is an indication of the neonate's remarkable capacity for maintaining homeostasis.

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During the early weeks of postnatal life, preterm infants are exceptionally unstable, requiring close monitoring of blood gas status. Pulse oximetry and blood gas measurements are the most widely used clinical methods for assessing pulmonary function in neonates and form the basis for diagnosis and management of cardiorespiratory disease.

Invasive Blood Gas Measurements

Partial Pressure of Alveolar Oxygen and Carbon Dioxide

Changes in partial pressure of alveolar oxygen (P_{AO_2}) and P_{ACO_2} can identify disordered pulmonary function in various clinical situations. P_{AO_2} and P_{ACO_2} values depend on the composition and volume of alveolar gas, the composition and volume of the mixed venous blood, and the mechanisms of pulmonary gas exchange impairment. Alveolar gas composition can be obtained from the equation

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R}\left[F_{IO_2} + \frac{1 - F_{IO_2}}{R}\right]$$

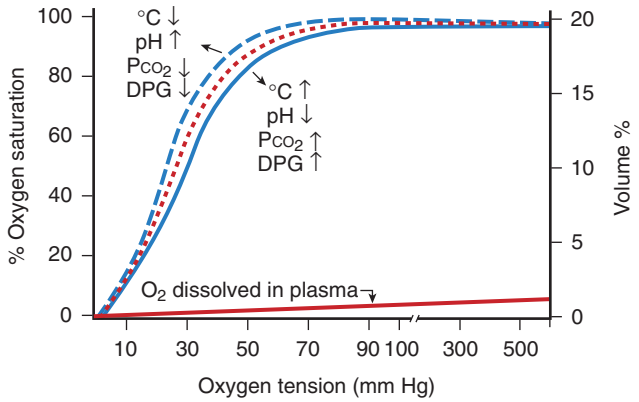
where P_{IO_2} is partial pressure of inspired oxygen ($P_{IO_2} = F_{IO_2} \times$ [barometric pressure − water vapor pressure]). At sea level, barometric pressure is 760 mm Hg; at 100% humidity, water vapor pressure is 47 mm Hg. P_{ACO_2} is the partial pressure of alveolar carbon dioxide, and R is the respiratory quotient (usually 0.8). The mechanisms of pulmonary gas exchange impairment include $\dot{V}/\dot{Q}$ mismatch, shunt, hypoventilation, and diffusion limitation. Appropriate matching of the alveolar gas with the mixed venous blood yields optimal gas exchange. Mixed venous blood composition and volumes are determined by the arterial blood gas content, cardiac output, oxygen consumption, and carbon dioxide production.

Techniques of blood gas determination in infants with RDS are discussed in Chapter 64. Gas exchange during assisted ventilation is discussed in Chapter 65. Acid–base physiology is discussed in Chapter 92.

Partial Pressure of Arterial Oxygen

Depending on the efficacy of gas exchange, the alveolar oxygen partial pressure (tension) tends to equilibrate with the mixed venous blood, resulting in the P_{aO_2}, which determines the degree of oxygen saturation of hemoglobin. In addition to its chemical combination with hemoglobin, oxygen is also dissolved in plasma and red blood cells (RBCs). Most of the oxygen in whole blood is bound to hemoglobin (measured clinically as oxygen saturation), whereas the amount of dissolved oxygen is only a small fraction of the total quantity carried in whole blood.

The quantity of oxygen bound to hemoglobin depends on the P_{aO_2} and the oxygen dissociation curve (Fig. 63.3). The blood is almost completely saturated at a P_{aO_2} of 90-100 mm Hg. The flattening of the upper portion of the S-shaped dissociation curve makes it virtually impossible to estimate oxygen tension greater than 60-80 mm Hg by using arterial oxygen saturation alone. The dissociation curve of fetal hemoglobin (compared with adult hemoglobin) is shifted to the left, and at any P_{aO_2} less than 100 mm Hg, fetal blood binds more oxygen. The shift appears to be the result of the lower affinity of fetal hemoglobin for 2,3-diphosphoglycerate. Note that pH, P_{aCO_2}, temperature, and diphosphoglycerate (DPG) content influence the position of the dissociation curve.



• **Fig. 63.3** Factors shifting the oxygen dissociation curve of hemoglobin. (Fetal hemoglobin is shifted to the left.) DPG, Diphosphoglycerate.

Arterial oxygen content (C_{aO_2}) is the sum of hemoglobin-bound and dissolved oxygen, as described by the following equation:

$$C_{aO_2} = (1.37 \times Hb \times S_{aO_2}) + (0.003 \times P_{aO_2})$$

where the arterial oxygen content is in mL/100 mL of blood, 1.37 is the approximate amount of oxygen (in milliliters) bound to 1 g of hemoglobin at 100% saturation, Hb is hemoglobin concentration (g/100 mL), S_{aO_2} is the percentage of hemoglobin bound to oxygen, and 0.003 is the solubility factor of oxygen in plasma (mL/mm Hg). In this equation, the first term ($1.37 \times Hb \times S_{aO_2}$) is the amount of oxygen bound to hemoglobin. The second term ($0.003 \times P_{aO_2}$) is the amount of oxygen dissolved in plasma and red blood cells.

Most of the oxygen in the blood is carried by hemoglobin. For example, if an infant has a P_{aO_2} of 80 mm Hg, an S_{aO_2} of 99%, and a hemoglobin concentration of 15 g/100 mL, C_{aO_2} is the sum of oxygen bound to hemoglobin ($[1.37 \times 15 \times 99]/100 = 20.3$ mL) plus the oxygen dissolved in plasma ($0.003 \times 80 = 0.24$ mL). In this example, just over 1% of oxygen in blood is dissolved in plasma and almost 99% is carried by hemoglobin.

The partial pressure of oxygen in arterial blood not only depends on the ability of the lungs to transfer oxygen as determined by alveolar ventilation but also is largely influenced by the $\dot{V}/\dot{Q}$. For normal gas exchange, the ventilation and perfusion should be proportional. The ratio should be very close to 1:1; that is, for every milliliter of gas that passes the alveoli, there should be a proportional volume of blood in the pulmonary capillary bed. If the $\dot{V}/\dot{Q}$ is decreased (as in RDS), only partial oxygenation and CO_2

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removal from the mixed venous blood will occur. Oxygen supplementation can largely overcome the hypoxemia when the $\dot{V}/\dot{Q}$ is decreased. If the $\dot{V}/\dot{Q}$ is high, as in overventilation, partial pressure of oxygen is increased slightly.

The mechanism of shunting becomes evident when blood bypasses the alveoli, as occurs in congenital cyanotic heart disease, persistent pulmonary hypertension, or atelectasis. Oxygen supplementation does not prevent the hypoxemia produced by such a shunt. Hypoventilation (e.g., caused by apnea) is a common cause of hypoxemia. Diffusion limitation can affect oxygenation slightly, but this mechanism is not a common cause of severe hypoxemia in neonates. Hypoxemia caused by either hypoventilation or diffusion limitation usually can be treated easily with oxygen supplementation.

Three indexes can be used to estimate the degree of oxygenation derangement (see Chapter 70). The *arterial–alveolar oxygen tension ratio* (PaO_2/PAO_2 or a/AO_2 ratio) has no units, decreases with worsening oxygenation, and can be obtained from the equation

$$P(a/A)O_2 = \frac{P_aO_2}{PiO_2 - \frac{PACO_2}{R}\left[FiO_2 + \left(\frac{1 - FiO_2}{R}\right)\right]}$$

where R is the respiratory quotient. Because $[FiO_2 + (1 - FiO_2)/R]$ approximates 1.0, and $PACO_2$ approximates $PaCO_2$, the equation can be simplified as follows:

$$P(a/A)O_2 \sim \frac{PaO_2}{PiO_2 - \frac{PaCO_2}{R}}$$

The *alveolar–arterial oxygen tension gradient* ($PAO_2 - PaO_2$ or $AaDO_2$) is expressed in mm Hg, increases with worsening oxygenation and can be obtained from the equation

$$P(A-a)O_2 = PiO_2 - PACO_2\left[FiO_2 + \left(\frac{1 - FiO_2}{R}\right)\right] - PaO_2$$

or

$$P(A-a)O_2 = PiO_2 - \frac{PaCO_2}{R} - PaO_2$$

The *oxygenation ratio* is expressed in mm Hg, decreases with worsening oxygenation, and can be obtained from the equation

$$\text{Oxygenation ratio} = \frac{PaO_2}{FiO_2}$$

The oxygenation ratio is less often used because it is subject to inaccurate assessment of the oxygenation derangement when $PaCO_2$ varies markedly. Often, it is necessary to correct the degree of oxygenation for the ventilatory support, because oxygenation is strongly influenced by mean airway pressure ($\bar{P}aw$) during assisted ventilation. The oxygenation index (OI) is useful under these circumstances. The OI, which increases with worsening oxygenation or increasing $\bar{P}aw$, has units of centimeters of water per mm Hg and can be obtained by the equation

$$OI = \frac{\bar{P}aw \times FiO_2}{PaO_2} \times 100$$

Partial Pressure of Arterial Carbon Dioxide

$PaCO_2$ is an important measure of pulmonary function in neonatal respiratory disease. Mechanisms responsible for impairment of pulmonary exchange of CO_2 include hypoventilation, $\dot{V}/\dot{Q}$ mismatch, and shunt. In addition, an increase in dead space, as occurs with alveolar overdistention or gas trapping, impairs CO_2 elimination. Because of the high solubility coefficient of CO_2, diffusion limitation rarely affects CO_2 exchange. As tissue levels of CO_2 increase above those of arterial blood, molecules diffuse into the capillaries and are transported in RBCs and plasma. Unlike the S-shaped dissociation curve for O_2, the relationship between CO_2 tension and content is almost linear over the physiologic range.

Noninvasive Blood Gas Measurements

See Chapter 37.

Carbon Dioxide

Noninvasive estimates of CO_2 by end-tidal or transcutaneous detectors provide a reasonable alternative to frequent blood gas sampling, allowing for continuous monitoring of CO_2 over prolonged periods of time. End-tidal CO_2 monitoring is a noninvasive technique that measures CO_2 concentration in the gas at the end of expiration. Quantitative measurements of end-tidal CO_2 have been shown to correlate well with arterial blood gases in term and preterm infants without pulmonary disease and can be useful for detection of rapid changes in exhaled CO_2 with data displayed on a breath-by-breath basis.[51] When there is minimal pulmonary disease, quantitative end-tidal CO_2 monitoring can assist in detection of hypercapnia and hypocapnia. However, with small tidal volumes and high respiratory rates it may underestimate the true alveolar gas in some neonates. Alternative designs, such as disposable colorimetric end-tidal CO_2 detectors, have a high diagnostic accuracy for confirmation of endotracheal tube placement.[76] A positive end-tidal CO_2 test confirms endotracheal tube placement, and a negative test strongly suggests esophageal intubation. However, many infants can have falsely negative results at birth.[62]

Transcutaneous CO_2 detectors have been shown to be superior to end-tidal CO_2 in ill neonates.[51] However, sensor preparation, taping, and the need for changes in sensor location may limit transcutaneous CO_2 usefulness. Despite the limitations of end-tidal and transcutaneous monitoring of CO_2, these methods provide critically important continuous information pertaining to changes in the respiratory system and minimize the need for blood gas analysis.

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Several randomized controlled trials have evaluated allowing CO_2 to rise to reduce lung injury. Evidence from these randomized controlled trials and meta-analyses indicates that a strategy of permissive hypercapnia using noninvasive respiratory support with CPAP instead of a conventional ventilatory approach reduces death or bronchopulmonary dysplasia (risk difference −0.04; 95% confidence interval −0.08-0.00, number needed to treat 25).[61]

Oxygen

Maintenance of oxygenation in an acceptable range requires constant monitoring that is not possible with intermittent blood gas measurements. This has led to the widespread implementation of pulse oximetry as a means of continuous noninvasive O_2 monitoring (see Chapter 37). Pulse oximetry measures the amount of hemoglobin molecules that is bound with oxygen. It has a rapid response time and can be used as an estimate of Pao_2 for detecting short intermittent hypoxic episodes. However, as shown by the oxyhemoglobin dissociation curve (see Fig. 63.3), oxygen saturation levels should remain below 95% in infants requiring supplemental O_2, as hyperoxic values of Pao_2 cannot be distinguished beyond that range.

Pulse Oximetry: Optimal Oxygen Saturation Target Range

The ideal oxygen saturation target range is currently unknown. The avoidance of oxygen saturations greater than 95% in very preterm infants is generally accepted as this target range has been associated with both increased pulmonary complications[3] and retinopathy of prematurity. In an attempt to improve optimal oxygen saturation targets, saturation targeting below 95% has been tested. Five randomized trials of targeting oxygen saturations of 85%-89% versus 91%-95% included almost 5000 extremely preterm infants.[61,67,72] The trials were well designed and conducted. The meta-analysis shows that the lower oxygen saturation target group had a higher rate of death at 18-24 months' corrected age (risk difference [RD] 0.03, 95% CI 0.01-0.05; 4873 infants), a higher rate of necrotizing enterocolitis, and a lower rate of ROP-receiving treatment compared to the higher oxygen saturation target group.[2] An increased number of intermittent hypoxemic events were reported in the low (85%-89%) target group.[20] Despite the increased risk of retinopathy, blindness and other visual outcomes were not affected.[2] Death or major disability to 18-24 months' corrected age did not differ between the two oxygen saturation target groups. Other major outcomes including patent ductus arteriosus receiving treatment did not differ between the treatment groups. The revised American Academy of Pediatrics guidelines state that target oxygen saturations of 90%-95% may be safer than 85%-89%. The previous recommended target range of 85%-95% is no longer recommended. Guidelines by professional societies and others in many countries have been updated accordingly. Studies combining pulse oximetry with automated adjustments in Fio_2 show promise in maintaining oxygen levels within the desired range, mainly by reducing exposure to hypoxemia.[8]

Pulse Oximetry: Screening for Critical Congenital Heart Disease

About 25% of infants with critical congenital heart disease (those who require surgery or catheter intervention during the first year of life) may not be symptomatic and diagnosed until after initial discharge from the newborn nursery if oxygen saturation screening is not performed. Multiple cohort studies have shown a reasonable detection rate of critical congenital heart disease with oxygen saturation screenings. A sensitivity of around 70%-75% with a specificity and negative predictive value of about 99.9% have been reported using a cutoff oxygen saturation of usually less than 95% at greater than 24 hours after birth as abnormal.[44,71] The sensitivity is not higher because oximetry screening is less effective at identifying newborns with obstructive left heart lesions, including hypoplastic left heart syndrome, aortic stenosis, and coarctation of the aorta. Overall, pulse oximetry is highly specific for detection of critical congenital heart disease. Pulse oximetry newborn screening before hospital discharge is widely employed in the United States.

Pulse Oximetry: Perfusion Index

The perfusion index (PI), a noninvasive estimate of tissue perfusion, is obtained by comparing the pulsatile signal with the nonpulsatile signal of the oxygen saturation waveform.[58] A perfusion index of less than or equal to 1.24 has been shown to be predictive of high illness severity in newborn infants.[17]

Hyperoxia–Hyperventilation Test

The hyperoxia test aids in differentiating between primary lung disease and congenital heart disease with right-to-left shunting. The test is performed by placing the infant in 100% oxygen for 5-10 minutes followed by monitoring oxygenation by arterial blood gas or noninvasive measures (see Chapter 64). In patients with primary lung disease, oxygen should diffuse into the poorly ventilated areas and improve oxygenation by 5-10 minutes of oxygen exposure. Persistent hypoxemia after this time period would suggest the presence of right-to-left shunting.

A modification of the hyperoxia test combining hyperoxia with hyperventilation can be used to distinguish between structural congenital heart disease and primary (or persistent) pulmonary hypertension of the newborn (PPHN), both of which have right-to-left shunting. Inhalation of 100% oxygen improves oxygenation in some patients with PPHN. In response to hyperventilation with 100% oxygen ($PaCO_2$ 25-30 mm Hg), more infants with PPHN achieve PaO_2 levels higher than 100 mm Hg. In contrast, patients with anatomically fixed right-to-left shunting rarely generate a PaO_2 well above 40-50 mm Hg, even with inhalation of 100% oxygen and hyperventilation.

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Evaluation of Shunting

Desaturated blood from the right side of the heart enters the main pulmonary artery and crosses the ductus arteriosus to the descending aorta when right-to-left ductal shunting occurs. Because the ductus arteriosus almost always enters the aorta after the origin of the right subclavian and carotid arteries, blood arriving at these two sites is well oxygenated, whereas blood from the aorta, and usually the left subclavian artery, is less oxygenated if there is a right-to-left ductal shunt. Thus preductal blood gases can be obtained from the right radial artery, whereas blood in the descending aorta, and usually the left radial artery, can include blood of postductal origin. Alternatively, placement of two pulse oximeters (one on the right hand and the other on the left hand or either foot) accomplishes the same effect in differentiating preductal and postductal Pao_2 or oxygen saturation.

Patients with PPHN sometimes have right-to-left shunting through the foramen ovale and the ductus arteriosus. Ductal shunting can be demonstrated by the presence of a simultaneous oxygenation gradient between preductal and postductal arterial blood, whereas foramen ovale shunting affects both preductal and postductal oxygenation. Echocardiography can be used to confirm foramen ovale and ductal shunts.

Respiratory Function

One of the principal functions of the first breaths is to transform the fluid-filled fetal lung from a gasless organ to one with an appropriate functional residual capacity (FRC) (see Chapter 31). The ability of the lungs to maintain a volume of gas at end-expiration depends on two factors. One is the chest wall, which acts as a support for the lungs, and the other is surfactant, which stabilizes the expanded alveoli. These two factors are not well developed in the premature infant.

The mechanisms responsible for initiation of breathing probably include both environmental and physiologic stimuli. After delivery, the infant is exposed to cold and tactile environment. In addition, interactions occur among pH, P_{O_2}, and P_{CO_2}, whose contributions to inducing breathing in the human neonate have yet to be determined. Once initiated, the negative intrathoracic pressure of the first breath must overcome the effects of viscosity of fluid in the airway, surface tension, and tissue resistance. Radiographic studies of the lung indicate that inflation with air occurs immediately with the first breath. Transient retention of lung fluid might underlie transient tachypnea of the newborn (see Chapter 66). Functional residual capacity is rapidly established, with little change throughout the first week of life.

Physiologic Measurements

Tests of cardiopulmonary function performed on sick neonates can assist in diagnosis and treatment. Radiographic evaluation of the chest is an integral part of the diagnostic evaluation of respiratory disorders and is discussed in Chapter 38. Measurements of central venous and pulmonary artery pressures could indirectly give useful information regarding pulmonary function but are rarely available in the clinical neonatal setting. Knowledge of pulmonary mechanics may be useful in identifying disease entities and in guiding treatments, whereas plots of airflow, volume, and pressure may provide additional information on a breath-by-breath basis.

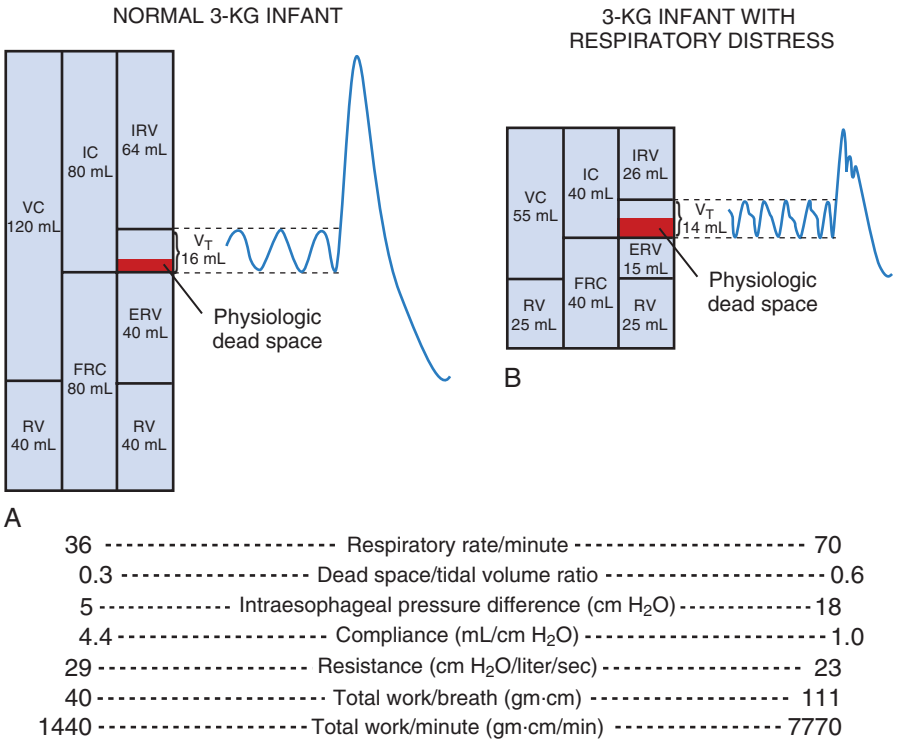
Airflow

Many devices are available for estimating airflow in infants. Noninvasive devices can be used for extended periods, yielding qualitative measurements of airflow that are sufficient for cardiorespiratory monitoring. These include devices to estimate chest wall expansion using electrical impedance, strain gauges, or respiratory inductive plethysmography and devices to estimate airflow at the nose by application of a thermistor, nasal cannula, or end-tidal CO_2 detector. These devices can give approximations of tidal volume and information regarding the presence or absence of airflow and, used in conjunction, can distinguish central from obstructive apnea. Respiratory inductive plethysmography is a noninvasive method that can be used to determine respiratory rate, timing, and asynchrony as well as estimate airflow and lung volumes. Precise quantitative measurements of airflow needed for analysis of pulmonary mechanics require an alternative group of devices placed at the nose such as a pneumotachometer or hot-wire anemometer. The pneumotachometer is the gold standard for quantitative measurement of airflow. To accurately measure flow, all air must pass through the pneumotachometer. In a ventilated patient, the pneumotachometer can be attached to an endotracheal tube with leaks minimized by repositioning the infant, using a cuffed tube, or applying gentle pressure to the neck. In a spontaneously breathing infant, the pneumotachometer must be incorporated into a nasal or oral mask that is tightly sealed around the patient's nose and mouth. The hot-wire anemometer may also become an alternate choice in the measurement of pulmonary mechanics as improvements in hot-wire anemometer design continue in terms of accuracy and response time (see Chapter 37). After reliable measures of flow are acquired, the flow signal is integrated to calculate volume.

Lung Volume

The total volume of gas in the lungs and airways can be measured and subdivided into various volumes (Fig. 63.4). The size of the lung compartments is related to the height, weight, and surface area of the subjects. *Functional residual capacity* (FRC) is the volume of gas in the lungs that is in direct communication with the airways at the end of expiration. The volume of gas in the FRC serves as an oxygen storage compartment in the body and a buffer so that large changes in alveolar gas tension are reduced. Helium dilution and nitrogen washout techniques have been adapted to

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• **Fig. 63.4** Partitioning of lung volumes and other measures of pulmonary function **(A)** in a normal infant and **(B)** in an infant with respiratory distress syndrome. ERV, Expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; VC, vital capacity; VT, tidal volume. (From Avery M, et al., eds. *The lung and its disorders in the newborn infant.* Philadelphia: Saunders; 1981, with permission.)

measure FRC in infants. The helium dilution technique uses the equilibration between a known volume and concentration of helium and the lung volume to be measured. After gas mixing and equilibration, FRC is calculated using the initial and final concentration of the helium and the initial volume of helium. Similarly, FRC can be estimated by measuring the volume of nitrogen washout from the lungs when nitrogen-free gas is inhaled.

Thoracic gas volume is the total volume of gas in the thorax at the end of expiration and, in contrast to FRC, includes gas that is not in communication with the airways (e.g., gas in pulmonary interstitial emphysema [PIE]). Thoracic gas volume is calculated by measuring pressure and volume changes during respiratory efforts against an occluded airway while the infant is inside a body plethysmograph. With an inspiratory effort, the gas in the lungs expands, the lung volume increases, and the pressure or volume in the box increases. Because the product of pressure and volume is constant, the pressure changes in the box can be used to determine the lung volume changes, which, when analyzed with the pressure changes in the airway, yield the thoracic gas volume.

Tidal volume, the volume of gas in and out of the lungs during a single breath, can be measured either with a pneumotachometer or a plethysmograph. *Vital capacity* (the total gas capacity of the lungs) cannot be measured in infants because of lack of cooperation, but crying vital capacity, the maximum volume of air expired in a single breath during crying, has been used as an alternative estimation.

Dead space, the portion of volume not involved in gas exchange, varies with the incidence of areas of high $\dot{V}/Q$. The dead space is divided into several compartments. *Anatomic dead space* is the airway volume not involved in gas exchange and is made up of the air passage from nares to terminal bronchioles. *Alveolar dead space* is the volume of gas in alveoli that are well ventilated but underperfused. *Physiologic dead space* is the sum of anatomic and alveolar dead space. In the normal newborn, physiologic dead space is 6-8 mL; smaller values are obtained in premature infants. The relationship of dead space to tidal volume (VT) is normally about 0.3. It is important to minimize the dead space added by apparatus for assisted ventilation or measurement of lung function to prevent rebreathing and inadvertent accumulation of carbon dioxide.

Pressure

Measurements of pressure that produce lung inflation are essential for pulmonary function testing. There are two ways to measure pressure, with the location of the measurement defining the system. Pressure can be determined by placing an esophageal balloon or catheter into the distal third of the esophagus. This measurement reflects pleural or alveolar pressure and is referred to as *transpulmonary pressure.* The accuracy of this measurement should be verified by demonstrating the absence of a pressure gradient between the airway and esophageal pressure tracings during airway occlusion.

In the case of mechanically ventilated patients, pressure can be measured at the airway opening. This reflects pressure of the entire respiratory system. This is equivalent to pleural or alveolar pressure plus the pressure component owing to the chest wall and is known as *transrespiratory pressure*. It is important to clarify the type of pressure measurement (transpulmonary versus transrespiratory) when

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making comparisons of respiratory mechanics between studies. As transrespiratory pressure includes the additional pressure component due to the chest wall, measurements of transrespiratory resistance (described in the following section) will always be higher when compared to transpulmonary resistance.

Respiratory Mechanics

The challenge of utilizing measures of respiratory mechanics in preterm infants in a clinical setting includes the large intersubject and intrasubject variability. The magnitude of both resistance and compliance may also be dependent on the algorithm chosen. More detailed descriptions of models used in newborn infants are shown in the following section.

Compliance

Compliance is a measure of elasticity or distensibility (e.g., of the lungs, chest wall, or respiratory system) and is defined as

$$\text{Compliance} = \frac{\Delta\text{Volume}}{\Delta\text{Pressure}}$$

Elastance is the reciprocal of compliance.

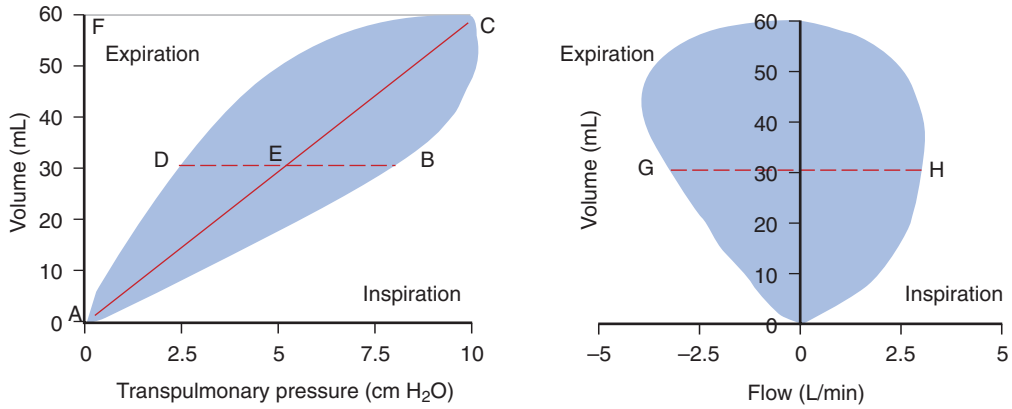
Lung compliance is measured either dynamically or statically depending on the absence or presence of relaxation of the respiratory muscles. *Dynamic lung compliance* can be measured during spontaneous breathing using devices to measure VT and esophageal pressure as described earlier. With this method, dynamic lung compliance is calculated by dividing the change in VT by the corresponding change in esophageal pressure at points of no airflow (e.g., between end-inspiration and end-expiration). This is represented by the line drawn from point C to point A in Fig. 63.5. End-inspiration and end-expiration are used as quasi static points of reference for pressure equilibration. At high respiratory rates or increased levels of resistance, pressure does not equilibrate between these two points, resulting in an underestimation of the true compliance.

Alternatively, *static lung compliance* can be calculated between points of no flow when the respiratory muscles are relaxed by employing occlusion of the airway. This allows for complete equilibration of pressure throughout the system. During the occlusion, static respiratory system compliance can be calculated by dividing the total exhaled volume by the pressure change during the occlusion minus the pressure at end-expiration (Fig. 63.6). An important advantage of this technique is that it does not require an esophageal balloon to measure pressure.

Both dynamic and static compliance, using a single occlusion, assume that compliance is constant throughout the breath. This may not be the case during periods of lung disease or overdistention of the lung during mechanical ventilation. Under these conditions, dynamic compliance underestimates the true compliance. True changes in compliance throughout a breath can be determined by expanding the single occlusion technique to include multiple brief interruptions during the expiratory phase of a breath, also known as the *multiple-interruption technique* (Figs. 63.7 and 63.8).[63] Using this technique, a decrease in compliance can be seen with increasing pressure as the lung becomes overdistended. In mechanically ventilated infants, compliance measurements should be acquired at the same PEEP and peak inspiratory pressure (PIP) to obtain values at the same section of the pressure-volume curve.

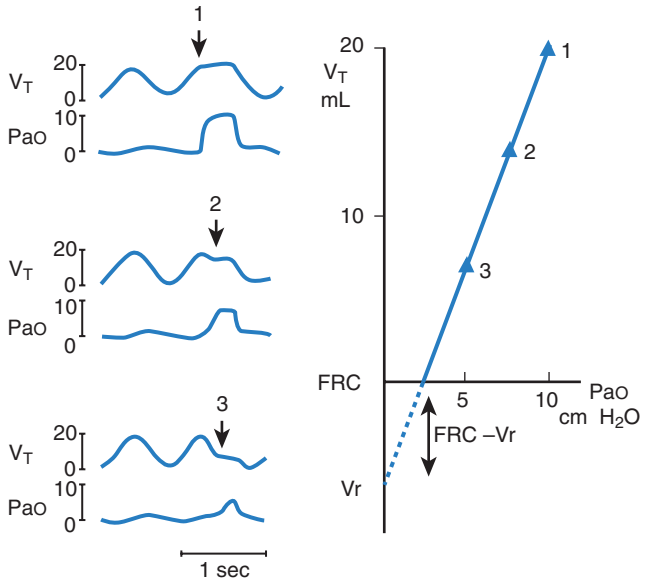
Because lung elasticity depends on lung volume, changes in FRC can alter lung compliance. The degree of elasticity corrected for lung volume or patient size is called *specific compliance*. Whereas specific lung compliance in the normal neonate (1-2 mL/cm H_2O per kilogram) is comparable with that of the adult when corrected for unit body weight, compliance of the chest wall is relatively much higher in infants.

In addition to compliance, expiratory occlusion can also be used to determine the lung volume above the relaxation volume of the respiratory system (see Fig. 63.6). Expiratory volume clamping is a modification of the occlusion technique in which exhalation is prevented during several

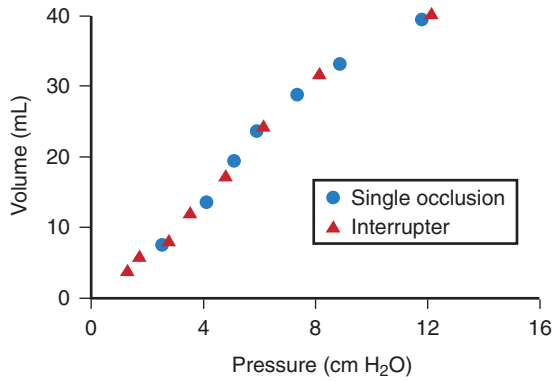


• **Fig. 63.5** Dynamic lung compliance can be calculated as the Δ volume/Δ pressure as shown by the slope of line AC. Work of breathing is represented as the area inside the section drawn by ABCFA. Resistance (using the Mead-Whittenberger technique) can be calculated as the change in pressure, shown by the difference between points D and B, divided by the change in flow, shown by the difference between points G and H at the same midvolume points.

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• **Fig. 63.6** Schematic representation (from actual records) of the changes in lung volume (V_T in milliliters) and airway pressure (Pao in cm H_2O) during one spontaneous breath and occlusion of the airways during the expiratory phase of the following breath in a ventilated infant. In the three examples shown, occlusion is performed (from top to bottom) at end-inspiration, in the first third of expiration, and in the last third of expiration. After the occlusions (indicated by *arrows*), Pao gradually rises to a plateau, corresponding to the recoil value of the respiratory system at that lung volume. *Right*, Plot of the changes in lung volume above the end-expiratory level (FRC) against the corresponding changes in Pao as obtained in the left panel. The slope of the function represents the compliance of the respiratory system, the intercept on the Pao axis represents the internal recoil of the respiratory system at FRC, and the intercept of the V_T axis represents the resting volume of the respiratory system (Vr). (From Mortola JP, et al. Measurements of respiratory mechanics in the newborn: a simple approach. *Pediatr Pulmonol.* 1987;3:123. With permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)



• **Fig. 63.7** A typical example of the volume-pressure relationships obtained with both the interrupter and single occlusion techniques. Each point represents the compliance at that particular volume within the breath.

breaths at increasing lung volumes. After plotting the corresponding volumes and pressures acquired during each occlusion, the slope of the function represents the compliance of the respiratory system. In addition, the intercept along the volume axis represents the resting volume of the respiratory system.

In neonates, lung compliance is the most important component, because the chest wall is very distensible. Lung compliance is low at the initiation of the first breath even in normal newborns. With the establishment of breathing and with gradual clearance of lung fluid during the first 3-6 hours after birth, FRC increases with concomitant improvement in lung compliance. Pathophysiologic factors that can increase the amount of fluid or impede the clearance of lung fluid could delay this improvement. The variability of compliance values in the first 2 hours after birth, in part the result of physiologic variation, could account for the frequent observations of higher respiratory rates in some infants during this period.

In distressed infants in whom lung compliance is markedly reduced, the compliant chest wall poses a disadvantage in that, as the infant attempts to increase negative intrathoracic pressure, the chest wall collapses (retracts). In addition, the more compliant neonatal airways could predispose the preterm infant to airway collapse during expiration and result in distal gas trapping.

Resistance

Pulmonary resistance is a measure of the friction encountered by gas flowing through the nasopharynx, trachea, and bronchi and by tissue moving against tissue. The basic definition of resistance states

$$\text{Resistance} = \frac{\Delta\text{Pressure}}{\Delta\text{Flow}}$$

Conductance is the reciprocal of resistance. Both airway resistance (the resistance caused by the airways) and viscous resistance (the resistance caused by tissues) contribute to total pulmonary resistance.

The most commonly used algorithm to calculate resistance in commercial devices for infants is the multiple linear regression technique also known as the *equation of motion* or *Rohrer's equation*.

The *equation of motion* defines the relationship between pressure, flow, volume, and the elastic, resistive, and inertial components of the respiratory system. It is represented as

$$P = \frac{1}{C} \times V + R \times \dot{V} + I \times \ddot{V}$$

where P is the pressure that produces lung inflation, C is compliance, V is volume, R is resistance, $\dot{V}$ is flow, I is inertance, and $\ddot{V}$ is acceleration. Because the inertial component is considered negligible for clinical considerations, the equation of motion is further simplified with the inertial component often dropped from the equation. This equation assumes a linear relationship that is not usually the case in the preterm infant. Yet, although not optimal, as nonlinear models have not led to improvements in clinically applicable values for respiratory mechanics, the equation of motion continues to be the mode of choice in the clinical and research setting.

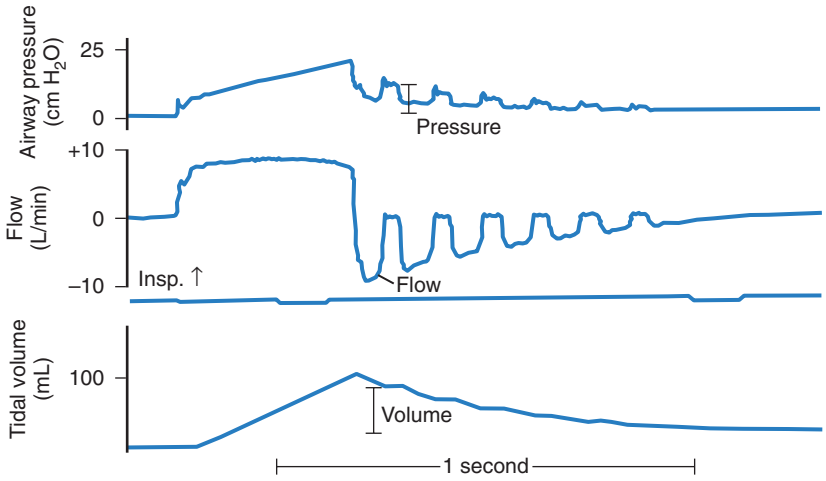
The *Mead-Whittenberger technique* uses the pressure-volume and flow-volume loops generated from pressure,

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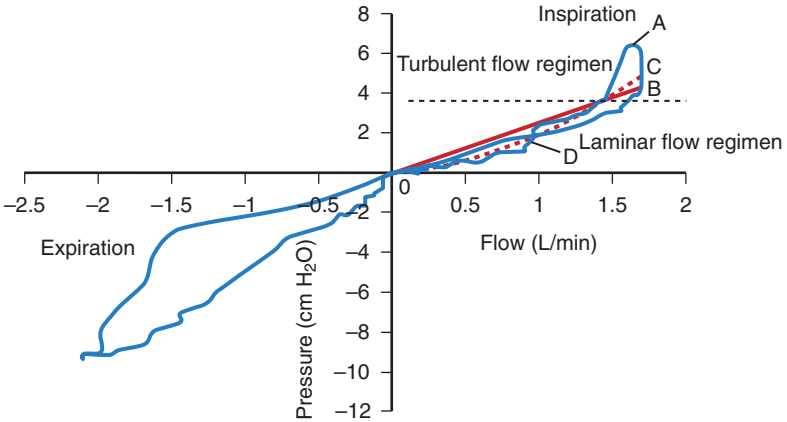
volume, and flow waveforms. By convention, resistance is calculated by dividing the change in pressure by the change in flow at the midvolume point of the breath (see Fig. 63.5). Resistance can be measured at additional volumes throughout the breath by using the *occlusion or multiple-interruption technique* as described earlier. In this case, resistance is calculated by dividing the pressure during the occlusion by the flow immediately preceding the occlusion (see Fig. 63.8). These points of pressure and flow can be plotted to represent resistance over a range of volumes throughout the breath. Furthermore, this technique can be used to partition the components of resistance into those due to airflow and those owing to viscous tissue resistance.

The model-dependent effects on resistance for a single breath are shown in Fig. 63.9. The Mead-Whittenberger technique gives the resistance at one point during the breath at midvolume, which approximates peak inspiratory flow. This will correspond to the highest value for resistance for a given breath. The equation of motion uses linear regression to acquire the best fit corresponding to an average overall resistance for the breath. The multiple-interrupter technique can be used to reveal changes in resistance within the breath by plotting multiple pressure and flow points for each breath (where Res = P/F at each point).

Possible conflicting values of resistance between multiple algorithms for the same breath are primarily owing to the presence or absence of a turbulent flow pattern. During periods of low pressure, the frictional contribution of the airway walls is minimized, the corresponding flow regimen is laminar, and the assumption that resistance is constant throughout the breath holds true (see Fig. 63.9). Under these conditions, the deviation among techniques is minimized. As the pressure increases further, the frictional contribution of the airway walls and the divergence of flow caused by branching of the smaller airways are no longer negligible. During this time the flow regimen changes from laminar to turbulent with a minimal increase in flow. In extreme cases, a point of flow limitation will occur where increasing pressure will be accompanied by no increase in flow. This is a common occurrence in both spontaneously breathing infants with lung disease and mechanically ventilated infants. During a turbulent flow regimen, resistance is no longer constant throughout the breath and is dependent on the technique used. Although discrepancies between algorithms have limited the application of resistance as a diagnostic tool in the clinical setting, useful information can be derived by using multiple techniques to compare breaths before and after an intervention. For example, a resistance measurement extrapolated from the linear portion of the pressure-flow curve will give information on changes in the mechanical structure of the airways (i.e., was there dilatation of the airway?). In contrast, resistance measurements



• **Fig. 63.8** Illustration of data collected with the interrupter technique. The top channel is airway pressure proximal to the interrupter valve. The middle and bottom channels represent flow and volume, respectively. Compliance is calculated by dividing the volume above the end-expiratory level by the pressure during the occlusion. Resistance is calculated by dividing this pressure by the flow that preceded the interruption.



• **Fig. 63.9** During a laminar flow regimen, resistance is constant throughout the breath and discrepancies between various techniques of measuring resistance are minimized. As the flow regimen changes from laminar to turbulent, resistance is no longer constant throughout the breath and becomes flow dependent. During this time, values of resistance between various techniques begin to diverge: **A,** Mead-Whittenberger (200 cm H_2O/L/sec); **B,** linear regression (152 cm H_2O/L/sec); **C,** nonlinear regression (32 cm H_2O/L/sec); and **D,** the linear portion of the curve (106 cm H_2O/L/sec). (From Di Fiore JM, et al. Respiratory function in infants. In: Haddad G, et al., eds. *Basic mechanisms of pediatric respiratory disease.* Toronto: Decker; 2002:165.)

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during the nonlinear portion of the pressure-flow curve will provide information on changes in resistance caused by dynamic flow patterns (i.e., did increasing PIP result in more turbulence in the airway?).

Time Constant

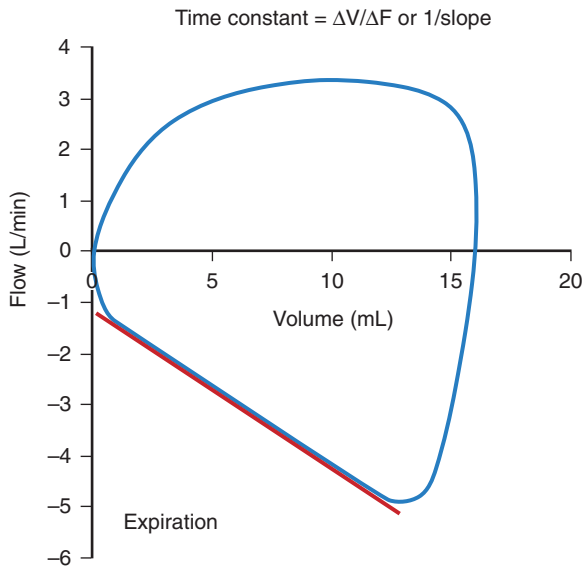
The *time constant* of the respiratory system is the duration (expressed in seconds) necessary for a step (e.g., pressure or volume) change to partially equilibrate throughout the lungs. A duration equivalent to one time constant allows for 63% of the equilibration of the change. Although one time constant is not a very useful parameter in the clinical environment, five time constants are equivalent to the amount of time needed for 99% equilibration of the system. This value can be useful in areas of patient care such as mechanical ventilation (see Chapter 65).

The time constant of the respiratory system can be calculated by using the relationship between the time constant, resistance, and compliance:

$$\text{Time Constant} = \text{Resistance} \times \text{Compliance}$$

Because both compliance and resistance are affected by different volumes and flows or by pulmonary disease, pulmonary mechanics change throughout the respiratory cycle, and a single time constant may not always accurately represent lung mechanics. However, for clinical purposes, linearity is assumed, and single values of compliance, resistance, and time constant usually suffice.

If resistance and compliance values are unknown, the time constant of the respiratory system can also be obtained from the flow-volume plot acquired during a passive exhalation. With this plot, 1/slope during the expiratory phase of the breath is equivalent to the time constant of the respiratory system (Fig. 63.10). Calculation of the time constant using the flow-volume curve assumes that the slope is linear



• **Fig. 63.10** The time constant of a breath can be represented by the change in volume divided by the change in flow during the expiratory phase of the breath.

throughout expiration. Flow limitation—as may occur with bronchoconstriction during expiration, postinspiratory activity of the respiratory muscles, or laryngeal adduction—can be identified by convexity toward the volume axis.[70] In this case, calculations of a single time constant are no longer valid. Although a numerical value for time constant cannot be accurately determined under these conditions, X-Y plots of flow and volume can be used to qualitatively characterize pulmonary function. Normal and abnormal flow-volume loops can be used to identify infants with airflow limitation patterns (Fig. 63.11).[13]

Forced Expiratory Maneuvers

There is increased interest in long-term airway reactivity and wheezing in preterm infants.[14] Measures of airway reactivity are most commonly quantified by the use of forced expiratory maneuvers. The maximal expiratory flow-volume relationship can be measured in uncooperative infants by using a respiratory jacket or cuff placed around the chest and abdomen that is suddenly inflated at the end of lung inflation to produce rapid thoracoabdominal compression and forced expiratory flow. Alternatively, sudden exposure of the inflated lung to a negative pressure at the airway opening can be used to produce a forced deflation. During this maneuver, peak expiratory flow, maximal flow at 1 sec (FEV_1) or at FRC, and the patterns of flow-volume curves can be measured using a pneumotachograph. Flow-volume curves can be used to evaluate intrathoracic airway abnormalities and can detect flow limitation missed by the passive expiratory techniques.[54]

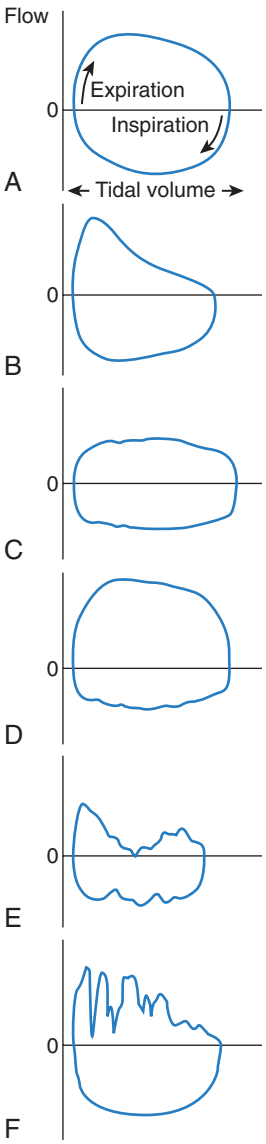
Forced Oscillation Technique

The forced oscillation technique (FOT) has the advantage of assessing lung function in a noninvasive manner by applying external pressure or flow-based excitation superimposed on spontaneously breathing or mechanically ventilated infants under apneic conditions. The FOT presents a measure of respiratory system impedance (Z), encompassing a real (resistance) and imaginary (reactance) component, which together summarize the dissipative and energy-storing properties of the respiratory system. Limited FOT data are available in preterm and wheezy infants.[54]

Work of Breathing

The work of breathing is a measure of the energy expended in inflating the lungs and moving the chest wall. In general terms, work is the cumulative product of pressure and the volume of gas moved at each instant. In the normal infant, total pulmonary work has been determined to equal an average value of 1440 g/cm per minute. In an infant with respiratory distress, the total pulmonary work can increase as much as sixfold. This becomes most important when considered in terms of the oxygen cost of breathing. The neonate requires a higher caloric expenditure to breathe than does the adult, and the distressed infant requires an even higher caloric expenditure for this function. In the full-term infant, the work of breathing is minimal when

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• **Fig. 63.11** Examples of the relationship between tidal flow and volume. **A,** Normal lemon-shaped loop; **B,** ski-slope loop observed with expiratory airflow limitation as seen in babies with bronchopulmonary dysplasia (BPD); **C,** cigar-shaped loops observed in babies with extrathoracic airway obstruction with inspiratory and expiratory airflow limitation as seen in babies with subglottic stenosis or narrow endotracheal tubes; **D,** bun-shaped loop observed in babies with intrathoracic inspiratory airflow limitation as seen in babies with intraluminal obstruction (close to the carina) or an aberrant vessel compressing the trachea; **E,** crumpled loop as observed in babies with unstable airways or tracheomalacia; and **F,** mountain-peaks loop is usually suggestive of an erratic airflow limitation as seen with airway secretions.

the infant has a respiratory rate of 30 breaths per minute. The pressure-volume loop can be used to calculate work of breathing as represented by the area inside the section drawn by ABCFA in Fig. 63.5.

Limitations

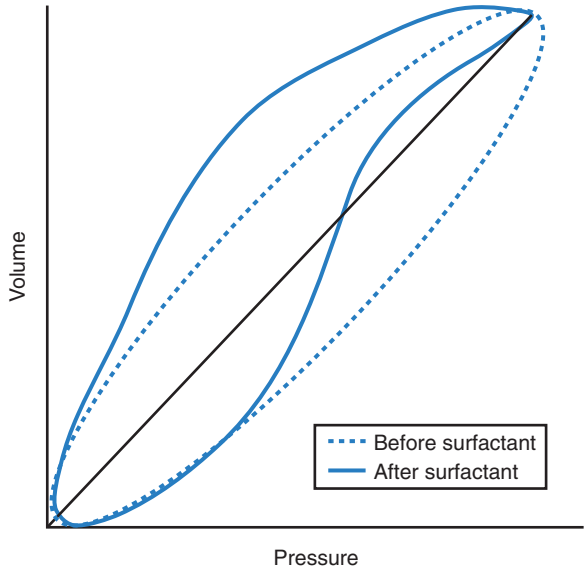
Before any measurements of pulmonary function can be made, a clear understanding of equipment performance is needed. Although beyond the scope of this chapter, a clear adherence to these guidelines is imperative to ensure that lung function measurements can be performed with an acceptable degree of safety, precision, and reproducibility.[28] Once data are acquired, there are a multitude of algorithms for measuring pulmonary mechanics available. As no algorithm is ideal, standards are available addressing a range of issues from equipment criteria[28,29] to testing procedures.[11,52,64,66] A review of the techniques for measuring pulmonary mechanics and function has been published by the American Thoracic Society and the European Respiratory Society.[1]

Because various algorithms yield different results for the same breath, a wide range of published values for any given patient population has resulted, making it extremely difficult to define ranges for comparison between normal and diseased states. Compounding the issue is the large intrasubject variability of compliance and resistance, which is minimized during mechanical ventilation. This is most likely caused by muscle relaxation and reduced fluctuations in respiratory rate and tidal volume compared with spontaneous respiration.

During mechanical ventilation, leaks around the endotracheal tube, a common occurrence in the neonatal intensive care unit setting, can result in overestimation of resistance and underestimation of elastance. This error is minimized during the expiratory phase of the breath. A leak of less than 10%-20% between the inspiratory and expiratory volume is generally considered acceptable to obtain reliable measurements of resistance and compliance.[41,45] Given these limitations, measurements of resistance and compliance during the expiratory phase of mechanical breaths with a leak of less than 10% should give the most precise and reproducible values.

Additional confounders that affect respiratory mechanics include sleep state,[56] posture,[12] endotracheal tube size,[47] FRC,[31] laryngeal braking,[33] gender,[67] race,[67] and respiratory patterns.[30] Errors in data calculation or interpretation can also occur if there are no compensatory modifications in mechanical ventilator settings in response to changes in lung function. This can occur because of overdistention of the lung as compliance improves in response to therapy if PIP is not decreased accordingly. As pressure-volume and flow-volume curves become more readily available on mechanical ventilators, they may become a useful tool, with or without measurements of respiratory mechanics, in distinguishing changes in pulmonary function. Fig. 63.12 shows a simulation of a pressure-volume curve for a mechanically ventilated infant before and after surfactant administration with no change in peak inspiratory pressure. A numerical representation for dynamic compliance would show no change in compliance in response to surfactant administration. In contrast, visualization of the graph reveals improvement in compliance at low pressures but overdistention of the lung at high pressures as the peak inspiratory pressure was not decreased.

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• **Fig. 63.12** A representation of the change in compliance in response to surfactant administration. Note that dynamic compliance, as represented by the line, reflects no change. In contrast, visualization of the graph shows improvement in compliance at low volumes and overdistention of the lung after surfactant administration, indicating the need to decrease peak inspiratory pressure.

Clinical Applications

The goal of respiratory support is to optimize oxygenation and CO_2 elimination with the lowest possible ventilator settings to minimize lung injury. The use of pulmonary function testing can be a valuable tool in achieving this goal and reducing the incidence of barotrauma.[57] Visualization of pressure-volume curves and measurements of compliance can be used to assist in identification of excessive PIP or PEEP, leading to lung overdistention,[26] and to distinguish between alveolar collapse and overdistention to assist in determining the most advantageous PEEP.[10] High compliance and low resistance have also been shown to be associated with the likelihood of extubation success in infants recovering from RDS.[6]

Pulmonary function measurements have been used to assess mechanical effects of pharmacologic interventions. To optimize the response, changes in resistance have been used to compare treatment modalities, with the meter-dosed inhaler and ultrasonic nebulizer being shown as superior modes of bronchodilator administration.[27] Although surfactant results in rapid improvement of gas exchange, early beneficial effects on respiratory mechanics have been shown in some studies[16] but other studies report variable responses. There has been interest in the effect of nitric oxide (NO) on the incidence of chronic lung disease. Although beneficial effects of NO are dependent on dose, time of administration, and disease severity, there is currently no evidence that NO leads to improvement in baseline respiratory mechanics.[4,18] However, infants who received inhaled NO for PPHN had maximal expiratory flows comparable to those who were treated with extracorporeal membrane oxygenation (ECMO) but lower flows than control subjects.[38] Inhaled NO to prevent BPD has resulted in decreased need for bronchodilator therapy at 1 year of age.[37] Inhaled NO reduced death or need for extracorporeal membrane oxygenation in term and near-term infants but did not reduce BPD or death in preterm infants.[9,15] Both postnatal and antenatal steroids enhance lung function,[5,49] although there is a diminished response to antenatal steroids if delivery occurs more than 7 days after therapy.[50] Last, diuretic administration has been shown to enhance lung function.[23,39] Interestingly, improvements in resistance and compliance did not always correlate with better oxygenation.[23]

Respiratory mechanics have been employed in longitudinal studies to evaluate the clinical course of pulmonary diseases. The occurrence of meconium aspiration syndrome during infancy has been associated with alveolar hyperinflation and airway hyperreactivity to exercise at 7 ± 2 years of age.[22] Measurements of pulmonary mechanics at 1-year follow-up showed no difference between survivors in trials of high-frequency ventilation versus conventional ventilation.[72,73] However, during adolescence, former preterm infants who were randomized to high-frequency oscillatory ventilation had improved respiratory function in several measures, including FEV_1, forced vital capacity, peak expiratory flow, diffusing capacity, and impulse-oscillometric findings.[77] Hypoxemic respiratory failure has been linked with an increased risk for impaired pulmonary function, particularly in the presence of congenital diaphragmatic hernia or ECMO.[46] Decreases in FRC, compliance, and conductance have been shown to be predictive of BPD,[13,34,43] with gradual improvements in this cohort as the lungs grow.[32,59] Therapeutic agents in evolving or established BPD (i.e., diuretics, bronchodilators, and steroids) have been shown to have short-term benefits on resistance and compliance, but potential adverse side effects limit their use in neonates.[35] Because BPD is a manifestation of prolonged oxygen exposure or barotrauma, pulmonary function measurements and graphical displays may be most helpful in this area to minimize ventilator settings and duration of ventilatory support.

Evidence suggests that preterm birth alone may have long-term adverse effects on pulmonary function. For example, former preterm infants have deficits in FEV_1 at both 8 and 16 years of age,[74] and this impairment can occur even in those who do not develop BPD.[42] Pulmonary function testing in children with a history of BPD shows persistent abnormalities in clinical moderate expiratory flow obstruction.[25] About 25%-50% of very low birth weight infants and over 50% of children born at less than 26 weeks of gestation continue to have abnormal spirometry as preadolescents.[24,53] Many have asthma and respond to bronchodilators. Increased pulmonary arterial resistance is also common during infancy in infants who develop BPD. However, survivors of BPD have comparable right and left ventricular function at 8-12 years of age when

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compared to preterm and term children without evidence of increased pulmonary arterial pressure even after hypoxic exposure.[68]

Even with the current limitations in methodology and confounders in the area of pulmonary function, diagnostic evaluations can be a useful tool in neonatal patient care. Ideally, clinical evaluation should include both numerical values for resistance and compliance in addition to visualization of flow-volume, pressure-volume, and pressure-flow curves. Application of these tools for pulmonary function measurements should complement clinical assessment in the care of infants with pulmonary disorders.

Key Points

- Methods developed to evaluate pulmonary function in neonates include physical signs, cardiovascular assessment, and physiologic measurements.
- Pulse oximetry and blood gas measurements are the most widely used clinical methods for assessing pulmonary function in neonates and form the basis for diagnosis and management of cardiorespiratory disease.
- Knowledge of pulmonary mechanics may be useful in identifying disease entities and in guiding treatments, whereas plots of airflow, volume, and pressure may provide additional information on a breath-by-breath basis.

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64

Respiratory Distress Syndrome in the Neonate

MEGAN LAGOSKI, AARON HAMVAS, AND JENNIFER A. WAMBACH

Enormous strides have been made in understanding the pathophysiology of respiratory distress syndrome (RDS) and the role of surfactant in its cause and treatment (see Chapter 62). Nevertheless, RDS, formerly referred to as hyaline membrane disease, remains a dominant clinical problem despite the introduction of pharmacologic acceleration of pulmonary maturity using antenatal corticosteroids and the development of surfactant replacement therapy.[31,67]

Because more of the sickest, most immature infants are surviving,[90] the incidence of complications in the survivors of RDS remains significant. These include intracranial hemorrhage, patent ductus arteriosus (PDA), pulmonary hemorrhage, sepsis, and bronchopulmonary dysplasia (BPD) as discussed later. It is often impossible to determine whether these disorders are the sequelae of RDS, its treatment, or the underlying prematurity. In this section, the clinical features and evaluation of infants with RDS are discussed, and therapeutic approaches other than assisted ventilation (see Chapter 65) are outlined.

Incidence

Respiratory distress syndrome is one of the most common causes of morbidity and mortality in preterm neonates, although lack of a precise definition among infants with very low birth weight necessitates cautious interpretation of statistics regarding incidence, mortality, and outcome.[10,65] The diagnosis can be established pathologically or by biochemical documentation of surfactant deficiency; nonetheless, most series refer only to a combination of clinical and radiographic features. Without biochemical evidence of surfactant deficiency, it is difficult to clinically diagnose RDS in infants with extremely low birth weight. The term *respiratory insufficiency of prematurity* had been used in some centers for infants who require oxygen and ventilator support in the absence of typical radiographic evidence of RDS. More recently, the term *respiratory instability of prematurity* has been proposed to describe very low birth weight infants who require some respiratory support but may have additional contributing factors such as inconsistent central respiratory drive or poor inspiratory effort.[10]

Respiratory distress syndrome occurs throughout the world and has a slight male predominance.[4] The greatest risk factors appear to be young gestational age and low birth weight; however, European descent, late preterm delivery (35-36 weeks), or elective delivery in the absence of labor are also prominent risk factors.[4,73,118] Given the associated adverse respiratory outcomes of late preterm and early term births, initiatives to delay elective deliveries until 39 weeks' gestation have been successful in reducing pulmonary and nonpulmonary morbidity in these infants.[28,105] Other risk factors include maternal diabetes and perinatal hypoxia-ischemia.

The incidence of RDS is inversely proportional to gestational age: nearly all infants born at 22-24 weeks' gestation have RDS,[100] decreasing to approximately 25% in infants with birth weights between 1251 and 1500 g.[32,101] Even infants of 34 weeks' gestation and greater, especially males of European descent, have a discernible risk of RDS that decreases from ~10% at 34 weeks to less than 1% at 37 weeks (Fig. 64.1).[4]

Pathophysiology

The lungs of infants who succumb from RDS have a characteristic uniformly ruddy and airless appearance, macroscopically resembling hepatic tissue. On microscopic examination, the striking feature is diffuse atelectasis such that only a few widely dilated alveoli are readily distinguishable (Fig. 64.2). An eosinophilic membrane lines the visible airspaces that usually constitute terminal bronchioles and alveolar ducts. This characteristic membrane (from which the term *hyaline membrane disease* is derived) consists of a fibrinous matrix of materials derived from the blood and contains cellular debris derived from injured epithelium. The recovery phase is characterized by regeneration of alveolar cells, including the type II cells, with a resultant increase in surfactant activity. The development of RDS begins with impaired or delayed surfactant synthesis and

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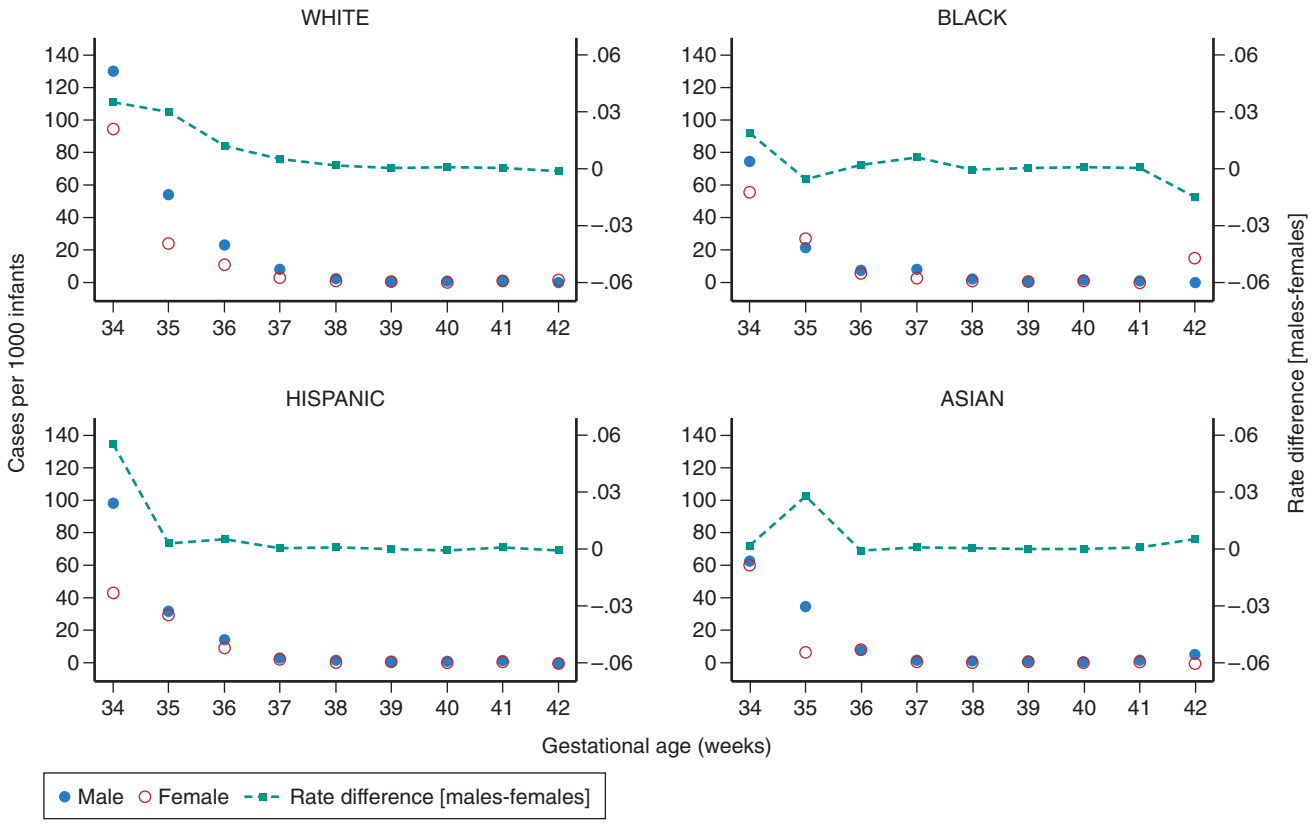
Abstract

Respiratory distress syndrome (RDS), formerly referred to as hyaline membrane disease, is one of the most common causes of morbidity and mortality among preterm infants. RDS results from a developmental deficiency of pulmonary surfactant production, and the incidence of RDS is inversely proportional to gestational age, affecting the majority of infants born less than 32 weeks' gestation. Late preterm status, male sex, European-descent ethnicity, maternal diabetes, cesarean section without labor, and genetic variants also contribute to disease risk. Infants with RDS typically present shortly after birth with clinical symptoms, including grunting respirations, tachypnea, chest retractions, nasal flaring, cyanosis, and increased oxygen requirement. Chest radiograph typically demonstrates a homogeneous, reticulogranular pattern with superimposed air bronchograms. Treatment includes delivery of positive pressure to maintain airway and alveolar expansion through invasive (intubation and mechanical ventilation) or noninvasive support (nasal continuous positive airway pressure), supplemental oxygen, exogenous surfactant therapy, and careful monitoring of gas exchange. Despite the use of pharmacologic acceleration of pulmonary maturity using antenatal corticosteroids, the development of exogenous surfactant replacement therapy, and invasive and noninvasive modes of respiratory support, RDS remains a dominant clinical problem in neonatology.

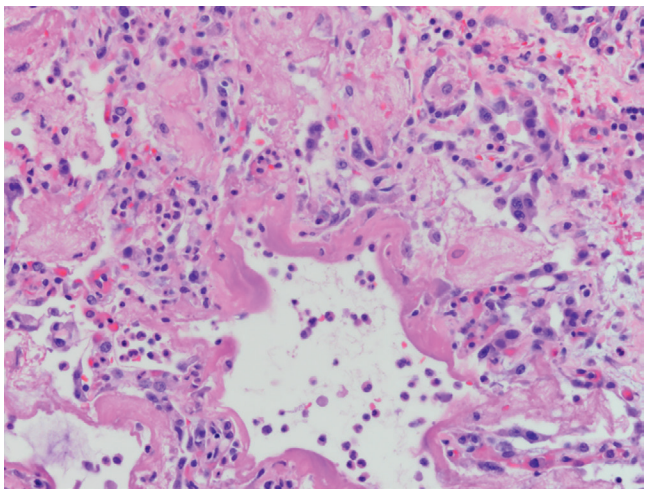
Keywords

respiratory distress syndrome
RDS
surfactant
hyaline membrane disease
HMD

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• **Fig. 64.1** Race and sex-specific risk of respiratory distress syndrome by gestational age (*circles*, left y-axis) and absolute difference in risk between sexes (*dashed line*, right y-axis) for infants born at 34 weeks and greater. White males have an increased risk of respiratory distress syndrome up to 38 weeks. (From Anadkat JS, Kuzniewicz MW, Chaudhari BP, et al. Increased risk for respiratory distress among white, male, late preterm and term infants. *J Perinatol*. 2012;32:780-785.)



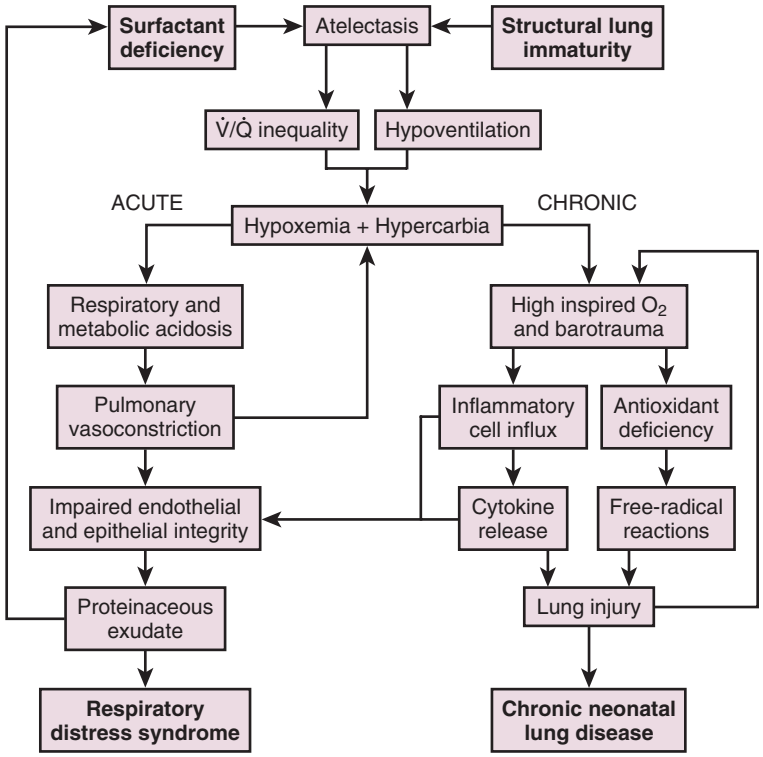
• **Fig. 64.2** Histologic appearance of the lungs in an infant with respiratory distress syndrome. Note the marked atelectasis and so-called hyaline membranes lining the dilated alveolar ducts.

secretion followed by a series of events that may progressively increase the severity of the disease for several days in the absence of exogenous surfactant replacement (Fig. 64.3). Surfactant synthesis is a dynamic process that depends on factors such as pH, temperature, and perfusion and may be compromised by cold stress, hypovolemia, hypoxemia, and acidosis. Other unfavorable factors, such as exposure to high inspired oxygen concentration and the effects of barotrauma and volutrauma from assisted ventilation, can trigger the release of proinflammatory cytokines and chemokines and further damage the alveolar epithelial lining, resulting in reduced surfactant synthesis and function. The leakage of proteins such as fibrin in the intra-alveolar space further aggravates surfactant deficiency by promoting surfactant inactivation. Deficiency of surfactant and the accompanying decrease in lung compliance lead to alveolar hypoventilation and ventilation-perfusion (V/Q) imbalance.

Severe hypoxemia and systemic hypoperfusion result in decreased oxygen delivery with subsequent lactic acidosis secondary to anaerobic metabolism. Hypoxemia and acidosis also result in pulmonary hypoperfusion secondary to pulmonary vasoconstriction, and the result is a further aggravation of hypoxemia due to right-to-left shunting at the level of the ductus arteriosus, the foramen ovale, and within the lung itself.

The relative roles of surfactant deficiency and pulmonary hypoperfusion in the overall clinical picture of RDS vary somewhat with each patient. The natural history of RDS is now almost invariably altered by a combination of antenatal corticosteroid administration, exogenous surfactant

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• **Fig. 64.3** Schematic representation of the complex series of acute and chronic events that lead to neonatal respiratory distress syndrome and the accompanying lung injury secondary to therapeutic intervention in these infants.

therapy, assisted ventilation, and in some cases, intrauterine inflammation.

Heritability of Respiratory Distress Syndrome

A genetic contribution to the risk of RDS has been suggested in twin studies where the concordance of RDS in monozygotic twins is greater than that in dizygotic twins and with isolated reports of recurrence in families.[69,81,94] With the application of molecular techniques, the contribution of genetic variations to the pathogenesis of respiratory disorders in newborns is rapidly emerging.[71,109]

Pathogenic mutations in genes encoding surfactant protein-B (SP-B, *SFTPB*), surfactant protein-C (SP-C, *SFTPC*), the ATP binding cassette subfamily A, member 3 (ABCA3, *ABCA3*), and the thyroid transcription factor (TTF-1, *NKX2-1*) represent rare monogenic causes of RDS.[49,83,84,95] Inherited SP-B deficiency is a recessive disorder that presents as severe respiratory failure in the immediate newborn period and is unresponsive to standard neonatal intensive care interventions. With a disease frequency of approximately 1 per million live births, the absence of SP-B, the presence of an incompletely processed proSP-C, and a generalized disruption of surfactant metabolism cause surfactant dysfunction and the clinical syndrome. Dominant mutations in *SFTPC* are present in significantly less than 0.1% of the population[42,109] and typically result in interstitial lung disease in infants older than 1 month of age, although an "RDS-like" presentation has been described.[17]

The accumulation of misfolded proSP-C within cellular secretory pathways results in activation of cell stress responses and apoptosis and impaired surfactant function.[80] Monoallelic, predicted deleterious variants in *ABCA3* are present in approximately 2%-4% of the population[109] and biallelic (recessive) mutations have been identified in association with progressive respiratory failure in newborns and with chronic respiratory insufficiency and interstitial lung disease in children.[26,95,108] Accumulating experience suggests that ABCA3 deficiency may be the most common of these disorders of surfactant homeostasis. Data from humans and mice suggest that ABCA3 mediates surfactant phospholipid transport (primarily phosphatidylcholine and phosphatidylglycerol) into lamellar bodies, and thus dysfunction of phospholipid transport into the lamellar body leads to reduced surfactant function.[36,41,45,75] Dominant mutations in *NKX2-1* were first identified in the context of benign hereditary chorea but since then have also been recognized in lethal and nonlethal neonatal RDS as well as interstitial lung disease in older children.[25,49,113] A triad of neurologic disease, characterized by hypotonia, developmental delay and movement disorders, congenital hypothyroidism, and RDS has been termed the *brain-thyroid-lung syndrome*, but any single organ presentation or combination thereof may be the initial and only manifestation of the syndrome.[49] Mutations in *NKX2-1* are rare, but the frequency of disease is unknown. Disruption in structural lung development and/or decreased expression of surfactant-associated genes are the postulated mechanisms of disease.

Large-scale cohort-based resequencing efforts have demonstrated an over-representation of monoallelic, predicted

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deleterious variants in *ABCA3* in newborns 34 weeks and greater with RDS, suggesting that these mutations are modifiers for the risk or severity of respiratory disease in developmentally susceptible newborns.[42,82,109,114] These efforts have failed to identify an unequivocal contribution of rare or common variants in the surfactant protein-B or -C genes to RDS in newborns, suggesting that if these genes play a role in RDS, it is likely to be through interactions with variants in other lung-associated genes.[50,109] Exome and genome sequencing are becoming more accessible and will yield additional insights into candidate genes that account for the heritability of RDS.[61,71]

Prevention: Pharmacologic Acceleration of Pulmonary Maturation

In the early 1970s, Liggins, while studying the effects of steroids on premature labor in lambs, noticed the lack of RDS and increased survival in preterm animals prenatally exposed to steroids. The effects of various catecholamines as well as aminophylline and thyroid hormone have been studied; however, the most successful method to induce fetal lung maturation is prenatal corticosteroid administration (see Chapter 62).[72]

If premature delivery of any infant appears probable or necessary, lung maturity can be hastened pharmacologically. Accelerated lung maturation occurs with physiologic stress levels of corticosteroids via receptor-mediated induction of specific developmentally regulated proteins, including those associated with surfactant synthesis. Steroids, when administered to the mother at least 24-48 hours before delivery, decrease the incidence and severity of RDS.[87] Corticosteroids appear to be most effective before 34 weeks of gestation and when administered at least 24 hours and no longer than 7 days before delivery. Because corticosteroid therapy for less than 24 hours is still associated with significant reductions in neonatal mortality, RDS, and intraventricular hemorrhage (IVH), antenatal steroids should always be considered unless immediate delivery is anticipated.[21] While antenatal corticosteroids have routinely been administered to women at risk for preterm delivery before 34 weeks' gestation since the 1990s, recent data suggest that late preterm infants born at 34-36 weeks' gestation may also benefit.[47] Late preterm infants exposed to antenatal betamethasone are less likely to require respiratory support after birth; however, they require close monitoring for hypoglycemia.[47] While preterm infants as early as 23 weeks' gestation may benefit from antenatal corticosteroid exposure, their use before 23 weeks' gestation remains controversial.[18,110]

Less clear are the effects of repeated courses of antenatal corticosteroids on the short- and long-term outcomes of preterm infants. Decreased fetal growth and poorer neurodevelopmental outcomes have been reported with exposure to multiple courses of antenatal corticosteroids in retrospective clinical studies.[11,111] Prospective data suggest benefit for a single rescue course for women less than 34 weeks' gestation who are at risk for preterm delivery within 7 days and whose prior steroid course was greater than 14 days.[39]

Concern about the possibility of increased infection in mother or infant appears to be unfounded. Indeed, even when corticosteroids are administered to women with prolonged rupture of membranes, there is no evidence of increased risk of infection, and the neuroprotective effects of corticosteroids are still evident. However, the use of a rescue course of corticosteroids in the setting of premature rupture of membranes remains controversial.[21,46] Maternal steroids may induce an increase in total leukocyte and immature neutrophil counts in the infant, which should be considered if neonatal sepsis is suspected.[12]

There is proven benefit from the combined use of prenatal corticosteroids and postnatal surfactant therapy in preterm infants (see Surfactant Therapy). Their effects appear to be additive in improving lung function. Antenatal steroids induce structural maturation of the lung, as evidenced by physiologic and morphometric techniques, that is not secondary to increases in alveolar surfactant pool sizes.[55] These structural changes translate into improved physiologic properties of the lung, such as increased lung volume, increased lung compliance, and increased response to exogenous surfactant treatment.

Antenatal corticosteroids appear to reduce the incidence of other co-morbidities associated with prematurity, including intracranial hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis.[19,70,112] The beneficial effect on intracranial hemorrhage does not correlate directly with improved pulmonary morbidity and may be secondary to stabilization of cerebral blood flow or a steroid-induced maturation of vascular integrity in the germinal matrix, or both.

In the 1990s, the observation that thyroid hormone could augment lung development and surfactant production *in vitro* prompted trials of antenatally administered thyrotropin releasing hormone (TRH). However, these trials failed to demonstrate a benefit and also raised concerns for adverse consequences on neurodevelopment, thereby significantly dampening enthusiasm for this therapy.[23]

Clinical Features

The classic clinical presentation of RDS includes grunting respirations, retractions, nasal flaring, cyanosis, and increased oxygen requirement, together with diagnostic radiographic findings and onset of symptoms shortly after birth. The respiratory rate is usually regular and increased well above the normal range of 30-60 breaths per minute. These infants usually show progression of respiratory symptoms and require supplemental oxygen. The presence of apneic episodes at this early stage is an ominous sign that could reflect thermal instability or sepsis but more often is a sign of hypoxemia and respiratory failure. This characteristic picture is modified in many infants with low birth weight as a result of the early administration of exogenous surfactant and immediate noninvasive or invasive assisted ventilation.

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Retractions are prominent and are the result of the compliant rib cage collapsing on inspiration as the infant generates high negative intrathoracic pressures to expand the poorly compliant lungs. The typical expiratory grunt is an early feature and may subsequently disappear. Grunting results from partial closure of the glottis during expiration and in this way acts to trap alveolar air and maintain functional residual capacity (FRC). Although these signs are characteristic for neonatal RDS, they can result from a wide variety of nonpulmonary causes, such as hypothermia, hypoglycemia, anemia, polycythemia, or sepsis; furthermore, such nonpulmonary conditions can complicate the clinical course of RDS.

Cyanosis is a consequence of right-to-left shunting in RDS and is typically relieved by administering a higher concentration of oxygen and ventilatory support. Impaired cardiac output resulting from respiratory effort that is asynchronous with the ventilator may further impede oxygen delivery and lead to poor peripheral perfusion or cyanosis. The consistency of the arterial waveform with invasive blood pressure monitoring or the pulse signal with oxygen saturation monitoring can provide information about the effectiveness of cardiac output. Acrocyanosis of the hands and feet is a common finding in healthy infants and should not be confused with central cyanosis, which always must be investigated. Peripheral edema, often present in RDS, is of no particular prognostic significance unless it is associated with hydrops fetalis.

During auscultation of the chest, breath sounds are widely transmitted and cannot be relied upon to reflect pathologic conditions. Nonhomogeneous aeration plus elevated endogenously or exogenously generated intrathoracic pressures can cause pulmonary air leaks. Thus, unilaterally decreased breath sounds (with mediastinal shift to the opposite side) or bilaterally decreased air entry could indicate pneumothorax and immediate transillumination should be performed. Chest radiography is also needed to confirm endotracheal tube placement if air entry sounds are asymmetric. The murmur of a PDA is most often audible during the recovery phase of RDS, when pulmonary vascular resistance has fallen below systemic levels and there is left-to-right shunting. Distant, muffled heart sounds should alert one to the possibility of pneumopericardium. Percussion of the chest is of no diagnostic value in preterm infants.

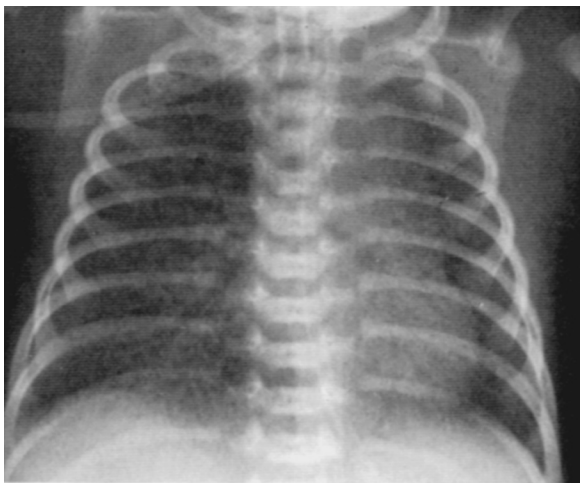
A constant feature of RDS is the early onset of clinical signs of the disease. Most infants present with signs and symptoms either in the delivery room or within the first 6 hours after birth. Inadequate observation can lead to the impression of a symptom-free period of several hours. The uncomplicated clinical course is characterized by a progressive worsening of symptoms, with a peak severity by days 2-3 and onset of recovery by 72 hours. Surfactant therapy often shortens this course as it reconstitutes the surfactant pool and prevents atelectasis until endogenous surfactant production is sufficient. When the disease process is severe enough to require assisted ventilation or is complicated by the development of air leak, significant shunting through a PDA, concomitant infection, or early signs of BPD, recovery can be delayed for days, weeks, or months (see Fig. 64.3). In the most affected patients, the transition from the recovery phase of RDS to BPD is clinically imperceptible.

Radiographic Findings

The diagnosis of RDS is based on a combination of the previously described clinical features, evidence of prematurity, exclusion of other causes of respiratory distress, and characteristic radiographic appearance (see Chapter 38). The typical radiographic features consist of a diffuse reticulogranular pattern, giving the classic ground-glass appearance in both lung fields with superimposed air bronchograms (Fig. 64.4). Although the radiologic appearance of RDS is typically symmetric and homogeneous, asymmetry has also been described, especially if surfactant therapy has been administered preferentially to one side.

The reticulogranular pattern is primarily caused by alveolar atelectasis, although there may be some component of pulmonary edema. The prominent air bronchograms represent aerated bronchioles superimposed on a background of nonaerated alveoli. An area of localized air bronchograms may be normal in the left lower lobe overlying the cardiac silhouette, but in RDS they are widely distributed, particularly in the upper lobes. In the most severe cases, a complete opacification of the lungs can be observed, with total loss of the cardiac borders. Heart size is typically normal or slightly increased. Cardiomegaly may herald the development of congestive cardiac failure from a PDA. After the administration of exogenous surfactant therapy, the chest radiograph usually shows improved aeration of the lungs bilaterally; however, asymmetric clearing of the lungs may occur.

The radiographic appearance of RDS, typical or atypical, cannot be reliably differentiated from that of neonatal pneumonia, which is most commonly caused by group B streptococcal or Gram-negative (e.g., *E. coli*) infection. This



• **Fig. 64.4** Typical radiographic appearance of respiratory distress syndrome with reticulogranular infiltrates and air bronchograms.

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problem has been the major reason for the widespread use of empiric antibiotics in the initial management of infants with RDS. Infants with RDS reportedly have a larger thymic silhouette than infants of comparable size without RDS. This supports the theory that patients with RDS have had reduced exposure to endogenous corticosteroids during fetal life.

Echocardiographic evaluation of selected infants with RDS may be of value in the diagnosis of a PDA to quantitate elevations in pulmonary artery pressure, to assess cardiac function, and to exclude congenital heart disease (e.g., obstructed total anomalous pulmonary venous return) (see Chapter 75).

Treatment

Therapy for RDS includes careful application of general supportive measures supplemented by respiratory support and selective use of surfactant therapy. Close and detailed supervision of small infants requires a dedicated, trained staff experienced and attuned to problems specific to the newborn and skillful in the unique technical procedures involved, such as CPAP administration, endotracheal intubation, titration of invasive and noninvasive respiratory support, and assessment of neonatal blood gases.

Positive-Pressure Ventilation

Delivery of distending pressure to maintain airway and alveolar expansion through invasive and noninvasive means is the mainstay of treatment for RDS (see Chapter 65). The most common approaches of invasive mechanical ventilation via an endotracheal tube utilize a time-cycled, pressure-limited mode, or volume-controlled mode with synchronized ventilated breaths. Alternatively, high-frequency jet ventilation or high-frequency oscillatory ventilation is utilized both as a primary means of ventilation and as rescue when conventional mechanical ventilation has failed.

There has been much enthusiasm for noninvasive methods of ventilation, especially nasal continuous positive airway pressure (nCPAP). The benefits of CPAP include maintenance of a constant airway opening pressure, establishment and maintenance of functional residual capacity, reduction of pharyngeal or laryngeal obstruction, improvement of oxygenation, and release of surfactant stores.[43,104] When compared to invasive mechanical ventilation, nCPAP reduces barotrauma, volutrauma, airway damage, and risk of secondary infections, and enhances mucociliary transport.[2,54,115]

Nasal CPAP used in combination with surfactant for the treatment of RDS among preterm infants is well established. Early studies demonstrated reduced need for mechanical ventilation among very preterm infants treated with surfactant and nCPAP.[107] Several randomized clinical trials have addressed the early-life respiratory management of extremely preterm infants (24-28 weeks) at risk for RDS. Taken together, these trials demonstrate that a subset of extremely preterm infants, especially those exposed to antenatal corticosteroids, can be stabilized with nCPAP shortly after birth and may avoid intubation, ventilation, and surfactant altogether.[30,79,103] Methods to identify this subset of infants before delivery or soon after birth remain an area of great interest.[37,88,96]

Although some extremely preterm infants can be treated with nCPAP, many infants fail this strategy because of persistent and severe apnea, desaturation, bradycardia, or respiratory acidosis. Noninvasive positive-pressure ventilation (NIPPV) combines nCPAP with intermittent ventilator breaths and can be administered through short binasal prongs. NIPPV increases tidal and minute volumes,[78] improves lung recruitment, decreases work of breathing,[1] may reduce apnea of prematurity,[68] and may reduce the need for mechanical ventilation among preterm infants.[86] NIPPV is superior to nCPAP in effectively weaning preterm infants with RDS from mechanical ventilation.[13,33,59,68,78] Caffeine also reduces risk of extubation failure for preterm infants.[33] However, despite increased use of less invasive ventilation strategies to avoid intubation and mechanical ventilation among extremely preterm infants, the frequency of need for supplemental oxygen at 36 weeks has not decreased, and pulmonary function during childhood has not significantly improved.[29]

Surfactant Therapy

First introduced in 1990, no intervention in the past 20 years has had more impact on the care of newborns with RDS than surfactant replacement therapy. A thorough history of the development of surfactant replacement therapy can be found in Chapter 62.[48] The discovery that surfactant deficiency was key in the pathophysiology of RDS led several investigators to administer artificial aerosolized phospholipids to infants with RDS. In these early studies, only limited therapeutic success was encountered. In contrast, animal models in which natural surfactant compounds were used yielded more promising results.

Because intact lung preparations were not available in Japan, Fujiwara and co-workers developed a mixture of both natural and synthetic surface-active lipids for use in humans.[38] Such a mixture might also afford alveolar stability with less potential risk for a reaction to foreign protein than would be the case with exclusively natural surfactant. When administered to an initial group of 10 preterm infants with severe RDS who were not improving despite artificial ventilation, a single 10-mL dose of surfactant instilled into the endotracheal tube resulted in a dramatic decrease in inspired oxygen and ventilator pressures. None of the infants in this uncontrolled series subsequently succumbed from RDS. Recovery, however, was complicated by clinical evidence of a PDA in nine of the infants, possibly the result of a prompt fall in pulmonary vascular resistance with the resultant left-to-right shunting after surfactant therapy.

Endotracheal administration of exogenous surfactant decreases complications of respiratory distress syndrome

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among preterm infants.[53] Multiple studies have administered synthetic and mixed natural-synthetic surfactant preparations as part of prevention (delivery room administration), early treatment (within first few hours of life), and rescue (administration for established RDS) protocols.[5,9,53] The current synthetic-only preparation uses a bio-engineered peptide-mimic of surfactant-associated protein B, which assists as a spreading and stabilization agent for dipalmitoylphosphatidylcholine at the air-fluid-alveolar interface in a monolayer.[56,76] The mixed-surfactant preparations contain extracts of minced or lavaged bovine or porcine lungs. Despite differences in their chemical composition, manufacturing methods, dosage amount, and frequency of dosing (Table 64.1), both animal-derived surfactant extracts and protein-free synthetic extracts are effective treatments for respiratory distress syndrome (Box 64.1).[5] More strikingly, mortality from RDS, and even overall mortality of ventilated preterm infants, is significantly reduced.[92] While animal-derived surfactant extracts are associated with greater early improvement in need for ventilator support, fewer pneumothoraces, and decreased mortality, there is no difference in risk for bronchopulmonary dysplasia compared to protein-free synthetic surfactant preparations.[5] While some studies have shown decreased risk of death or bronchopulmonary dysplasia with higher initial dosing of porcine minced lung surfactant extract as compared to bovine minced lung surfactant extract, it is unclear whether these differences are caused by dosing regimen or source (porcine vs. bovine) because of lack of dose-equivalent, appropriately powered comparative trials.[97]

Early selective surfactant administration (within the first few hours after birth) given to infants with RDS requiring assisted ventilation leads to decreased risk of pneumothorax, pulmonary interstitial emphysema, chronic lung

TABLE 64.1 Surfactant Preparations Available in the United States[97]

Name of Surfactant	Derivation	Components and Concentration per mL	Dosage	Maximum Number of Doses	Frequency
Beractant (Survanta)	Bovine minced lung extract	25 mg/mL phospholipids (11-15.5 mg DPPC) <1 mg SP-B + SP-C	4 mL/kg	4	Every 6 hours
Calfactant (Infasurf)	Bovine lavage extract	35 mg/mL phospholipids (16 mg DPPC) 0.7 mg SP-B + SP-C	3 mL/kg	4	Every 6-12 hours
Poractant Alfa (Curosurf)	Porcine minced lung extract	76 mg/mL phospholipids (30 mg DPPC) 1 mg SP-B + SP-C	2.5 mL/kg (1st dose) 1.25 mL/kg (2nd/3rd doses)	3	Every 12 hours
Lucinactant (Surfaxin)	Synthetic	30 mg/mL phospholipids (22.5 mg DPPC) 0.862 mg SP-B analog	5.8 mL/kg	4	Every 6 hours

Information obtained from package inserts of products. All surfactant preparations are only FDA approved to be given intratracheally via an endotracheal tube.

• BOX 64.1 Surfactant Therapy for Respiratory Distress Syndrome

Resolved

- Improved mortality from respiratory distress syndrome (RDS).
- Greatest benefit when antenatal corticosteroids are also employed.
- Exogenous surfactant does not inhibit endogenous surfactant synthesis.
- Retreatment may be required in severe RDS.
- Major component for lowering surface tension: phosphatidylcholine.
- Endotracheal intubation required for administration of fluid suspension.
- Improvement in oxygenation, functional residual capacity, and lung compliance.
- Protein-containing preparations show a faster therapeutic response.
- Decrease in incidence of air leaks.
- Early use of CPAP with subsequent selective surfactant administration in extremely preterm infants.
- Early use of surfactant in infants who require endotracheal intubation and mechanical ventilation soon after birth.
- Efficacy of surfactant therapy, early extubation, noninvasive ventilation strategy.

Unresolved

- Role of surfactant in etiology and treatment of pulmonary hemorrhage.
- Optimal ventilatory strategy to maximize surfactant response.
- Effect on incidence and severity of bronchopulmonary dysplasia.
- Role of surfactant proteins as modulator of the immune system and inflammatory response.
- Role for recombinant surfactant protein-based preparations.
- Role for aerosolized surfactant preparations.
- Endotracheal administration via a narrow-bore catheter as an alternative to endotracheal intubation.
- Efficacy of synthetic peptide surfactant preparations.

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disease, and mortality compared with delaying treatment until RDS is well established.[9] Given the increased use of antenatal corticosteroids and success of postdelivery stabilization on nCPAP, selective administration of surfactant to infants requiring intubation is now a preferred alternative to prophylactic surfactant administration.[89] In contrast with the impressive improvement in mortality, the incidence of BPD appears unaltered in most studies.[29,53] Although individual studies have shown a decreased incidence of BPD, these results have not been substantiated by meta-analysis of large randomized trials.[5] This could be a consequence of the enhanced survival caused by surfactant administration to infants who are very preterm but is more likely because BPD is unlikely to be a direct consequence of RDS as many infants who are preterm develop BPD without significant antecedent RDS.

Data from the early trials suggested slightly higher pulmonary hemorrhage rates in association with surfactant therapy in the smallest and most immature infants.[40] However, these findings have not been consistent throughout the literature, and controversy still exists. Generally, an acute deterioration in oxygenation and ventilation accompanied by variable degrees of cardiovascular compromise constitute the typical clinical findings. Several studies have reported an association of PDA and pulmonary hemorrhage among preterm infants.[35,60] One of the major hurdles encountered in defining the magnitude of the problem has been the lack of precise diagnostic criteria. In surfactant-treated infants, there tends to be extensive intra-alveolar hemorrhage, in contrast to infants not exposed to surfactant therapy, in whom hemorrhages occur as interstitial hemorrhage and localized hematomas. Although surfactant therapy has been proposed to contribute to pulmonary hemorrhage, the latter may inactivate surfactant and be an indication for its administration.[3]

Some infants do not exhibit the anticipated favorable response to surfactant therapy. The need for high oxygen concentration and ventilatory pressures during the early stages of RDS has been identified as a risk factor for an inadequate response. Animal studies have shown that even a few large tidal volume breaths in a surfactant-deficient lung are associated with alveolar accumulation of protein-rich edema fluid and decreased response to surfactant treatment.[52] Thus, it is unclear if lack of response is secondary to the initial severity of the disease or to the damage induced by short periods of aggressive ventilation before surfactant replacement. Furthermore, reactive oxygen species in preterm infants with poorly developed antioxidant defenses (e.g., superoxide dismutase, catalase, and reduced glutathione) may inactivate endogenous and exogenous surfactants. Finally, intrauterine inflammation or genetically determined factors may disrupt lung development or endogenous surfactant metabolism, thereby influencing response to surfactant therapy.

Data from large numbers of infants in the United States and Europe indicate no adverse effects of surfactant administration on physical growth, respiratory symptoms, or neurodevelopmental outcome. In a systematic review of randomized controlled trials, surfactant treatment was associated with a reduction in the combined outcomes of death or severe disability at 1 year of age.[98] Furthermore, this improvement in mortality and morbidity induced by surfactant therapy is accompanied by significant cost savings.[91]

Currently, all formulations of surfactant are approved solely for endotracheal administration. The most accepted method for this is via an endotracheal tube with assisted mechanical ventilation, although other methods have been attempted (Table 64.2). As mechanical ventilation is known to increase the risk of injury to the lungs, the INSURE technique (INtubate, SURfactant, Extubate) method gained popularity, as it has demonstrated a decreased need for reintubation and mechanical ventilation.[15] A more recently introduced method (less invasive surfactant administration or LISA) administers surfactant via a small catheter inserted into the trachea by direct laryngoscopy while the patient remains on nCPAP with a resultant decrease in need for intubation and mechanical ventilation.[24,44,62] Pilot studies of an aerosolized form of synthetic surfactant have shown similar results,[34,57] and a randomized clinical trial is currently underway (Clinicaltrials.gov, NCT02294630).[53]

Surfactant has also been used as a vehicle because of its lipid interface and ease at widespread distribution in the lungs. As postnatal steroids have been shown to reduce the incidence and severity of BPD, but are linked to neurodevelopmental impairment at higher doses, a combination of inhaled steroids and surfactant has been recently investigated[116,117] (NCT02907593). Early data suggest this combination is safe and decreases the risk of BPD or death at 36 weeks without affecting growth or neurodevelopment.[63]

Although no adverse immunologic consequences of foreign tissue protein administration have been reported in the recipients of natural surfactant therapy, concerns for transmitted disease prompt the desire to develop synthetic, non-animal-based products. Preparations that contain synthetic peptides that mimic the biophysical properties of SP-B or SP-C have been studied in newborns (SP-B) and adults (SP-C) but have not found their way into general use.[58,99] SP-A and SP-D, although not essential for surface-lowering activity, could play a significant role in the lung's innate immune response and modulation of inflammation. It is not yet known whether the use of purified SP-A or recombinant SP-D has a therapeutic role in neonatal lung disease. The combination of a new generation of surfactants along with a gentler ventilatory approach could hold the key to optimal pulmonary outcomes in the future.

Inhaled Nitric Oxide Therapy

Inhaled nitric oxide (iNO), currently approved for treatment of hypoxic respiratory failure in near-term and full-term infants, has been proposed as a potential intervention in preterm infants at risk for developing BPD or in RDS that is complicated by pulmonary hypertension (see Chapter 70). Although individual trials have exhibited variable results

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TABLE 64.2 Modes of Surfactant Administration

Mode of Surfactant Administration	Level of Studies Completed	Brief Description	Advantages	Disadvantages
Intratracheal via endotracheal tube (ETT)	• FDA approved • Multiple phase 3 randomized control trials (RCTs)	Surfactant administered most commonly through 5F or 8F catheter threaded through ETT in bolus dosing with continuing mechanical ventilation or positive pressure ventilation	• Most evidence • Easiest way to ensure dose is administered • Uniform distribution	• Airway trauma • Requires appropriately positioned ETT to ensure uniform distribution • Difficult to maintain functional residual capacity (FRC) depending on method of instillation • Hemodynamic instability
Thin catheter/ less invasive surfactant administration (LISA)[24,44,62]	• Not FDA approved • 3 RCTs • 4 observational studies • 1 recruiting phase 4 RCT	5F catheter is threaded into trachea via forceps. Laryngoscope is removed and catheter remains in place during administration of surfactant.	• Decreased risk of airway trauma • May avoid mechanical ventilation and volutrauma/ barotrauma from aggressive positive pressure ventilation	• Accidental removal of catheter during laryngoscope removal • Slower instillation of surfactant • Increased incidence of reflux of surfactant • Dependent on adequate, spontaneous breathing
Aerosolized[34,57]	• Not FDA approved • 2 RCTs • One pilot study • One recruiting phase II study	Aerosolized surfactant is given while patient is receiving nasal CPAP. Dose and frequency varies.	Theoretical avoidance of intubation, mechanical ventilation, volutrauma/ barotrauma	• Small number of patients enrolled • No significant difference in number of infants progressing to intubation

in survival without BPD, meta-analyses and randomized clinical trials have failed to clearly demonstrate improved respiratory or neurodevelopmental outcomes associated with routine use of iNO in preterm infants.[20,27,51] However, there may be select cases in which iNO may be of benefit.[8] When pulmonary hypertension accompanies RDS, or with decreased vascular surface area and pulmonary hypoplasia resulting from oligohydramnios and prolonged rupture of membranes, early use of iNO may improve oxygenation and survival.[8]

Assessment of Blood Gas Status

The ability to accurately monitor gas exchange is essential in all cases of neonatal respiratory disease (see Chapter 37 and Chapter 63). In its most basic form, this involves intermittent arterial sampling, usually via an indwelling umbilical arterial catheter or, less commonly, a peripheral (e.g., radial) arterial line. Infants with acute respiratory distress requiring a significantly increased inspired oxygen concentration or assisted ventilation should have blood gases sampled as often as their clinical condition dictates. A strategy of "permissive hypercapnia" has been used in attempts to reduce lung injury in preterm infants.[74] In general, $Paco_2$ is maintained in the 45-55 mm Hg range with pH at least 7.25, although in the most immature infants these ranges have been relaxed to minimize the degree of ventilatory support in an effort to decrease ventilation-associated morbidity.[74,77]

Noninvasive Monitoring: Pulse Oximetry

Risk of infection and other complications has prompted early umbilical line removal and increased the reliance on noninvasive methods for measuring gas exchange. Pulse oximetry is a well-established technique for indirectly determining oxygenation in a noninvasive and continuous manner. For infants with mild respiratory distress, pulse oximetry is extremely valuable and could make an umbilical arterial catheter unnecessary, provided intermittent assessments of pH and PCO_2 are made. Generally, this is not the case in infants with moderate or severe respiratory disease in whom noninvasive measurement remains an important adjunct rather than a substitute for arterial blood gas sampling. One should bear in mind that a normal arterial oxygen tension or saturation does not ensure adequate tissue oxygen delivery, because oxygen delivery is dependent on cardiac output and oxygen content of the blood. Hence, interpretation of gas exchange should always be correlated with a thorough clinical assessment.

Continuous noninvasive measurement of arterial hemoglobin oxygen saturation (pulse oximetry) has gained

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widespread acceptance. Pulse oximetry typically employs a microprocessor-based pulse oximeter consisting of a light-emitting probe attached to a distal extremity of the infant. Oxygen saturation is computed from the light absorption characteristics of the pulsatile flow (containing both oxygenated and nonoxygenated hemoglobin) as it passes beneath the probe. The monitor readings closely correlate with saturation measurements obtained from arterial samples.

The major disadvantage of pulse oximetry is that changes in saturation are small on the flat portion of the hemoglobin dissociation curve at PaO_2 values greater than about 60 mm Hg (depending on the fetal hemoglobin content and other factors affecting position of the hemoglobin dissociation curve). This is not a substantial problem in infants with BPD when oxygen saturation is generally maintained in the low to mid 90s and these infants are unlikely to be at risk for hyperoxemia. Significant decreases in severe forms of retinopathy of prematurity have been seen when oxygen saturation limits are constrained between 85% and 89%; however, more restricted oxygen supplementation may increase mortality.[7,102] Therefore, values of O_2 saturation persistently less than 90% should be avoided.[102] Significant variability in even resting oxygen saturations in some infants provides a significant challenge to administer the appropriate amount of oxygen to remain within these constraints.

Pulse oximeters are technically easy to use, do not require calibration or heating of the skin, and provide immediate data on arterial oxygenation. Unfortunately, this ease of use can allow misinterpretation of potentially erroneous measurements.[85] Placement must not be associated with excess pressure, and peripheral perfusion must be adequate, although pulse oximeters are less dependent on peripheral perfusion than the previously widely used transcutaneous PaO_2 probes. Pulse oximeters are quite sensitive to sudden changes in background signal such as those owing to body movements. It is, therefore, important to ensure that the pulsatile waveforms from which oxygen saturation is derived are not distorted. This is typically done by comparing pulse rate from the oximeter with heart rate obtained from a cardiorespiratory monitor; these values should be identical. Newer signal extraction technology has significantly improved the accuracy and reliability of pulse oximetry measurements.

A major effect of pulse oximetry has been the ability to rapidly optimize respiratory care and drastically reduce the time required to determine optimum inspired oxygen concentrations, levels of CPAP, and respirator settings. Other benefits include the ability to assess responses to all procedures, including surfactant instillation, as well as excessive handling. Complications such as pneumothorax, endotracheal tube dislodgement, disconnection from oxygen supply, or ventilator malfunction will be rapidly recognized so that immediate corrective treatment can be initiated. Episodes of hypoxemia or desaturation can occur spontaneously or accompany feeds and have complex etiologies, as discussed in Chapter 67. Noninvasive monitoring of oxygenation allows such episodes to be identified and their relationship to apnea and bradycardia recorded.

Noninvasive Carbon Dioxide Monitoring

Although not used as universally as pulse oximetry, noninvasive methods for monitoring carbon dioxide levels can also provide an important adjunct to blood gas monitoring (see Chapter 37). Capnography has become the standard of care in resuscitation situations for accurately and rapidly demonstrating that the endotracheal tube is in the airway. End tidal CO_2 monitoring, although routinely used during anesthesia, is useful for following trends but is not always reliable in very low birth weight infants. Transcutaneous PcO_2 monitoring is also very useful for monitoring trends, especially when trying to optimize the ventilatory settings when initiating conventional or high-frequency ventilation. The possible association of $PaCO_2$ levels of less than 30 mm Hg with periventricular leukomalacia in preterm newborns demonstrates the need for careful CO_2 monitoring.[93]

Arterial Sampling

Umbilical catheterization should be performed by an experienced operator and under strict surgical sterile technique. Once the umbilical arteries have been identified by their anatomic characteristics, one of the vessels is dilated with the use of an iris forceps. The catheter is then gently advanced to a predetermined length that will place its tip at a high (T6-T8) or at a low (L3-L4) position. Several methods have been developed to estimate the length of catheter to be inserted to achieve proper placement; however, radiologic confirmation of catheter position is still imperative.

Although umbilical artery catheters still form the basic means of arterial sampling in infants with RDS, the list of catheter-related complications is formidable. The most common visible problem from an umbilical or radial line is blanching or cyanosis of part or all of a distal extremity or the buttock area, resulting either from vasospasm or a thrombotic or embolic incident. This complication may be reduced in the case of an umbilical catheter by high placement, with the catheter tip at the level of T7 or T8 as opposed to lower placement at L3 or L4 just above the aortic bifurcation.

Tyson and associates observed thromboatheromatous complications resulting from umbilical artery catheters in 33 of 56 neonates at autopsy.[106] Small amounts of heparin added to the continuous infusion appear to reduce the risk of arterial thrombi. Hypertension can result if a renal artery is involved. A rare complication of indwelling arterial umbilical catheters is aneurysmal dilation with dissection of the abdominal aorta, which can be diagnosed by careful ultrasound examination. Retrograde blood flow into the proximal aorta can occur during flushing of radial and umbilical artery lines and result in transient blood pressure elevation; therefore, routine flushing should be performed with a small volume over a period of several seconds.

The risk of catheter-associated bloodstream infection increases significantly as the days in place increase; thus,

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limiting the number of days these catheters remain in place reduces the risk of infection and catheter-associated thrombosis.[16] All these complications illustrate the importance of applying rigid criteria for the insertion and removal of indwelling arterial catheters and the need for less hazardous methods of monitoring blood gases.

If a peripheral arterial catheter is to be used, an Allen test should be performed before the insertion of a radial artery line to establish the presence of adequate collateral circulation to the fingers.

Acid–Base Therapy

A change in acid–base balance should prompt a rapid determination of the type of imbalance, respiratory or metabolic, and a thorough evaluation of the cause (see Chapter 92). Acidosis, respiratory or metabolic, especially when coupled with hypoxia, can cause pulmonary arterial vasoconstriction and ventilation-perfusion abnormalities, decreased cardiac output, or both. A metabolic acidosis out of proportion to the degree of respiratory distress might signify hypoperfusion, sepsis, or IVH. Although sodium bicarbonate was historically used to correct metabolic acidosis, its routine use has not been shown to improve neonatal morbidity or mortality among preterm infants[66] and may be associated with increased risk for adverse neonatal outcomes.[6] Treatment of metabolic acidosis depends on the underlying etiology (e.g., lactic acidosis, renal tubular acidosis), and therapy should be targeted accordingly.

Respiratory acidosis requires assisted ventilation, and serial blood gases should be performed to titrate respiratory support. Administration of sodium bicarbonate to infants with respiratory acidosis is not indicated and could further increase the P_{CO_2}.

Cardiovascular Management

Comprehensive management of patients with RDS includes a close evaluation and monitoring of the cardiovascular system. An in-depth understanding of the physical and physiologic interactions between the cardiovascular and pulmonary systems in the mechanically ventilated patient is paramount. For example, after surfactant administration, with the improvement in the mechanical properties of the lungs, an unrecognized overdistension of the lungs by excessive mechanical ventilation support can decrease systemic venous return to the heart and result in a decrease in cardiac output. Radiographically, a typical squeezed-heart silhouette and flattened diaphragm are found. A thorough clinical evaluation should include sequential assessment of vital signs, peripheral pulses, capillary refill, and urine output as surrogate markers of adequate cardiac output.

Myocardial dysfunction secondary to ischemia or hypoperfusion may be present and could lead to decreased peripheral perfusion with lactic acidemia and metabolic acidosis. Systemic hypotension is common in the early stages of RDS; thus, continuous monitoring of systemic blood pressure by means of an indwelling arterial catheter is of utmost importance in the moderately to severely ill infant. Noninvasive intermittent monitoring of systemic blood pressure should be reserved for the mildly affected neonate. Judicious use of crystalloids for intravascular expansion and vasopressor support are often indicated. In patients with persistent hypotension not responsive to fluid therapy or pressors (e.g., dopamine), serum cortisol levels should be measured and treatment with stress doses of hydrocortisone should be considered.

Failure of the ductus arteriosus to close is a common complication in infants with RDS and has been linked to worsening respiratory distress and acidosis. Clinically, the presence of a PDA is heralded by a widened pulse pressure, an active precordium, and bounding peripheral pulses. A heart murmur on the left subclavicular area and the back is often present. On the chest radiograph, cardiomegaly might signal the presence of a hemodynamically significant PDA with congestive heart failure. With clinical suspicion, a confirmatory echocardiogram, which should demonstrate evidence of pulmonary overcirculation such as left atrial enlargement, is usually obtained. The decision whether to proceed with pharmacologic closure of the ductus arteriosus with a prostaglandin synthesis inhibitor such as indomethacin or ibuprofen remains controversial.[14] Fluid restriction, vasopressors, and a loop diuretic (e.g., furosemide) may be indicated for the medical management of a hemodynamically significant PDA with congestive heart failure (see Chapter 74).

Antibiotics

Neonatal pneumonia (most commonly caused by group B streptococci or gram-negative organisms) can be indistinguishable from RDS both clinically and radiographically. Such infection usually is acquired around the time of delivery either through ascending infection or passage through a colonized genital tract. The potentially fulminant course of neonatal pneumonia, especially in preterm infants, and the difficulty in distinguishing it from RDS have led to the practice that infants with significant respiratory distress receive antibiotics after appropriate cultures.

Prenatal features suggestive of neonatal infection include maternal fever, prolonged rupture of membranes, and clinical evidence of chorioamnionitis. The suspicion for bacterial infection is raised by a history of maternal genital colonization with group B streptococcus in an inadequately treated mother.

In the newborn, persistent hypotension, metabolic acidosis, early onset of apnea, neutropenia, or neutrophilia accompanied by an increase in immature neutrophils (left shift) are clinical findings suggestive of systemic infection. Nonetheless, the absence of these features does not exclude the diagnosis of pneumonia. Penicillin combined with an aminoglycoside is the antibiotic regimen of choice and may be discontinued after 48 hours based on culture results and clinical course of the infant. However, for medically

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indicated preterm deliveries in the absence of risk factors for infection, antibiotic use may not be necessary. Furthermore, longer treatment with antibiotics without a clear source of infection has been associated with increased risk of morbidity.[22,64]

Despite substantial improvements in the treatment of RDS, prevention of preterm birth is still the ultimate goal and will have significant impact on the prevention of RDS. In the meantime, understanding the interactions of the intrauterine environment and genetic determinants of lung development with the pathogenesis of RDS is essential to develop mechanism-specific interventions.

Key Points

- Antenatal corticosteroids enhance surfactant production and reduce co-morbidities such as intraventricular hemorrhage.
- RDS results from a developmental deficiency of pulmonary surfactant production that may be aggravated by maternal diabetes and perinatal hypoxia-ischemia.
- Respiratory distress syndrome (RDS) and its associated complications are one of the most common causes of morbidity among preterm infants.
- Various techniques of surfactant replacement, respiratory support including CPAP, and other supportive therapy are the mainstays of treatment.

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65

Assisted Ventilation of the Neonate and Its Complications

STEVEN M. DONN AND MOHAMMAD A. ATTAR

Mechanical ventilation has been used to treat neonatal respiratory failure for more than a half century. The earliest applications began as modifications of adult ventilators, treating babies of modest size and prematurity by today's standards.[23] Most devices were time-cycled, pressure-limited ventilators. Landmark advances in respiratory care occurred in the 1970s. Antenatal corticosteroids were shown to enhance fetal lung maturity, and transcutaneous oxygen monitoring taught us much about the vulnerability of the preterm infant. The 1980s brought pulse oximetry and high-frequency ventilation, which greatly expanded the therapeutic armamentarium. The surfactant replacement era began in the 1990s and was accompanied contemporaneously by patient-triggered ventilation, real-time pulmonary graphics, and a host of pharmacologic agents. Finally, in the new millennium, the microprocessor was incorporated into neonatal ventilators to greatly expand capabilities, monitoring, safety, and efficacy. This technological revolution has extended survival to infants born extremely prematurely as well as those with severe pulmonary disease that was heretofore lethal.

Mechanical ventilation can now be provided in many permutations. Clinicians can alter target variables, waveforms, cycling mechanisms, and modes simply by adjusting a dial. This has led to the development of disease-specific strategies to deal with the wide spectrum of neonatal respiratory failure. Similar to the rapidity of change in the computer industry, advances have been rapid and are often introduced into clinical practice without much of an evidence base, causing further confusion and consternation. This chapter reviews the classification and principles of both noninvasive ventilation and mechanical ventilation, with an emphasis on nomenclature and terminology.

Continuous Positive Airway Pressure and Noninvasive Ventilation

Although mechanical ventilation had been the primary treatment for respiratory failure in most preterm babies, there continues to be a concern that it is a major contributor to lung injury. This has led to a growing interest in noninvasive forms of respiratory support in the belief that this will reduce the need for mechanical ventilation and its associated complications. The noninvasive neonatal respiratory support modalities fall into two broad groups: single-level pressure support, such as continuous positive airway pressure (CPAP), and high-flow nasal cannula (HFNC) support, or bilevel positive airway pressure in the form of nasal small pressure difference (bilevel CPAP [BiPAP] or synchronized bilevel CPAP [SiPAP]) and in the form of nasal intermittent positive-pressure ventilation (NIPPV). NIPPV uses a high pressure difference and can be either synchronized or nonsynchronized.

Physiology of CPAP

When used to treat respiratory distress syndrome (RDS), CPAP prevents collapse of the alveoli at end-expiration, maintaining some degree of alveolar inflation. It thus decreases the work of breathing in accordance with LaPlace's law, in which the pressure required to overcome the collapsing forces generated by surface tension is reduced, because the radius of curvature is greater when the alveolus is partially inflated. In this way, CPAP helps to maintain functional residual capacity and to facilitate gas exchange. In addition, CPAP helps to maintain upper airway stability by stenting the airway and decreasing obstruction. It may also augment stretch receptors and decrease diaphragmatic fatigue and thus be useful in treating apnea of prematurity.

Nasal Continuous Positive Airway Pressure

Continuous positive airway pressure is a form of continuous distending pressure (CDP), which is defined as the maintenance of increased transpulmonary pressure during the expiratory phase of respiration. When positive pressure is applied to the airways of spontaneously breathing infants, it is called continuous positive airway pressure

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Abstract

Neonatal respiratory failure is the most common disease entity in the neonatal intensive care unit. Treatment options range from administration of supplemental oxygen to continuous distending pressure to assisted ventilation. This chapter addresses aspects of assisted ventilation and its complications. Principles of mechanical ventilation, monitoring of the infant, and short- and long-term outcomes are discussed.

Key words

newborn
respiratory failure
noninvasive ventilation
mechanical ventilation
complications

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• BOX 65.1 Clinical Indications for Continuous Positive Airway Pressure (CPAP)

- Delivery room resuscitation
- Management of respiratory distress syndrome (RDS)
- Postextubation support
- Apnea
- Mild upper airway obstruction

• BOX 65.2 Methods of Providing Continuous Positive Airway Pressure (CPAP)

- Ventilator-derived CPAP
- Flow-driven CPAP
- Bubble (underwater) CPAP
- High-flow nasal cannula CPAP

(CPAP), whereas distending pressure applied to a mechanically ventilated infant is called positive end expiratory pressure (PEEP). Thus, both CPAP and PEEP are types of CDP (although not technically a form of ventilation) that provide low-pressure distension of the lungs and prevent the collapse of alveoli at the end of expiration. Continuous distending pressure helps to maintain functional residual capacity (FRC) and thus facilitates gas exchange throughout the respiratory cycle. In addition, CPAP supports the breathing of premature infants in a number of other ways, including abolition of upper airway occlusion and decreasing upper airway resistance, enhancement of diaphragmatic tone and activity, improvement in lung compliance and decrease in lower airway resistance, increase in tidal volume delivery by improving pulmonary compliance, conservation of surfactant at the alveolar surface, and reduction in alveolar edema.[48]

CPAP may be administered invasively through an indwelling endotracheal tube, or it may be provided noninvasively using a variety of different nasal interfaces. This is referred to as nasal CPAP (NCPAP). Single nasal prongs are usually cut from endotracheal tubes and passed 1-2 cm into one nostril with about 3 cm residing externally. Resistance along the length of the cannula adds to the loss of pressure from the other nostril. Nasal masks are now used in the belief that they reduce trauma to the nostrils. However, it is often difficult to produce a good seal without undue pressure, which may still cause injury in the region between the nasal septum and the philtrum. Short binasal prongs are available in several designs; all have two short tubes that provide the least resistance of any other nasal interface. They may be more effective at maintaining extubation and preventing reintubation than single nasal prongs as shown in a recent meta-analysis of controlled studies.[2]

Clinical Indications for CPAP in Newborns

The clinical use of NCPAP in the neonate falls into one of several groups: (1) early use in resuscitation, (2) management of RDS, (3) postextubation care, (4) treatment of apnea, and (5) management of mild upper airway obstruction (Box 65.1).

Methods of Generating Continuous Positive Airway Pressure

The gas mixture delivered by CPAP is derived from either continuous or variable flow (Box 65.2). Continuous-flow CPAP consists of gas flow generated at a source and directed against the resistance of the expiratory limb of the circuit. Ventilator-derived CPAP and bubble or underwater CPAP are examples of continuous-flow devices, whereas infant flow drivers (flow-driven CPAP) and Benveniste valve CPAP are examples of variable-flow devices.

Flow-Driven CPAP

Flow-driven CPAP is a prototype of variable-flow CPAP. It uses a dedicated flow driver and gas generator with a fluidic-flip mechanism to deliver variable-flow CPAP. The principle is the Bernoulli effect, which directs gas flow toward each nostril, and the Coanda effect, which causes the inspiratory flow to flip and leave the generator chamber via the expiratory limb during exhalation. This assists spontaneous breathing and reduces the work of breathing by lowering expiratory resistance and maintaining stable airway pressure. Flow-driven CPAP can be delivered using binasal prongs or a nasal mask.

Bubble CPAP

Underwater bubble continuous positive airway pressure (BCPAP) is a continuous-flow system used since the early 1970s. In this method, the blended gas is heated and humidified and then delivered to the infant through a secured low-resistance nasal prong cannula. The distal end of the expiratory tubing is immersed in water, and the CPAP pressure generated is equal to the depth of immersion of the CPAP probe. It has also been proposed that chest vibrations produced by the bubbling may contribute to gas exchange. BCPAP is an effective and inexpensive option to provide respiratory support to premature babies.[48]

Ventilator-Derived CPAP

Ventilator-derived CPAP is another conventional way to administer continuous-flow CPAP. The CPAP is increased or decreased by varying the ventilator's expiratory orifice diameter. The exhalation valve works in conjunction with other controls, such as flow control and pressure transducers, to maintain the CPAP at the desired level.

Sustained Inflation at Neonatal Resuscitation

Sustained inflation (SI) uses pressures of 20-30 cm H_2O for 5-15 seconds during resuscitation to recruit lung airspaces immediately after delivery and to establish functional residual capacity. Thus far, studies have failed to demonstrate a benefit of presumed lung recruitment (and a decrease in the

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rates of death or BPD). More randomized controlled studies are underway to evaluate the efficacy and safety of SI.[43,84]

CPAP Immediately After Birth

In a meta-analysis of randomized controlled trials comparing CPAP started in the immediate postnatal period in very low birth infants at risk for RDS, to support with mechanical ventilation (including 3123 babies), Subramaniam et al. found CPAP to decrease the need for mechanical ventilation and surfactant treatment and to reduce the incidence of BPD at 36 weeks and the incidence of death or BPD.[99]

High-Flow Nasal Cannula (HFNC)

Flow of gas in excess of 1 L/min, and up to 8 L/min, through a small nasal cannula might provide some degree of CPAP. The physiologic benefits of HFNC are attributed to washout of the nasopharyngeal dead space, possible reduction of the inspiratory resistance, and provision of a degree of CPAP.[19] However, a major problem is that the CPAP level is usually not measurable in clinical practice and has been shown to be highly variable depending on the leak at the nose and/or mouth. The cannula tips should not be more than 50% of the internal diameter of the nares to allow optimal washout of the dead space.[54] This leak around the nasal cannula affects the measured CPAP in an in vitro study.[95] In another study of preterm infants, a flow of 2 liters/minute generated 9.8 cm H_2O pressure (measured by an esophageal balloon) when a nasal cannula of certain diameter was used (0.3-cm outer diameter), emphasizing the potential risk of inappropriate size selection of the nasal cannula.[68] Utilization of this technique has increased in many units as a result of the simpler patient interface compared to CPAP, and because the use of HFNC appears to be associated with less nasal trauma.[63,70] HFNC in preterm infants has been used as a primary mode of support shortly after birth, postextubation, and for apnea. In general, HFNC was no worse than CPAP in a meta-analysis of controlled trials. However, there is a paucity of evidence in the extremely preterm infant.[63] In a large randomized, controlled, noninferiority trial, published subsequently, early (after birth) use of HFNC for primary support for RDS in infants older than 27 weeks was associated with more frequent treatment failures compared to CPAP.[82] Additional studies are needed to demonstrate safety and efficacy for HFNC under various clinical conditions.[19,116]

Noninvasive Nasal Ventilation

Methods of noninvasive ventilation include nasal intermittent positive-pressure ventilation (NIPPV), synchronized nasal intermittent positive-pressure ventilation (SNIPPV), and synchronized bilevel CPAP (SiPAP). In all of these modalities, ventilator inflations augment NCPAP while PEEP, peak inspiratory pressure (PIP), respiratory rate, and inspiratory time can all be manipulated. Terminology used to describe NIPPV is not standardized and may be confusing. SiPAP, a form of NIPPV, is also termed biphasic or bilevel nasal CPAP.

The mechanism of action of NIPPV remains unclear. It is not known whether mechanical inflations during NIPPV are transmitted to the lungs; clinical studies show contradictory results. Other trials also found no differences in tidal volume or minute volume when comparing NCPAP with SNIPPV. Similarly, there are conflicting reports on work of breathing, pulmonary mechanics, and thoracoabdominal synchrony during comparisons of NCPAP with SNIPPV.[78]

Clinical Indications for NIPPV

Several studies have compared nonsynchronized NIPPV with NCPAP for treatment of apnea in premature infants and showed no advantage of NIPPV. Trials have also compared SNIPPV with NCPAP following extubation and found a significant reduction in extubation failure using SNIPPV. Studies have also assessed NIPPV as a primary strategy to treat RDS to avoid intubation. Investigators reported improved carbon dioxide removal, reduced apnea, and shorter duration of ventilation in the NIPPV group. Nonetheless, these are small studies and used sufficiently different protocols that prevent generalizable conclusions. A large randomized controlled trial consisting of more than 1000 babies of less than 30 weeks' gestation and birth weight less than 1000 g did not show any advantage of NIPPV over CPAP either as a means of early respiratory support to treat RDS or to facilitate extubation.[72] This is now further supported by another large multicenter study.[61] Lemyre et al. reported a meta-analysis of randomized controlled trials comparing NIPPV to CPAP. NIPPV was associated with a reduction in the need for re-intubation, and that benefit was persistent in all the trials that synchronized NIPPV (although they used different methods of synchronization).[66] The authors cautioned that their data were not sufficiently robust to support the added benefits of synchronization.

New Modes of NIPPV

Other forms of NIPPV have been introduced to overcome the limited pneumatic synchrony (flow or pressure) from air leaks at the patient interface. The noninvasive neurally adjusted ventilator assist (NIV-NAVA) uses a trigger that incorporates electrical activity of the diaphragm (Edi) by placing a probe at the gastroesophageal junction to trigger and proportionally pressure-assist each breath depending on the level of the measured diaphragmatic activity. In preclinical studies of NIV-NAVA, mechanical breaths are synchronized to the initiation, size, and termination of each patient breath.[42,97] Data from clinical studies using NIV-NAVA are limited and report mainly about infant-ventilator synchrony.[42]

The use of high-frequency ventilators with a nasal interface (high-frequency nasal ventilation, HFNV) theoretically eliminates the need for synchrony by delivering

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high-frequency, small tidal volume ventilation. Clinical reports of HFNV in human neonates are emerging,[42,115] but no recommendations can be made yet.

CPAP and Surfactant Administration

Intubation with surfactant administration, followed by extubation (INSURE), is a way for surfactant administration to premature infants supported with CPAP. Dani et al. described variation in the threshold for surfactant treatment in multiple studies using this technique of surfactant administration, with the lower threshold seemingly better.[20] Less invasive surfactant administration (LISA) describes administering surfactant to spontaneously breathing premature infants without traditional endotracheal intubation. LISA is used with the hope of decreasing exposure to mechanical ventilation and subsequently to decrease the risk for lung injury.[64] A meta-analysis of six randomized studies, enrolling 895 infants, demonstrated that LISA was associated with a lower need for mechanical ventilation and a reduction in the composite outcome of death or BPD.[1]

Practical Problems of NCPAP

Despite its widespread use, a number of problems still persist.[67] Nasal prongs rarely fit tightly into the nares, thus resulting in gas leak and inability to maintain a baseline pressure. The set CPAP level is rarely maintained in the pharynx. The best way to reduce nasal leak is to ensure that the prongs are of sufficient size to snugly fit the nostrils without making them blanch. A chin strap can be used to reduce leaks around the mouth, but it is not simple to use in practice.

Complications of CPAP

Nasal trauma is a common problem with NCPAP especially in very premature infants. Proposed interventions include alternating binasal prongs with a nasal mask and using a nasal barrier dressing.[53] Excessive CPAP may contribute to lung overinflation and increase the risk for air leaks. CPAP can increase intrathoracic pressure and decrease venous return and cardiac output. If set too high, CPAP may result in carbon dioxide retention and impaired gas exchange. Gastric distension is a commonly encountered problem and can be at least partially alleviated by placement of an orogastric tube.

Postextubation CPAP

Ferguson et al., in a meta-analysis of studies that evaluated rates of successful extubation, found that continuous positive pressure reduces extubation failure compared to headbox oxygen, NIPPV was superior to CPAP, and that HFNC had similar efficacy to CPAP.[41] Lemyre's meta-analysis did not find enough evidence to demonstrate superiority of synchronized over nonsynchronized NIPPV after extubation, although a postextubation benefit was consistently observed in studies using synchronized NIPPV.[66]

Discontinuing CPAP

There are several methods of discontinuing NCPAP, including transition to HFNC. A gradual decrease in CPAP before discontinuing it was associated with success in the initial trial off NCPAP in two randomized controlled studies of very low birth weight infants.[4,105]

Long-Term Outcomes

The use of CPAP immediately after birth and selective surfactant treatment has generally replaced the practice of prophylactic or early surfactant replacement in preterm infants. This change in practice was influenced by the evidence from multiple randomized trials that used CPAP for initial stabilization and demonstrated a decreased risk of death or BPD compared to prophylactic surfactant therapy. That change in practice also included using the INSURE strategy in surfactant administration in an attempt to decrease exposure to mechanical ventilation. There has been an increase in the use of noninvasive forms of pulmonary support over time in an attempt to decrease exposure to mechanical ventilation and to decrease the risk for lung injury and potentially decrease the risk of death or BPD. The temporal increase in the use of noninvasive ventilation was demonstrated in longitudinal studies using single-center and regional datasets. Vliegenthart et al., in a single center in the Netherlands, reported a decrease in the rate of intubation and a decrease in the duration of mechanical ventilation over two epochs spanning 2004-2011, but there was no significant decrease in BPD. However, the investigators reported a significant decrease in the rate of death or neurodevelopmental impairment at 24 months.[111]

A regional Australian evaluation that compared pulmonary support and outcomes in three periods, 1991-1992, 1997, and 2005, demonstrated a longitudinal increase in duration of noninvasive pulmonary support without a significant change in duration of endotracheal mechanical ventilation and no significant decrease in duration of oxygen therapy or in the rate of oxygen dependence at 36 weeks. In addition, survivors of that population born in the most recent time period had lower expiratory volumes, suggesting more airflow obstruction at their 8-year evaluation.[36] Although these longitudinal evaluations have many limitations, they are not showing the hoped-for pulmonary benefits of the increased use of noninvasive pulmonary support. It seems that more work needs to be done to identify better noninvasive pulmonary support practices and the ideal patient population.

Indications for Assisted Ventilation

Mechanical ventilation is intended to take over or assist the work of breathing in babies who are unable to support

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• BOX 65.3 Indications for Assisted Ventilation

Absolute Indications

- Failure to initiate or sustain spontaneous breathing
- Persistent bradycardia despite bag/mask ventilation
- Presence of major airway or pulmonary malformations
- Sudden respiratory or cardiac collapse with apnea/bradycardia

Relative Indications

- High likelihood of subsequent respiratory failure
- Surfactant administration
- Impaired pulmonary gas exchange
- Worsening apnea unresponsive to other measures
- Need to maintain airway patency
- Need to control carbon dioxide elimination
- Medication-induced respiratory depression

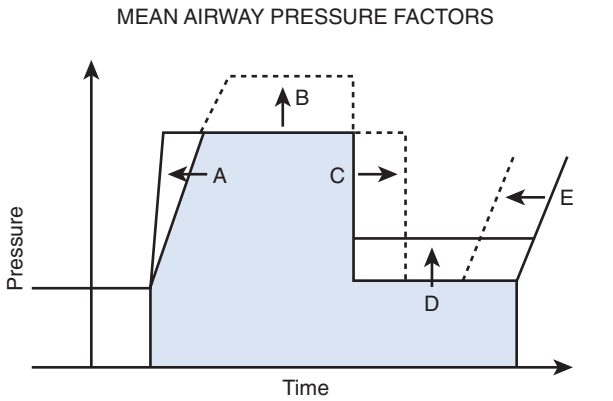
effective pulmonary gas exchange on their own. The causes for respiratory insufficiency may be pulmonary, such as respiratory distress syndrome or meconium aspiration syndrome; extrapulmonary, such as airway obstruction or compression; or neurologic, such as central apnea or neuromuscular disease. Respiratory failure may also accompany other systemic derangements, including sepsis or shock.

Indications for assisted ventilation may be thought of as absolute and relative (Box 65.3). Absolute indications include entities encountered in the delivery room, such as the failure to establish spontaneous breathing despite bag and mask ventilation, persistent bradycardia despite positive-pressure ventilation by mask, or the presence of major anomalies such as diaphragmatic hernia or severe hydrops fetalis, where there is a high likelihood of immediate respiratory failure. In the neonatal intensive care unit, sudden respiratory or cardiac collapse with apnea and bradycardia unresponsive to mask ventilation and massive pulmonary hemorrhage are two examples of absolute indications.[47]

Relative indications may be based on clinical judgment, such as intubating very preterm babies for prophylactic or early surfactant administration, or they may be based on an objective assessment of impaired gas exchange as evidenced by abnormal blood gases. Various recommendations exist to define respiratory failure severe enough to warrant assisted ventilation. In general, the easiest of these is the so-called "50-50 rule," whereby hypoxemia is defined as a failure to maintain an arterial oxygen tension of 50 mm Hg with a fraction of inspired oxygen of 0.5 or greater, and hypercapnia is defined as an arterial carbon dioxide tension greater than 50 mm Hg. Some have suggested that the arterial carbon dioxide tension criterion should be coupled with a pH value, such as less than 7.25. Additional relative indications for assisted ventilation include the stabilization of infants who are at risk for sudden deterioration, such as preterm infants with apnea unresponsive to CPAP or methylxanthines; severe systemic illness such as sepsis; the need to maintain airway patency, such as meconium aspiration syndrome or tracheobronchomalacia; the need to maintain

• BOX 65.4 Determinants of Oxygenation

- Fraction of inspired oxygen
- Mean airway pressure
- Positive end expiratory pressure (PEEP)
- Peak inspiratory pressure (PIP)
- Inspiratory time
- Frequency
- Gas flow rate



• **Fig. 65.1** Graphic representation of determinants of mean airway pressure. The mean airway pressure is the area under the curve (*shaded*). Note the effects of increasing the rise time (**A**), peak inspiratory pressure (**B**), inspiratory time (**C**), and positive end expiratory pressure (**D**), and of increasing the expiratory time (**E**).

control of carbon dioxide elimination, such as persistent pulmonary hypertension; following severe hypoxic-ischemic brain injury; or for the management of drug-induced respiratory depression, such as maternal magnesium sulfate therapy, general anesthetics, or analgesics.

General Principles of Assisted Ventilation

Oxygenation

The two major factors that are responsible for oxygenating the blood are the fraction of inspired oxygen and the pressure to which the lung is exposed (Box 65.4). The role of inspired oxygen can be understood from the alveolar gas equation (see Chapter 63). Oxygenation is also proportional to mean airway pressure (mean Paw), which is the average pressure applied to the lungs during the respiratory cycle and is represented by the area under the curve for the pressure versus time waveform. Inflation of the lung recruits more airspaces and exposes more of the pulmonary surface area to alveolar gas. Thus, those factors that increase mean airway pressure will, up to a certain point, improve oxygenation (Fig. 65.1).[13]

The most direct impact comes from positive end expiratory pressure (PEEP), because it is applied throughout the respiratory cycle. PEEP is the baseline pressure, the lowest level to which airway pressure falls. It is used to take advantage of LaPlace's law by maintaining some degree

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of alveolar inflation during expiration, thus reducing the pressure necessary to further inflate the alveolus during inspiration. There is a 1 : 1 relationship between PEEP and mean Paw; for every 1-cm H_2O increase in PEEP, there is a 1-cm H_2O increase in mean Paw. Excessive PEEP is potentially harmful. It may overdistend the alveoli, increasing the risk of air leaks; it may impede venous return and cardiac output; and it may decrease the amplitude, leading to carbon dioxide retention (see Complications of CPAP).[107]

Peak inspiratory pressure (PIP) will also increase the mean Paw, but this will be proportional to the inspiratory time (T_I) or duration of positive pressure. PIP is the driving pressure and also establishes the upper limit of the amplitude. Excessive PIP poses many of the same risks as excessive PEEP, including hyperinflation (overdistension) of the lung, leading to excessive stretch of the alveolar units (baro- or volutrauma); high intrathoracic pressure with decreased venous return and cardiac output; and air leaks. Additionally, if PIP and/or PEEP is/are inadequate, there may be alveolar atelectasis and resultant damage to the lung from cyclic opening and closing of lung units, a process referred to as atelectrauma.[17]

Mean Paw is also affected by T_I and the duration of positive pressure. As T_I increases, the mean Paw will also increase if all other parameters are held constant. Similarly, on machines wherein the inspiratory:expiratory (I:E) ratio is adjusted, mean Paw will increase as the inspiratory phase is lengthened or the expiratory phase is shortened. If the T_I is too long, however, there is an increased risk of gas trapping, inadvertent PEEP, and air leak. If it is too short, there may be inadequate lung expansion, air hunger, and patient-ventilator asynchrony, leading to inefficient gas exchange.

Changes in the ventilator rate will have a slight effect on mean Paw. At faster rates, the mean Paw will rise, because there are more breaths delivered per minute and the cumulative area under the curve per unit of time increases. Rapid rates may result in incomplete emptying of the lung, with gas trapping, inadvertent PEEP, and lung hyperinflation.

Finally, circuit gas flow will also impact mean Paw. If the T_I is held constant, more volume (and hence higher pressure) will be delivered as flow is increased. If the flow is set too high, turbulence, incomplete emptying of the lung, inadvertent PEEP, and hyperinflation may occur.[76] If the flow is set too low, air hunger and asynchrony will result. The injurious effects of improper airway flow have been referred to as *rheotrauma*.[32]

Ventilation

Ventilation refers to carbon dioxide removal. Its two primary determinants are tidal volume and frequency (Box 65.5).[106] Tidal volume is determined by the amplitude of the mechanical breath, or the difference between the peak (PIP) and baseline (PEEP) pressures. During conventional ventilation, carbon dioxide removal is the product of tidal volume and frequency. Clinically, this is usually expressed as the minute volume, or mL/kg/min, of exhaled gas. It is also important to consider the contribution of spontaneous breathing to minute ventilation (which is not always measured) and that pulmonary blood flow is also a key element in carbon dioxide removal, as well as oxygenation. During high-frequency ventilation, carbon dioxide removal is the product of frequency and the square of the tidal volume.[11] Thus, small changes in amplitude may have a profound effect on arterial carbon dioxide tension (see later).

• BOX 65.5 Determinants of Ventilation

Minute Volume

- Tidal volume
- Amplitude (PIP–PEEP)
- Frequency
- For conventional ventilation:
  Minute volume = frequency × tidal volume
- For high-frequency ventilation:
  Minute volume = frequency × (tidal volume)^2
- Expiratory time (or I : E ratio)

Control of ventilation during patient-triggered ventilation requires an understanding of the physiology of gas exchange. Most newborns will have intact chemoreceptors and will seek to maintain normocapnia. This is accomplished by adjustments in minute ventilation. Thus, if the amplitude is set too low, the baby will compensate by increasing the spontaneous (and hence, triggered) breathing rate. Conversely, if the amplitude is set too high, the infant's hypercapnic drive will be abolished, and the baby will "ride" the ventilator rate.[31]

Carbon dioxide tension is affected by minute ventilation, which in turn is the product of tidal volume and frequency during conventional mechanical (tidal) ventilation (CMV). Of these two parameters, adjustment in tidal volume (by adjusting the amplitude) has a more predictable effect on minute ventilation.[107]

Time Constant

Use of mechanical ventilators requires an understanding of the respiratory time constant. The respiratory time constant refers to the time required to allow pressure and volume equilibration of the lung. Mathematically, the time constant is the product of compliance and resistance. When the lung is stiff (low compliance) and has limited expansibility, such as occurs during RDS, it takes less time to fill and empty than it does at higher compliance. This pattern is clinically illustrated by observing the spontaneous breathing pattern of an infant with RDS not requiring assisted ventilation. Early on, when compliance is poor, the baby will breathe rapidly and take shallow breaths. As the disease process remits, compliance improves, and the baby breathes more slowly and takes deeper breaths.

If expiratory time is set at one time constant, approximately 63% of the change in pressure or volume will occur; if it is lengthened to three time constants, changeover will

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increase to 95%; and at a five time constant-length, it will approach 99%. Thus, setting the expiratory time at less than 3-5 times the length of the time constant will increase the risk of gas trapping and potentially inadvertent PEEP and alveolar rupture.[12]

Classification of Mechanical Ventilators

Over the past decade, newer mechanical ventilation devices have been introduced into neonatal practice and devices that are based on sound physiologic principles. The proliferation of devices and techniques has caused confusion about nomenclature and classification, which are frequently device specific. In a general sense, mechanical ventilators can be divided into two groups: those that deliver physiologic tidal volumes, often referred to as conventional mechanical ventilators, and those that deliver tidal volumes that are less than physiologic dead space, referred to as high-frequency devices, which will be discussed later.

Among conventional mechanical ventilators, it is advisable to use a simple hierarchical classification to describe devices according to the variables they utilize (Fig. 65.2). These variables fall into two categories: those that control the type of ventilation (called *ventilatory modalities*) and those that determine the breath type (called *ventilatory modes*).[106] Recently, Chatburn, El-Khatib, and Mireles-Cabodevila proposed a taxonomy for mechanical ventilation. This system utilizes the defining of the control variable, breath sequence, targeting scheme, and mode classification to describe what is happening. This scheme, if adopted, could eliminate the widespread inconsistencies in nomenclature and terminology that presently exist among different devices and manufacturers.[14,15]

Control Variables (Ventilatory Modalities)

At any one time, the ventilator can control only a single variable—time, pressure, or volume. However, the same ventilatory device can operate using different control variables at different times. Ventilatory modalities can target either pressure or volume as the primary variable. Because volume is the integral of flow, volume- and flow-controlled ventilation are actually the same. When pressure is controlled, volume will fluctuate according to the compliance of the lungs, and conversely, when volume is controlled, pressure will fluctuate as a function of compliance.[14,106]

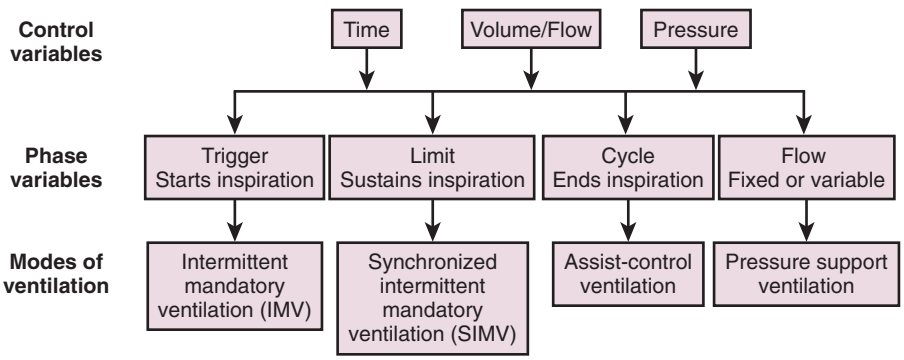
Phase Variables (Ventilatory Modes)

The mechanical breaths delivered by the ventilator have four phases, and more than one variable can be used to design the type of breath to suit the underlying lung mechanics and/or pathophysiology. The first of these is the variable that initiates or triggers inspiration (trigger). The second is the variable that is used to limit the inspiratory gas flow (limit). The third is the variable that changes inspiration to expiration and vice versa (cycle). The final is the variable that maintains the baseline pressure during expiration (PEEP).[106]

A number of variables can be used to trigger a breath. In the past, most neonatal ventilators used time to start inspiration. The clinician programmed either a set inspiratory time or ventilator rate and inspiratory:expiratory ratio, and the exhalation valve would open and close according to the lapse of time. More recently, other triggering variables have been introduced, allowing for the synchronization of the onset of mechanical breaths to spontaneous breathing. The clinician can set a threshold flow or pressure, above which the ventilator initiates a mechanical breath. These variables are used as a surrogate for spontaneous effort and include pressure or flow, with time as a backup. Most present ventilators use flow-triggering devices for newborns, because this requires less effort to trigger and is thus associated with less work of breathing.[33]

The limit variable restricts the inspiratory flow to a preset value. Traditionally, pressure has been used as a limit variable, but volume and flow are other variables that can limit inspiratory flow. True volume limitation is difficult to achieve, because cuffed endotracheal tubes are seldom used, and there is almost always some degree of volume loss around the endotracheal tube.

The cycling mechanism is the variable used to end inspiration. Most neonatal ventilators, including high-frequency ventilators, are time cycled, but changes in airway flow may also be used to end the inspiratory phase.[30] Termination of inspiration occurs when decelerating inspiratory flow has reached a preset percentage of peak inspiratory flow. At this point, the exhalation valve opens and expiration



• **Fig. 65.2** Hierarchical classification of conventional mechanical ventilators.

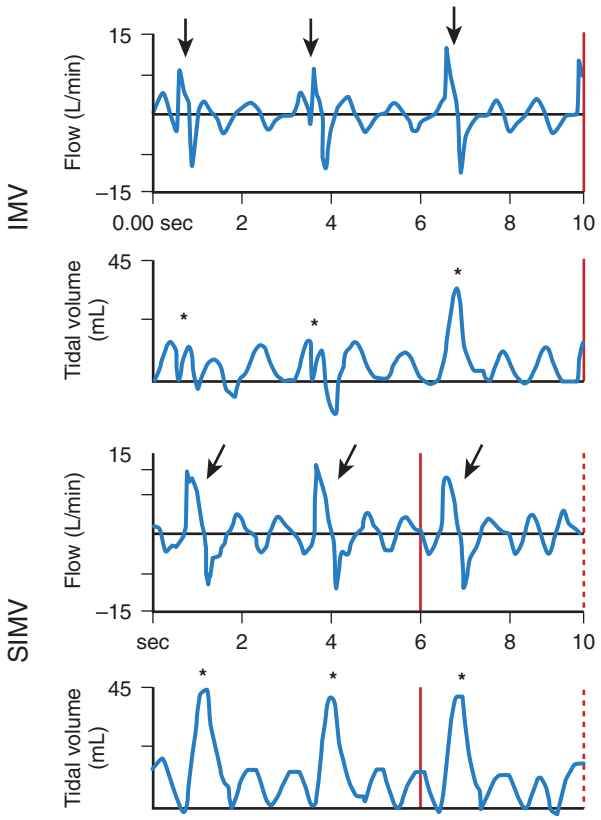
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begins. Flow cycling more accurately mimics the physiologic breathing pattern and allows for the mechanical breath to be fully synchronized to the spontaneous breath during both inspiration and expiration. Changes in transthoracic electrical impedance that occur during spontaneous respiration can also be used to generate a trigger signal.[110] Thus, triggering during both active inspiration and active expiration can achieve total synchronous breathing between the baby and the ventilator.

A recent addition to neonatal ventilation has been Neurally Adjusted Ventilatory Assist. This modality uses the electrical activity of the diaphragm to trigger, cycle, and control the level of support.[9] Although there is a paucity of clinical data, the method appears promising but will require further investigation.

Modes of Ventilation

Using different phase variables, which are interchangeable, a variety of ventilatory modes can be generated that are applicable to both pressure- and volume-controlled modalities. The commonly used ventilatory modes are intermittent mandatory ventilation (IMV), synchronized intermittent mandatory ventilation (SIMV), assist/control (A/C) ventilation, and pressure support ventilation (PSV).[50] Fig. 65.3 is a graphic comparison of IMV and SIMV demonstrating the effects of asynchronous ventilation.



• **Fig. 65.3** Comparison of tidal volume delivery and flow during intermittent mandatory ventilation (IMV) and synchronized intermittent mandatory ventilation (SIMV). Note the tremendous variability in delivered tidal volume (*noted by asterisks*) during IMV breaths (*vertical arrows*) and SIMV breaths (*diagonal arrows*). Dyssynchronous breathing during IMV leads to inefficient gas exchange.

Intermittent Mandatory Ventilation

Intermittent mandatory ventilation delivers mechanical breaths at a rate set by the clinician. Inflations are provided at regular intervals and are not influenced by spontaneous breathing. The baby may breathe spontaneously with, between, or even against the mechanical breath, supported only by PEEP, and patient-ventilator asynchrony can be a major problem, resulting in a wide variability in delivered tidal volume. Efforts to reduce asynchrony include increasing the rate to override the spontaneous drive and "capture" the baby, generous use of sedatives, and in some instances, the administration of skeletal muscle relaxants. Virtually all forms of synchronized ventilation have been shown to be superior to IMV, and the latter should only be used when there is a complete cessation of spontaneous breathing.

Synchronized Intermittent Mandatory Ventilation

Synchronized intermittent mandatory ventilation is a mode in which the onset of mechanical breaths is synchronized to the onset of spontaneous breaths if the patient begins to breathe within a timing window. As a result, mechanical breaths are not delivered as regularly as in IMV but vary slightly according to the baby's own breathing pattern. In between the mechanical breaths, the baby may breathe spontaneously, but again, the spontaneous breaths are supported only by PEEP unless pressure support is utilized (see later). In time-cycled SIMV, synchrony between mechanical and spontaneous breath occurs only during inspiration, because the inspiratory time for both mechanical and spontaneous breaths may be different. This discrepancy can be offset by using flow cycling, where synchrony occurs during both inspiration and expiration.

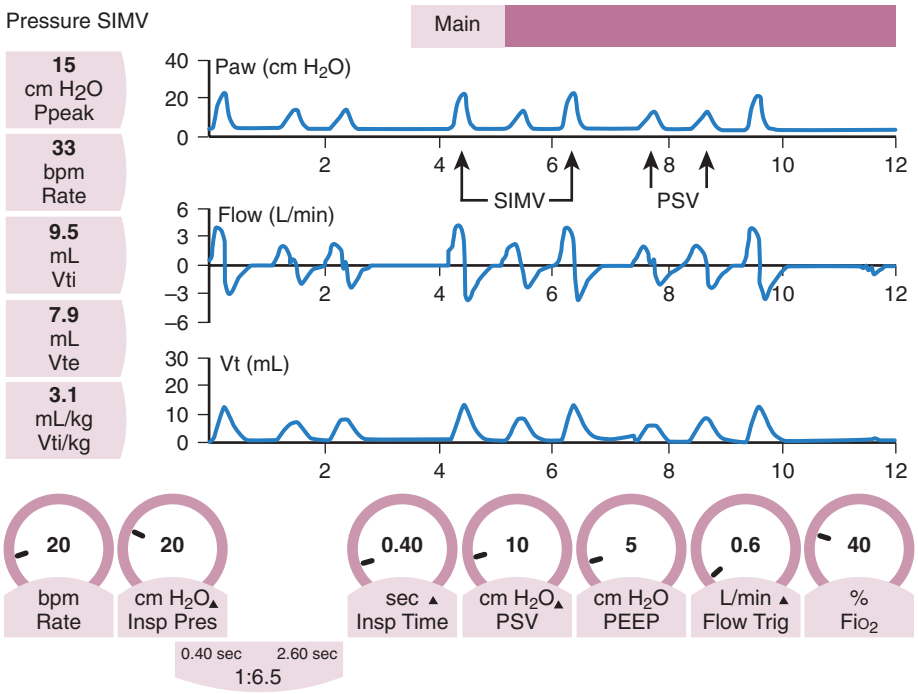
Assist/Control Ventilation

In the A/C mode, the ventilator delivers a mechanical breath each time the patient's inspiratory effort exceeds the preset threshold criterion. When the patient triggers the ventilator to deliver a mechanical breath, the breath is said to be assisted. This mode also provides the safety of a guaranteed minimal mechanical breath rate (the control rate, set by the operator) in case no patient effort occurs or none is detected. A/C breaths can be time-cycled or flow-cycled. During A/C ventilation, as long as the baby breathes above the control rate, lowering the control rate will have no effect on the total respiratory rate, and thus the reduction of pressure should be the primary weaning strategy (see later).[86,91]

Pressure Support Ventilation

Pressure support ventilation (PSV) was developed to help intubated patients overcome the imposed work of breathing created by the narrow lumen (high-resistance) endotracheal tube, circuit dead space, and demand valve (if one is being used). It is, however, a *spontaneous* breath mode.

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• **Fig. 65.4** Graphic representation of the combined use of synchronized intermittent mandatory ventilation (SIMV) and pressure support ventilation (PSV), where additional inspiratory pressure is applied to spontaneous breaths to help overcome the imposed work of breathing.

Spontaneous breaths that exceed the trigger threshold result in the delivery of additional inspiratory pressure to a limit set by the clinician. These breaths are flow-cycled, but for safety purposes they may be time limited. Most commonly, PSV is used in conjunction with SIMV to support spontaneous breathing between SIMV breaths with something more substantial than PEEP (Fig. 65.4). If the pressure limit of the PSV breath is adjusted to provide a full tidal volume breath, it is referred to as PS_{max}. If the pressure applied is just enough to overcome the imposed work of breathing, it is referred to as PS_{min}. PSV is a relatively new neonatal mode, but it is gaining acceptance.[77,79] It appears that it is most commonly used as a weaning strategy with low rate SIMV.[83]

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is a fully adaptive modality, which attempts to provide a breath in total synchrony with the patient. The ventilator will also adapt the inspiratory flow to provide a breath waveform that matches what the patient is attempting to do. To achieve this, the ventilator continuously measures the respiratory effort of the baby, proportionally adjusting pressure and flow. Unfortunately, there is a paucity of clinical data.

Pressure-Targeted Modalities

Pressure-targeted modalities are characterized by limiting the amount of pressure that can be delivered during inspiration. The clinician sets the maximum pressure, and the ventilator will not exceed this level. The volume of gas delivered to the baby will vary according to lung compliance and the degree of synchronization between the baby and the ventilator. If compliance is low, less volume will be delivered than if compliance is high.[90,93,94] In IMV, tidal volume will fluctuate depending on whether the baby is breathing with the ventilator or against it.

There are three main pressure-targeted modalities: pressure-limited ventilation (PLV), pressure control ventilation (PCV), and pressure support ventilation (PSV), which is also a mode. All three are pressure limited. Some devices allow both PLV and PCV to be time or flow cycled. Traditional PSV is flow cycled but time limited. Inspiratory flow during PLV is continuous and is set by the clinician. During both PCV and PSV, inspiratory flow is variable and is related to lung mechanics and patient effort. It accelerates rapidly early in inspiration then decelerates quickly, producing a characteristic waveform.[26] Some devices allow modulation of the accelerating portion by offering an adjustable rise time. This enables "fine tuning" of flow to avoid pressure overshoot or flow starvation and helps to achieve optimal hysteresis of the pressure-volume loop.

Pressure-limited ventilation has been used to treat neonatal respiratory failure for a half century. It was developed from adult ventilators by adding continuous flow to the bias circuit to allow the baby to have a fresh source of gas from which to breathe between mechanical inflations. It is relatively easy to use and was presumed to be safe, because the delivered inspiratory pressure could be limited, thus reducing the risks associated with barotrauma. Although the inspiratory pressure is very consistent on a breath-to-breath basis, the delivered tidal volume will fluctuate, as noted above. In the postsurfactant era, lung compliance may vary considerably following the administration of surfactant, and

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unless the clinician is vigilant, increasing tidal volume can lead to overexpansion and volutrauma.

Recently, PCV was introduced into neonatal ventilators. It differs from PLV primarily in the manner in which flow is regulated. PCV produces a waveform that accelerates rapidly then quickly decelerates. A rapid rise in flow early in inspiration leads to earlier pressurization of the ventilator circuit, and delivery of gas to the baby occurs early in inspiration. Intuitively, this should be beneficial in disease states characterized by homogeneity and the need for a higher opening pressure, such as early RDS. Variable flow should be advantageous when resistance is high, such as when a small endotracheal tube is used. The relative novelty of PCV has thus far precluded adequate comparison with PLV.

Both PLV and PCV are used as mandatory modes (IMV, SIMV, or A/C). PSV is a spontaneous mode; that is, it is applied only to spontaneous breaths the baby takes between mandatory mechanical inflations to support spontaneous breathing and overcome the imposed work of breathing created by the narrow lumen endotracheal tube, circuit dead space, and demand valve (if one is used). Because it is patient triggered and flow cycled, it is completely synchronized to the baby's own breathing, thus the baby controls the rate and the inspiratory time. The clinician sets the pressure level to augment spontaneous breathing. PSV can be used in conjunction with SIMV, or in patients with reliable respiratory drive, it may be used as a primary mode.[27] There is an evolving body of evidence that PSV is both safe and efficacious.[45,49,56,81,107] Still to be determined is the best way to apply PSV as a weaning tool. Table 65.1 compares the characteristics of pressure-targeted modalities.

Volume-Targeted Modalities

Broadly speaking, volume-targeted ventilation can be provided in several ways. Volume-controlled ventilation (VCV) targets a set tidal volume, which is delivered irrespective of lung compliance or the pressure required to deliver it (pressure may be limited for safety reasons). Hybrid ventilators are essentially pressure-targeted but aim to deliver the tidal volume within a set range using computer-controlled feedback mechanisms. Finally, standard pressure-targeted ventilation can function in a quasi–volume-targeted capacity if strict and vigilant attention is paid to volume delivery.[22]

TABLE 65.1 Characteristics of Pressure-Targeted Modalities

Parameter	Pressure Limited	Pressure Control	Pressure Support
Limit variable	Pressure	Pressure	Pressure
Inspiratory flow	Fixed	Variable	Variable
Cycle mechanism	Time or flow*	Time or flow*	Flow (time limited)

*Device specific and not available on all machines.

Volume-Controlled Ventilation

The first ventilator designed specifically for volume-targeted ventilation in infants was the Bourns LS 104-150, which was modified from an adult ventilator. Because of a multiplicity of problems, including a high trigger sensitivity, long response time, lack of continuous flow during spontaneous breathing, limited rate, poor circuit design, and the inability to measure small tidal volumes, this device (and VCV) fell out of favor in the early 1980s. Technologic advances in the 1990s enabled reintroduction of VCV to neonatal and pediatric patient populations. The new ventilators incorporate sophisticated devices to trigger, deliver, and accurately measure the tiny tidal volumes required by infants weighing as little as 500 g.

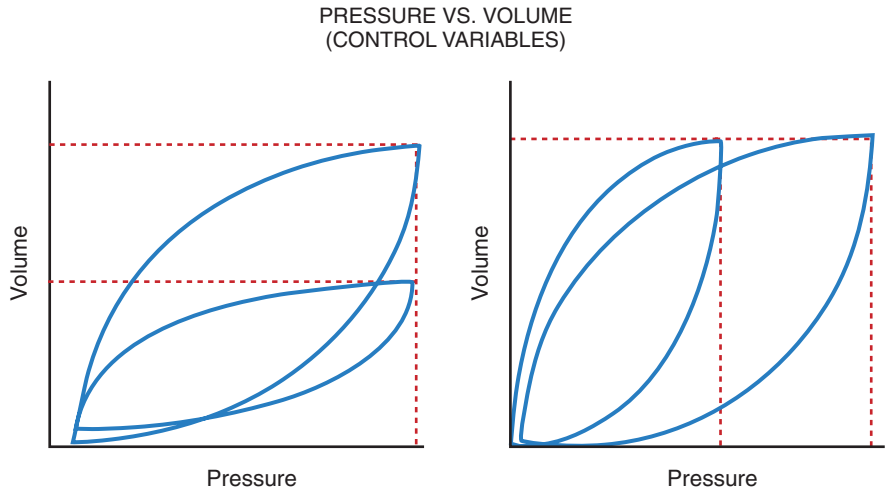
Volume-controlled ventilation for newborns differs from "adult" volume-cycled ventilation, where inspiration is terminated and the machine is cycled into expiration when the specific target tidal volume has been delivered. However, the use of uncuffed endotracheal tubes in newborns results in some degree of gas leak around the tube and precludes the ability to cycle based on a true delivered tidal volume. Thus, *volume cycling* is a misnomer in neonatal ventilation, and the terms *volume-controlled*, *volume-targeted*, or *volume-limited* better describe this modality. Many current ventilators provide the option of utilizing a leak compensation algorithm to at least partially offset this problem.

During VCV, there is also a discrepancy between the volume of gas leaving the ventilator and that reaching the proximal airway, which results from compression of gas within the ventilator circuit. This is referred to as *compressible volume loss*, which is greatest when pulmonary compliance is lowest. The use of semirigid circuits may help to offset this. Compressible volume is also affected by humidification. It is, therefore, critical that the delivered tidal volume is measured as close to the proximal airway as possible (i.e., at the patient wye piece).

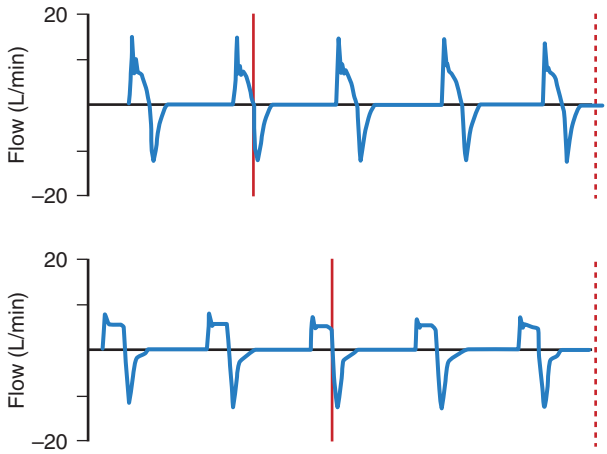
The principal feature of VCV is that it delivers the set tidal volume irrespective of the underlying lung compliance by automatically adjusting the peak inspiratory pressure (Fig. 65.5). Another important feature of VCV that differentiates it from PLV is the way that gas is delivered during the inspiratory phase.[94,102] In traditional VCV, a square flow waveform is generated and peak volume and pressure delivery are achieved at the end of inspiration (Fig. 65.6). These may be thought of as "back end" loaded breaths. In comparison, in PLV the gas flow pattern accelerates rapidly, then decelerates, resulting in the achievement of peak pressure and volume delivery early in inspiration. This produces a "front end" loaded breath. Because these are very different, certain disease states might be more amenable to one form than the other.

Detractors of VCV have argued that unlike the limited pressure used in PLV, VCV may utilize a high inflation pressure to deliver the preset volume in cases of decreased compliance. This anxiety in the past arose because of the perceived risks of barotrauma and its consequences associated with high PIP. However, since it has become clear that

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• **Fig. 65.5** Responses to changes in compliance in pressure- versus volume-targeted ventilation. In pressure-targeted, change in pulmonary compliance results in a change in delivered tidal volume while pressure remains constant (*left panel*). In volume-targeted ventilation, changes in compliance result in a change in pressure, while delivered tidal volume remains constant (*right panel*).



• **Fig. 65.6** Flow waveforms for pressure-targeted (*top*) and volume-targeted ventilation (*bottom*). Pressure-targeted produces a spiked waveform with rapid acceleration and deceleration of flow, producing peak pressure and volume delivery early in inspiration. Volume-targeted ventilation produces a characteristic "square wave," with constant or plateau flow. This results in peak pressure and volume delivery at the end of inspiration.

it is not necessarily the high pressure, but rather the excessive tidal volume (volutrauma) that causes lung injury,[37] attention to controlling tidal volume delivery has become an essential part of neonatal ventilation. It should also be realized that high peak pressure associated with fixed-flow delivery in VCV is a reflection of proximal airway pressure rather than alveolar pressure. When the compliance of the patient's lungs improves (increases), the ventilator generates less pressure to deliver the same tidal volume, thus leading to an automatic reduction of the PIP. It is also a misconception that pressure-limited ventilation of infants is superior to VCV, because it maintains a constant airway pressure in the presence of leaks around uncuffed endotracheal tubes. The reasoning seems to be that constant pressure implies that the delivered volume remains constant, but this is not true, because leaks around the uncuffed endotracheal tube also occur with PLV. Some VCV devices provide a way to compensate for leaks by adding additional flow to the circuit to automatically maintain a stable baseline pressure.

Like PLV, VCV can be provided as IMV, SIMV, and A/C ventilation. It may also be combined with PSV during SIMV and even A/C in some devices.[90]

Hybrid Volume-Targeted Ventilation

Some newer devices use a blended approach to volume targeting. They are primarily pressure-targeted ventilators but involve computerized servo-controlled ventilation, wherein a ventilator algorithm adjusts the rise and fall of pressure to produce tidal volume delivery within a set range. These include volume guarantee (VG), pressure-regulated volume control (PRVC), and volume-assured pressure support (VAPS). These hybrid forms try to achieve the same goal, the optimization of tidal volume delivery, although each has a different mechanism. Clinicians must familiarize themselves with the specific features of individual machines to maximize safety and efficacy.

Volume Guarantee Ventilation

Volume guarantee ventilation is a commonly used form of volume targeting.[58] It is a dual-loop, synchronized, pressure-targeted modality of ventilation with microprocessor-based adjustments in pressure to ensure adequate tidal volume delivery. The operator chooses a target tidal volume and selects a pressure limit up to which the inspiratory pressure (the working pressure) may be adjusted. The machine uses the exhaled tidal volume of the previous breath as a reference to adjust the working pressure up or down over the next breath to achieve the target volume. The auto feedback mechanism is an improvement in design but has some limitations. For example, if adjustments to PIP are made in small increments to avoid overcompensation and are based on the exhaled tidal volumes, the delivered tidal

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volume may not compensate for large breath-to-breath fluctuations in the presence of large leaks. Moreover, if catch-up adjustments in pressures occur every few breaths, it may not work if the ventilator rate is set at low levels such as those used during weaning. In this context, the term *guarantee* is somewhat misleading.

On some devices, VG can only be used in conjunction with patient-triggered modes, that is, A/C, SIMV, and PSV, but newer devices also offer the use of VG with nontriggered continuous mandatory ventilation. The inspiratory pressure is set at the upper desired pressure limit. If this pressure is reached and the set tidal volume has not been delivered, an alarm will sound. Automatic pressure changes are made in increments to avoid overcompensation. No more than 130% of the target tidal volume is supposed to be delivered. The usual starting target is a tidal volume of 4-5 mL/kg. The pressure limit is set approximately 15%-20% above the peak pressure needed to constantly deliver the target tidal volume. Most infants can be extubated when they consistently maintain tidal volume at or above the target value with delivered PIP less than 10-12 cm H_2O and with good sustained respiratory effort.[62]

Pressure-Regulated Volume Control Ventilation

Pressure-regulated volume control ventilation is another modality of ventilation that attempts to combine the benefits of PLV and VCV.[9] It is a flow-cycled modality that offers the variable flow rate of pressure control ventilation with a targeted tidal volume. Like VG, PRVC is also a form of closed-loop ventilation in which pressure is adjusted according to the tidal volume delivered. The clinician selects a target tidal volume and the maximum permissible pressure to deliver the tidal volume. The microprocessor of the ventilator attempts to use the lowest possible pressure with a decelerating flow waveform to deliver the set tidal volume. The first breath is delivered at 10 cm H_2O above PEEP and is used as a test breath to enable the microprocessor to calculate the pressure needed to deliver the selected tidal volume based on the patient's compliance. The next three breaths are delivered at a pressure of 75% of the calculated pressure needed. If the targeted tidal volume is not achieved, the inspiratory pressure is increased by 3 cm H_2O for each breath until the desired tidal volume is reached. If targeted tidal volume is exceeded, the inspiratory pressure is decreased by 3 cm H_2O. Inspiratory pressure is regulated by the ventilator between the PEEP level and 5 cm H_2O below the clinician-set upper pressure limit. In PRVC, the pressure is adjusted based on the average of four breaths, so variations in delivered tidal volume still occur.

Volume-Assured Pressure Support Ventilation

Volume-assured pressure support ventilation is a hybrid modality of ventilation that optimizes two types of inspiratory flow patterns (VAPS = PSV + VCV), thus combining the advantages of both pressure and volume ventilation within a single breath and on a breath-to-breath basis.[24] It is best described as *variable flow volume ventilation*. VAPS can be used in either A/C or SIMV modes, or alone in babies with reliable respiratory drive. Spontaneous breaths begin as PSV breaths. The ventilator measures the gas volume delivered when the inspiratory flow has decelerated to the minimal set value. As long as the delivered volume exceeds the desired level (set by the clinician), the breath behaves like a pressure support breath and is flow cycled. If the preset tidal volume has not been achieved, the breath will transition to a volume-controlled breath; the set flow will persist and the inspiratory time will be prolonged (and pressure may increase slightly) until the desired volume has been reached. VAPS can be used both in the acute phase of respiratory illness, in which the patient requires a substantial level of ventilatory support, and when a patient is being weaned from the ventilator, especially in the face of unstable ventilatory drive. The optimal flow acceleration varies with patient dynamics, patient demand, and patient circuit characteristics. Pulmonary graphics are an essential tool for making the appropriate adjustments with VAPS.

Volume Support Ventilation

Volume support ventilation is another hybrid modality combining features of PSV and PRVC.[9] It is intended for patients who are breathing spontaneously with sufficient respiratory drive. Similar to PRVC, breath rate and tidal/minute volume are preselected by the clinician; however, inspiratory time is determined by the patient. Like PRVC, the ventilator algorithm increases or decreases the pressure limit by no more than 3 cm H_2O at a time. Adjustments are made in sequential breaths until the target tidal volume is achieved. The flow, pressure, and volume graphics for a volume-supported breath are similar to those of pressure-supported breaths; however, evidence for efficacy of volume support can only be assessed by evaluating sequential graphic presentations over time, as in PRVC. The tidal volume waveform will increase in a stepwise fashion until the targeted volume is reached.

Pressure Augmentation

This is also a hybrid modality, which offers the benefit of matching the patient's flow demand while guaranteeing a minimal tidal volume. Pressure augmentation differs from PRVC in the following ways: (1) the preset tidal volume is only a minimum, and the patient can breathe above this level; (2) the minimum tidal volume is guaranteed by adjustment in flow rather than pressure, which is fixed at preselected level; and (3) adjustment to flow is made within each breath rather than several sequential breaths. Pressure augmentation is interactive with the patient and is dependent upon the patient's flow demand and lung dynamics. Pressure augmentation can be utilized in either the A/C or SIMV modes, in which volume-controlled breaths are selected.

A meta-analysis of volume- versus pressure-targeted ventilation demonstrates a number of advantages of volume targeting. The duration of ventilation was shorter, the incidence of air leaks was significantly less, and there were

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fewer severe neuroimaging abnormalities. There is also a statistically significant reduction in bronchopulmonary dysplasia in infants treated with volume targeting.[112] One study demonstrated better consistency and less variability in tidal volume delivery during volume targeting, which may explain some of these differences.[102]

Suggested Ventilatory Management Guidelines

Initiation of pressure-targeted ventilation is aimed at achieving adequate pulmonary gas exchange at the least possible pressure. Selection of pressure-limited or pressure control ventilation should be based on the pathophysiology of the respiratory failure. When the lungs are very stiff (poor compliance), such as in RDS, and there is a need for a high opening pressure, pressure control may be advantageous because of the rapid pressurization of the ventilator circuit and delivery of gas flow early in inspiration. If parenchymal disease is less heterogeneous, pressure-limited ventilation with slower inspiratory flow may be safer. Rapidly moving gas will preferentially ventilate the more compliant areas of the lung, perhaps contributing to ventilation-perfusion mismatch.

Pressure should be adequate enough to cause a visible rise in the chest wall during inspiration, and adequate breath sounds should be appreciated on auscultation. If measured, tidal volumes should be 4-6 mL/kg in preterm infants and 5-8 mL/kg in term infants.[69] Generally, PEEP is initiated at 4-6 cm H_2O, although higher levels are sometimes necessary. Remember that each baby is different and one setting does not fit all. The selection of a mode is usually based on personal preference, although A/C offers the most support. The rate should be adjusted to normalize minute ventilation and achieve normocapnia. It should not be too high, as this discourages spontaneous breathing.

The inspiratory time should be chosen according to the respiratory time constant. Small babies with stiff lungs generally require short inspiratory times, which tend to be proportional to birth weight.[86] Care must be taken to avoid gas trapping (see later).

The circuit (bias) flow rate should be adjusted to assure that it is adequate to meet the PIP within the allotted inspiratory time, but it should not be too high or it may cause turbulence, inefficient gas exchange, inadvertent PEEP, and lung overdistension.

Brief summaries of the clinical management protocol for VCV and VG are given in Table 65.2 and Box 65.6. In VCV (see Table 65.2), ventilation is generally initiated in the A/C mode using a desired inspiratory tidal volume of 4-6 mL/kg (measured at the proximal endotracheal tube) as the reference range to achieve the target blood gases. However, for monitoring and further adjustments in tidal volume delivery, expired (exhaled) tidal volume should be used as the reference, because it provides a more accurate measurement of the gas delivery to the lungs. To start weaning, a combination of low rate SIMV (6-20 breaths/minute) and PSV to augment spontaneous breathing seems best, because it compensates for the imposed work of breathing. In the beginning, the amount of pressure support should deliver a full tidal volume breath (PS_{max}), and with further improvement in spontaneous breathing, the PSV support can be reduced sequentially until a tidal volume of 3-4 mL/kg is

TABLE 65.2 Suggested Methods for Using Volume-Controlled Ventilation

Initial mode	Start in volume assist-control mode. Adjust volume at the machine to deliver 4-6 mL/kg (measured at proximal endotracheal tube).
Time limit (A/C)	Use flow to adjust inspiratory time to 0.2-0.4 seconds.
Target arterial blood gas range	pH: 7.25-7.4 P_{CO_2}: 40-60 mm Hg p_{O_2}: 50-80 mm Hg
Weaning	Wean by reducing volume as tolerated, but continue in A/C with control rate to assure normocapnia and tidal volume delivery at 3-4 mL/kg. Switch to SIMV/PS when control rate is <30 breaths/min. Load with a methylxanthine.
Weaning to extubation	Decrease SIMV rate to 10-20 breaths/min. Decrease pressure support to maintain tidal volume at 3-4 mL/kg.
Trial of extubation	Consider when pressure has been weaned to provide 3-4 mL/kg tidal volume and baby is breathing spontaneously at low rate SIMV.

A/C, Assist control; SIMV, synchronized intermittent mandatory ventilation.

• BOX 65.6 Suggested Methods for Using Volume Guarantee®

1. Press Vent Mode and select triggered mode of ventilation (SIMV, SIPPV = AC, PSV).
2. Set trigger sensitivity at most sensitive.
3. Set T_I, T_E (therefore, backup rate for apnea), FiO_2, P_{INSP}, PEEP, flow rate.
4. Press <VG>, preset V_T set by – and + buttons (starting value 4-6 mL/kg)
5. Connect infant to ventilator.
6. Select <Meas 1> or <VG> screen.
7. Check to see delivered V_T and PIP to delivery target V_T.
8. Adapt P_{INSP} (maximum allowed pressure) to actual peak inspiratory pressure.

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reached (PS_{min}). Most babies can be extubated from this level of support if they are showing regular respiratory drive.

In VG, the initial ventilation is started in the synchronized intermittent positive-pressure ventilation (SIPPV) mode with a trigger sensitivity set at 1, the most sensitive setting (see Box 65.6). This may need subsequent adjustment to reduce the effect of leak-induced auto-triggering. The starting tidal volume reference range is 4-6 mL/kg, which can be adjusted based on blood gas analyses. It takes between six and eight breaths to reach the targeted tidal volume; the exact number depends upon the respiratory rate. If the PIP being used to deliver the desired tidal volume is several cm H_2O below P_{INSP} (where P_{INSP} is the maximum allowed pressure), then the set P_{INSP} may be left as is. This extra available peak pressure can be used by the ventilator if lung compliance decreases (or resistance increases, endotracheal tube leak increases, or respiratory effort decreases). If the PIP used by the ventilator is close to or equal to the set P_{INSP}, the set P_{INSP} should be increased by at least 4-5 cm H_2O. This will allow the ventilator some leeway to deliver the desired tidal volume in the event that compliance decreases. Once appropriate levels of tidal volume have been established, weaning should be an "automatic" process, with the amount of pressure deployed by the ventilator to provide the set tidal volume decreasing as the infant recovers. When the peak airway pressure used is very low, the infant may be ready for extubation.[58]

Weaning Infants From Assisted Ventilation

Weaning is the process in which the work of breathing is shifted from the ventilator to the patient (Box 65.7). Signs that an infant is ready to be weaned include improved gas exchange and pulmonary mechanics,[109] more spontaneous breathing,[113] and greater assumption of the work of breathing by the baby.[34] The most common reason for failure to wean is failure to wean.

There are physiologic requisites for weaning.[108] First, the baby must have adequate spontaneous drive to sustain alveolar ventilation. This can be assessed by observation (how easily the baby appears to be breathing), and measurement of tidal volume and frequency, and thus calculation (or measurement) of minute ventilation. Second, the baby must be able to overcome the respiratory system load, which can be defined as the forces necessary to overcome the elastic and resistive properties of the lungs and airways.[34] Additionally, there are defined elements of weaning (see Box 65.7). Tidal volume determinants include amplitude, inspiratory time, gas flow rate, and pulmonary compliance. Frequency determinants include chemoreceptor function and carbon dioxide production, as well as acid-base balance. Minute ventilation is determined by the product of tidal volume and frequency, and both spontaneous and mechanical components need to be evaluated. The work of breathing refers to the force or pressure necessary to overcome those forces that oppose gas flow and expansion of the lung during inspiration. It may be estimated by the product of pressure and volume, or graphically as the integral of the pressure-volume loop; it is thus proportional to compliance, but it may also be elevated if there is increased resistance. It is an indirect measurement of energy expenditure or oxygen consumption. Finally, there are nutritional aspects. Adequate calories need to be provided to fuel the work of breathing and avoid catabolism. However, an excess of non-nitrogen calories may increase carbon dioxide production and impede weaning.[34]

Clinicians should also recognize impediments to successful weaning (see Box 65.7). These should be avoided or treated, if present, to provide the best possible chance for the baby to be successfully weaned and extubated. Adjunctive therapies, including corticosteroids, diuretics, and bronchodilators, are often utilized to facilitate weaning, but only methylxanthines have sufficient evidence to be recommended.[8]

Weaning Strategies

Because infants are placed on assisted ventilation for differing reasons, and because different primary strategies are utilized for the different causes of respiratory failure, it is nearly impossible to design a "one size fits all" strategy. It has become even more confusing in the era of patient-triggered ventilation. In earlier times, when IMV was the only available mode, the usual strategy was to sequentially lower the rate and allow the baby to assume a greater burden of gas exchange by spontaneous breathing. During triggered ventilation, as long as the baby breathes above the control rate, lowering the ventilator rate has no effect on gas exchange.

In general, it is probably best to reduce the potentially most harmful parameter first. With the exception of HFOV, it is best to limit changes to one parameter at a time to

• BOX 65.7 Weaning From Assisted Ventilation

Physiologic Requisites

- Adequate spontaneous respiratory drive
- Overcome respiratory system load

Elements of Weaning

- Maintenance of alveolar ventilation
- Tidal volume
- Frequency
- Assumption of work of breathing
- Nutritional aspects

Impediments to Weaning

- Infection
- Neurologic/neuromuscular dysfunction
- Electrolyte imbalance
- Metabolic alkalosis
- Congestive heart failure
- Anemia
- Sedatives/analgesics
- Malnutrition (inadequate calories or excessive non-nitrogen calories)

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better assess its impact on the baby's respiratory status. Avoid changes of a large magnitude, and be sure to document the baby's responses to changes so that subsequent care providers will be able to continue or adjust the plan.

Weaning and Ventilator Modes

For pressure-targeted A/C ventilation the primary strategy should be decreasing the PIP. It should be adjusted to keep tidal volume and P_{CO_2} in a reasonable range. If it is reduced too much, and alveolar ventilation is inadequate, it will be reflected by an increase in the spontaneous (and hence mechanical) ventilator rate. Increasing the assist sensitivity to increase the patient effort to trigger might be an alternative method, but there are no data to date to support this. Babies may be extubated directly from A/C, or they may be switched to SIMV or low-rate SIMV with PSV.

The goal of weaning in SIMV is to maintain minute ventilation while reducing the level of mechanical support. This can be accomplished by reductions in either the PIP or the SIMV rate, using the spontaneous rate as the monitored variable. As the SIMV rate is lowered, the baby may require additional support of spontaneous breathing to overcome the imposed work of breathing, either by increasing the PEEP, flow rate, or inspiratory time, or by adding PSV.

SIMV and PSV

The combined use of SIMV and PSV is analogous to A/C ventilation, except that changes can be made independently. Physiologic studies have demonstrated that if spontaneous breaths are fully supported with PSV (sufficient pressure to deliver a full tidal volume breath), lower SIMV rates can be used and weaning is faster.[49] In addition, the PSV breaths are fully synchronized, because they are patient triggered and flow cycled. If babies demonstrate reliable respiratory drive, PSV can even be used alone as a weaning strategy, with extubation occurring when the delivered tidal volumes are in the 3- to 5-mL/kg range.

Assessment for Extubation

In the past, predictive indices, such as blood gas or pulmonary mechanics testing, have not been adequately sensitive or specific in assessing readiness for extubation.[6,92] Part of the problem is not knowing what will happen to the airway once the endotracheal tube is removed, and obstructive apnea is common. Attention to spontaneous breathing while receiving only endotracheal CPAP has been shown to have a high positive predictive value for successful extubation. This can be accomplished by examining the relationship of spontaneous to mechanical ventilation[44,113] or simply by observing patient stability during a 10-minute period of CPAP.[55]

Postextubation Care

The care of the infant after extubation usually reflects clinician or institution preference. Most infants are extubated and placed on some form of continuous pressure provided by either nasal CPAP or nasal cannula, with or without supplemental oxygen. Most clinical trials support the use of CPAP to avoid postextubation failure.[21] Prone positioning has also been shown to improve gas exchange, perhaps by stabilizing the chest wall and allowing abdominal viscera to fall away from the diaphragm. Postextubation stridor is a relatively common occurrence from narrowing of the upper airway from swelling. It is usually transient, but it may require reintubation. Some affected infants will benefit from inhalational sympathomimetics or a short course of corticosteroids.

High-Frequency Ventilation

High-frequency ventilation (HFV) refers to a form of assisted ventilation in which the delivered gas volumes are less than the anatomic dead space volume and are provided to the patient at very rapid rates. During HFV, carbon dioxide removal is the product of frequency and approximately the square of the tidal volume, and thus the pressure required to set the amplitude can be considerably less than that used during conventional mechanical (tidal) ventilation (CMV). In addition, because the inspiratory times are much shorter, the duration of positive pressure is less and the alveoli are potentially exposed to less barotrauma. Because carbon dioxide removal can be achieved at lower amplitudes compared to conventional ventilation, HFV allows the clinician to use a higher PEEP with a wider margin of safety.[11] The two most commonly used forms of HFV are high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV)[16] (Table 65.3).

High-frequency ventilation has been used to treat lung conditions that have been challenging for CMV, including air leaks, refractory hypoxemia, and respiratory insufficiency after cardiac surgery. It also differs from CMV in not trying to mimic normal spontaneous breathing, and because of its unique flow characteristics, it provides a different pattern of gas distribution within the lungs, whereby airway resistance, and not compliance, is the major determinant of gas distribution. Because gas flow is more rapid during HFV than

TABLE 65.3 Characteristics of High-Frequency Ventilation

	HFJV	HFOV
Rate	360-450 bpm	480-900 bpm
T_I	20 msec	10-20 msec
Exhalation	Passive	Active
Tandem CMV	Yes	No
Gas delivery	High velocity injector	Piston

bpm, Breaths per minute; CMV, conventional mechanical (tidal) ventilation; HFJV, high-frequency jet ventilation; HFOV, high-frequency oscillatory ventilation.

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during CMV, the gas-flow profile is more laminar or parabolic. Thus, inspiratory gas tends to remain in the center of the airways, enabling it to penetrate more deeply into the lung and to bypass airway disruptions, such as bronchopleural or tracheoesophageal fistulas,[35] or other thoracic air leaks, such as pneumothorax or pulmonary interstitial emphysema (PIE).[59]

Although the basic principles of mechanical ventilation are essentially the same for HFV as for CMV, HFV enables better uncoupling of oxygenation and ventilation. During CMV, adjustments made to improve oxygenation often adversely affect ventilation and vice versa. This phenomenon is much less apparent during HFV, particularly during oscillatory ventilation.

Although both HFJV and HFOV have been in use for more than 25 years, there is a relative paucity of evidence for either modality. A thorough review by Lampland and Mammel summarizes the clinical evidence.[65]

High-Frequency Jet Ventilation

This form of HFV involves pulses of high-velocity gas injected directly into the upper airway, either by a special endotracheal tube adapter (proximally) or a specialized triple-lumen endotracheal tube (distally). It is used in tandem with a conventional ventilator, which provides PEEP and can be used to deliver "sigh" breaths and maintain lung expansion.

High-frequency jet ventilation is similar to CMV in that inspiration is active and expiration is passive, meaning that exhaled gas flow results from the elastic recoil of the lungs. Theories of gas exchange during HFJV suggest that there may be some facilitation of expiratory gas flow by countercurrent energy imparted by the inspiratory flow. HFJV rates range from 240-660 breaths per minute; most commonly, rates of 360-450 are used in clinical practice. Inspiratory time is usually set at 0.02 seconds (20 msec). Gas volumes delivered during HFJV are considerably smaller than those delivered during CMV.[57]

Different strategies for using HFJV have been proposed for different diseases. A "low pressure" strategy is adopted for conditions in which air leak is the predominant pathophysiology. Here, the use of lower PIP allows for healing. If oxygenation is problematic, higher PEEP or more CMV support can be offered. The "optimal volume" strategy is used for conditions in which there is a tendency for the alveoli to collapse, such as RDS. HFJV is used to optimize the lung volume and improve ventilation/perfusion matching. Clinicians must be aware that because two ventilators are being used, there are usually two oxygen blenders, and both must be adjusted when a change in the fraction of inspired oxygen is made.

Clinical experience has demonstrated that HFJV is superior to rapid rate IMV in the management of preterm infants with pulmonary interstitial emphysema.[59] It has also been used to treat other types of intractable air leaks, such as esophageal atresia/tracheoesophageal fistula complicated by RDS.[35] One trial comparing HFJV to IMV for the early management of RDS showed less oxygen dependency at discharge when HFJV was used.[60]

High-Frequency Oscillatory Ventilation

This is another form of HFV. Its major distinguishing feature is the addition of active exhalation, whereby removal of exhaled gas is facilitated by negative pressure applied during expiration. Typical rates vary between 8 and 15 Hz (480-900 breaths per minute). Depending upon the nature of the device, I:E ratios vary from 1:1 to 1:2, and the clinical implication is that inspiratory times and tidal volumes are very short and small, respectively.

The general principles of mechanical ventilation also apply to the oscillator. Mean Paw is used to inflate the lung and recruit alveoli for oxygenation. This may be thought of as continuous distending pressure, because the lung remains inflated throughout the respiratory cycle. Ventilation is accomplished by adjusting the amplitude, which in turn regulates gas delivery during inspiration and gas removal during expiration.

High-frequency oscillatory ventilation has been used both as a primary strategy for the initial treatment of respiratory failure and as a rescue strategy for infants who fail to respond to CMV. Some centers prefer to wean and extubate directly from HFOV, whereas others prefer to transition to and wean from CMV. HFOV appears to be the best way to deliver inhaled nitric oxide because of its ability to recruit lung volume and match ventilation and perfusion.

The major drawback to HFOV is the inability to monitor the baby as closely as is possible with CMV. Proper settings are verified by blood gases, the degree of lung expansion on the chest radiograph, and by an assessment of chest wall movement during HFOV, referred to as the *chest wiggle factor*. Because intrathoracic pressure can be high, close attention needs to be paid to cardiac output and perfusion. In addition, care must be taken to avoid gas trapping in babies requiring a high amplitude for adequate ventilation, which can result in the collapse of the smaller airways, described as "choke points," during active exhalation.[17]

Monitoring of Ventilated Infants

Babies requiring assisted ventilation require close monitoring to assess underlying lung pathology, response to treatment, and surveillance for associated complications. Monitoring may be considered in five broad categories: (1) clinical evaluation; (2) assessment of gas exchange; (3) chest imaging; (4) pulmonary function and pulmonary mechanics testing; and (5) extrapulmonary monitoring, such as echocardiography and indicated imaging studies to screen for complications known to contribute to mortality and morbidity in ventilated infants.

Clinical Evaluation

Clinical examination of the cardiorespiratory system includes observations for general physical condition, chest

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wall movement, equality of air entry, and the presence of abnormal sounds such as rales, rhonchi, or heart murmurs. The clinician must evaluate the interaction between positive-pressure ventilation and the baby's spontaneous breaths to detect asynchrony, which can interfere with gas exchange and lead to gas trapping and air leaks. Rapid, shallow breathing and the presence of subcostal/intercostal retractions in ventilated babies may suggest air hunger or increased work of breathing, which can be corrected by adjustments of ventilator parameters. A hyperactive precordium, tachycardia, easily felt peripheral pulses, and the presence of a cardiac murmur appearing on day two or three suggests a left-to-right shunt through a patent ductus arteriosus. In contrast, right-to-left shunting causing cyanosis (and desaturation on pulse oximetry) suggests persistent pulmonary hypertension of the newborn. Assessment of cardiac function, blood pressure, and tissue perfusion is an important part of evaluation, because they have a direct effect on the respiratory status. Blood pressure measurements should be interpreted in conjunction with other indices of tissue perfusion, such as capillary refill time, acid-base status, urinary output, and echocardiographic evaluation of myocardial contractility and cardiac output.[40] Bedside transillumination by a bright fiberoptic light source applied to the chest wall is a useful and effective way to detect pneumothorax, pneumomediastinum, and pneumopericardium, which may require urgent attention.[28] Other systemic clinical evaluation includes examination of abdomen for tenderness or distension and an assessment of the neurologic status by assessing the tone, posture, and movement.

Assessment of Gas Exchange

Blood Gases and Acid-Base Balance

Clinical interpretation of blood gases alone conveys relatively little information and must be interpreted in a clinical context, taking into account factors such as the work of breathing, recent trends, and the stage of illness. For example, a $Paco_2$ of 65 mm Hg is a genuine source of concern in an infant in the first few hours of life, but may be perfectly acceptable in an infant who is chronically ventilated for bronchopulmonary dysplasia (BPD). There is also a wide range of "normal" blood gas values, depending upon gestational age, postnatal age, source (arterial, venous, or capillary), and disease state. In most infants with respiratory disease, the goal is not to make blood gases entirely normal but to keep them within a target range appropriate for the clinical status.[25]

Analysis of gas exchange also requires an understanding of respiratory physiology. Oxygenation is dependent on ventilation-perfusion matching, whereas movement of CO_2 from the blood into the alveoli is dependent on alveolar ventilation (the product of alveolar tidal volume and respiratory rate). The pH of arterial blood is determined primarily by $PaCO_2$, lactic acid (produced by anaerobic metabolism), and buffering capacity, particularly serum or plasma bicarbonate and plasma hemoglobin concentration.

Arterial blood gases remain the gold standard for assessment, but analysis can only be performed intermittently. Moreover, arterial catheters are invasive, and intermittent arterial sampling requires skill and is painful for the patient. These limitations have led to increasing acceptance of noninvasive techniques, such as transcutaneous oxygen monitoring ($tcPO_2$) and oxygen saturation monitoring using pulse oximetry (see Chapter 37). There are no data to show that any one method is superior. A $tcPO_2$ value of more than 80 mm Hg is associated with a higher incidence of retinopathy of prematurity. A correlation between $tcPO_2$ and pulse oximetry (SpO_2) showed that oxygen saturation above 92% carries a risk of hyperoxia and thus an increased risk of retinopathy of prematurity (ROP) in preterm babies receiving supplemental oxygen.[103] One disadvantage of pulse oximetry is that it is not reliable in cases of severe hypotension or marked edema. Pulse oximeters measure either functional saturation or fractional saturation, which are device specific. Before interpreting an SpO_2 reading, the quality of signal should be assessed by observing the accompanying arterial pulse waveform. Interpretation also needs to take the signal averaging time into consideration. Long signal averaging times may result in the failure to detect brief periods of desaturation or the interpretation of a cluster of short events as a single, prolonged episode, overestimating the incidence of longer episodes.[104]

A recent technological advance has been closed-loop control of oxygen delivery to ventilated infants. This device controls the fraction of inspired oxygen based on a value derived from the pulse oximeter. If saturation falls, the device increases the oxygen concentration to bring the saturation back to the desired range. Conversely, if the saturation is too high, the oxygen concentration will be lowered to avoid hyperoxia. In a multicenter trial evaluating the short-term use of the device, with infants serving as their own controls, a greater proportion of time was spent in the desired range during automatic control. Importantly, there was a highly statistical reduction in the number of manual interventions required during the automated phase.[18] Although not yet approved for use in the United States, the device is gaining widespread acceptance in Europe.

The ventilatory parameters that affect oxygenation include FiO_2, PIP, PEEP, inspiratory time, tidal volume, and flow rate. Persistent hypoxemia despite appropriate adjustments in ventilatory parameters may indicate inadequate pulmonary blood flow or perfusion or right-to-left shunting. Another important factor that affects arterial oxygen tension is altitude, and this is relevant to air transport of sick babies.

Transcutaneous partial pressure of carbon dioxide ($tcPCO_2$) can be measured noninvasively and continuously using a special skin electrode. One of the factors influencing measurements is sensor temperature, which is optimal at 42°C. If $tcPCO_2$ is used in combination with a $tcPO_2$ sensor, a sensor temperature of 44°C can be used without jeopardizing the precision of the $tcPCO_2$ measurement. Measurements of $tcPCO_2$ are relatively independent of sensor site

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and skin thickness. $tcPCO_2$ may be falsely high in severe shock, and precision may be affected if $PaCO_2$ is more than 45 mm Hg and/or arterial pH is less than 7.30, but there is no systemic over- or underestimation of $PaCO_2$ under these conditions. Sensitivity of $tcPCO_2$ in detecting hypercapnia and hypocapnia is 80%-90%.

Base Deficit

In the healthy term infant, the base deficit is usually 3-5 mEq/L. However, base deficit can vary significantly. In patients with a base deficit between 5 and 10 mEq/L, assuming reasonable tissue perfusion, no acute intervention is generally needed. However, a base deficit greater than 10 mEq/L should prompt a careful assessment of the infant for evidence of hypoperfusion. In most cases, correcting the underlying cause of metabolic acidosis is far more effective and less dangerous than administering sodium bicarbonate.

Capnometry or End-Tidal Carbon Dioxide Monitoring

End-tidal carbon dioxide ($ETCO_2$) is an alternative method of measuring carbon dioxide and is called *capnometry*.[117] Depending on the gas-sampling techniques, devices are either mainstream or sidestream capnometers. Capnometry measurements are less reliable than $tcPCO_2$ monitoring, especially when the ventilation-perfusion relationship is not uniform within the lungs, as in infants with RDS or persistent pulmonary hypertension of the newborn.

Partial pressure of CO_2 is affected by minute ventilation, which in turn is the product of tidal volume and frequency during CMV. Of these two parameters, adjustment in tidal volume (by adjusting the amplitude) has a more predictable effect on minute ventilation changes.

Radiography and Other Chest Imaging

Chest radiography is the most commonly used imaging modality on neonatal intensive care units, both for diagnosing and following the course of a disease process. However, the specificity of chest radiography is poor and should always be interpreted in context with clinical information. The findings on chest radiographs are mostly suggestive of pathology and are not always diagnostic.

Ultrasound is a very popular imaging modality because of its portability and scope of repeated examination without any ionizing radiation. Although use of ultrasound for diagnosis of primary respiratory disorders is limited, it can be used to evaluate diaphragmatic excursion and position in suspected cases of phrenic nerve paresis or paralysis. It may also be useful in assessing lung fluid dynamics and differentiating pulmonary edema from atelectasis. Computerized tomography and magnetic resonance imaging have limited use in the neonatal intensive care unit because of practical difficulties but are helpful in certain conditions such as congenital pulmonary adenomatoid malformation, pulmonary sequestration, or complex congenital heart disease when there is insufficient information from echocardiography (e.g., total anomalous pulmonary venous return). Color Doppler echocardiography is now routinely used for assessment of cardiac function and hemodynamic assessment, which may impact the respiratory status in ventilated infants.

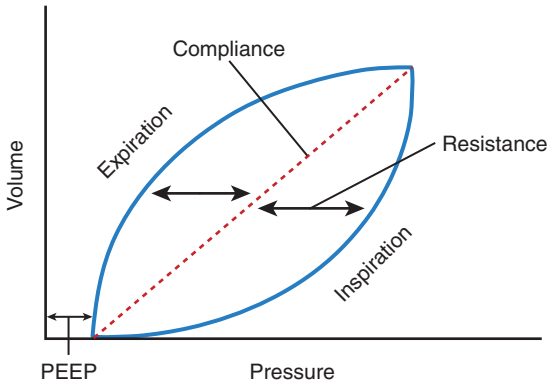
Real-Time Pulmonary Graphic Monitoring

Real-time graphic analysis of pulmonary mechanics in infants receiving assisted ventilation has emerged as a valuable tool to aid clinical decision making.[29] A working knowledge of pulmonary mechanics also improves understanding of pulmonary physiology and pathophysiology. Pulmonary mechanics monitoring consists of measurements of several parameters that define different aspects of lung function. Specifically, clinicians are interested in the *pressure* necessary to cause a *flow* of gas to enter the airway and increase the *volume* of the lungs. From these variables, several other measures of pulmonary mechanics can also be derived, such as pulmonary *compliance* (Fig. 65.7) and *resistance*, and resistive work of breathing (energetics). From this information, displayed as either numerical values or graphic representations, useful information can be obtained and used for diagnosing specific lung pathology, evaluating the disease progression, and determining the response to therapeutic interventions. Besides assessment of acute respiratory distress and evaluation of mechanical ventilation, other potential benefits of pulmonary graphics include assessment of suitability for weaning and the objective determination of the efficacy of pharmacologic treatments.

The two representations of pulmonary graphics most commonly used in clinical practice are waveforms and loops. Both patterns display the relationships between pressure, volume, and flow and time.

Volume and Pressure Waveforms

Measurement of tidal volume is becoming increasingly important in ventilatory management. The desired inspiratory tidal volume for a ventilated breath ranges from 4-7 mL/kg; for spontaneous breaths, a tidal volume of 3-4 mL/kg generally indicates suitability for weaning or



• **Fig. 65.7** Schematic representation of a pressure-volume loop denoting derivation of dynamic compliance and features of the relationship between pressure, volume, and time.

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extubating. Minute ventilation (tidal volume × frequency) is another predictor of weaning, especially in small infants who have short inspiratory times and a higher frequency. Normal values are generally between 240 and 360 mL/kg/min. Breath-to-breath variability and longer-term trends are useful in selecting the mode and modality of ventilation and designing individualized strategies based on pulmonary pathophysiology.

Flow Waveform

Flow is the volume of gas delivered per unit of time. Inspiratory flow is plotted above (positive) and expiratory flow is plotted below the abscissa (negative). The duration and shape of the inspiratory and expiratory flow waveforms are affected by many factors, including type of ventilation, I:E ratio, impedance and resistance to gas flow (Fig. 65.8), and the effect of therapeutic agents such as bronchodilators. The flow waveform can be used to determine if gas trapping is present (Fig. 65.9).

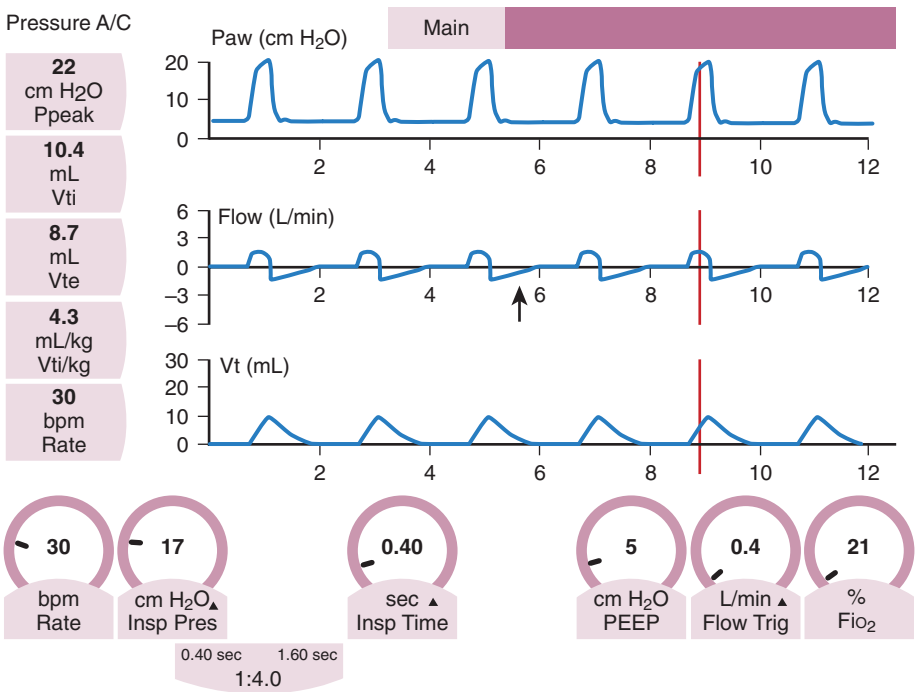
Pulmonary Mechanics (Loops)

Loops are commonly used to demonstrate correlations between airway pressure and volume, and airflow and lung volume (see Chapter 63). Pressure-volume (P-V) loops graphically depict the correlation between the ventilator inspiratory pressure and the volume of gas entering the lungs on a breath-to-breath basis. A line connecting the points of zero flow (the changeover from expiration to inspiration) is the compliance axis, and the slope of this line reflects pulmonary compliance (a measure of the change in volume per unit of added pressure). An estimate of compliance can be made by looking at the slope of the compliance axis; a 45-degree slope indicates a compliance of 1.0. If this slope is more toward vertical, compliance is improving, and conversely, if the axis moves nearer to horizontal, compliance is decreasing. Be sure that the scale of each axis is equal.

Increased resistance, as is seen in conditions such as meconium aspiration syndrome and BPD, causes a bowing around the compliance line and is an indirect measure of the work of breathing, which can be estimated by the P-V loop and the area to its left, as measured from the highest point. The P-V loop may also be used to determine the optimal PEEP. Pressure-volume loops that appear "boxlike" indicate the need for a higher opening pressure, and the shape can be normalized by increasing the PEEP and PIP. Another potentially dangerous condition, lung hyperinflation, can also be detected graphically (Fig. 65.10).

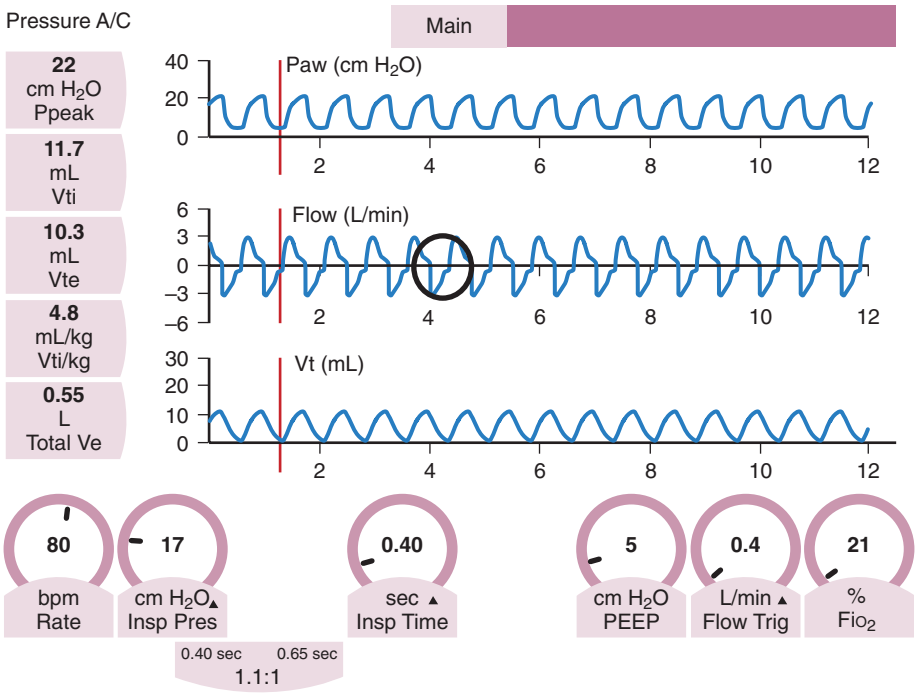
Another valuable measurement is resistance. This can be assessed by observing the flow-volume (F-V) loop, which graphically displays the relation between change in volume and change in airflow (Fig. 65.11). A normal flow-volume loop should be rounded or oval and should appear symmetrical with respect to the abscissa. Identification and measurement of endotracheal tube leaks is possible with graphic monitoring. Increased resistance and turbulent gas flow from excessive condensation in the ventilator circuit or secretions in the airway can also be identified by the appearance of a noisy flow signal.

It should be realized that graphic monitoring is largely pattern recognition and should be used to trend data. Appropriate scaling of axes is crucial to proper interpretation. However, if properly calibrated, the real-time

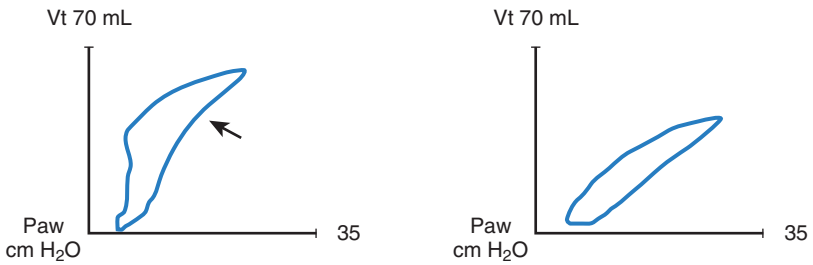


• **Fig. 65.8** Flow waveform demonstrating increased expiratory resistance. Note the decreased peak expiratory flow and the prolonged time to return to baseline (*arrow*).

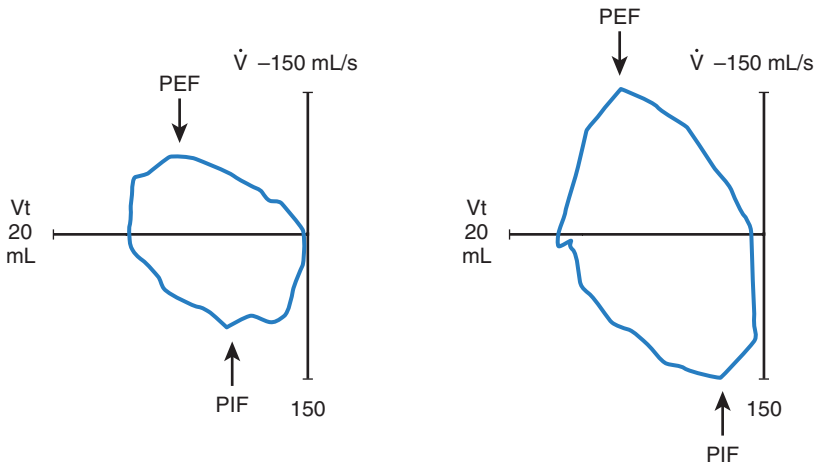
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• **Fig. 65.9** Flow waveform showing gas trapping (*circle*). Note that the expiratory portion of the flow waveform fails to reach the baseline (*zero flow state*) before the next breath is initiated.

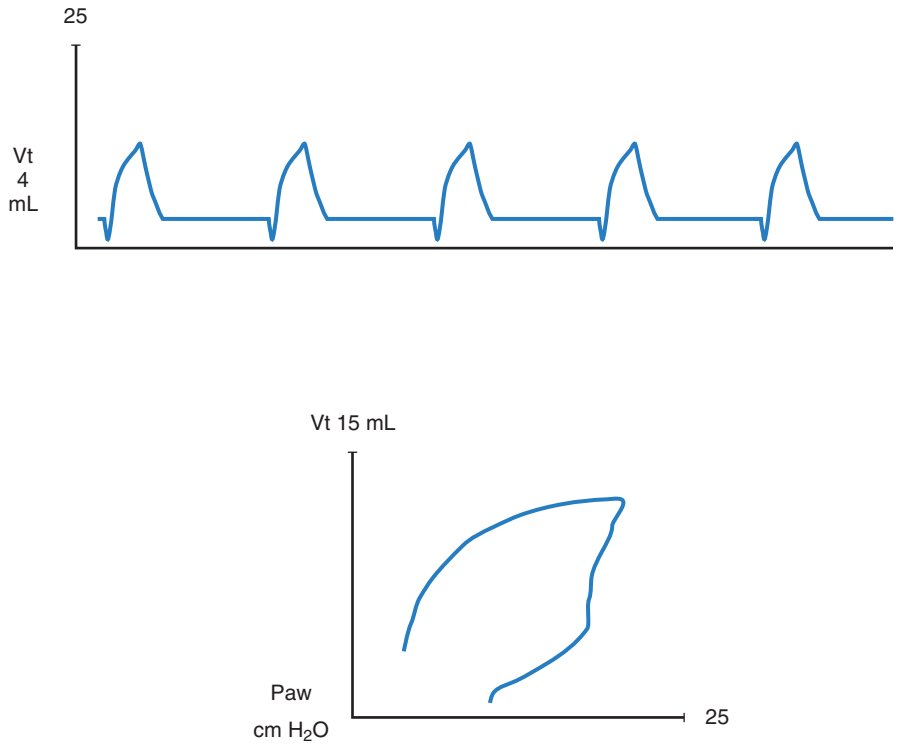


• **Fig. 65.10** Pressure-volume loops. The loop on the left shows hyperinflation. Note the upper inflection point (*arrow*). Above this point, incremental pressure is producing less change in lung volume per unit pressure than below it. On the right, peak inspiratory pressure has been reduced, and the loop now shows normal hysteresis.



• **Fig. 65.11** Flow-volume loops. On the left, increased resistance produces a smaller loop, with decreased peak inspiratory flow (PIF) and peak expiratory (PEF) flow. On the right, successful treatment with a bronchodilator decreased resistance and improved both PIF and PEF.

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• **Fig. 65.12** Large endotracheal tube leak. Note that the pressure-volume loop (*top*) fails to close, and the volume waveform fails to reach the baseline (*bottom*).

breath-to-breath view of pulmonary mechanics and respiratory waveforms allows the clinicians to fine-tune ventilator settings and provides constant surveillance for many potential complications such as gas trapping and lung overdistension before they become clinically apparent. Endotracheal tube leaks may also be detected graphically (Fig. 65.12).

Complications of Assisted Ventilation

Airway

Placement of an endotracheal tube into the airway can potentially damage the mucosal and submucosal tissues, causing injury that can obstruct gas exchange, lead to other functional disabilities, and create cosmetic deformities. Some of these are idiosyncratic, whereas others relate to the duration of ventilation, frequency of intubations, and associated complications such as infection. (Box 65.8 lists complications of assisted ventilation.)

Upper Airway

Procedural complications of endotracheal intubation are generally traumatic in nature and result from mechanical damage to structures in the naso- or oropharynx, trachea, and larynx. These injuries include superficial mucosal erosion, damage to the alveolar ridge (with subsequent dental problems),[75] perforation of the esophagus or trachea,[85,98] injury to the vocal cords,[114] and injury related to fixation devices such as tape. Long-term nasotracheal intubation may cause erosion of the nasal septum and nasal deformities.[46] Acquired palatal grooves[39] and even cleft palate[38] have been described after long-term orotracheal intubation.

Trachea

Less serious problems, which tend to resolve spontaneously over time, include tracheal and laryngeal mucosal metaplasia, subglottic cysts, tracheal enlargement, and tracheobronchomalacia. The latter is being increasingly recognized by the pediatric pulmonary follow-up of former preterm infants with lung injury.[52] Subglottic stenosis is a life-threatening condition generally requiring tracheostomy. Its etiology is still not completely understood, but associations have been demonstrated for duration of intubation, number of intubations, and the degree of prematurity.[87] Necrotizing tracheobronchitis was another highly lethal acquired entity.[10] This disorder was seen most commonly in the early days of HFJV and was felt to be related to the effects of insufficient humidification of inspired gas. It has all but disappeared since refinements in humidification systems.

Lungs

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is a disease entity defined as pneumonia characterized by the presence of new and persistent focal radiographic infiltrates in a ventilated infant appearing more than 48 hours after admission to the neonatal intensive care unit (see Chapters 48 through 50).

Ventilator-associated pneumonia is a commonly observed complication in babies requiring mechanical ventilation. It

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• BOX 65.8 Complications of Assisted Ventilation

Airway

Upper Airway

- Trauma
- Abnormal dentition
- Esophageal perforation
- Nasal septal injury (nasotracheal tubes)
- Acquired palatal groove (orotracheal tubes)

Trachea

- Tracheal and laryngeal mucosal metaplasma
- Subglottic cysts
- Tracheal enlargement
- Tracheo-bronchomalacia
- Tracheal perforation
- Vocal cord paralysis/paresis
- Subglottic stenosis
- Necrotizing tracheobronchitis

Lungs

- Ventilator associated pneumonia (VAP)
- Air leaks
  - Pneumomediastinum
  - Pneumothorax
  - Pulmonary interstitial emphysema
  - Pneumopericardium
  - Pneumoperitoneum (trans-diaphragmatic)
- Ventilator induced lung injury (VILI)
- Bronchopulmonary dysplasia (chronic lung disease)

Miscellaneous

- Imposed work of breathing
- Patent ductus arteriosus

Neurologic

- Intraventricular hemorrhage (IVH)
- Periventricular leukomalacia (PVL)
- Retinopathy of prematurity (ROP)

results from either dissemination of micro-organisms from colonized mucosal sites or aspiration of gastric contents. Repeated and prolonged endotracheal intubation, as well as suctioning, can disrupt mucosal integrity and promote dissemination. Occasionally microorganisms may be transmitted from contaminated equipment. The reported incidence of VAP is 0.3-1.6 cases per 1000 ventilator days in Level 2 and 3 NICUs in the United States.[51] A number of risk factors and associations have been identified, including prematurity; use of corticosteroids, H2 blockers, antacids, and proton pump inhibitors; overcrowding; understaffing; and inadequate disinfection of equipment.

One should suspect VAP in a ventilated infant if there is deterioration in the respiratory status unexplained by other events or conditions. Blood cultures may or may not be positive in infants with VAP. Sepsis and/or pneumonia should also be considered when there is unexplained temperature instability, hyper- or hypoglycemia, acidosis, feeding intolerance, or abdominal distension. Radiographic findings are nonspecific and may be difficult to distinguish from chronic lung disease in the older baby. Bacterial and fungal pathogens are the most common agents. Tracheal aspirates for culture are not helpful in the diagnosis of pneumonia and may merely reflect colonization. Laboratory investigations such as abnormal blood counts and elevated acute phase reactants such as CRP suggest the diagnosis of sepsis/pneumonia.[51]

Management of VAP includes broad-spectrum antibacterial and/or antifungal agents, hemodynamic support, and provision of adequate nutrition. Respiratory support should be maintained as necessary. If hypoxemia is refractory despite maximal ventilatory support, consideration should be given to use of inhaled nitric oxide and/or extracorporeal membrane oxygenation for term and late-preterm infants, if they meet criteria. Benefit from the use of additional surfactant is unproved, but anecdotal reports suggest efficacy with preparations that contain surfactant proteins A and D. A study by Aly et al. suggests that more frequent positioning of babies on their sides, as opposed to supine, may decrease the incidence of VAP.[3]

Air Leaks

Thoracic air leaks are collections of pulmonary gas residing outside the pulmonary air spaces. They include pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema (PIE), pneumoperitoneum, and subcutaneous emphysema. Pneumothorax often results from high inspiratory pressure and unevenly distributed ventilation. The ventilator parameters that are contributory to the development of pneumothorax include: (1) a prolonged inspiratory time and/or an inversed I:E ratio, (2) high PIP or mean Paw, (3) high flow rates, and (4) patient-ventilator asynchrony. There is also higher incidence of pneumothorax in the presence of certain disease conditions, such as meconium and other aspiration syndromes, cystic fibrosis, and pulmonary hypoplasia, which are characterized by uneven lung compliance and alveolar overdistension.

Pneumothorax in patients receiving positive-pressure ventilation can manifest in three ways: (1) asymptomatic, where it is first detected on a routine chest radiograph without or with subtle clinical signs; (2) deterioration in laboratory or bedside monitoring findings, without an obvious change in the patient's clinical condition, but is suspected because of worsening blood gases and increasing ventilatory requirements; and (3) acute clinical deterioration with tension, which is the most common presentation in ventilated infants. Infants with tension pneumothorax present with agitation and increasing respiratory distress, hypotension, and other signs of cardiovascular collapse. Auscultation of the chest reveals diminished or absent breath sounds on the affected side, with a contralateral shift of heart sounds and the point of maximum impulse. Breath sounds on the contralateral side may also be decreased as tension worsens and compresses the unaffected lung. Arterial blood gases may show respiratory or mixed acidosis and hypoxemia. Transillumination will reveal increased

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transmission of light on the involved side. Chest radiography is confirmatory. Tension pneumothorax is a medical emergency and requires prompt treatment. Needle aspiration (thoracentesis) can be used as a temporizing measure but generally needs to be followed by placement of a chest tube (thoracostomy) for resolution. Smaller gas collections may resolve spontaneously without further intervention but are likely to recur with ongoing mechanical ventilation.

The incidence of pneumothorax has diminished over the years. This may be related to a number of factors, including antenatal corticosteroid treatment, surfactant therapy, and the increased use of prenatal ultrasound, which has enabled the diagnosis of conditions such as congenital diaphragmatic hernia and pulmonary hypoplasia with predisposition to pneumothorax. Various ventilatory strategies have also been employed to reduce the risks of air leak. Rapid rate IMV (>60 breaths/min) has been utilized to decrease inspiratory time and the duration of positive pressure (and hence tidal volume) and to produce less asynchronous breathing. However, rapid-rate ventilation can also cause inadvertent PEEP and gas trapping. Synchronized ventilation, such as SIMV or A/C, may reduce the incidence of air leak by avoiding patient-ventilator asynchrony. The use of flow cycling enables complete synchronization, even during expiration. In rare instances, neuromuscular paralysis may be needed when a patient is actively "fighting" the ventilator despite adequate sedation.

Pulmonary interstitial emphysema often precedes the development of pneumothorax and can be localized or widespread throughout one or both lungs. It develops when the most compliant portion of the terminal airway ruptures, allowing gas to escape into the interstitial space. Gas may accumulate in the interstitium, compressing both the airway and adjacent alveoli. PIE alters pulmonary mechanics by decreasing compliance, increasing resistance, contributing to gas trapping, and increasing ventilation-perfusion (V/Q) mismatch; it also impedes pulmonary blood flow. Diagnosis is based on the chest radiograph, which shows fine linear or radial radiolucencies. Unilateral PIE that is less severe may respond to decubitus positioning. Left-sided PIE may be alleviated by selective intubation of the right main bronchus if the infant can tolerate single lung ventilation. Management of generalized PIE should aim to reduce inspiratory time and/or pressure. An often used strategy is to increase the PEEP in an attempt to stent the airways and allow more complete emptying of the alveoli during expiration. Alternatively, HFJV has been shown to decrease time to resolution and to improve survival in VLBW infants compared to rapid-rate IMV.[59]

Pneumomediastinum is usually of little clinical importance and usually does not need to be drained. However, its presence should alert the clinician of an increased risk for subsequent symptomatic air leaks. Symptomatic infants are often placed in 100% oxygen for up to 24 hours (nitrogen washout). Although this may make the infant more comfortable and potentially decrease the air leak, there is no evidence to support the practice.

Pneumopericardium occurs when air from the pleural space or mediastinum enters the pericardial sac through a defect that is often located at the reflection near the ostia of pulmonary veins. The diagnosis should be suspected from rapid clinical deterioration, which includes respiratory compromise and cardiovascular collapse, with a narrow pulse pressure and diminished perfusion. It can be diagnosed by transillumination and confirmed by radiography, which shows the air completely encircling the heart. Cardiac tamponade is a life-threatening event and requires immediate drainage. Needle aspiration (pericardiocentesis) via the subxiphoid route may be used to drain the air as a temporizing measure, but a pericardial drain is usually necessary. The majority of cases occur in infants ventilated with high PIP, high mean Paw, and long inspiratory times.

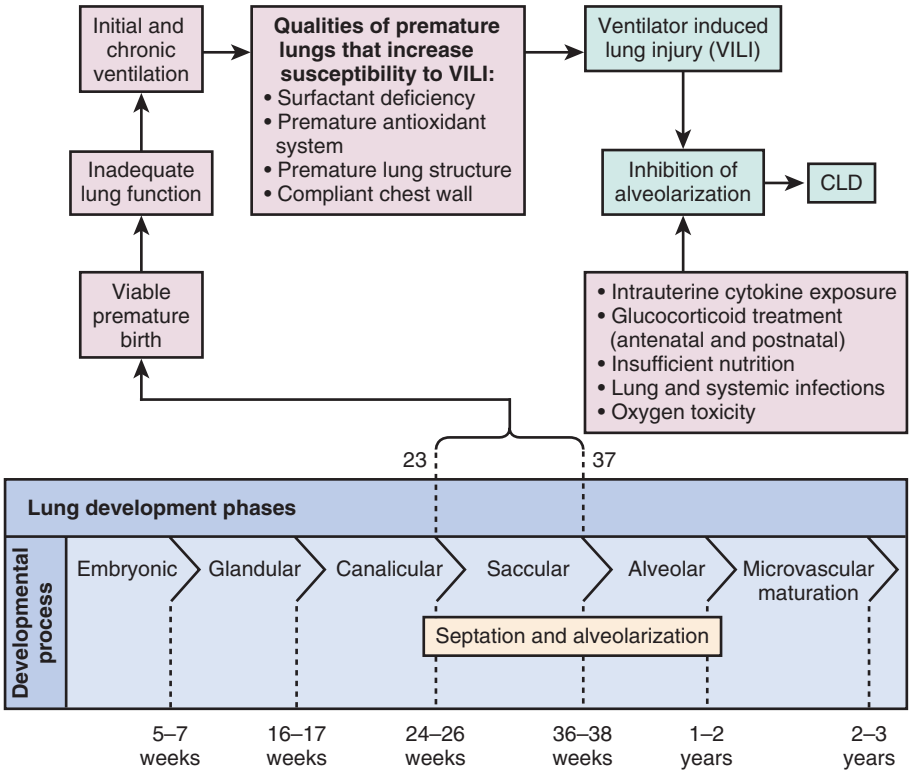
Pneumoperitoneum usually results from rupture or perforation of an abdominal viscus, but on rare occasions, gas from a thoracic leak can dissect trans-diaphragmatically to an abdominal location. Recognition of this phenomenon can avoid an unnecessary laparotomy. A sample of the abdominal gas may be aspirated by abdominal paracentesis and analyzed for its oxygen concentration (provided the baby is receiving more than room air). If the FiO_2 is greater than 0.21, the likely source is thoracic.

Ventilator-Induced Lung Injury

Despite the introduction of advanced ventilatory techniques based on sound physiologic principles, the incidence of chronic lung disease remains unacceptably high among babies who require mechanical ventilation, particularly for those born extremely prematurely. Bronchopulmonary dysplasia is multifactorial and involves a number of overlapping factors, such as prematurity, oxidant injury, inflammation, and injury related to mechanical ventilation, referred to as ventilator-induced lung injury (VILI).[5]

Various terms, such as *the pulmonary injury sequence*, have been used to describe the individual components of VILI (Fig. 65.13); these are interrelated and likely to act synergistically to damage the developing lung as part of the sequence.[5] Barotrauma, or excessive pressure, may disrupt airway epithelium and alveoli. Volutrauma refers to injury related to overdistension or stretching of the lung units by delivering too much gas. Atelectrauma refers to the damage caused by the repetitive opening and closing of the lung units (the cycle of recruitment and subsequent derecruitment). *Biotrauma* is a collective term to describe infection and inflammation, as well as the role of oxidative stress on the delicate tissue of the developing lung. *Rheotrauma* refers to damage evoked by inappropriate airway flow. If flow is excessive, inefficient gas exchange, inadvertent PEEP, turbulence, and lung overinflation may occur. On the other hand, if flow is inadequate, it may lead to air hunger (flow starvation) and increased work of breathing. The cumulative effect of both endogenous and exogenous insults to the developing lung is a reduction in alveolarization and diminished pulmonary surface area capable of effective gas exchange.

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• **Fig. 65.13** Pulmonary injury sequence leading to ventilator-induced lung injury and chronic lung disease (CLD). (Reproduced from Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. *Sem Neonatol*. 2002;7:353-360. Copyright, Elsevier Science Ltd, with permission).

With the introduction of newer techniques of mechanical ventilation, including pulmonary graphic monitoring, clinicians have now initiated strategies to avoid VILI. Monitoring of tidal volume delivery, irrespective of whether the target variable is volume or pressure, has become much more important in recent years. Indeed, delivering a physiologic tidal volume during conventional ventilation seems prudent. Of equal importance is the ability to customize ventilator settings to the specific needs of the patient.[33]

Bronchopulmonary Dysplasia (Chronic Lung Disease)

Despite high utilization of antenatal steroids, surfactant replacement therapy, and newer ventilation techniques, chronic lung disease remains the major problem of neonatal intensive care (see Chapter 69). Bronchopulmonary dysplasia is a severe form of chronic lung disease and is generally characterized by the presence of chronic respiratory insufficiency, a supplemental oxygen requirement, and an abnormal chest radiograph at 36 weeks' postmenstrual age. When Northway et al. originally described BPD in 1967, the affected infants ranged from 32-39 weeks' gestation and weighed 1474-3204 g at birth. Most had required high airway pressures and significant concentrations of supplemental oxygen. Their chest radiographs showed typical overinflation and cystic emphysema. More than a quarter of a century later, the demographics of BPD have changed. It occurs in more immature and very low birth weight babies who required only modest supplemental oxygen and ventilatory support. Their chest radiographs are also different and are characterized by diffuse haziness and a fine, lacy pattern. Infants with the "new" BPD do not seem to have had typical RDS, and many do not require ventilation during the first few days of life.[7]

Because BPD is associated with mechanical ventilation, some have advocated for the avoidance of assisted ventilation and the alternative use of noninvasive respiratory support such as NIPPV or NCPAP. However, randomized controlled trials that included more than 3000 preterm babies and compared noninvasive forms of respiratory support to mechanical ventilation through an endotracheal tube have not shown any reduction in either death or BPD, which were the primary outcome measures of these trials.[73,74,100,101] Attempts have also been made to use "gentler" ventilation by allowing "permissive hypercapnia" as a protective lung strategy.[71] The rationale for permissive hypercapnia is that by using less ventilation, there may be less volutrauma, a reduction of the duration of positive-pressure ventilation, and decreased alveolar ventilation. Although the secondary goals appear to be achievable, this approach has thus far failed to show a reduction in the incidence of BPD. In addition, it is very difficult to accomplish in the era of patient-triggered ventilation, because the baby with intact chemoreceptors will increase his minute ventilation to try to achieve normocapnia.

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There is compelling evidence that excessive tidal volume causes lung injury, so targeting tidal volume in a normal range (4-6 mL/kg) is gaining support within the neonatal community. In one randomized clinical trial, babies receiving volume-controlled ventilation were shown to have a trend toward reduction in BPD compared with those managed with pressure-limited ventilation.[89] A 20-month follow-up study of these infants also showed a reduced frequency of respiratory symptoms and need for treatment in the babies who had received volume-controlled ventilation.[88] This has been confirmed in a subsequent meta-analysis.[80]

High-frequency ventilation is often used as an alternative to conventional ventilation, and there is a large pool of data, both from animal and human studies, suggesting that this form of ventilation may have an advantage over conventional tidal ventilation in reducing lung injury. However, the cumulative evidence from clinical trials does not show a reduction in BPD.[65,96]

Unfortunately, clinical investigation has not yet demonstrated a beneficial effect from any form of ventilation in preventing lung injury associated with mechanical ventilation. This may be the result of a number of other factors, including the underlying immaturity of the lung itself, which is more susceptible to the damaging effects of extrinsic factors.

Miscellaneous Complications

Imposed Work of Breathing

Infants placed on mechanical ventilation assume additional burdens of breathing. First, there is an increase in airway resistance because of the placement of the narrow lumen endotracheal tube. Resistance to airflow is proportional to the fourth power of the radius of the tube and is linearly related to tube length. Second, there is an increase in dead space created by tubing and connectors. Finally, if a demand system is used, there is effort required to open the demand valve. Collectively, these have been referred to as the imposed work of breathing, primarily affecting spontaneous breaths taken by the baby between mechanical breaths. These spontaneous breaths are supported only by PEEP, unless the baby is receiving assist/control or pressure support ventilation, which was developed to overcome the imposed work of breathing and enhance patient comfort and endurance.

Patent Ductus Arteriosus

Patency of the ductus arteriosus (PDA) is a common problem in preterm infants. Its incidence varies inversely with gestational age and may be as high as 60% in infants less than 28 weeks' gestation (see Chapter 74). Its relationship to lung disease and mechanical ventilation is well established. Preterm infants have an immature closure mechanism, decreased sensitivity to normal constrictors such as oxygen tension, and increased sensitivity to prostaglandin-E_2, all of which promote patency. Other factors that have been associated with a PDA include severe lung disease, exogenous surfactant therapy, phototherapy, high fluid administration, early use of furosemide, and lack of antenatal glucocorticoid exposure.

The pathophysiologic effects of a PDA are determined by the direction of shunting. When pulmonary vascular resistance is high, such as with early RDS or meconium aspiration syndrome, shunting will be in a right-to-left direction, resulting in mixing of deoxygenated and oxygenated blood and resultant hypoxemia. When pulmonary vascular resistance is less than systemic vascular resistance, shunting will be left-to-right. Overperfusion of the lungs can alter pulmonary mechanics, causing a need for higher levels of supplemental oxygen and ventilatory support and an increase in the cardiac workload. A diastolic steal may also occur, reducing blood flow to organs and increasing the risk of ischemic complications. Persistent PDA is also associated with increased risks for apnea, BPD, congestive heart failure, and impaired weight gain. Diagnosis and treatment of PDA is discussed in detail in Chapter 74.

Neurologic Complications

Intraventricular Hemorrhage and Periventricular Leukomalacia

Premature babies requiring mechanical ventilation are at increased risk of brain injuries (see Chapters 52 and 53). The spectrum of brain injuries observed in these infants includes periventricular-intraventricular hemorrhage (PV-IVH) and periventricular leukomalacia (PVL). The main reason for the increased susceptibility to hemorrhagic or ischemic brain injuries is the unique anatomical and physiologic immaturity of the brain. Absent or reduced autoregulation of cerebral blood flow creates pressure-passive cerebral circulation and thus renders the brain prone to damage during periods of systemic hypotension and hypertension. Cerebral circulation (and autoregulation) is also affected by changes in $Paco_2$ and to a lesser extent pH. A rise in $Paco_2$ (hypercapnia) during the first 3-4 days of life is a recognized risk factor for PV-IVH. Conversely, hypocapnia (Pco_2 <35 mm Hg) is also potentially dangerous, because it may cause cerebral ischemia and PVL, especially if $Paco_2$ decreases rapidly as can sometimes occur with the institution of HFV. Another recognized risk factor for PV-IVH is the fluctuation in cerebral blood flow observed in babies who fight the ventilator (asynchronous breathing). The use of high PIP or PEEP can result in lung overdistension leading to increased central venous pressure, which is transmitted to cerebral veins. Increased intrathoracic pressure can also decrease venous return to the heart and thus reduce cardiac output. Additional threats to central nervous system function may come from a patent ductus arteriosus, with right-to-left shunting; from focal or systemic infections, which initiate the inflammatory responses associated with white matter damage; and from pneumothorax or PIE, which may also aggravate respiratory failure and hemodynamic function. Concerns also exist that cerebral perfusion may be

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jeopardized during routine procedures, such as endotracheal tube suctioning or re-intubation.

Retinopathy of Prematurity

Retinopathy of prematurity is a condition confined to the developing retinal vessels in very premature infants (see Chapter 96). The major risk factors for ROP are the degree of prematurity and a high arterial oxygen content. There is a higher incidence of ROP in low birth weight babies who require mechanical ventilation and supplemental oxygen. Hyperoxia, hypoxemia, and fluctuations of arterial oxygen content, even within the normal range, have all been implicated as etiologic factors. Many other risk factors have also been suggested, including vitamin E deficiency, exchange transfusions, necrotizing enterocolitis, treatment for patent ductus arteriosus, and other complications of prematurity. Despite meticulous neonatal care, ROP is not entirely preventable. Maintaining early arterial oxygen tension between 60 and 80 mm Hg and pulse oximetry between 88% and 92% has been shown to reduce the incidence of ROP in babies who receive oxygen treatment. With advancing postnatal age, it has been proposed that a higher target diminishes intermittent hypoxia and the neovascularization process in ROP. Nonetheless, the ideal level of oxygen saturation in ventilated preterm babies remains unknown.

The Neonatal Research Network SUPPORT trial utilized a factorial design to randomize infants between 24 and 28 weeks' gestation to either a higher or lower pulse oximetry range. Although the incidence of ROP was significantly reduced in the lower saturation group, there was a small but statistically significant increase in mortality. The reasons for this are unclear, and the optimal saturation range remains elusive.[100]

Key Points

- Newborn infants with respiratory failure will require ventilatory assistance, which ranges from supplemental oxygen to continuous distending pressure to assisted ventilation.
- No respiratory intervention is without risk to the baby, and it is the obligation of clinicians to minimize risk and maximizing benefit.
- Patients and diseases are all different, and a standard "one size fits all" strategy is no longer appropriate. Therapy must be customized to the individual patient.
- The principles of assisted ventilation are relatively simple. Mean airway pressure impacts oxygenation; amplitude impacts ventilation.
- The present popularity of noninvasive ventilation has not brought about the desired reduction in bronchopulmonary dysplasia. Additional investigation will be necessary to achieve this.

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66

Neonatal Respiratory Disorders

MOIRA A. CROWLEY

Multiple pathophysiologic mechanisms can present with pulmonary manifestations in term and preterm infants. The clinical picture is most commonly dominated by respiratory distress, which presents as tachypnea, grunting, flaring, retractions, cyanosis, and hypoxemia. However, apnea and hypoventilation are also common. In preterm infants, these manifestations are commonly associated with respiratory distress syndrome (RDS) as discussed in Chapter 64. Nonpulmonary etiologies of respiratory distress include thermal instability, circulatory problems, cardiac disease, neuromuscular disorders, sepsis, anemia or polycythemia, and methemoglobinemia (Box 66.1). This section presents an overview of the many other respiratory disorders that can affect preterm and term infants.

Developmental Diseases

Pulmonary Underdevelopment: Pulmonary Agenesis, Aplasia, and Hypoplasia

Abnormal lung development varies from mild hypoplasia, which can either be a primary or secondary defect, to agenesis of a single lobe or whole lung.[21,136] Agenesis of the lung is a rare congenital anomaly defined as the total absence of pulmonary parenchyma, its supporting vasculature, and bronchi after the bifurcation.[20,109] Complete agenesis of the lung is usually unilateral (90%), although dysgenesis of the other lung has been reported.[40] Pulmonary aplasia can be classified as a subset of pulmonary agenesis, defined by the presence of a blind-ending, rudimentary bronchus without associated lung parenchyma or pulmonary vasculature.[18] It has been hypothesized that pulmonary agenesis is vascular in origin, most likely resulting from a disruption of the dorsal aortic arch blood flow during the fourth week of gestation. Although lung agenesis can be an isolated finding, in as many as 50%-76% cases it is associated with other congenital malformations, including urogenital, vertebral, cardiac, and gastrointestinal, as well as malformations of the first and second branchial arch derivatives and radial ray defects.[20,40,133] As a result, pulmonary agenesis has been considered a subset of the VACTERL (*v*ertebral, *a*nal atresia, *c*ardiac defect, *t*racheo-*e*sophageal fistula, *r*enal anomalies, *l*imb anomalies) sequence and Goldenhar syndrome. Malformations of the first and second branchial arches and/or radial ray malformations are the most common malformations associated with pulmonary agenesis, and all cases are ipsilateral to the pulmonary malformation. Those who do not have facial or radial ray anomalies appear to fit the VACTERL association.[40]

Diagnosis is confirmed on antenatal ultrasound by the presence of mediastinal shift in the absence of a diaphragmatic hernia. Antenatal echocardiogram reveals total absence of the pulmonary artery or one of its branches on the affected side. Magnetic resonance imaging (MRI) examination can confirm the diagnosis, evaluate the size of the remaining lung, and evaluate the presence of other congenital malformations. After delivery, diagnosis of infants with unilateral pulmonary agenesis can be suspected by decreased breath sounds and displacement of the mediastinum to the affected side. Some breath sounds, however, may be audible over the affected side if a portion of normal lung, which usually has undergone compensatory hypertrophy, has herniated across the midline into the affected hemithorax. The radiographic appearance of a radiopaque hemithorax helps confirm the diagnosis, and accompanying vertebral defects are not uncommon (Fig. 66.1). Treatment is largely supportive, and the prognosis depends on the presence or absence of other anomalies; those with isolated pulmonary agenesis have better survival.[133]

Pulmonary hypoplasia is the result of deficient or incomplete development of the lung parenchyma leading to decreased number of distal airways, alveoli, and associated pulmonary vessels. It can be classified as either *primary*, caused by intrinsic failure of normal lung development, or *secondary*, caused by a multitude of different pathologic processes that interfere with normal lung development. The pathophysiology of secondary pulmonary hypoplasia includes (1) oligohydramnios secondary to renal malformations, prolonged early amniotic fluid leak, placental abnormalities, or intrauterine growth restriction; (2) space-occupying lesions compressing the lungs and preventing normal growth as seen with congenital diaphragmatic hernia (which is thought to have some evidence of primary pulmonary hypoplasia as well), cystic lung disease, or cardiac malformations with extreme cardiomegaly (e.g., tricuspid

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Abstract

Multiple pathophysiologic mechanisms can present with pulmonary manifestations in term and preterm infants. The clinical picture is most commonly dominated by respiratory distress, which presents as tachypnea, grunting, flaring, retractions, cyanosis, and hypoxemia. However, apnea and hypoventilation are also common. In preterm infants, these manifestations are commonly associated with respiratory distress syndrome (RDS) as discussed in Chapter 64. Nonpulmonary etiologies of respiratory distress include thermal instability, circulatory problems, cardiac disease, neuromuscular disorders, sepsis, anemia or polycythemia, and methemoglobinemia. This section presents an overview of the many other respiratory disorders that can affect preterm and term infants.

Keywords

congenital lung lesions
CDH
MAS

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• BOX 66.1 Classification of Extrapulmonary Causes of Respiratory Distress

Neuromuscular Disorders (see Chapter 56)

- Central nervous system: asphyxia, hemorrhage, malformations, drugs, infection
- Spinal cord: cord injury, spinal muscular atrophy
- Nerves: phrenic nerve injury, cranial nerve palsy
- Neuromuscular plate: myasthenia gravis
- Muscular: dystrophies

Obstructive-Restrictive Disorders

- Airway obstruction (see Chapter 68)
  - Intrinsic: choanal atresia, floppy epiglottis, laryngeal web, cord paralysis, laryngospasm, malacia, tracheal stenosis
  - Extrinsic: tubes, secretions, Pierre Robin syndrome, macroglossia, goiter, vascular ring, cystic hygroma, mediastinal and cervical masses
- Rib cage abnormalities
  - Thoracic dystrophies
  - Rickets and bone disease
  - Fractures
  - Pectus excavatum

Diaphragmatic Disorders

- Congenital eventration
- Abdominal distention

Hematologic Disorders (see Chapter 79)

- Anemia
- Polycythemia
- Methemoglobinemia

Metabolic Disorders (see Part 15)

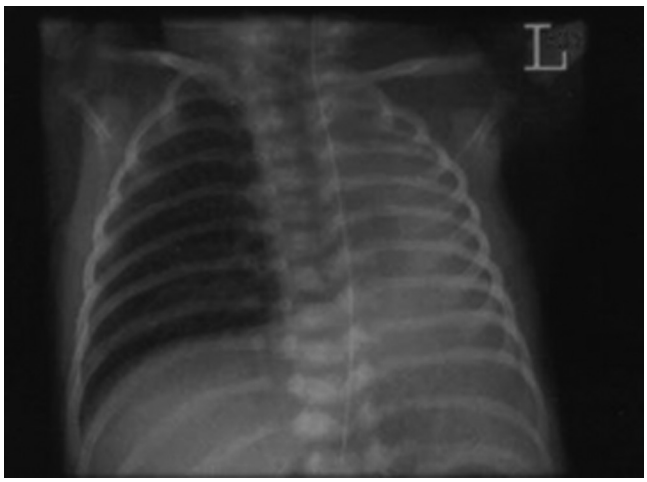
- Metabolic acidosis
- Hypoglycemia
- Hypocalcemia

Cardiovascular Disorders (see Part 12)

- Increased pulmonary flow
  - Patent ductus arteriosus
  - Ventricular septal defect
  - Transposition of the great arteries
  - Truncus arteriosus
- Decreased pulmonary flow
- Persistent pulmonary hypertension
  - Pulmonary atresia
  - Tetralogy of Fallot
  - Tricuspid atresia
- Cardiomegaly
  - Tricuspid atresia
  - Ebstein anomaly
- Left heart obstruction (e.g., coarctation, mitral atresia, total anomalous pulmonary venous return)
- Hypotension

Miscellaneous (see Parts 6 and 9)

- Sepsis
- Pain
- Hypothermia
- Hyperthermia



• **Fig. 66.1** Unilateral left lung agenesis. (From Greenough A, Ahmed J, Broughton S. Unilateral pulmonary agenesis. *J Perinat Med*. 2006;34:80, with permission.)

atresia or Ebstein anomaly); and (3) absence or abnormal diaphragmatic activity (which is essential for lung development) resulting from a central or peripheral nervous system disorder or musculoskeletal disease, which can prevent chest wall expansion and breathing movements.

Diagnosis of pulmonary hypoplasia is made pathologically by measuring the lung-to-body ratio; however, this truly only captures those with lethal pulmonary hypoplasia. Methods to diagnose pulmonary hypoplasia antenatally in those fetuses at risk for developing pulmonary hypoplasia because of associated findings have been reported and include the use of prenatal ultrasound techniques, both two- and three-dimensional, as well as fetal MRI. Ultrasound measurement techniques include thoracic circumference (TC) corrected for gestational age or femur length, TC:abdominal circumference ratio, and thoracic:heart area. These techniques, however, measure the thoracic wall rather than lung parenchyma itself and have inadequate positive and negative predictive values to be a reliable tool for predicting pulmonary hypoplasia in isolation. More recently, measurement of lung volume using three-dimensional ultrasound has been reported, but even in the most experienced hands, 8%-48% of cases did not have a calculable lung volume on at least one side.[159] MRI has shown promise in predicting pulmonary hypoplasia, especially in the setting of congenital diaphragmatic hernia (CDH), but seems to be no better for other causes of pulmonary hypoplasia.[159] Pathologic examination of the hypoplastic lung can show a low ratio of lung to body weight, low DNA content, or decreased radial alveolar count. Peripheral bronchioles are decreased in number, as are the pulmonary arterioles, which often exhibit hypertrophy of medial smooth muscle, a predisposition to persistent pulmonary hypertension.

Secondary pulmonary hypoplasia is most commonly encountered in oligohydramnios and congenital

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diaphragmatic hernia (CDH). Survival of infants with pulmonary hypoplasia depends on the degree to which lung growth is restricted and the underlying cause of hypoplasia. It is not uncommon for these patients to present with severe respiratory distress associated with bilateral pneumothorax as well as hypoxia from both fixed and reactive pulmonary hypertension. Pulmonary hypoplasia is present in up to 33% of patients with oligohydramnios and can be associated with a high mortality rate (55%-100%) depending on the severity of hypoplasia[100] (see Chapter 24). Patients with pulmonary hypoplasia secondary to prolonged premature rupture of membranes (PPROM) starting in the second trimester have been shown to have a better prognosis than initially expected. In four retrospective series of mid-trimester PPROM (18 0/7 to 24 6/7 weeks' gestation), higher survival rates of 68%-73%[52,102,167] to as high as 90%[22] have been reported. This is thought to be secondary to improved obstetrical (prenatal steroids) and modern neonatal therapies. However, among survivors, 36%-46% had bronchopulmonary dysplasia. Both human and animal studies have shown that some of these infants who present with early severe respiratory failure consistent with pulmonary hypoplasia may benefit from inhaled nitric oxide (iNO).[138,167] Supportive therapy with gentle ventilation is the mainstay of therapy. Serial amnioinfusion has been proposed as a potential therapy to mitigate the effects of oligohydramnios/anhydramnios and pulmonary hypoplasia caused by both PROM and renal abnormalities. When used in the setting of PROM, there is no improved survival,[162] but success has been reported in a few case series when used for renal abnormalities.[16,66] At this time, no randomized control trials exist to prove its efficacy in either case.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) results from a developmental defect during the formation of the diaphragm that permits abdominal contents to herniate into the thoracic cavity. In some cases, the herniated viscera are covered with a membranous sac. Defects of the diaphragm are classified according to the anatomic region of the diaphragm that is defective. The most common defect involves the posterolateral diaphragm (Bochdalek) and accounts for 70% of diaphragmatic hernias. Anterior diaphragm defects (Morgagni) account for 25%-30% of diaphragmatic hernias, and central diaphragmatic defects are rare, occurring in 2%-5% of cases.[84] The incidence of CDH is 1 in 2000-3000 live births, and it occurs most commonly on the left side (85%), whereas bilateral hernias are rare (1%) and usually fatal. In CDH, there are fewer alveoli that have thickened septae, resulting in markedly diminished alveolar airspace and gas exchange surface area. Vascular development parallels that of the airways, thus there also are reduced number of vessels, adventitial thickening, medial muscle hyperplasia, and peripheral extension of the muscular layer into the smaller intra-acinary arterioles, resulting in a fixed increase in pulmonary vascular resistance. Both lungs are affected, the ipsilateral one more than the contralateral one. After delivery, these morphologic changes compromise effective gas exchange, resulting in respiratory failure and pulmonary hypertension.

To explain the severe respiratory failure at birth owing to pulmonary hypoplasia, a *dual hit hypothesis* has been proposed. Traditionally, it was thought that the pulmonary hypoplasia associated with CDH was caused by compression of the lungs by the herniated abdominal viscera during early development. However, as our understanding of the pathophysiology grew, it has been demonstrated that pulmonary development has already been disturbed prior to diaphragm development and before compression from abdominal organs can occur. Thus, the dual hit hypothesis has emerged to explain the severe pulmonary hypoplasia often seen in this condition.[86] The first insult affects both lungs before diaphragm development is complete. The second insult affects the growth of the ipsilateral lung because of compression of that lung by the herniated viscera. The origin of the diaphragmatic defect lies in the disruption of the mesenchymal substrata of the pleuroperitoneal folds, which form the scaffold for the eventual migration of muscular precursor cells into the nascent diaphragm. In human embryology, this would point to a defect as early as 4-5 weeks' gestation, long before the formation of the "muscular" diaphragm.[31,115]

The pathogenesis of CDH and associated pulmonary hypoplasia are slowly being unraveled in part owing to animal models, which have confirmed that developmental regulation of the lung and diaphragm are controlled by some of the same genes. The nitrofen mouse model has proposed that CDH is a result of a disturbance in the retinoic acid pathway. A defect in the retinoid signaling pathway, specifically, inhibition of retinal dehydrogenase-2 (Raldh2), has been proposed as the likely etiology of the embryonic disruption resulting in CDH.[60,63,69,115] However, despite convincing animal data, the use of nitrofen and retinol have not been linked to human CDH.[84]

Congenital diaphragmatic hernia is either an isolated defect or can be associated with other congenital anomalies, including cardiac, urogenital, chromosomal, and musculoskeletal. Most reports estimate that 40%-60% of patients with CDH have non-hernia-related anomalies, designated CDH+.[171] In a review of 3062 patients with CDH, the Congenital Diaphragmatic Hernia Study Group reported a 28% incidence of severe malformations (major cardiac, syndromal, and chromosomal disorders) in patients who did not undergo surgical repair secondary to unsalvageable hernia compared with 7% in repaired patients.[156] In some of these CDH+ infants, the constellation of anomalies suggests a well-described genetic syndrome, the most frequent of which is Fryns syndrome, which has an autosomal recessive inheritance pattern. Another proportion of these CDH+ infants have been found to have chromosomal rearrangements including aneuploidy (trisomies 13, 18, 21, and Turner syndrome), segmental deletions, or duplications and rearrangements. Genetic analysis has identified a

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CDH critical region on chromosome 15q26, which codes for four genes involved in diaphragmatic morphogenesis. Microdeletions in this region have been described in several patients with nonisolated CDH and are associated with very high mortality. Other CDH "hot spots" include 1q41-q42, 3q22, 4p16, 8p23, 8q22, and 11p13. Haploinsufficiency or decreased expression of one or more genes encoded in these regions may cause or predispose to the development of CDH.

Recent advances in genetic diagnostic modalities along with the use of knockout mice have shed some light on specific genes that may be involved in the pathogenesis of CDH, including clues for both the diaphragmatic defect as well as the associated pulmonary hypoplasia. Several genes including Wilms tumor 1 (*Wt-1*) and members of the sonic hedgehog (*Shh*) pathway (*Shh*, *Gli2*, *Gli3*) have been implicated in CDH. *Wt-1*-, *Gli2*-, and *Gli3*-null mice have all been shown to have diaphragmatic defects. *Shh* has been demonstrated to be downregulated in human hypoplastic lungs of CDH patients. Another growth factor–related gene, platelet-derived growth factor (*PDGFRα*), was demonstrated to play a role in posterolateral diaphragm and lung development, but the mice knockouts demonstrate features of Fryns syndrome; thus *PDGFRα* may be involved in nonisolated CDH. As advances are made in molecular genetics, more candidate genes are being discovered.[82]

For all the reasons aforementioned, it is important to adequately evaluate for associated malformations in patients with CDH as well as genetic testing antenatally, if not then postnatally. About half of CDH cases are diagnosed antenatally. Antenatal diagnosis is associated with a poor prognosis, but the data suggest that infants with a prenatal diagnosis have a better chance of survival if they are born in a tertiary center with reported survival rates of isolated, operative CDH cases approaching 70%-90%.[105] Several antenatal parameters have been evaluated for their ability to predict survival and morbidity in cases of isolated CDH. Most of these predictors rely on the indirect assessment of the size of the contralateral lung as a proxy for pulmonary hypoplasia. Methods used include lung area to head circumference ratio (LHR) between 22 and 28 weeks' gestation, the presence of the liver in the chest (which has been thought to be most predictive), and estimated fetal lung volume by MRI.[24,68,75,77,110] Because it has been reported that the LHR increases exponentially with gestational age, some experts have advocated that the LHR should be corrected for gestational age and have used an observed:expected LHR (O/E LHR) based on the LHR in the CDH patient compared with what is considered normal for that gestational age.[74] When using the corrected LHR, the CDH registry has quoted the following numbers based on 184 fetuses with isolated left-sided CDH evaluated between 22 and 28 weeks' gestation[46]:

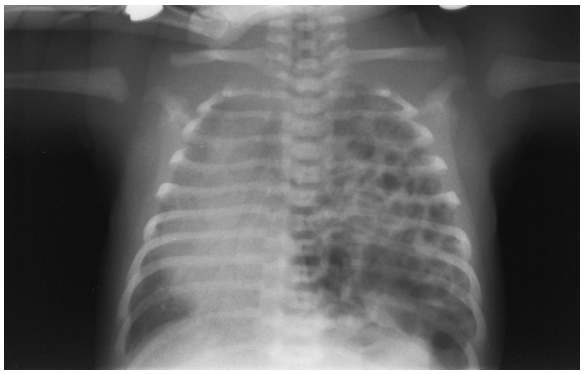
- Fetuses with O/E LHR less than 15% have extreme pulmonary hypoplasia, with virtually no survivors.
- Fetuses with O/E LHR between 15% and 25% have severe pulmonary hypoplasia, with a predicted survival of 20%. (Those with liver completely down in the abdomen fare better than those with liver herniated up into the chest.)
- Fetuses with O/E LHR between 26% and 35% and those with O/E LHR between 36% and 45%, but liver in the chest, have moderate pulmonary hypoplasia, with expected survival between 30% and 60%.
- Fetuses with O/E LHR between 36% and 45% with liver down and those with an O/E LHR greater than 45% have mild hypoplasia and are likely to survive (>75%).

More recently, authors have focused on the use of MRI to evaluate total lung volume (TLV), observed to expected TLV (O/E TLV), and the percentage of liver herniated into the chest (%LH) to predict survival and/or need for extracorporeal membrane oxygenation (ECMO) support. When using O/E TLV, thresholds of <25%, 25%-35%, and >35% were predictive of 0%-25%, 25%-69%, and 75%-89% survival respectively.[120] And when combining o/e TLV and %LH, severe CDH defined as an O/E TLV <32% and %LH >21% carried a 50% mortality; mild CDH were those with an o/e TLV >32% and %LH <21% had only an 8% risk of mortality.[131]

The ability of these parameters to predict survival has not been consistent. This is mostly secondary to the small number of patients in each series, challenges in measurement consistency among operators, lack of correlation with actual and functional lung volume and pulmonary vasculature size, inconsistent measures for survival or morbidity, and differences in postnatal management and survival. Nevertheless, these tools give clinicians some data to use when counseling families faced with the diagnosis of CDH.

The clinical presentation of patients with CDH can vary from asymptomatic in mild cases to severe respiratory failure at birth. Diagnosis should be suspected in previously undiagnosed patients by the presence of severe respiratory distress, cyanosis, scaphoid abdomen, and failure to improve with ventilation. Physical examination reveals absence of breath sounds on the affected side with displacement of heart sounds to the contralateral side, and occasionally bowel sounds can be heard over the thorax. Once the diagnosis is made or suspected, patients should be immediately intubated and an orogastric tube placed to evacuate the stomach. Aggressive ventilatory strategies should be avoided (see later). Chest radiograph shows the presence of bowel loops in the affected chest cavity with shifting of the heart to the contralateral side (Fig. 66.2). If the stomach is included in the hernia, the tip of the orogastric tube will be seen within the thorax. The presence of liver in the chest is suspected by deviation of the umbilical venous line. Late presentation of Bochdalek hernia occurs in less than 3% of cases.[91] These patients can be asymptomatic at birth and usually present later in life with respiratory or gastrointestinal symptoms. High index of suspicion is needed in these cases to prevent unwarranted and potentially dangerous interventions such as the insertion of a chest tube for suspected pleural effusion or pneumothorax. Diagnosis can be made after nasogastric tube insertion, contrast upper

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• **Fig. 66.2** Left-sided diaphragmatic hernia in a 1-day-old term infant.

• BOX 66.2 Management of Congenital Diaphragmatic Hernia

- Accept preductal saturations greater than or equal to 85%, $PaCO_2$ less than or equal to 65 mm Hg, and pH greater than or equal to 7.25.
- Identify preset ventilatory limits that are not to be exceeded.
- Use high-frequency oscillatory ventilation if conventional mechanical ventilation fails.
- Use ECMO per preset criteria.
- Delay surgery until persistent pulmonary hypertension improves.

gastrointestinal study, or chest computed tomography (CT) scan. Prognosis for cases with late presentation is excellent once the correct diagnosis is made.

Improved survival has been reported using a consistent approach in the management of CDH that can be facilitated by the development of multidisciplinary standardized treatment guidelines, including input from neonatology, pediatric surgery, ECMO specialists, and respiratory therapy (Box 66.2). Predetermined criteria for the use of ECMO and an underlying protect-the-lung strategy are essential components in the care of these infants and can be as important as the specific medical interventions chosen. Whereas animal studies have suggested lung immaturity and surfactant deficiency in models of CDH, the use of antenatal steroids and surfactant replacement has not been shown to be beneficial.[161] A systematic review of strategies associated with improved survival among infants with CDH in 13 centers that cared for at least 20 patients and reported a survival rate of 75% or more has described multiple successful treatment strategies associated with this improved survival.[105] Although these centers used different mechanical ventilation strategies, most of these targeted the use of gentle ventilation or permissive hypercapnia. The basic elements of this treatment strategy are:

1. Ventilation of the patient with low peak inspiratory pressures (PIP) to minimize lung injury. The goal of PIP is usually less than 25 cm H_2O.
2. Accepting preductal saturations of greater than or equal to 85%, regardless of postductal saturation, and higher $PaCO_2$ levels of less than or equal to 65 with a pH of at least 7.25 as long as there is evidence of adequate tissue perfusion and oxygenation.
3. Instituting high-frequency oscillatory ventilation (HFOV) or high-frequency positive pressure ventilation once the preset limit failed to achieve adequate ventilation, although HFOV was used by some as the primary mode of ventilation.
4. Even though iNO might produce short-term benefits, the routine use of iNO is not supported by current data and might actually be associated with a worse outcome (see Chapter 70).
5. Using ECMO as rescue therapy with variable indications in different centers, including persistent oxygenation index (OI) greater than 40, persistent hypoxemia, or failure of ventilatory management to support oxygenation, ventilation, or tissue perfusion (see Chapter 70).
6. Delaying surgical repair until physiologic stabilization and improvement of PPHN.

Surgical repair is delayed until the pulmonary hypertension is resolved or significantly improved such that, if need be, support may be escalated postoperatively if necessary. The procedure often involves either a primary closure of the diaphragmatic defect, or if too large, the use of a prosthetic patch. Recently, centers are reporting on thoracoscopic closure, but no trials comparing the methods exist.

Postnatal survival rate at tertiary centers has improved with reported rates of 70%-92%.[47,57,58,83,107,118] However, the survival data might underestimate hidden mortality secondary to termination, stillborn, and referral pattern for outborn patients. With improvement in survival, there has been a focus on improving long-term morbidity of survivors. Infants born with CDH have multiple long-term morbidities affecting the pulmonary, gastrointestinal, neurologic, and skeletal systems. Respiratory complications include pulmonary vascular abnormalities presumably causing pulmonary hypertension, a higher incidence of obstructive airway disease, and a restrictive lung function pattern that continues into adulthood.[146] Gastroesophageal reflux disease (GERD), sometimes in combination with failure to thrive, is a well-recognized complication in patients with CDH, and several patients require antireflux surgery. It is unknown whether GERD has an effect on pulmonary function in this population. Pulmonary hypoplasia and PPHN predispose children born with CDH to a high risk for hypoxemia, which may result in neurodevelopmental delay. It has been reported that infants with CDH are at higher risk to have neuromotor delay, hypotonia, and delayed language skills.[29] There is also a high percentage of these infants with sensorineural hearing loss.[42] Chest wall deformities and scoliosis are more common among CDH patients, although deformities are mild and surgery is rarely required.[121] These data emphasize the need for a multidisciplinary team approach in the postoperative management and follow-up of all survivors of CDH. The American Academy of Pediatrics (AAP) section on surgery has provided a suggested schedule for follow-up for these children.[137]

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More recently, fetal therapies, namely fetoscopic tracheal occlusion (FETO) in the most severe cases (where survival was nil given prenatal predictors), have shown some promise in improving survival in those cases, including improved lung growth in utero, less pulmonary hypertension, and overall improved survival when compared to expectant management. However, some of these successes have come at a cost of increased preterm delivery, although with improved techniques, the rate of preterm birth is declining.[76,132] There are several US centers trialing this approach now, and a large, international, multicenter, randomized control study is underway to evaluate not only FETO for severe CDH but also for moderately severe CDH and effectiveness performing fetoscopic tracheal occlusion at later gestational ages (30-32 weeks); this is the Tracheal Occlusion To Accelerate Lung Growth Trial.[27]

Alveolar Capillary Dysplasia

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) is a rare, often fatal pulmonary disease that presents in the newborn period, usually within the first 48 hours of life with severe hypoxemia and PPHN unresponsive to treatment.[17] The true incidence of the disease is unknown, because the diagnosis is made by pathology, and if there is no autopsy or antemortem lung biopsy, the diagnosis cannot be made; thus, what is reported in the literature likely underestimates the true incidence of the disease. Histologically, ACD/MPV is characterized by paucity of capillaries proximal to the alveolar epithelium, anomalous distended pulmonary veins within the bronchovascular bundle (rather than within the interlobular septae), and immature alveolar development with medial thickening of small pulmonary arteries and muscularization of the arterioles, and in approximately one-third of cases, lymphangiectasis. These characteristic findings are diffuse in 85% of patients and patchy in the remainder. Although the mechanisms underlying the pathogenesis of ACD/MPV and its associated pulmonary hypertension are not fully understood, it has been suggested that it is related to a failure of fetal lung vascularization with capillary hypoplasia and discontinuity of these capillaries and pulmonary veins impairing pulmonary blood flow, as well as a component of reactive pulmonary vasoconstriction mediated by hypoxia.[39,145] More recently, the role of prominent right-to-left intrapulmonary vascular shunt pathways have been identified and implicated in the severe hypoxia seen in these patients.[59] Extrapulmonary findings are present in 50%-80% of cases, most commonly affecting the gastrointestinal, genitourinary, and cardiovascular systems.[11,140] Although the disease is mostly sporadic, reports of multiple affected siblings in subsets of families suggest an autosomal recessive inheritance pattern.[139,141] Mutations of the *FOXF1* gene located on chromosome 16q24.1 have been identified in 70%-90% of patients with ACD/MPV, and more recently, there is evidence that genomic imprinting plays a role in the development of ACD/MPV.[155] This may allow for prenatal genetic testing of high-risk families; however, it will not identify all cases of ACD.[147]

Most patients with ACD/MPV present within the first few hours of life. These infants are usually born at term and have appropriate size and normal Apgar scores. Although these babies might be asymptomatic at delivery, respiratory distress, cyanosis, and hypoxemia progress quickly to respiratory failure in more than half of these patients within hours after delivery. About 14% of these patients do not present with symptoms until 2-6 weeks of life. Treatment is always unsatisfactory. Although a transient response to iNO might be observed, PPHN is not responsive to medical treatment, and the disease progression is that of a fulminant course and rapid progression to death, although there are reports of survival beyond the neonatal period. High index of suspicion and diagnostic lung biopsy are required to avoid the use of more invasive and futile treatments, including ECMO.

Congenital Pulmonary Lymphangiectasia

Congenital pulmonary lymphangiectasia (CPL) is a pulmonary disorder first described by Virchow in 1856, characterized by dilation of lymphatic vessels in multiple areas of the lungs. Most cases of CPL are sporadic with a predilection for male involvement (2:1). However, familial presentations have been described, suggesting an autosomal recessive inheritance pattern. The incidence is difficult to estimate as few cases are reported in the literature. Congenital pulmonary lymphangiectasia is classified as primary or secondary. Primary CPL can present as either a primary pulmonary developmental defect that can be localized or diffuse or as a part of a more generalized lymphatic developmental defect. Patients with generalized lymphangiectasia tend to have less severe pulmonary involvement. Secondary cases of CPL are often associated with cardiac malformations with obstructed pulmonary venous return, including obstructed total anomalous pulmonary venous return, hypoplastic left heart syndrome, and cor triatriatum. Congenital pulmonary lymphangiectasia has also been described in multiple syndromes, including Noonan, Down, and Ullrich-Turner. The characteristic pathologic finding of CPL is pulmonary lymphatic dilation in the subpleural, interlobar, perivascular, and peribronchial lymphatics. It may be associated with nonimmune hydrops fetalis and congenital chylothorax.[15]

The etiology of CPL is not clear but is thought to be secondary to a failure of regression of lymphatics that normally occurs between 16 and 20 weeks' gestation. Multiple genes have been found to be involved in lymphatic development, including *FOXC2*,[158] vascular endothelial growth factor 3,[148] and integrin a9b1 genes. Mice homozygous for a null mutation in the integrin a9 subunit gene died of respiratory failure caused by bilateral chylothorax within 6-12 days after birth with pathologic features similar to those in CPL.[71]

Patients with CPL usually present with intractable respiratory failure, cyanosis, and hypoxia associated with bilateral

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chylothoraces in the first few hours of life, although diagnosis can be delayed for several weeks in cases of unilobar involvement. Nonimmune hydrops is also a well-recognized presentation in patients with CPL. Examination of the pleural fluid shows characteristic findings of chylothorax, including a lymphocytosis and elevated triglycerides, although elevated triglycerides might be absent in nonfed infants (see later). Chest radiograph reveals hyperinflation of the lung with bilateral interstitial infiltrates and bilateral pleural effusions. High-resolution computed tomography demonstrates diffuse thickening of the peribronchovascular interstitium and the septa surrounding the lobules. Definitive diagnosis is made by lung biopsy showing the characteristic features: increased fibrous tissue with dilation of cystic lymphatic spaces and collapsed alveoli, although differentiation from lymphangiomatosis can be difficult.[15]

Treatment is mostly supportive. Intubation and mechanical ventilation; drainage of pleural and peritoneal effusions; and correction of hypoxia, acidosis, and shock might be needed in the delivery room for stabilization. Persistent chylothorax might require chest tube placement. Nutritional therapy with medium-chain triglycerides and total parenteral nutrition has been successful in the treatment of CPL. Case reports of using octreotide and antiplasmin to treat CPL as well as intestinal lymphangiectasia have been reported with success.[15] Pleurodesis with sclerosing agents has been used to treat persistent chylothoraces associated with the disease. More recently, reports of using lymphangiogram with ethiodized oil as a successful treatment modality have been reported.[61] The prognosis appears to depend on the severity of symptoms in the immediate newborn period. Although traditionally thought to be fatal, there are reports of survival in some patients presenting with respiratory failure, chylothorax, and hydrops fetalis in the immediate neonatal period. Later presentation carries a better prognosis with the possibility of spontaneous resolution, although respiratory morbidity might be common.

Chylothorax

Chylothorax is the accumulation of lymphatic fluid (chyle) in the pleural cavity. It is the most common cause of pleural effusion in neonates and can be primary (congenital) or secondary (acquired). It is a rare entity, with a reported incidence of 1:10,000 births, and affects males more than females (2:1).[49] Congenital chylothorax, which accounts for less than 10% of all chylothoraces, may be associated with abnormalities of the lymphatic system; congenital malformations such as congenital heart disease or mediastinal malignancies; or chromosomal abnormalities such as trisomy 21, Noonan syndrome, or Turner syndrome. Secondary chylothoraces are most commonly associated with trauma during thoracic surgery but can also be the result of increased superior vena caval pressure caused by venous thrombosis.

Clinical presentation is that of respiratory distress secondary to lung compression, pulmonary hypoplasia, or symptoms of the underlying pulmonary or cardiac disease. Many cases of congenital chylothorax are diagnosed by prenatal ultrasound, and antenatal management consists of thoracocentesis or thoracoamniotic shunt placement to try to prevent the development of pulmonary hypoplasia. However, even with prenatal treatment, these infants can still present with significant respiratory distress at birth as fluid reaccumulates, requiring postnatal treatment.

Physical examination is significant for decreased breath sounds on the affected side with shifting of the cardiac apex to the contralateral side. Chest radiograph shows a pleural effusion, compression of the lung on the affected side, and displacement of the heart to the opposite side. Diagnosis is established by analysis of the pleural fluid. In neonates with established feedings, chylothorax appears milky in color; however, in nonfed neonates, it is clear. Buttiker and colleagues have proposed the following criteria for establishing the diagnosis of chylothorax: absolute cell count of greater than 1000/μL with a lymphocyte fraction of greater than 80% and triglyceride levels greater than 1.1 mmol/L.[23]

Optimal treatment for chylothoraces has not been defined but is mostly supportive while awaiting resolution of the effusion. Mechanical ventilation and drainage of the chylothorax might be needed in patients with large effusions, and nutritional support using total parenteral nutrition is essential. When feedings are started, formulas containing a high percentage of medium-chain triglycerides (MCTs) are recommended, because lymphatics are not needed for MCT absorption. In most cases, spontaneous resolution occurs within 4-6 weeks. Several treatment strategies have been described for cases with persistent chylothorax, including pleurodesis, ligation of the thoracic duct, and pleuroperitoneal shunt.[10] Whereas povidone-iodine pleurodesis has been used successfully in persistent chylothorax, it has also been associated with renal failure. There is growing evidence from uncontrolled case studies suggesting a markedly positive effect of somatostatins, particularly octreotide, in the treatment of chylothorax with minimal side effects. In the absence of a controlled trial evaluating safety and efficacy, this therapy should be reserved for persistent and severe cases and not as first line of treatment.[130,143,170] Case reports of successful treatment with oral sildenafil, perhaps by generation of new lymphatic vessels, have been reported.[45,108] An emerging therapeutic modality is embolization of the thoracic duct with lipiodol; however, this procedure is in its infancy and will need further study before becoming a first-line therapy.[72]

Congenital Cystic Pulmonary Malformations

Congenital cystic lung disease encompasses a broad spectrum of rare, but clinically significant, developmental abnormalities that include congenital pulmonary airway malformation (CPAM; previously known as congenital cystic adenomatoid malformation CCAM), bronchopulmonary sequestration (BPS), bronchogenic cyst (BC),

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TABLE 66.1 Characteristics of Congenital Pulmonary Airway Malformation versus Bronchopulmonary Sequestration

	Congenital Pulmonary Airway Malformation	Bronchopulmonary Sequestration
Classification	Types 0-4, microcystic and macrocystic	Intralobar and extralobar
Connection to tracheobronchial tree	Yes	No
Systemic blood supply	No	Yes
Associated malformation	Common	Less common
Location	Either lower lobe	Left lower lobe
Malignant transformation	Yes	Yes
Spontaneous regression of antenatally diagnosed cases	15%	75%

and congenital lobar emphysema (CLE). These lesions are rare with an estimated incidence of 1 per 11,000-35,000 births.[13,95] They were originally thought to be separate entities; however, the description of coexistence of multiple lesions (bronchogenic cyst, CPAM, and extralobar BPS) in the same patient as well as reports of bronchial atresia in some specimens of all four entities suggests a common embryologic origin. These lesions can be identified on prenatal ultrasound, but the classification of the lesion should wait until postnatal examination and histology are available. These lesions should be followed closely in utero as some of these lesions can predispose the fetus to develop hydrops, and when this occurs in the second trimester, fetal intervention is warranted. Intervention includes repeated cyst aspiration, thoracoamniotic shunting, sclerotherapy, fetal surgery, or more recently, maternal betamethasone treatment. However, fetal intervention is relatively rarely needed, as many of these cystic lung lesions appear to regress in utero.

Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformation (CPAM) constitutes multiple different hamartomatous lesions arising from the abnormal branching of the immature bronchial tree. This entity was first described by Ch'in and Tang in 1949,[28] and since then, the term has been evolving as our understanding of the entity improves. For the past 40 years, Stocker has classified the lesions into three types: I, II, and III.[152] Stocker has since described two new types, 0 and 4, and has revised his original term congenital cystic adenomatoid malformation, and now refers to this entity of cystic lung lesions as *congenital pulmonary airway malformations* (CPAM) to reflect the site of suspected development of the malformation in the tracheobronchial tree, and that only three types (1, 2, and 3) are adenomatoid and only types 1, 2, and 4 are cystic.[150] However, the term CCAM will still appear in the literature.

Congenital pulmonary airway malformation is the most common congenital cystic lung disease, occurring in 1 in 11,000-30,000 live births and affecting more males.[142] Both lungs are affected equally, and the disease is most commonly unilobar with predilection for the lower lung lobes. Unlike BPS, it is connected to the tracheobronchial tree and has a pulmonary blood supply (Table 66.1). Congenital pulmonary airway malformation develops during the pseudoglandular phase (7-17 weeks' gestation) of fetal lung development. In addition to the classification system described in the preceding, some have suggested classifying the lesions, at least during the prenatal period, as microcystic versus macrocystic based on the gross anatomy and antenatal ultrasound appearance. Whereas the latter classification has poor correlation with histologic features, it has a much better prognostic value, with microcystic lesions (cysts <5 mm) having a poorer prognosis than macrocystic lesions (>5 mm).[5]

Type 0 CPAM is the rarest form and arises from the trachea or bronchus and contains multiple small cysts. These infants also have other associated lesions, including cardiovascular anomalies, renal hypoplasia, and focal dermal hypoplasia. The lung itself is hypoplastic, weighing only 30%-50% of the expected weight. Microscopically, the tissue consists almost entirely of irregular bronchial-like structures lined by pseudostratified ciliated columnar epithelium surrounded by thick cartilage plates and bundles of smooth muscle fibers. Usually all lobes of the lung are involved; thus, this diagnosis is usually lethal.[150]

Type 1 CPAM is the most common form, representing 60%-70% of all CPAMs.[151] These lesions consist of large cysts (1-10 cm) surrounded by multiple small cysts that arise from the distal bronchus or proximal bronchiole and are rarely associated with other congenital malformations. These CPAMs can be large and can have significant mass effect in utero, which can lead to fetal hydrops and pulmonary hypoplasia. However, many of these cysts collapse as pregnancy progresses, allowing normal lung growth of the unaffected lobes. Radiographically, they appear as either a single or multiple air-filled or air/fluid-filled cysts in one or (much less frequently) multiple lobes. Depending on size,

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there can be flattening of the diaphragm, mediastinal shift, and compression of adjacent lung. Overall, these lesions have a good prognosis. However, a number of reports describe the occurrence of a bronchioloalveolar carcinoma, especially when the CPAM is not fully resected, with a malignant transformation risk of 1%.[166]

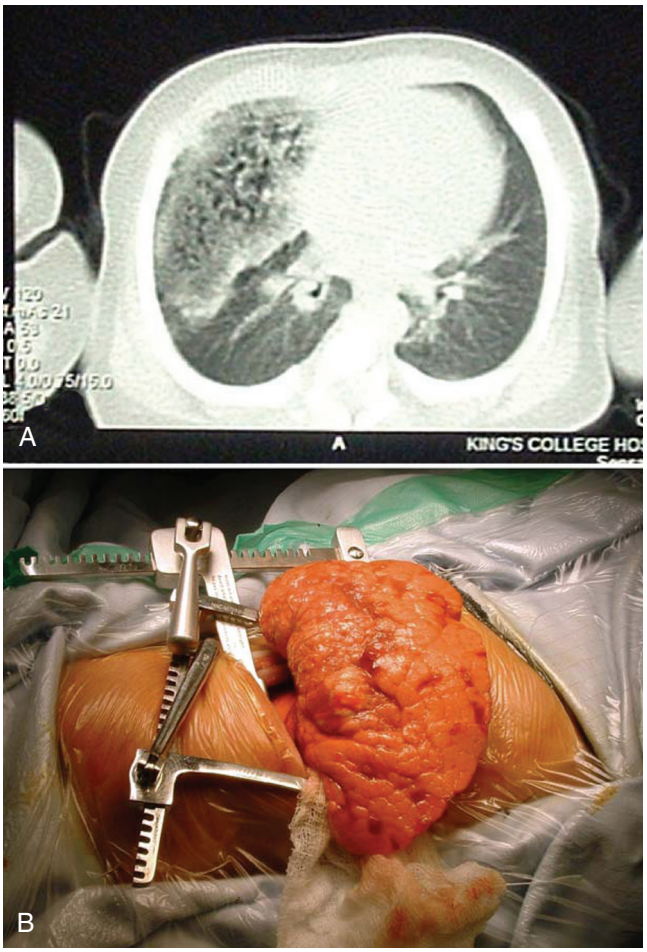
Type 2 CPAM accounts for 15% of all CPAMs and is the second most frequent type of CPAM. These malformations are of bronchiolar origin and consist of multiple small cysts (0.5-2 cm) and are often (≈50%) associated with other congenital anomalies, including renal agenesis/dysplasia, cardiovascular anomalies, congenital diaphragmatic hernia, and extralobar sequestrations.[32,150] Radiographically, they are characterized by multiple small cysts that may not even be visible on chest x-ray. Prognosis is usually related to the severity of the associated anomalies.

Type 3 CPAM accounts for 5%-10% of all CPAMs. These are of bronchiolar/alveolar duct origin and almost exclusively seen in males. These lesions were the original congenital adenomatoid malformation described by Ch'in and Tang in 1949.[28] They consist of multiple smaller cysts (rarely >0.2 cm) and appear as a solid mass that is associated with a significant risk of hydrops and polyhydramnios resulting from caval obstruction and cardiac compression secondary to mediastinal shift. This also leads to pulmonary hypoplasia, because unlike type 1 CPAMs, this lesion does not regress with progression of pregnancy. The extent of the pulmonary hypoplasia is the primary determinant of survival.

Finally, type 4 CPAM accounts for approximately 10% of CPAMs and is of distal acinar origin. The lesion primarily consists of large (up to 10 cm), air-filled, thin-walled cysts usually located at the lung periphery. This lesion can be asymptomatic at birth and presents from the neonatal period to 4 years of age. Often, this will be an incidental finding on an x-ray that was taken for other reasons, such as acute respiratory distress related to a tension pneumothorax, or pneumonia. This lesion can be confused with pleuropulmonary blastema; therefore, blastemas must be looked for histologically. Surgical resection of the lobe is accompanied by an excellent prognosis.[150]

With improvement in prenatal imaging, most of these lesions are diagnosed prenatally, but some may not present until the postnatal period either as acute respiratory distress or as an incidental finding on a chest x-ray that was obtained for other reasons. Although the diagnosis of a congenital lung lesion is able to be made on prenatal ultrasound, it is difficult to distinguish CPAM from other cystic lung lesions. Adzick et al. proposed the classification of antenatal cystic lung lesions based on their appearance on ultrasound as either macrocystic (cysts ≥5 mm) or microcystic (cysts <5 mm).[5]

Understanding of the natural history of CPAMs continues to evolve. Up to 15% of these lesions appear to "disappear" in the prenatal period, usually after 28 weeks' gestation when the growth of these lesions tends to plateau; however, in most all cases, postnatal CT scan or fetal MRI will show persistence of the anomaly (Fig. 66.3). The unpredictability of the in utero growth of these lesions requires careful follow-up. Midgestation, these lesions can grow quite rapidly, which can cause mediastinal shift, pulmonary hypoplasia, and impaired venous return leading to hydrops. It has been well established that the diagnosis of fetal hydrops associated with CPAM portends a poor prognosis, with mortality near 100%.[3,4,164] In 2002, it was hypothesized that the volume of the lesion would predict whether hydrops would develop in the fetus. The CPAM volume ratio (CVR) was developed as a prognostic tool and is calculated by measuring the three dimensions of the lung lesion and dividing by the head circumference. A CVR greater than or equal to 1.6 at initial diagnosis was found to reliably predict a subgroup of fetuses at increased risk for developing fetal hydrops and is now used to evaluate which infants might benefit from in utero interventions.[38] Fetal surgery using thoracoamniotic shunting or cyst aspiration has been successful for macrocystic lesions, with survival rates in hydropic fetuses of 50% and 69%, respectively.[26] Microcystic lesions require open fetal surgery in the presence



• **Fig. 66.3** **A,** Computed tomography scan showing right-sided microcystic congenital pulmonary airway malformation (CPAM). **B,** Lung resection of predominantly solid and small cysts (type 2 CPAM). (Adapted from Stanton M, Davenport M. Management of congenital lung lesions. *Early Human Dev*. 2006;82:289, with permission.)

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of hydrops with a survival rate of 52%[38,64,164] (see Chapter 13). Patients who are not suitable for surgery benefit from antenatal steroids, which have been shown to decrease the size of microcystic CPAMs as well as resolve the hydrops in several case series.[125] The ex utero intrapartum treatment (EXIT) procedure should be considered in patients with significant mediastinal shift and cardiac and lung compression at time of delivery.[12,89] Recently, Ehrenberg-Buchner and colleagues report that the maximum and final CVR are independent predictors of respiratory morbidity at the time of delivery and need for neonatal intervention. According to their work, a maximum CVR >1 portends a 75% likelihood of having respiratory distress at birth; thus, these babies should be delivered at a tertiary care center. If the maximum CVR is <1, nearly 100% of those infants are asymptomatic at birth.[50]

Postnatally, all CPAMs should have surgical evaluation. If the infant is symptomatic, surgical excision is indicated. However, there is still some debate over the appropriate management of those lesions that are asymptomatic at birth. All infants with CPAM should have a chest x-ray in the immediate neonatal period and chest CT scan at 4-6 weeks of age to evaluate the mass. There are justifications for prophylactic surgery: preventing chest infections and sepsis; preventing malignancy; early rather than delayed surgery may encourage compensatory lung growth; and reduction in postoperative complications (compared with emergency surgery).[81,92] The majority opinion seems to favor elective resection at 2-6 months of age; however, this continues to be debated in the surgical arena. Following successful resection, the long-term functional outcome of children with CPAM is excellent, with no physical limitations or increased risk for infection.[12]

Bronchopulmonary Sequestration

Bronchopulmonary sequestrations (BPSs) are microscopic cystic masses of nonfunctioning lung tissue thought to arise from the primitive foregut. Usually, these structures are not connected to the main airway, and their blood supply arises from the systemic circulation. Two forms are recognized: intralobar sequestration (ILS) and extralobar sequestration (ELS). Intralobar sequestration occurs when the accessory bud arises before the establishment of the pleura and is contained within the normal lung. If the accessory lung bud arises after the pleura are established, it has its own pleural covering and is completely separated from the normal lung and is classified as an ELS. Extralobar sequestrations are usually located supradiaphragmatic; however, a small portion (<10%) are located infradiaphragmatic.[55,97] This is dependent on the level of the foregut at which they arise.

On antenatal ultrasound, sequestrations appear as well-defined, solid, echogenic masses very similar to type 3 CPAM. A distinguishing feature of BPS is the documentation of systemic blood supply by color Doppler. If unclear, ultrafast MRI can establish the blood supply, define the lesion, and identify other associated malformations. It is difficult to distinguish ELS from ILS on prenatal ultrasound unless it is surrounded by a pleural effusion or is located below the diaphragm, which can only be features of an extralobar sequestration. Intra-abdominal ELS appears as a suprarenal solid mass and should be differentiated from other suprarenal masses, including neuroblastoma and mesoblastic nephroma.[142] Antenatal or postnatal echocardiography can show associated cardiac malformation. Bronchopulmonary sequestration appears on chest radiograph as a posterior thoracic mass mostly on the left. Chest CT scan or even MRI might be needed to further delineate systemic blood supply.

Like CPAMs, sequestrations, extralobar more so than intralobar, can be associated with multiple congenital malformations, including congenital diaphragmatic hernia, congenital heart disease, and vertebral anomalies. A feature unique to BPS is high-output cardiac failure owing to the sequestration's redundant circulation and occasionally massive left-to-left shunt. Like a CPAM, BPS can also cause fetal hydrops, either from the mass effect or from a tension hydrothorax that is the result of either fluid or lymph secretion from the BPS or from high-output cardiac failure. If there is significant in utero compromise of the fetus, fetal intervention may be necessary in the form of a thoracoamniotic shunt for decompression of pleural effusion, surgical excision, or EXIT procedure.[2,34,44]

The natural history of BPS is still being learned. Most BPSs (68%) dramatically decrease in size as pregnancy progresses.[2] Thus, most sequestrations are usually asymptomatic in the neonatal period. If the sequestration is large, it can act as a space-occupying lesion and present as respiratory insufficiency either from pulmonary hypoplasia or lung compression and may require emergent surgical repair. If asymptomatic in the neonatal period, sequestrations can present later with recurrent pneumonia, atelectasis, bleeding, or high-output congestive heart failure. It is felt that asymptomatic patients should undergo elective resection to prevent complications of malignancy or infection.[34]

While discussing CPAMs and BPSs, it should be noted that there are lesions, referred to as hybrid lesions, that exhibit clinical and histologic features of both entities, most commonly characteristics of ILS and type 2 CPAM.[55,97]

Bronchogenic Cyst

A bronchogenic cyst is a single cyst lined by respiratory epithelium and covered with elements of the tracheobronchial tree, including cartilage and smooth muscle. Bronchogenic cysts originate from an abnormal budding of the ventral surface of the primitive foregut between the 26th and 40th day of fetal life, a budding that does not undergo further branching, resulting in a blind cyst that may or may not communicate with the airways. These cysts are mostly found in the mediastinum near the carina but can occur within the lung parenchyma, pleura, or diaphragm.[111]

In the neonatal period, most patients with bronchogenic cysts are asymptomatic, and diagnosis is usually made on prenatal ultrasound and fetal MRI or incidentally on a chest radiograph after birth. On chest radiograph, bronchogenic

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cysts can appear as radiopaque areas if they are fluid filled, but if connected to the airway, an air-fluid level may be seen. A CT scan is the study of choice before undergoing surgery and provides a thorough characterization of the lesion and its relation to mediastinal structures.

Symptoms, if present, are secondary to mass effect on the airways, gastrointestinal tract, or cardiovascular system. Even though major airway obstruction is uncommon, subcarinal lesions can present with severe obstruction. On the other hand, obstruction of smaller airways can cause air trapping, overdistension, and a clinical picture mimicking congenital lobar emphysema. Cases not diagnosed in the neonatal period usually present in older children or adults with pneumonia, hemoptysis, pneumothorax, dysphagia, or signs of caval obstruction.

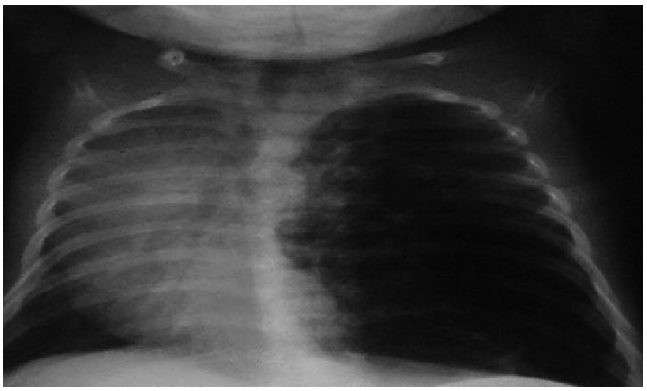
Treatment of all cases of bronchogenic cysts is complete surgical excision. In symptomatic patients, this is performed after immediate clinical stabilization. Simple aspiration should be considered as a temporizing measure in patients with severe compromise, but complete resection is subsequently required. In asymptomatic newborns, surgery can be done electively at a few months of age. Patients who undergo resection of a bronchogenic cyst have an excellent outcome. Only a few patients develop life-threatening complications before surgery and have a poorer outcome. There are no long-term complications related to the resection of a bronchogenic cyst.[96]

Congenital Lobar Emphysema

Congenital lobar emphysema (CLE) is a rare anomaly of the lung that is characterized by postnatal overdistension of one or more segments or lobes of the lung. The mechanism underlying CLE is that of intrinsic or extrinsic obstruction of the airways resulting in air trapping, overdistension, and subsequent emphysema. Multiple mechanisms have been described to explain the development of CLE, including dysplastic bronchial cartilage, inspissated mucus, aberrant cardiopulmonary vasculature, and infection. In half of the cases, no underlying pathology is identified. The left upper lobe is most frequently affected (42%), followed by right middle lobe (35%) and the right upper lobe (21%). The lower lobes are involved in 1% of the cases. Congenital lobar emphysema is three times more common in males.[149]

Patients usually present in the neonatal period with respiratory distress (80% within the first month of life); however, later presentations have been described. The severity of the clinical picture depends on the size of the CLE and the degree of compression of the normal lung. Physical examination might be indistinguishable from that of a pneumothorax with decreased air entry, bulging of the affected hemithorax, and in severe cases, shifting of the apical heartbeat to the contralateral side. However, these children are often hemodynamically stable, thus differentiating it from a tension pneumothorax.

Congenital lobar emphysema can be detected at midgestation using a combination of ultrasonography and ultrafast fetal MRI, although differentiation from CPAM might be difficult. Diagnosis is usually made by chest radiograph that may show an early opaque mass due to delayed clearance of lung fluid followed by a hyperlucent, overexpanded area of lung with atelectasis of the adjacent lobes of the lung, depression of the diaphragm, and mediastinal shift to the opposite side (Fig. 66.4). The distinction of CLE from pneumothorax is essential to prevent attempted aspiration and potential development of tension pneumothorax. The presence of alveolar air markings throughout the emphysematous area is supportive of CLE. The emphysematous segment may also herniate anterior to the heart and great vessels. A CT scan of the chest is a useful adjunct.



• **Fig. 66.4** Congenital lobar emphysema with marked tracheal and mediastinal shift in a patient who required emergency lobectomy. (From Shanmugam G, et al. Congenital lung malformations—antenatal and postnatal evaluation and management. *Eur J Cardiothorac Surg*. 2005;27:45, with permission.)

Treatment of CLE depends on the severity of symptoms. Conservative and supportive management should be considered in milder cases. Surgical resection of the affected area should be considered in patients with life-threatening, progressive pulmonary insufficiency from compression of the adjacent normal lung. Once the emphysematous area is resected, the long-term prognosis is excellent.[94]

Pulmonary Arteriovenous Malformation

Intrapulmonary arteriovenous malformation is a rare vascular anomaly of the lung that is associated with cyanosis and may lead to significant morbidity. Such malformations are direct communications between the smaller pulmonary arteries and veins, allowing blood to bypass the capillary system.[6] Over 70% are associated with hereditary hemorrhagic telangiectasia[35] and present with cyanosis not responding to medical management. Antenatal diagnosis of an intrapulmonary arteriovenous malformation is possible and allows early treatment. Postnatal diagnosis is confirmed by angiography. Traditionally, treatment has been by surgical resection. More recently these lesions have been successfully managed by embolization with coils or endovascular plugs.[88] If left untreated, they can be complicated by strokes and cerebral abscesses.[36,119]

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Acquired Neonatal Pulmonary Diseases

Meconium Aspiration Syndrome

Meconium is comprised of desquamated fetal intestinal cells, bile acids, minerals, and enzymes, including alpha$_1$ antitrypsin and phospholipase A_2, as well as swallowed amniotic fluid, lanugo, skin cells, and vernix caseosa. Antenatal passage of fetal intestinal contents into the amniotic fluid is common in early gestation, stopping by 20 weeks, when there is innervation of the anal sphincter; thus meconium passage between 20 and 34 weeks is an infrequent occurrence.[127] Most babies who pass meconium during the labor process are term or post-term.

Meconium-stained amniotic fluid (MSAF) occurs in approximately 13% of normal pregnancies, and ~5% of these infants will develop respiratory distress.[168] Risk factors for MSAF include postmaturity (gestational age beyond 41 weeks), small for gestational age (SGA), fetal distress, and in utero conditions that can compromise fetal well-being, such as placental insufficiency and cord compression. The mechanisms underlying meconium passage in utero are not completely understood; however, there is evidence of increased parasympathetic activity causing increased peristalsis and relaxation of the anal sphincter secondary to enhanced vagal output during cord compression. Corticotropin-releasing factor, a known mediator of colonic motility, has been implicated in the pathogenesis of hypoxia-induced MSAF in a rat model.[98]

Meconium aspiration syndrome (MAS) is defined as respiratory distress and an oxygen requirement in an infant born through MSAF whose symptoms cannot be otherwise explained. This definition correctly implies that respiratory distress might occur in infants born through MSAF for a variety of reasons other than MAS. Infants born through MSAF were found to have a 100-fold increase in the likelihood of developing respiratory distress compared with those born through clear amniotic fluid, even in those with normal fetal heart tracing and Apgar scores. Meconium aspiration syndrome occurs in only 5% of infants born through MSAF, and it is unclear why only some infants born through MSAF develop MAS. The incidence of MAS has decreased secondary to improved obstetric standards, especially secondary to a decrease in the number of deliveries beyond 41 weeks' gestation in developed countries. Two large studies from the United States and Australia/New Zealand confirmed that the incidence of MAS increases with increasing gestational age for infants between 37 and 41 weeks in a study cohort involving more than 14 million babies. The incidence of MAS (United States) and MAS requiring intubation (Australia) in this cohort increased twofold to threefold at 41 weeks' gestation compared with neonates born at an earlier gestation.[43,173]

Pathophysiology

The pathophysiology of MAS, although extensively studied, remains incompletely understood. During normal fetal breathing, pulmonary fluid moves predominantly outward from the airways into the oropharynx. However, severe asphyxia in utero can induce gasping and aspiration of amniotic fluid and particulate matter into the large airways. The meconium inhaled by the fetus may be present in the trachea or larger bronchi at delivery. Meconium and squamous epithelium have been found as far as the alveoli in stillborn infants, and it is widely recognized that meconium aspiration can occur antenatally. After air breathing has commenced, especially if accompanied by gasping respirations, there is a rapid distal migration of meconium within the lung. Thick meconium-stained amniotic fluid, nonreassuring fetal heart tracing, low Apgar score at 5 minutes, instrumental delivery, especially emergency cesarean section, and planned home delivery are associated with increased risk for development of MAS.[43,90]

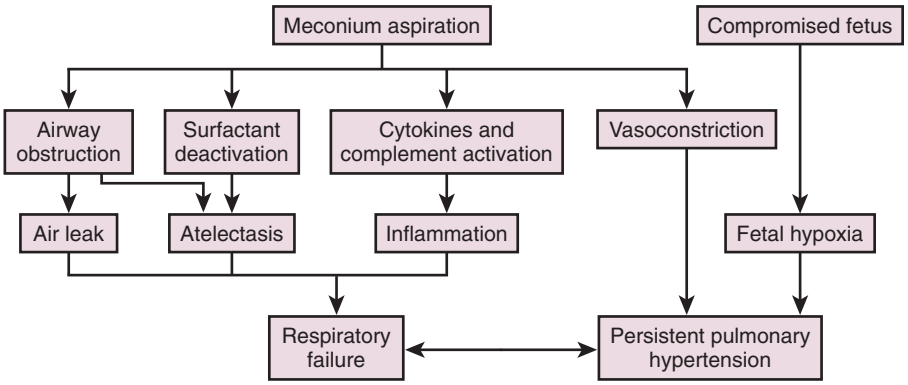
MAS can be regarded as a multifactorial disease resulting from the cumulative effect of aspiration of MSAF in an already compromised infant. Therefore, the underlying pathology is that of fetal compromise, discussed elsewhere, and pulmonary injury secondary to aspiration of meconium. Meconium aspiration causes injury to lung tissues through a variety of mechanisms, including complete or partial obstruction of airways, inflammation, complement activation and cytokine production, inhibition of surfactant synthesis and function, apoptosis of epithelial cells, and increased pulmonary vascular resistance (Fig. 66.5).

Aspiration of meconium particles can result in complete or partial obstruction of the airways. Complete obstruction causes collapse of the lung tissue distal to the obstruction and subsequent atelectasis and ventilation-perfusion mismatch. The effect of partial obstruction, however, has been traditionally thought of as a ball-valve effect, wherein air can enter during inspiration but is unable to escape during expiration. The resultant air trapping and overdistension increase the incidence of pneumothorax, which can occur in as many as 10%-30% of affected infants.[168,169]

The various components of meconium have been shown to induce inflammation and cytokine activation. Within hours, neutrophils and macrophages are found in the alveoli, larger airways, and the lung parenchyma. This is associated with activation of proinflammatory cytokines, tumor necrosis factor TNF-α, γ-interferon, and interleukins (IL)-1β, IL-6, and IL-8. Furthermore, meconium was found to activate the lectin and alternative complement pathways, and administration of complement 1 inhibitors efficiently reduced the level of these proinflammatory factors, thus adding a potential therapeutic target for the treatment of MAS.[134] Excessive activation of cells leads to oxidative damage of the lung tissue through release of cytotoxic and immune cell–activating agents such as reactive oxygen and nitrogen species.

The complex oxidative processes and inflammation via meconium and plasma proteins leaking through the alveolar-capillary membrane may destroy the alveolar type II cells, thus decreasing the production and function of surfactant,

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• **Fig. 66.5** Pathophysiology of meconium aspiration syndrome.

which may result in increased surface tension, atelectasis, decreased lung compliance, and subsequent hypoxia.[78,112]

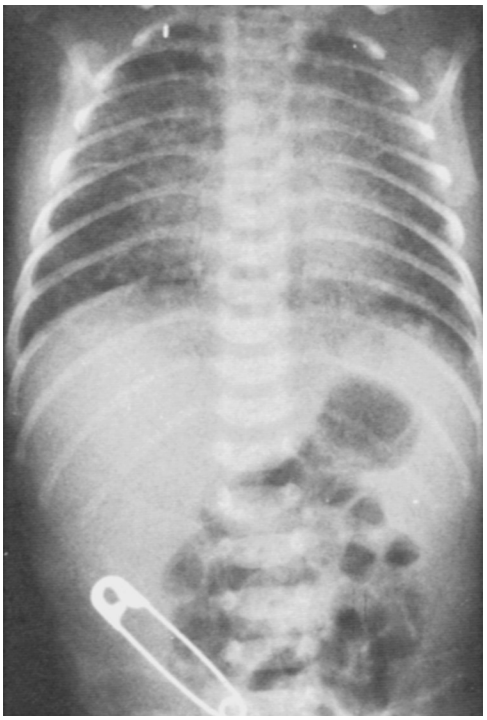
Severe persistent pulmonary hypertension often complicates cases of MAS. The mechanism of pulmonary vasoconstriction in these patients is not clear but thought to be induced, in part, by fetal and neonatal hypoxia. The direct effect of meconium on the pulmonary vasculature is controversial. In vitro studies observed relaxation of tracheal and pulmonary vasculature smooth muscles in response to meconium exposure in rats. However, in vivo administration of meconium caused increased contractility of vascular and tracheal smooth muscles, suggesting that meconium induces pulmonary vasoconstriction through lung release of pulmonary vasoconstrictor humoral factors. The potent vasoconstrictors thromboxane A_2 and angiotensin II, as well as cytokines, have been implicated in this mechanism.

Clinical Features

The infant with MAS often exhibits the classic signs of postmaturity, with evidence of weight loss; cracked, peeling skin; and long nails, together with heavy staining of nails, skin, and umbilical cord with a yellowish pigment. These infants often are depressed at birth. In fact, the initial clinical picture can be dominated by neurologic and respiratory depression secondary to the hypoxic insult precipitating the passage of meconium. Respiratory distress with cyanosis, grunting, flaring, retractions, and marked tachypnea soon ensue.

Characteristically, the chest appears overinflated ("barrel-chested"), and rales can be audible on auscultation. The chest radiograph shows coarse, irregular pulmonary densities with areas of diminished aeration or consolidation (Fig. 66.6). Pneumothorax and pneumomediastinum are common in infants with severe MAS. Hyperinflation of the chest and flattening of the diaphragm secondary to air trapping are sometimes noted on chest radiograph. Cardiomegaly might be observed as a manifestation of the underlying perinatal hypoxia.

Arterial blood gases characteristically reveal hypoxemia with evidence of right-to-left shunting. Hyperventilation can result in respiratory alkalosis, although infants with severe disease usually have a combined respiratory and metabolic acidosis secondary to hypoxia and respiratory failure.



• **Fig. 66.6** Chest radiograph showing multiple linear streaks of meconium aspiration pneumonia.

One should be alert to the possible development of PPHN, which frequently accompanies MAS and can contribute substantially to morbidity.

Management

In the Delivery Room

Successful management of patients with MAS depends on close observation during and immediately following labor in at-risk mothers as well as appropriate intervention in newborns born through meconium-stained amniotic fluid (Box 66.3). This requires a collaborative effort by the obstetric and neonatology teams. Mothers at a gestational age of 41 weeks or greater with thick MSAF and nonreassuring fetal heart tracing require careful monitoring. Fetal scalp oximetry is a technique of fetal monitoring that might improve the accuracy of detecting newborns at risk. Fetuses with nonreassuring fetal heart rate patterns and fetal oxygen

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• BOX 66.3 Management of Meconium Aspiration Syndrome

Delivery Room

- Women at risk should deliver in a center where immediate neonatal care is available.
- Meconium aspiration can develop in utero.
- Amnioinfusion for meconium-stained amniotic fluid (MSAF) in the setting of standard peripartum surveillance is not routinely indicated.
- Routine suctioning via endotracheal tube is no longer indicated.
- Routine suctioning of the oropharynx at the perineum is not recommended.

Neonatal Intensive Care Unit

- Surfactant administration may be beneficial.
- Inhaled nitric oxide is indicated for associated persistent pulmonary hypertension.

Unresolved Issues

- The use of amnioinfusion for MSAF when routine surveillance is not available, such as in developing countries
- The administration of surfactant as a bolus versus lavage
- The utility of anti-inflammatory agents

saturation below 30% had a high correlation with a scalp pH value of less than 7.2.[93]

Amnioinfusion refers to the instillation of normal saline or lactated Ringer's solution into the uterus through a catheter for the purpose of replacing amniotic fluid in cases of oligohydramnios and MSAF. Amnioinfusion might decrease the incidence of MAS by two mechanisms: diluting meconium consistency and decreasing cord compression, thereby resolving asphyxia and gasping. A meta-analysis of 13 studies demonstrated that the use of prophylactic intrapartum amnioinfusion for moderate or thick MSAF shows two distinct patterns. When standard peripartum and expert neonatal care are available, amnioinfusion does not improve outcome. In contrast, where antenatal and neonatal care is limited, such as underserved African communities, 75% of MAS is prevented. Furthermore, amnioinfusion decreased the frequency of cesarean section rate (OR, 0.74), meconium below the vocal cords (OR, 0.18), and neonatal acidemia (OR, 0.42) with no increase in the rate of chorioamnionitis (OR, 0.47).[124] A large, multicenter, randomized trial involving 1998 women concluded that in clinical settings with standard peripartum surveillance, amnioinfusion in the presence of thick MSAF did not reduce the risk of perinatal death, moderate or severe MAS, or other serious neonatal disorders.[56] This led the American College of Obstetricians and Gynecologists to issue an opinion statement: "Based on current literature, routine prophylactic amnioinfusion for the dilution of meconium-stained amniotic fluid should be done only in the setting of additional clinical trials. However, amnioinfusion remains a reasonable approach in the treatment of repetitive variable decelerations, regardless of amniotic fluid meconium status."[1]

Suctioning of the oropharynx upon delivery of the head and before delivery of the shoulders is used commonly in obstetric practices to decrease the possibility of meconium aspiration with the first breath. A multicenter, randomized, prospective study concluded that antepartum suctioning is not warranted and does not decrease the incidence of MAS even in high-risk infants. On the contrary, it may lead to added complications including bradycardia, desaturations, and increased incidence of pneumothorax.[160] Vain et al. also showed, in a prospective randomized trial, that routine intrapartum oropharyngeal and nasopharyngeal suctioning of term infants born through MSAF does not prevent MAS. With this evidence, the International Consensus on Cardiopulmonary Resuscitation currently does not endorse the routine intrapartum oropharyngeal and nasopharyngeal suctioning of infants born with clear or meconium-stained amniotic fluid.[122]

Routine endotracheal intubation is no longer recommended for infants born through MSAF even if the infant is not vigorous. Current NRP recommendations state that if a neonate born through MSAF presents with poor tone or respiratory effort, the initial steps of resuscitation should be performed and bag-mask ventilation initiated when/if appropriate. Routine intubation and suctioning is not recommended due to insufficient evidence to support this therapy.[123] Unfortunately, an appropriately powered randomized clinical trial to address optimal management of the nonvigorous meconium-stained infant has not been performed.[167a]

In the Neonatal Intensive Care Unit

Management of patients with MAS consists mainly of supportive respiratory and cardiovascular care. Maintaining normal blood pressure, adequate perfusion, and preventing hypoxia are essential to decrease complications. The use of antibiotics is indicated until infection is ruled out because MSAF could be the first sign of fetal sepsis or pneumonia, which may be indistinguishable from MAS on chest x-ray examination. Ventilatory support is indicated in the presence of respiratory failure or persistent hypoxemia not responsive to high fractional inspired oxygen. There is no clear evidence or consensus of an advantage of one ventilatory strategy. However, in the presence of air leak or failure of conventional ventilation, HFOV should be considered in units familiar with this ventilatory strategy. Pao_2 should be maintained such that there is minimal hypoxia-induced pulmonary vasoconstriction while not inducing hyperoxic injury.

Surfactant administration should be considered in severe cases of MAS. In a Cochrane review of available data, surfactant decreased the need for ECMO in patients with MAS (relative risk 0.64, 95% CI 0.46, 0.91), and the number needed to treat to prevent one ECMO case was 6.[51] Although surfactant administration in one study was associated with reduced hospital stay with a mean difference

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of 8 days, it did not affect mortality, days on a ventilator or oxygen, BPD, pneumothorax, or pulmonary interstitial emphysema. Dargaville et al. conducted a randomized, controlled trial of ventilated infants with MAS to look at the effects of surfactant lavage therapy. Those treated with surfactant had a decreased risk of death or ECMO, but there was no difference in the duration of respiratory support. They concluded that the use of surfactant lavage may reduce mortality, especially in units not offering ECMO.[43] The most effective method of delivering surfactant, bronchoalveolar lavage versus bolus administration, as well as which surfactant to use, remains controversial.

In cases complicated by PPHN, iNO should be considered. Extracorporeal membrane oxygenation can be lifesaving in patients with continued hypoxia despite aggressive treatment. Survival rates among infants with MAS treated with ECMO are high and are discussed in Chapter 70.

Observational studies in infants with MAS showed some improvement of pulmonary function with the use of inhaled or systemic steroids. However, a Cochrane meta-analysis of data in 2003 concluded that there is insufficient evidence to assess the effects of steroid therapy in the management of MAS. Future directions for treatment of MAS aimed at reducing inflammation and cytokine production are promising. Recent animal studies instilling budesonide with surfactant have demonstrated improved respiratory status and decreased inflammation and may be a therapeutic option in the future if results are replicated in humans.[113]

The ultimate prognosis of infants affected with MAS depends not so much on the pulmonary disease but on the accompanying asphyxial insult and treatment required. No specific long-term deficits in pulmonary function have been attributed to this disorder, although BPD can result from prolonged assisted ventilation. Compromised infants born through MSAF have an increased incidence of acute otitis media, probably secondary to meconium contamination of the middle ear.

Other Aspiration Syndromes

Respiratory distress can develop in the newborn infant secondary to aspiration of other amniotic fluid material, including purulent amniotic fluid, vernix caseosa, and maternal blood. The clinical picture is that of respiratory distress as described in the preceding. X-ray findings can be indistinguishable from MAS, although lack of MSAF and other risk factors for MAS help in the diagnosis.

Aspiration of maternal blood can be difficult to differentiate from pulmonary hemorrhage, especially if there is no history of antepartum hemorrhage. However, infants with pulmonary hemorrhage are usually sicker, with cardiovascular compromise including hypotension, poor perfusion, coagulopathy, and low platelets. Furthermore, the presence of swallowed blood in the stomach of affected infants suggests aspiration. Treatment with antibiotics is indicated if pneumonia is suspected secondary to aspiration of infected amniotic fluid.

Postnatal aspiration is most likely to be seen in preterm infants, those with disorders of swallowing, and infants with esophageal atresia and tracheoesophageal fistula. Small preterm infants are at greatest risk when fed excessive volumes per gavage or through misplaced orogastric tubes. These infants might initially present with cyanosis, desaturation, or apnea and subsequent respiratory distress. Over subsequent hours, pulmonary infiltrates may become visible on radiographs. The severity of disease varies and can be indistinguishable from an inflammatory pneumonitis. Aspiration syndromes associated with disorders of swallowing may be suspected from the perinatal history (asphyxia, polyhydramnios), feeding history (cyanosis, excessive drooling, poor suck), and physical examination. The precise cause, however, might not be readily apparent, and these infants require extensive neurologic evaluation. Infants with recurrent aspiration, particularly those with disorders of the swallowing mechanism, present complex management problems and require good care coordination to optimize care and prevent recurrent events.

Neonatal Pneumonia

Neonatal pneumonia continues to account for significant morbidity and mortality, especially in developing countries. Although mortality rates from pneumonia have declined over the past decade, neonatal pneumonia continues to be a global health issue that disproportionately affects developing countries.[54] At autopsy, pneumonia, diagnosed by the presence of inflammation, has been diagnosed in 20%-60% of stillbirths and liveborn neonatal deaths.[129]

Etiology

Neonatal pneumonia is classified as *early*, presenting within the first 3-7 days of life, and *late*, presenting after 7 days of life. Congenital pneumonia is one subset of early pneumonia that is acquired in utero and usually presents immediately after delivery. Congenital pneumonia is acquired through aspiration of infected amniotic fluid, ascending infection through intact or ruptured membranes, or hematogenous spread through the placenta. Early pneumonia can also be acquired during labor secondary to aspiration of infected amniotic fluid or bacteria colonizing the birth canal. Late neonatal pneumonia, which includes ventilator-associated pneumonia (VAP), is usually a nosocomial infection and occurs most commonly in ventilated neonates, although infection through hematogenous spread can also occur.

Whereas bacterial, viral, and fungal agents can cause pneumonia, the etiologic agent is usually related to the timing of occurrence of pneumonia. Group B *Streptococcus* (GBS) is the most common cause of early pneumonia. However, the overall incidence of GBS sepsis has decreased dramatically since the introduction of universal screening and intrapartum antibiotic prophylaxis.[163] The impact of the decreased incidence of GBS sepsis on the incidence of GBS pneumonia is not clear; however, the incidence of gram-negative

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sepsis, especially that caused by *Escherichia coli* (*E. coli*), has increased following the implementation of the revised AAP guidelines and is the most significant pathogen in preterm infants.[19,153] Other bacterial causes of pneumonia include: *Klebsiella*, *Enterobacter*, group A streptococci, *Staphylococcus*, and *Listeria monocytogenes*. Anaerobes such as *Bacteroides* are occasionally recovered, but the contribution of these organisms to early-onset pneumonia is minimal.

Herpes simplex is the major cause of early viral pneumonia and is usually acquired during labor. Pneumonia is associated with 33%-54% of disseminated herpes infection and is usually associated with a high mortality rate. Other causes of early viral pneumonia include adenovirus, enterovirus, mumps, and rubella, whereas early pneumonia is an unusual presentation of congenital cytomegalovirus (CMV) infection. Other TORCH infections, including syphilis and toxoplasmosis, can also present with early-onset pneumonia. Up to 70% of disseminated candidal infections are associated with pneumonia, especially in premature infants.

Late-onset pneumonia is usually caused by organisms that colonize the newborn during the hospital stay. These include *Staphylococcus* species, including coagulase-negative staphylococci and *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *E. coli*, *Klebsiella*, *Serratia*, *Enterobacter cloacae*, *Pseudomonas*, *Bacillus cereus*, and *Citrobacter*, all of which can cause severe pneumonia, especially in preterm infants. When *Chlamydia trachomatis* infection is acquired during labor, it usually manifests as pneumonia at 2-4 weeks of life because of its long incubation period. Respiratory syncytial virus is the most common viral agent causing late-onset pneumonia, although incidence and severity have decreased secondary to passive immunoprophylaxis. Other viral causes of late pneumonia include adenovirus, enteroviruses, parainfluenza, rhinoviruses, and influenza viruses and can result in severe disease. Cytomegalovirus pneumonia should always be considered in babies with congenital infection presenting with late respiratory decompensation. Prolonged courses of antibiotics and corticosteroids can increase the risk of candidal pneumonia, especially in colonized infants with extremely low birth weight.

Clinical Presentation

Risk factors for early pneumonia are similar to those for neonatal sepsis and include prematurity, prolonged rupture of membranes, GBS colonization, chorioamnionitis, and intrapartum maternal fever. However, in one study, 22% of neonatal cases did not have risk factors, and in almost half, the only risk factor was early onset of labor. Therefore, risk factors should not determine whether to start antibiotics in neonates with respiratory distress, especially infants with extremely low birth weight. The presence and duration of mechanical ventilation and central venous lines were the main risk factors for development of late-onset pneumonia.[37] Other risk factors include abnormal neurologic conditions predisposing to aspiration pneumonia, poor nutrition, severe underlying disease, and prolonged hospitalization.

Clinical manifestations of early-onset pneumonia can be nonspecific; therefore, a high index of suspicion should always be exercised. These symptoms include temperature instability, lethargy, apnea, tachycardia, metabolic acidosis, abdominal distention, poor feeding, and neurologic depression. Respiratory distress can present in the form of tachypnea and retractions in more than two-thirds of affected neonates. Cough is an unusual symptom in neonatal pneumonia and was present in less than one-third of neonates.[48] Delay in diagnosis and treatment can lead to PPHN and septic shock.

Differential diagnosis for early neonatal pneumonia includes transient tachypnea of the newborn (TTN), RDS, MAS, and pulmonary congestion secondary to obstructed anomalous pulmonary venous return or other left heart obstructive lesions. Radiographic findings characteristic of pneumonia are nonspecific and thus do not help differentiate pneumonia from the disorders mentioned in the preceding. Chest x-ray findings might include unilateral or bilateral streaky densities, confluent mottled opacified areas, or a diffusely granular appearance with air bronchograms. Differentiation from RDS is difficult in preterm infants, especially because preterm labor is a risk factor for pneumonia. Radiographic findings of TTN usually resolve by 48 hours and those of RDS are markedly improved after surfactant treatment, whereas radiologic changes of pneumonia may persist for weeks.

Late-onset pneumonia usually presents with nonspecific changes in the overall condition of the infant in the form of new-onset or increased apnea, abdominal distension or feeding intolerance, temperature instability, respiratory distress, hyperglycemia, or cardiovascular instability. Patients receiving ventilatory assistance usually present with an increased oxygen requirement or mechanical support.

The diagnosis of pneumonia requires a high index of suspicion in any infant with new onset of symptoms suggestive of sepsis. Sepsis work-up, including blood culture, blood count, and differential should be obtained before starting antibiotics. The presence of an elevated C-reactive protein, neutropenia, immature white blood cells, and thrombocytopenia is highly suggestive (although not diagnostic) of infection in newborn babies with risk factors. Tracheal Gram stain and culture should be considered in infants who require mechanical ventilation. A positive tracheal culture in the first 8 hours of life may correlate with a positive blood culture. After 8 hours, a positive tracheal culture might be secondary to colonization. Analysis and culture of pleural fluid, if present in adequate amount, can aid in the diagnosis in infants not responding to empiric therapy. Specific studies for viral or unusual bacterial infections should be obtained if suspected. Diagnosis of ventilator-associated pneumonia (VAP) can be troublesome, especially in preterm infants with underlying lung disease. Typically, these infants' tracheas are colonized, discounting the validity of tracheal cultures. The Centers for Disease Control and Prevention has proposed stringent diagnostic criteria to diagnose VAP in infants younger than 1 year of age that

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rely on increased ventilator support, temperature instability, new onset of purulent tracheal secretions or a change in the character of sputum, leukopenia or leukocytosis, clinical signs of respiratory distress, bradycardia or tachycardia, and new changes in chest radiograph that persist in at least two consecutive films. However, the validity of these criteria in diagnosing VAP in preterm infants with underlying lung disease has not been substantiated. Further studies are clearly needed to better diagnose and treat pneumonia in ventilated infants with low birth weight.

Management

Successful treatment depends on identification of the causative organism, institution of early and adequate antibiotic therapy, and supportive care. Empirical antibiotic therapy is usually started before isolation of the organism. In early-onset pneumonia, ampicillin and gentamicin are adequate initial therapy. However, with the increasing incidence of antibiotic-resistant Gram-negative bacteria, this regimen may need to be altered based on specific institutional susceptibility data. Empiric therapy with vancomycin (for coagulase-negative staphylococci) and gentamicin is usually started for late-onset pneumonia. To decrease the possibility of developing vancomycin-resistant bacteria, an empirical regimen for late-onset sepsis/pneumonia may include nafcillin and gentamicin, and vancomycin is started if coagulase-negative *Staphylococcus* is identified or the clinical picture is deteriorating. In intubated infants, antibiotic coverage depends on the specific bacteria colonizing the trachea. When the causative organism is isolated, specific therapy is started according to susceptibility profile. The duration of therapy is dependent on the causative organism and response to treatment; however, in uncomplicated pneumonia, 10-14 days of therapy are usually adequate.

Whereas antibiotic therapy is the mainstay of treatment, supportive care is essential and has been shown to decrease the mortality and morbidity associated with pneumonia in developing countries. In the acute stage, circulatory support with fluids and inotropes might be needed, and mechanical ventilation and oxygen should be administered to correct hypoxemia. Special attention to correct acidosis, hypoglycemia, and other possible electrolyte imbalance is also warranted. Parenteral nutrition with amino acids, carbohydrates, and lipids can provide adequate nutrition and prevent protein catabolism as well as amino and fatty acid deficiency. Feeding should be started as soon as possible to supply adequate calories. In the absence of respiratory distress or abdominal pathology with concern for aspiration, gavage feedings can be started.

Transient Tachypnea of the Newborn

Transient tachypnea of the newborn is a common physiologic disorder of the newborn resulting from pulmonary edema secondary to inadequate or delayed clearance of fetal alveolar fluid. The initial clinical picture is usually completely resolved by 48-72 hours, hence the term *transient*. However, TTN continues to represent a diagnostic dilemma secondary to the inability to differentiate its initial presentation from that of other causes of respiratory distress, including pneumonia. The incidence has been estimated at 5.7 per 1000 births in term infants. Risk factors for development of TTN include premature or elective cesarean delivery without labor, large birth weight, maternal diabetes, maternal asthma, twin pregnancy, and male gender. The incidence of pulmonary pathology including TTN was found to be two- to threefold higher in infants born after planned cesarean delivery compared with a planned vaginal delivery.[67]

Fetal alveolar fluid is continuously secreted during pregnancy through an epithelial chloride secretion mechanism, and the rate of secretion decreases a few days before delivery. At birth, the balance of fluid movement in the alveolus switches from chloride secretion to sodium absorption, causing resorption of intra-alveolar fluid. Absorption occurs in two steps. First, sodium moves from the alveolar lumen into the cell by passive movement across a concentration gradient maintained by the Na-K-ATPase pump. Next, sodium is actively transported into the interstitium by amiloride-sensitive epithelial sodium channels (ENaC). Thereafter, the sodium and fluid are cleared through the lymphatic and vascular systems.

The mechanisms underlying failure or delay in clearance of intra-alveolar fluid in patients with TTN are not totally understood. The mechanical force of birth canal squeeze, originally thought to be the major factor in lung fluid resorption, is now believed to be only a minor contributor. Immaturity of ENaC has been shown, both in animals and neonates, to impair fluid resorption, and as ENaC expression is developmentally regulated, this is especially relevant in the late preterm infant. Hormonal changes associated with spontaneous labor, especially the surge of catecholamines and endogenous steroids, and activation of the β-adrenergic system seem to be important in increasing the expression and activity of ENaC, which partially accounts for the higher incidence of TTN in elective cesarean section cases not preceded by spontaneous labor.[73]

The clinical picture of patients with TTN is secondary to the decrease in lung compliance associated with pulmonary edema. Collapse of airways might also occur in response to fluid accumulation in the interstitium and peribronchial lymphatics. The net result is variable degrees of hypoxemia and respiratory acidosis.

Patients with TTN usually present very early after birth with symptoms of respiratory distress. Tachypnea is the most consistent finding, although increased work of breathing with expiratory grunting, nasal flaring, and retractions may also be present. Hypoxemia necessitating modest oxygen requirement (usually <40%), together with hypercapnia, can occur, whereas respiratory failure requiring CPAP is unusual. The most characteristic feature of TTN is the transient nature of this disease. In most patients, rapid continuous improvement in the clinical condition occurs within

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24-48 hours of life, although in some patients, symptoms might persist beyond 72 hours of life. Characteristic radiographic findings consist of perihilar streaking that represents engorgement of the periarterial lymphatics and fluid-filled interlobar fissures. Both the horizontal and oblique fissures can be affected, although the horizontal is affected more commonly. Fluid-filled alveoli can present as fluffy bilateral infiltrates. Atelectasis and pleural effusion can also be seen. Although these radiographic changes can readily be distinguished from classic changes of RDS, TTN can conceivably accompany RDS in preterm infants. Radiographic changes are essentially resolved by 48 hours. Ultrasound has recently been described to be useful in the diagnosis of TTN as well as prediction of the need for respiratory support in infants affected by TTN.[33,103,126]

Treatment of TTN is supportive. However, because it is difficult to differentiate TTN from other disorders, most patients are usually started on antibiotics that can be discontinued after 48 hours if cultures are negative and the diagnosis is more clear. Lasix has no role in the treatment of TTN. Recently, the use of antenatal steroids prior to late preterm delivery has demonstrated decreased rates of TTN among other respiratory morbidities[65] perhaps through enhanced fluid resorption from alveolar spaces through increased transcription and activation of ENaC. However, this is not practice beyond 36 6/7 weeks' gestation. Exogenous steroids or catecholamines do not seem to provide benefit after birth once the patient is symptomatic, because recovery usually precedes the action of these agents. The use of inhaled β-agonist therapy has been suggested, but this is based on small observational studies, thus there is not enough evidence to support its routine use.[87,116] Delaying elective cesarean section until 39-40 weeks' gestation or until spontaneous labor starts will decrease the incidence of TTN. However, this should be weighed against possible complications of delaying a needed cesarean section.[62] Although TTN is considered a self-limited transient condition, there are increasing data to suggest that TTN increases a newborn's risk for developing a wheezing syndrome early in life.[101]

Pulmonary Hemorrhage

Pulmonary hemorrhage is a serious complication in neonates with RDS and has been associated with higher morbidity and mortality. Serious pulmonary hemorrhage has been defined as a gush of blood through an endotracheal tube in intubated neonates associated with a worsening clinical picture, requiring increased ventilatory support and blood product transfusion. The incidence of such severe hemorrhage is about 5% in very low birth weight infants and 10.2% in extremely low birth weight infants. Risk factors for development of pulmonary hemorrhage include extreme prematurity, surfactant administration, patent ductus arteriosus (PDA) with left-to-right shunting, multiple birth, and male gender. Other risk factors include severe systemic illness, coagulopathy, and asphyxia. More than 80% of cases of serious pulmonary hemorrhage occur before 72 hours of life with a median of 40 hours; however, some babies might present after 1 week of life.[157]

The pathophysiology of pulmonary hemorrhage is believed to be secondary to a sudden decrease in pulmonary vascular resistance, causing increased left-to-right shunting and pulmonary vascular engorgement, pulmonary edema, and ultimately, rupture of pulmonary capillaries. This is especially true in patients with a PDA after surfactant treatment. In a post hoc analysis of patients enrolled in the trial for indomethacin prophylaxis in premature infants, a reduced risk for PDA accounted for 80% of the beneficial effect of prophylactic indomethacin on serious pulmonary bleeds.[8] However, pulmonary hemorrhage can also occur in patients who never received surfactant or had a PDA, highlighting the importance of other etiologies in the pathogenesis of pulmonary hemorrhage, including aggressive suctioning, especially using a closed-circuit system.

Patients with pulmonary hemorrhage usually present with cyanosis, bradycardia, apnea, gasping, hypotension, increased work of breathing, hypoxia, and hypercapnia, requiring increased ventilatory support. In almost one-third of patients, serious pulmonary hemorrhage was preceded by prodromal episodes of suctioning frothy blood-tinged tracheal secretions. Chest radiographs demonstrate acute and varying degrees of worsening of the underlying pulmonary disease, ranging from bilateral fluffy infiltrates to complete whiteout in severe cases.

Treatment of pulmonary hemorrhage is mostly supportive. Increased ventilatory support, especially positive end-expiratory pressure (PEEP), serves two purposes: it is needed for adequate ventilation and oxygenation, and it acts to tamponade and stop the bleeding. Suctioning should be limited during the acute hemorrhage. The efficacy of instillation of epinephrine, although used clinically, has not been proved in clinical trials. Transfusion of blood products and correction of underlying or secondary coagulopathy is essential. Pulmonary hemorrhage can cause deactivation of surfactant, and exogenous surfactant administration has been used successfully.[9] Prophylactic indomethacin decreased the incidence of pulmonary hemorrhage by 26% in infants with extremely low birth weight.[135]

Pulmonary hemorrhage is associated with mortality approaching 50% in infants with extremely low birth weight. Whereas initial retrospective studies did not show worse neurodevelopmental outcomes in survivors of pulmonary hemorrhage, one study showed increased incidence of cerebral palsy and cognitive delay (OR 2.86 and 2.4, respectively).[8] Pulmonary hemorrhage was also associated with increased incidence of periventricular leukomalacia and seizures at 18 months of age.

Pulmonary Air Leak Syndromes

Air leak occurs more commonly in the newborn period than any other period of life. One to two percent of all live

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births of term infants were found to have a pneumothorax on consecutive chest radiographs in 1930. The incidence increases with decreasing gestational age. Although the incidence was 6.3% in 1999 in very low birth weight infants in the Vermont-Oxford Network database, it approached 15% in those with a birth weight of 501-750 g.[70] Air leak syndromes include pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, and pneumopericardium, and less commonly, pneumoperitoneum and subcutaneous emphysema. Even though air leaks can occur spontaneously, they mostly occur in patients with lung pathology, including MAS, pneumonia, RDS, diaphragmatic hernia, and pulmonary hypoplasia, especially when positive-pressure ventilation is required. The introduction of surfactant for treatment of RDS has caused a decrease in the incidence of air leaks. Conversely, the increasing practice of elective cesarean section before 39 completed weeks' gestation is associated with increased incidence of pneumothorax when compared with emergent cesarean section (OR 4.2) or vaginal delivery (OR 7.95).[172]

Pathophysiology

Air leaks occur when overdistended alveoli rupture into the perivascular bundle, from where air tracks toward the hilum or pleura, causing pneumomediastinum or pneumothorax, respectively. In the preterm infant in whom the interstitium is more abundant and less dissectible, air can stay in the perivascular sheets, causing pulmonary interstitial emphysema (PIE). Alveolar overdistension might occur in the presence of uneven alveolar ventilation or air trapping. Atelectasis in RDS and plugged small airways in MAS cause unequal distribution of the ventilated volume and transpulmonary pressure to the more distensible areas of the lung, increasing the risk of rupture and air leak. Partial obstruction during MAS causes air trapping when inspired air is not completely evacuated during exhalation. Further accumulation during subsequent breaths can rupture the alveolar space.

Different ventilatory strategies have been associated with the development of pneumothorax, including higher peak inspiratory pressure especially in the 24 hours preceding pneumothorax, long inspiratory time (>0.5 seconds), and frequent suctioning in the 8 hours before pneumothorax. Elective initial use of high nasal CPAP (8 cm H_2O) in infants at 25-28 weeks' gestation was associated with increased incidence of air leak from 3%-9% when compared with intubated infants who received surfactant therapy. However, there was no difference in the incidence of BPD or mortality rate between the two groups.[117] Use of CPAP (5 cm H_2O) in the delivery room in extremely low gestational age infants was associated with a decreased need for intubation and postnatal corticosteroids for BPD and fewer days of mechanical ventilation when compared with initial intubation and surfactant administration within 1 hour after birth, without an increase in the incidence of pneumothorax.[154] Factors possibly associated with decreased incidence of pneumothorax include positive-pressure ventilation (rate >60) and volume-targeted ventilation. The use of HFOV following pneumothorax was associated with a decreased incidence of secondary pneumothorax.[114]

Clinical Presentation

Although pneumothorax can be the presenting diagnosis, more commonly, it complicates underlying lung pathology. Sudden worsening in respiratory distress should always raise the suspicion of the development of a pneumothorax. Tachypnea, grunting, flaring, and retractions occur most commonly. Hypoxemia with cyanosis and increased oxygen requirement occur early in the course of pneumothorax while hypercapnia follows. Hypoxemia develops secondary to hypoventilation and ventilation-perfusion mismatch as the affected lung collapses. Physical examination reveals distant breath sounds, overdistension of the chest wall, and bulging abdomen on the affected side secondary to downward displacement of the diaphragm in patients with unilateral pneumothorax. The cardiac apex is displaced away from the affected side, as is the trachea.

Larger volumes of leaked air can cause significant increase in intrathoracic pressure, which impairs venous blood return and compromises cardiac output, causing poor tissue perfusion and metabolic acidosis. Although bradycardia and hypotension were not seen in a piglet model of moderate pneumothorax (30 mL of air), they can develop with a severe tension pneumothorax. The decreased cardiac output may cause a compensatory increase in carotid blood flow as the body tries to protect vital organs. The resultant increase in cerebral blood flow together with impairment of cerebral venous return secondary to increased central venous pressure might explain the increased incidence of intraventricular hemorrhage (IVH) in patients with pneumothorax.

Pneumomediastinum is often asymptomatic if not associated with pneumothorax and is mostly found on radiographic evaluation of patients with respiratory distress or distant heart sounds. Dissection of air through the anterior mediastinum into the neck can cause subcutaneous emphysema that is most commonly felt as subcutaneous crepitus in the face, neck, or supraclavicular notch area.

Pneumopericardium is a rare and serious complication probably caused by dissection of leaked air through the vascular bundle of great vessels. Trapped air in the limited pericardial space can quickly cause cardiac tamponade, decreasing venous return, and cardiac output. Pneumopericardium should be suspected in patients with an air leak and sudden cardiovascular compromise associated with a narrow pulse pressure. The clinical picture consists of worsening respiratory distress, hypotension, bradycardia, pallor, and/or cyanosis. Cardiac sounds are distant or muffled on auscultation and a pericardial rub might also be heard. Low voltage QRS complexes can also be seen.

Pneumoperitoneum occurs when an intrathoracic air leak decompresses into the abdomen. It is typically asymptomatic and usually diagnosed on radiographic evaluation. It should, however, be differentiated from free

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abdominal air secondary to a ruptured viscus in which patients are usually symptomatic with signs and symptoms of peritonitis.

Diagnosis

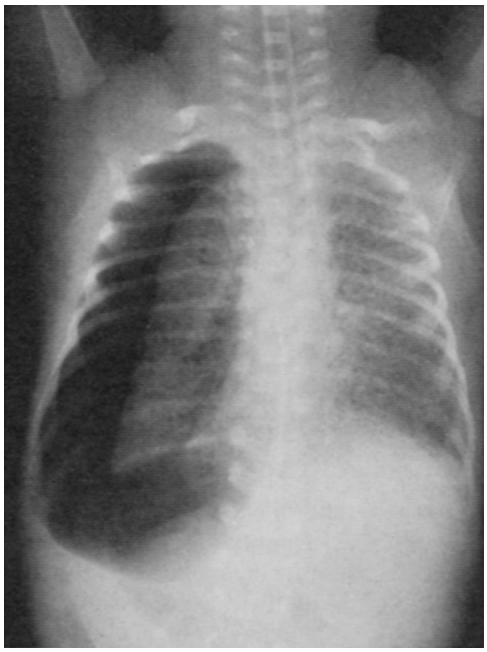
In unstable neonates with progressive deterioration of their clinical status, transillumination of the chest might provide a quick bedside diagnostic tool and allow for immediate intervention before x-ray confirmation. The technique involves the use of a fiberoptic light probe that is placed on the infant's chest wall while the room is darkened. In the presence of a large pneumothorax, the entire hemithorax on the affected side lights up and the opposite side shows diminished transillumination because of lung compression on that side. In such cases, decompression should be accomplished without awaiting radiographic confirmation. However, in stable neonates, radiographic confirmation should always be sought before intervention. Inconclusive results or inexperience with the use of transillumination should also be confirmed by x-ray before intervention. This allows for proper localization of the pneumothorax, as well as excluding other disorders that do not need evacuation, such as pneumomediastinum, congenital lobar emphysema, or diaphragmatic hernia.

The diagnosis is clear on radiographic evaluation of patients with a large or tension pneumothorax. Air accumulates between the parietal and visceral pleura, separating the lung from the chest wall and collapsing the ipsilateral lung. This can be seen as a curvilinear line silhouetting the collapsed lung (Fig. 66.7). External artifacts can also appear as a curvilinear line on chest radiograph; however, artifact can be differentiated from a pneumothorax by its tendency to extend beyond the chest cavity in either direction. With a tension pneumothorax, the mediastinal structures, including the heart, are shifted away from the affected side. Lung collapse might not be complete despite a severe pneumothorax in patients with RDS secondary to poor compliance of the affected lung. Smaller pneumothoraces might appear as a small sliver of free air lateral to the lung or above the diaphragm, causing the edge of the diaphragm or costophrenic angle to appear crisp. An anterior pneumothorax causes the affected lung to look translucent compared with the contralateral side. Confirmation of a small pneumothorax can be obtained with a lateral decubitus chest radiograph, where the unaffected side is dependent. As the free air rises, the reflection of the parietal pleura is seen clearly as a curvilinear line beyond which no lung markings are seen. This might also identify any contralateral pneumothorax or pneumomediastinum.

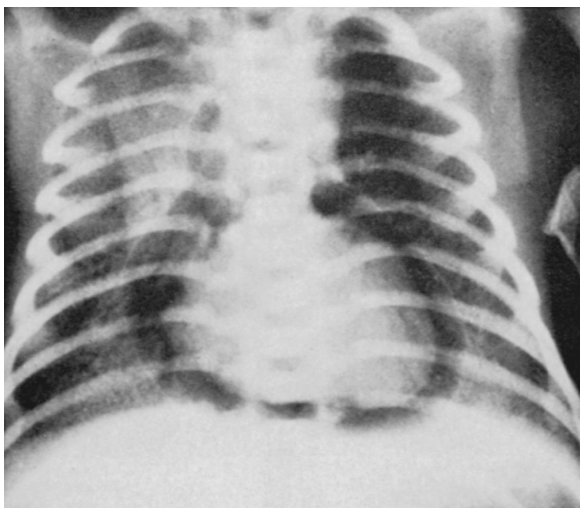
Pneumomediastinum can be diagnosed on chest radiograph by elevation of the edge of the thymus from the pericardium by mediastinal free air in a characteristic crescent or spinnaker sail configuration. A large pneumomediastinum can be differentiated from a pneumothorax by lateral decubitus radiographs as described earlier.

Pneumopericardium appears on plain chest radiograph as free air completely surrounding the heart but not extending beyond the aorta or pulmonary artery into the upper mediastinum. Although difficult to differentiate from a large pneumomediastinum, the presence of air between the heart and diaphragm is diagnostic of pneumopericardium (Fig. 66.8).

Pulmonary interstitial emphysema (PIE) is seen on chest radiograph as coarse, nonbranching radiolucencies that project toward the periphery of the lung in a disorganized fashion. This appearance must not be confused with an air bronchogram, a classic radiographic sign of respiratory distress syndrome. Air bronchograms show long, smooth, branching radiolucencies that follow normal anatomic distributions similar to the bronchial tree. Pathologically, PIE is seen in lung tissue as multiple irregular, air-filled cysts



• **Fig. 66.7** Tension pneumothorax on the right. An endotracheal tube is in place.



• **Fig. 66.8** Pneumopericardium in a newborn.

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varying in diameter from 1 mm-1 cm, localized to interlobular septa, and extending radially from the hilum. Pulmonary interstitial emphysema can be localized to one lung or a lobe of a lung or can be diffuse bilateral disease. There is usually hyperinflation on the affected side that persists even after weaning ventilatory support.

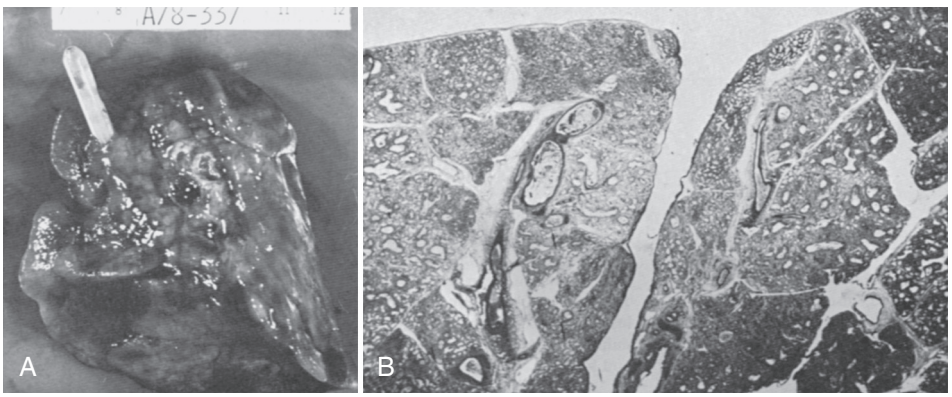
Management

Treatment of a pneumothorax depends on the severity of clinical presentation and whether it occurs during mechanical ventilation. In asymptomatic patients without underlying pulmonary disease, no treatment is required; however, close observation for worsening pneumothorax and development of respiratory symptoms is clearly needed. The pneumothorax usually resolves spontaneously in 1-2 days. Follow-up radiographs can be obtained as mandated by the clinical picture. The association of symptomatic spontaneous pneumothorax with congenital renal malformations and the need for renal ultrasound evaluation in these patients is controversial. A review of 80 patients with spontaneous pneumothorax compared with normal controls showed no difference between the two groups in the rate of congenital renal malformations.[7]

Only supportive care is needed in the treatment of symptomatic patients with a mild pneumothorax without evidence of respiratory failure. Theoretically, 100% oxygen given by a hood might lead to nitrogen washout and resolution or decrease in the size of the pneumothorax. Recent retrospective reviews showed no difference in time to resolution of pneumothorax in infants treated with 21% oxygen vs. 100% oxygen vs. somewhere in between.[30,144] Oxygen is generally given only as needed to provide adequate oxygen saturations. Thoracocentesis is used for emergency evacuation of a large pneumothorax in unstable infants and might be the only treatment needed in nonventilated babies. However, recurrence of the pneumothorax should prompt the insertion of a chest tube. Thoracocentesis can also be used as a temporizing measure before chest tube insertion in ventilated infants.

In ventilated patients with a large or tension pneumothorax, the initial management is to wean PIP and PEEP to decrease further air leak while preparing for chest tube placement. Deciding on which brand of chest tube and which insertion technique to use depends most importantly on experience and comfort level. The tube should be inserted under complete aseptic technique and positioned anterior to the affected lung. The position of the tube should be confirmed by anteroposterior and lateral chest radiographs. When placed correctly, there is immediate improvement in oxygenation in affected patients, and the tube should be connected to an underwater seal with continuous suctioning at 10-20 cm H_2O. The chest tube should be secured when correct positioning is confirmed, with special attention given to prevent tension on the tube causing it to dislodge, particularly during radiologic examination. Chest tube insertion can be complicated by lung damage, which is usually diagnosed at autopsy, diaphragmatic paralysis secondary to phrenic nerve damage, or bleeding (Fig. 66.9). The use of a trocar or other sharp instrument during insertion should be avoided to decrease the chance of these complications. Once air bubbling stops, the chest tube should be clamped or put to water seal overnight, and if the pneumothorax does not reaccumulate, the tube can be successfully removed. Isolated pneumomediastinum is usually self-limiting and does not need intervention. However, these patients should be closely observed because a pneumothorax could develop.

Management of PIE can present a challenge. Increased support may lead to enlargement of the more compliant PIE cysts, which in turn compresses the relatively normal adjacent alveoli, causing worsening hypoxia and hypercapnia. The treatment strategy instead should target decreasing mean airway pressure while accepting higher CO_2 levels and oxygen requirement to allow for collapse of the dilated interstitial cystic lesions and expansion of the normal alveoli. High-frequency oscillatory ventilation is an acceptable ventilatory strategy for PIE because of the lack of inflating volumes that tend to worsen the PIE. In the case of failure of conservative management and persistent PIE, different treatment strategies have been tried, especially in unilateral cases, with varying degrees of success, including single-lung ventilation.[128]



• **Fig. 66.9** Perforation of the lung associated with insertion of chest tube by means of trocar and cannula. **A,** Gross appearance. **B,** Histologic features demonstrating tract into the lung.

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The occurrence of air leak is associated with increased incidence of mortality and morbidity. Together with the increased incidence of IVH mentioned earlier, very low birth weight infants who develop pneumothorax in the first 24 hours of life were 13 times more likely to die or develop bronchopulmonary dysplasia. Furthermore, extremely low birth weight infants with a pneumothorax who had a normal head ultrasound were more likely to develop cerebral palsy after controlling for other factors (OR 2.3).[99] Therefore, management strategies directed at avoiding the development of a pneumothorax should always be sought, including using minimal effective inspiratory pressures, low inspiratory time, high-frequency positive pressure ventilation, volume-targeted ventilation, early administration of surfactant in eligible patients, and rapid weaning of mechanical ventilation.

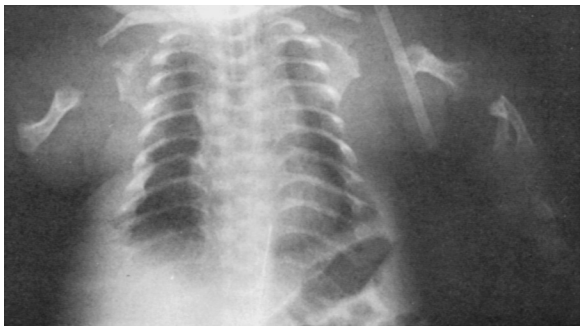
Rib Cage Abnormalities

Thoracic cage and skeletal abnormalities are a rare group of conditions that can cause respiratory distress by restriction of thoracic volume. They include a number of entities incompatible with life. In this group of diseases are those with hypoplasia of the ribs and thorax, including asphyxiating thoracic dystrophy (Jeune syndrome), thanatophoric dysplasia, achondrogenesis, homozygous achondroplasia, osteogenesis imperfecta (severe form), Ellis-van Creveld syndrome (chondroectodermal dysplasia), hypophosphatasia, spondylothoracic dysplasia, and rib-gap syndrome.

Respiratory distress caused by structural abnormalities of the chest wall should be readily apparent. However, marked narrowing of the thorax can result in what appears to be a distended abdomen, and the respiratory problem can be erroneously attributed to an intra-abdominal pathologic condition. The presence of other associated anomalies, for example, short-limbed dwarfism, together with close observation of respiratory excursions, examination of the bony thorax, and measurement of the circumference of the chest, establishes the diagnosis even before a review is made of the thoracic and skeletal radiographs.

With structural abnormalities of the chest wall, asphyxia and respiratory distress are present from birth. The infants are cyanotic and tachypneic and demonstrate severe retractions and characteristically, a virtually immobile chest. Diaphragmatic excursions are prominent; thus respiration appears entirely abdominal. Pulmonary hypoplasia accompanies the thoracic dystrophy, and radiographically, the lungs can appear airless.

Infants with asphyxiating thoracic dystrophy, thanatophoric dwarfism, achondrogenesis, homozygous achondroplasia, or Ellis-van Creveld syndrome have thoracic radiographs with a squared-off appearance, and the posterior rib arcs all appear to be the same length. The clavicles appear very high, and the diaphragms are low (Fig. 66.10). The transverse diameter of the thorax can appear diminished in comparison with the vertical diameter. On a lateral view, the ribs are very short and can appear clubbed anteriorly. The anteroposterior diameter of the thorax is decreased. The lungs may be poorly aerated, infiltrates are often present, and the heart might appear enlarged. Differentiating among the various syndromes of thoracic cage and skeletal abnormalities usually is accomplished by means of a skeletal survey. Multiple fractures and bone demineralization are characteristic of osteogenesis imperfecta and hypophosphatasia.



• **Fig. 66.10** Radiographic appearance in thanatophoric dwarfism showing the narrow thorax, low diaphragm, and foreshortened humeri.

Asphyxiating Thoracic Dystrophy (Jeune Syndrome)

Jeune syndrome is a rare autosomal recessive skeletal dysplasia with multiorgan involvement. Mutations in *WDR19*, *DYNC2H1*, *TTC21B*, and *IFT80* genes encoding intraflagellar protein have been identified in a small subset of Jeune syndrome patients.[14,165] The hallmarks of asphyxiating thoracic dystrophy are extreme constriction and narrowing of the thorax, short ribs, and variable shortening of the limbs with abnormalities of the bones of the pelvis and extremities. The thorax is relatively immobile, and the ribs are horizontally directed and short with bulbous ends. In addition to the thoracic abnormalities, the infants have trident iliac bones with a double-notch appearance of the acetabulum. Associated anomalies include polydactyly and deformed teeth. Renal abnormalities may be present, and renal failure can occur later in life.

These infants usually present with respiratory distress and recurrent respiratory infections during the neonatal period. It has been reported that 60%-80% of cases are fatal in early childhood, but if they survive the early years, the respiratory problems tend to decrease with age, and a subset of children affected by this disorder can have long-term survival.[41]

Thanatophoric Dysplasia

Thanatophoric dysplasia (see Chapter 30) was differentiated from achondroplasia in 1967. The disorder has been generally fatal in the perinatal period, with rare exceptions,

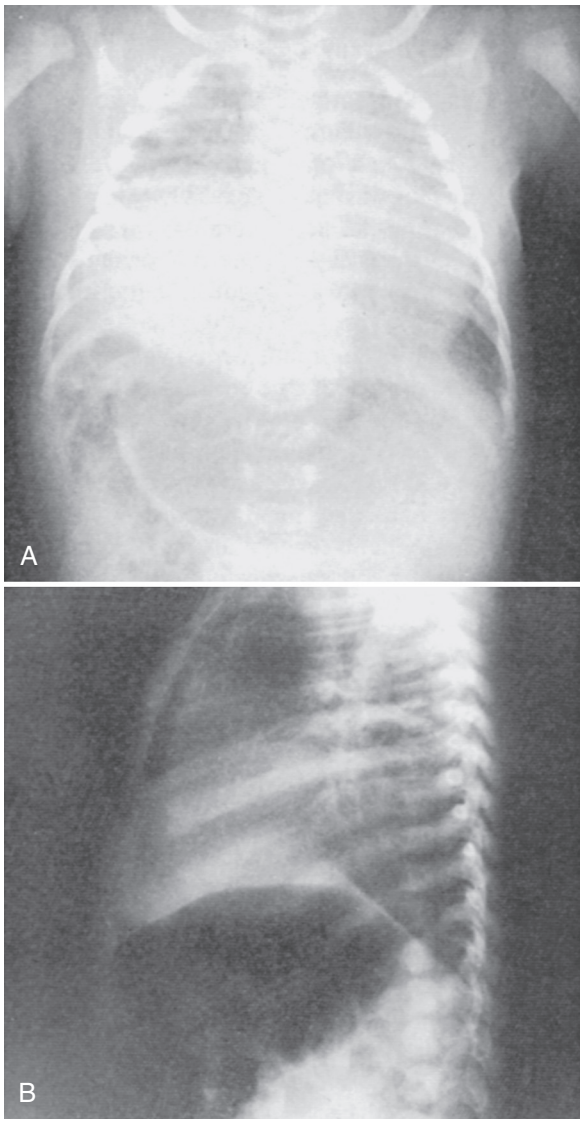
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and probably is the most common form of lethal neonatal dwarfism. It is caused by de novo mutations in the *FGFR3* gene (fibroblast growth factor receptor 3) and is an autosomal dominant condition.[79] Appearance at birth is characteristic and includes striking micromelia in association with a normal trunk, a large head, and a narrow thorax. The radiographic findings include severely flattened vertebral bodies with markedly widened intervertebral disk spaces, small iliac rings, and flaring of the metaphyses of the long bones. There is a high incidence of polyhydramnios, and the infants often present in the breech position.

Infants present at birth with severe pulmonary insufficiency, requiring mechanical ventilation and intensive neonatal care. Immediate and accurate diagnosis is important in guiding medical decisions about continuation of support.

Phrenic Nerve Injury

Phrenic nerve injury with paralysis of the diaphragm is an unusual cause of respiratory distress. It is most commonly present on the right side following birth trauma; thus, an associated brachial plexus injury or Horner syndrome can coexist in approximately 75% of the patients. However, injury can also occur after cardiovascular or thoracic surgeries or following invasive procedures. The injuries are observed in infants who are large for gestational age, especially following shoulder dystocia or difficult breech extractions. Fractures of the humerus or clavicle are often observed. The nerve roots of C3 to C5 are stretched, with lateral hyperextension and traction on the neck. Recovery depends on the degree of injury; avulsion results in permanent injury, and diaphragmatic eventration secondary to muscle atrophy ensues. Lesser injury or edema of the nerve roots results in a spectrum of respiratory symptoms that can include cyanosis, weak cry, tachypnea, or apnea. On radiographic examination, the involved hemidiaphragm is elevated, and atelectasis usually is observed on that side. The heart and mediastinum are shifted away from the affected side (Fig. 66.11). Ultrasonographic or fluoroscopic evaluation should be diagnostic and reveal paradoxic movement of the diaphragm with elevation during inspiration and descent with expiration. Congenital eventration of the diaphragm also results in an elevated hemidiaphragm with paradoxical movement. Secondary pneumonia is the major source of morbidity and mortality. Treatment of phrenic nerve palsy initially is supportive and, in the absence of avulsion, spontaneous resolution is to be expected. Surgical plication of the diaphragm might be required for selected infants with avulsion.



• **Fig. 66.11** Phrenic nerve palsy. **A,** Note the elevated right dome of the diaphragm. **B,** Lateral view.

Key Points

- Not all respiratory distress after birth is due to respiratory distress syndrome.
- The degree of respiratory distress due to these other causes is dependent on the timing of the insult and the degree to which it causes pulmonary hypoplasia and decreased pulmonary vascular growth.
- Symptoms and outcomes can vary widely in this group of disorders and our therapies are ever evolving to improve the long-term morbidities and mortality associated with them.

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67

Neonatal Apnea and the Foundation of Respiratory Control

MARY ELAINE PATRINOS

Breathing results in the exchange of oxygen and carbon dioxide between the lungs and the environment while maintaining homeostasis and control of blood pH. Energy-consuming breathing movements do occur in utero. Maturation of breathing is a continuous process that bridges fetal and neonatal life. Especially for premature infants, immature fetal breathing responses result in irregular respiratory effort, apnea, bradycardia, and hypoxemia.

Fetal Breathing

Fetal breathing activity has been described in many species and is present very early in gestation. Breathing activity in the human fetus can be detected by 11 weeks' gestation using ultrasound. Although the placenta is the site of gas exchange in utero, fetal breathing is important for lung growth and development. Moreover, decreased diaphragmatic activity has been associated with pulmonary hypoplasia. Fetal breathing movement (FBM) has also been shown to significantly increase fetal cardiac output and blood flow to a number of vital organs, including the heart, brain, and placenta. FBM changes from early continuous movement that seems to originate from the spinal cord to a phasic pattern that occurs only during rapid eye movement (REM) in the third trimester with total cessation of breathing during non-REM sleep, possibly secondary to descending inhibitory pontine input to the medullary rhythm-generating center. The mechanisms underlying loss of phasic FBM and the establishment of continuous breathing after birth are not clear. However, several factors have been implicated, including serotonin, γ-aminobutyric acid (GABA), corticotrophin-releasing factor, and prostaglandins.[2]

Fetal hypercapnia increases the incidence and depth of FBM only during REM sleep without affecting breathing frequency. This response is present from 24 weeks' gestation, and CO_2 sensitivity increases with advancing gestational age (GA). In contrast, fetal hypocapnia causes a decrease or disappearance of FBM, which implies that a baseline CO_2 level is essential for the presence of FBM. Although the fetus lives in a relatively hypoxemic state (PaO_2 23-27 mm Hg), oxygen delivery in utero is adequate, because it matches oxygen consumption and allows for fetal activity and growth. Unlike adults, the fetus responds to hypoxia with a decrease in breathing activity. The cause of this hypoxic ventilatory depression in utero appears to be central in origin. Brainstem transection or lesions in the lateral upper pons allow acute hypoxemia to stimulate FBM even in the absence of the carotid bodies. This is consistent with the concept that hypoxic depression is the result of descending pontine or suprapontine inhibition. Unlike the fetal breathing response to hypercapnia, the hypoxic response is logical in the sense that an increase in fetal respiratory activity in response to hypoxia would be counterproductive.

Postnatal Development of Respiratory Control

Although better developed than the fetal pattern, the degree of maturity of respiratory control in the newborn is directly related to gestational age at birth. Immaturity manifests in almost every aspect of respiratory control, from peripheral afferent input to central respiratory output and respiratory muscle responses. There seems to be an overriding inhibitory influence of central origin in the control of breathing in the neonate. This is manifested by a decreased response to CO_2, a paradoxical response to hypoxia, an exaggerated reflex apnea, and irregularities of breathing. The origin of this inhibitory effect on neonatal breathing could be secondary to increased inhibitory pathways, decreased excitatory pathways, or a combination of both.

Neonatal Breathing Pattern

Neonatal respiratory activity is irregular with spontaneous changes alternating between eupnea, apnea, periodic breathing, and tachypnea. Respiratory frequency, often inversely proportional to body weight, may be quite variable in the preterm infant. Periods of slow respiratory rates are secondary to prolongation of expiratory time (T_E),

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Abstract

Maturation of breathing is a continuous process that bridges fetal and neonatal life. Especially for premature infants, immature fetal breathing responses result in irregular respiratory effort, apnea, bradycardia, and hypoxemia. Caffeine in conjunction with continuous positive airway pressure or other forms of noninvasive respiratory support are effective measures to reduce apnea severity and its consequences. The lack of consensus regarding the definition of a clinically significant cardiorespiratory event can impact length of stay and complicate hospital discharge.

Keywords

apnea
bradycardia
hypoxia
BRUE
SUID
reflux

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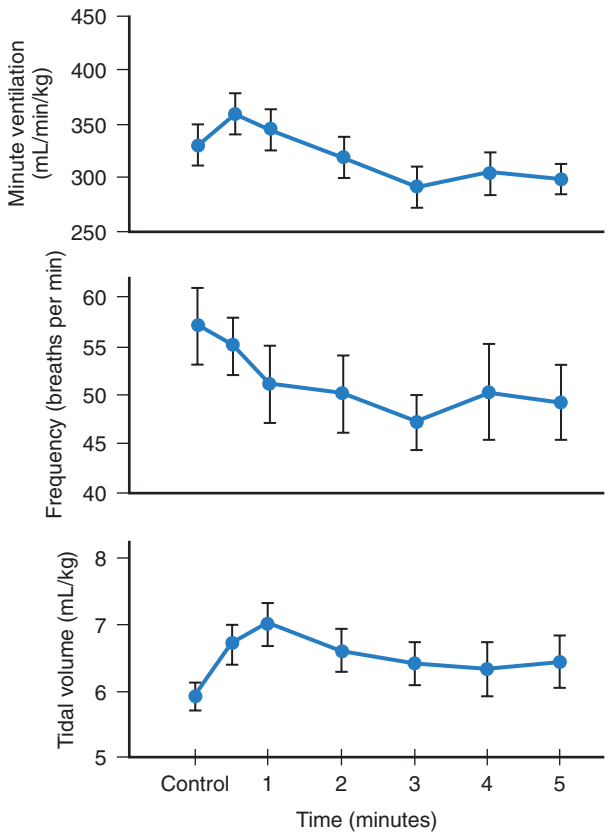
whereas inspiratory time (T_I) remains relatively unchanged during development. Extreme prolongation of T_E results in respiratory pauses and apnea, which occur frequently in preterm and, to a lesser extent, in healthy term neonates. Paradoxical inward movement of the rib cage during inspiration is especially common in preterm infants. The mechanism behind this paradoxical movement is related to a combination of a highly compliant rib cage and diminished intercostal muscle tone opposed by diaphragmatic contraction. The effort required to produce a tidal volume during these paradoxical movements is substantially greater than during "normal" breathing, which further hinders an already immature respiratory system. Because of chest wall instability and immature lung development, the preterm infant often compensates with a shortened expiratory time and expiratory breaking to maintain expiratory lung volume. Occasional sigh breaths re-open areas of atelectasis. Apnea often leads to a loss in lung volume, decrease in functional residual capacity (FRC), and reduction in oxygen stores.[12] The incidence of central apnea decreases with advancing gestational age and is present in almost all infants with a birth weight less than 1000 g or gestational age less than 28 weeks. At 43-44 weeks' corrected gestational age, the incidence of apnea is comparable to that of a term neonate. Apnea is not exclusively confined to preterm babies. Healthy term infants may also have apnea exceeding 20 seconds on home monitoring.[43]

Hypercapnia and Acidosis

Small increases in arterial P_{CO_2} resulting in central acidosis increase ventilation dramatically. The ventilatory response to CO_2 is the net result of activation of both peripheral and central chemoreceptors. The contribution of the peripheral chemoreceptors, mainly through the carotid body, is 10%-40% of the total hypercapneic response. Central chemoreceptors originally thought to be confined to the ventrolateral medulla have been found to be widespread in the brainstem, including the retrotrapezoid nucleus, the region of the nucleus tractus solitarius, the region of the locus coeruleus, the rostral aspect of the ventral respiratory group, and the medullary raphe.[34] Other sites of chemoreception include the fastigial nucleus of the cerebellum and the pre-Botzinger complex. The ventilatory response to CO_2 is impaired in preterm infants relative to term newborns and adults; however, it increases with advancing postnatal and gestational age. It has been demonstrated that, unlike adults, preterm infants and newborn animals are less able to increase their respiratory rate in response to CO_2, but tidal volume increases appropriately.[5] Possible mechanisms for this impaired response to CO_2 include changes in the mechanical properties of the lung, maturation in the peripheral or central chemoreceptors, or changes in the central integration of chemoreceptor or other neuronal signals. Multiple studies have indicated a central origin for the attenuated CO_2 response in preterm babies, in particular those with apnea. However, a cause-and-effect relationship between apnea of prematurity and the attenuated response to CO_2 has not been clearly established, and both might simply represent facets of a decreased respiratory drive.

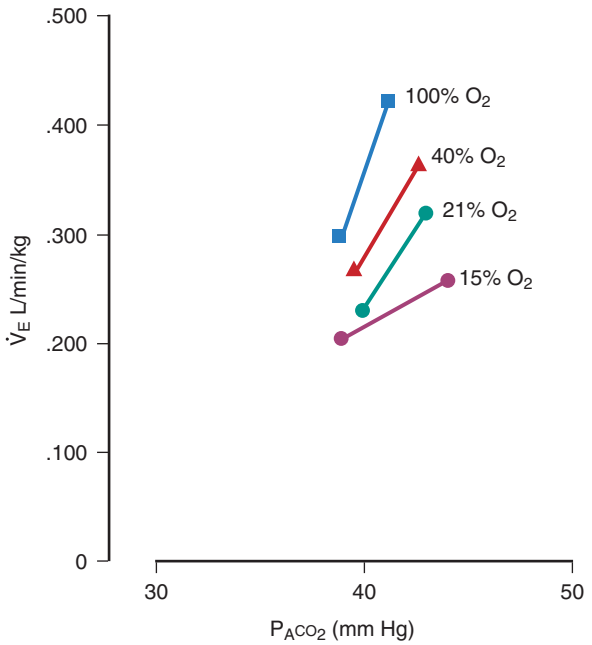
Hypoxia

Unlike adults who express a sustained response to hypoxia, the neonatal hypoxic ventilatory response is biphasic, with an initial increase in ventilation that lasts 1-2 minutes, followed by a decline that falls below baseline ventilation in preterm infants (Fig. 67.1). This late decline has been traditionally termed *hypoxic ventilatory depression*. Although the increase in tidal volume is sustained, breathing frequency decreases during hypoxic exposure, hence the biphasic response. The increase in ventilation occurs through activation of peripheral chemoreceptors located primarily in the carotid body and is eliminated by carotid body denervation. During development, the initial rise increases, while the late depression decreases with advancing postnatal age; however, in one study, hypoxic ventilatory depression persisted in convalescing preterm neonates at 4-6 weeks of age.[32] Several mechanisms have been postulated to explain the pathogenesis of late respiratory depression, including a time-dependent decrease in carotid body stimulation, hypocapnea secondary to the initial hyperventilation, and a decrease in metabolism. Increasing evidence, however, suggests a central origin for hypoxic ventilatory depression,



• **Fig. 67.1** The ventilatory response to 15% hypoxia in 4- to 6-week-old preterm infants.

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• **Fig. 67.2** Steady-state carbon dioxide response curves at different inspired oxygen concentrations. The more hypoxic the infant is, the flatter the response to carbon dioxide.

probably through interaction of multiple neurotransmitters, including adenosine, GABA, and endorphins, or through descending inhibitory pontine tracts. Consistent with these findings is the observation that a progressive decrease in inspired oxygen concentration causes a significant flattening of carbon dioxide responsiveness in preterm infants (Fig. 67.2).

Laryngeal and Pulmonary Afferent Reflexes

Stimulation of the laryngeal mucosa, either chemically (water, ammonium chloride, or acidic solutions) or mechanically, causes inhibition of breathing and apnea in neonates and newborn animals. This reflex-induced apnea, known as the *laryngeal chemoreflex* (LCR), is usually associated with glottic closure, swallowing, bradycardia, and hypotension, and has been shown to undergo maturational changes with age. Although it may serve a protective function, preterm infants express an exaggerated LCR as evidenced by prolonged apnea response to instilling saline in the oropharynx. The mechanisms underlying such maturational change in reflex-induced apnea are not known but seem to be related to a decrease in central neural output or a dominance of inhibitory pathways. The inhibitory neurotransmitters adenosine and GABA have both been implicated where blockade of $GABA_A$ receptors prevented, and activation of adenosine A_{2A} exaggerated, the LCR.[3]

Lung afferents play an important role in regulating respiratory timing and may play a role in apnea of prematurity. Stimulation of pulmonary stretch receptors through increasing lung volume causes shortening of inspiratory time, prolongation of expiratory time, or both. This reflex is known as the *Hering-Breuer reflex*. The decrease in respiratory frequency and prolongation of expiratory time following institution of nasal continuous positive airway pressure (CPAP) is mediated through activation of this reflex. This probably serves to prevent lung overdistention on CPAP. The Hering-Breuer deflation reflex is activated on deflation of the lung and results in inspiratory augmentation. However, unlike term infants, preterm infants are less likely to initiate breathing and tend to have respiratory pauses on deflation of the lung, thus making them less likely to recover from an apnea event.

Neurotransmitters and Neuromodulators

There are limited data regarding the balance of excitatory and inhibitory neurotransmitters during development of respiratory control. Because invasive studies cannot be performed in newborn infants, most studies on the relationship of neurotransmitters to respiratory control are based on the effect of these substances or their inhibitors on the breathing responses to hypoxia, hypercapnia, and reflex apnea in animal models. The most widely studied neurotransmitters in relation to disturbances in control of breathing include adenosine, GABA, prostaglandins, endorphins, and serotonin.

GABA is the major inhibitory neurotransmitter in the central nervous system (CNS). It has been implicated in the attenuated ventilatory responses to hypoxia, hypercapnia, and LCR. Blocking $GABA_A$ receptors prevented hypoxic ventilatory depression and the decrease in breathing frequency in response to CO_2 and attenuated the LCR. Both structural and functional differences in $GABA_A$ receptors have been observed during development. $GABA_A$ receptors are hetero-oligomers assembled from five subunits. During embryonic and early postnatal development, the brainstem has a much higher $GABA_A$ receptor density than does the adult brainstem, and the "mix" of $GABA_A$ receptor subunits differs from that in adults. Therefore, GABA has the potential to play a key role in the vulnerability of preterm infants to disturbed breathing, including apnea of prematurity. Of interest is the observation that GABA may switch from an excitatory to inhibitory neurotransmitter during the transition from fetal to neonatal life.

Adenosine is a product of ATP that is ubiquitous to most brain tissue as well as the cerebrospinal fluid (CSF). Adenosine is known to depress neural function and respiration, and its level has been shown to increase during hypoxia in brain tissue, CSF, and plasma. Furthermore, adenosine antagonists reversed hypoxic depression in anesthetized newborn piglets. The role of adenosine in apnea of prematurity is suggested by the ability of the methylxanthines, theophylline, and caffeine, which are nonspecific adenosine receptor inhibitors, to decrease the incidence of apnea of prematurity. However, the exact mechanism and location of action of adenosine, as well as the interaction of adenosine with other neurotransmitters, remain to be identified. Adenosine receptors may be inhibitory (A_1) or excitatory

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(A_{2B}). An interaction between adenosine and GABA in the regulation of breathing has been documented. Blockade of $GABA_A$ receptors abolished the inhibition of phrenic activity and the exaggerated LCR induced by adenosine A_{2A} agonist. Furthermore, A_{2A} receptors were found to co-localize on GABAergic neurons in the medulla oblongata of both piglets and rats. These data suggest that the mechanism of action of methylxanthines in the prevention of apnea of prematurity is through central blockade of either inhibitory A_1 receptors or excitatory A_2 adenosine receptors on GABAergic neurons.[3] In either case, respiratory inhibition is diminished.

Exogenous endorphin and enkephalin analogues have been shown to produce a consistent decrease in respiration in fetal and neonatal animals. Endorphin levels are elevated in the human neonate at birth, and endogenous opioids were found to modulate the hypoxic ventilatory response in newborn infants and animals. Furthermore, the opioid antagonist naloxone produced an improvement in apnea and periodic breathing in infants in whom β-endorphin–like immunoreactivity in the CSF was elevated. Although these data support a role for opioids in respiratory control in neonates, the effect of anesthesia in such studies and the interaction of opioids with other inhibitory neurotransmitters need to be clarified. Infusion of prostaglandin E_1 (PGE_1) may produce respiratory depression in infants during treatment for critical congenital heart disease. Prostaglandin E_1 has been shown to decrease, and indomethacin has been shown to enhance, phrenic activity in newborn piglets.

The involvement of serotonin in respiratory control is well established; however, the nature of this involvement is complex. Both activation and inhibition of breathing have been described with different doses and routes of administration. The different responses may owe, in part, to the effect on different subtypes of serotonin receptors preferentially expressed on respiratory neurons. Serotonin has been implicated as a regulatory factor in the production of apneusis. Blocking $5\text{-}HT_{1A}$ receptors has been shown to reverse apneustic breathing, which might result during hypoxia or ischemia. There is increasing evidence to suggest an important role for serotonergic neurons in the raphe nuclei in maturation of central chemoreception. This has been highlighted by findings in cohorts of sudden infant death syndrome (SIDS) victims (Japanese, African-American, and white) in whom there was a significant positive association with the presence of a homozygous gene that encodes for the long allele of the 5-HT transporter promoter (5-HTT), as well as the long allele itself. In both studies, SIDS victims were more likely than control subjects to express the long allele of 5-HTT, as well as to miss the short allele of 5-HTT.[53] Therefore, it is possible that a delay in maturation of serotonergic neurons or overexpression of the long allele for 5-HTT in the arcuate nucleus, as well as in other respiratory groups, might contribute to a failure of arousal and inadequate respiratory response to a life-threatening event. There is increasing evidence that this may be the underlying mechanism in the pathogenesis of SIDS.

Neonatal Apnea, Bradycardia, and Hypoxemia

Definition and Epidemiology

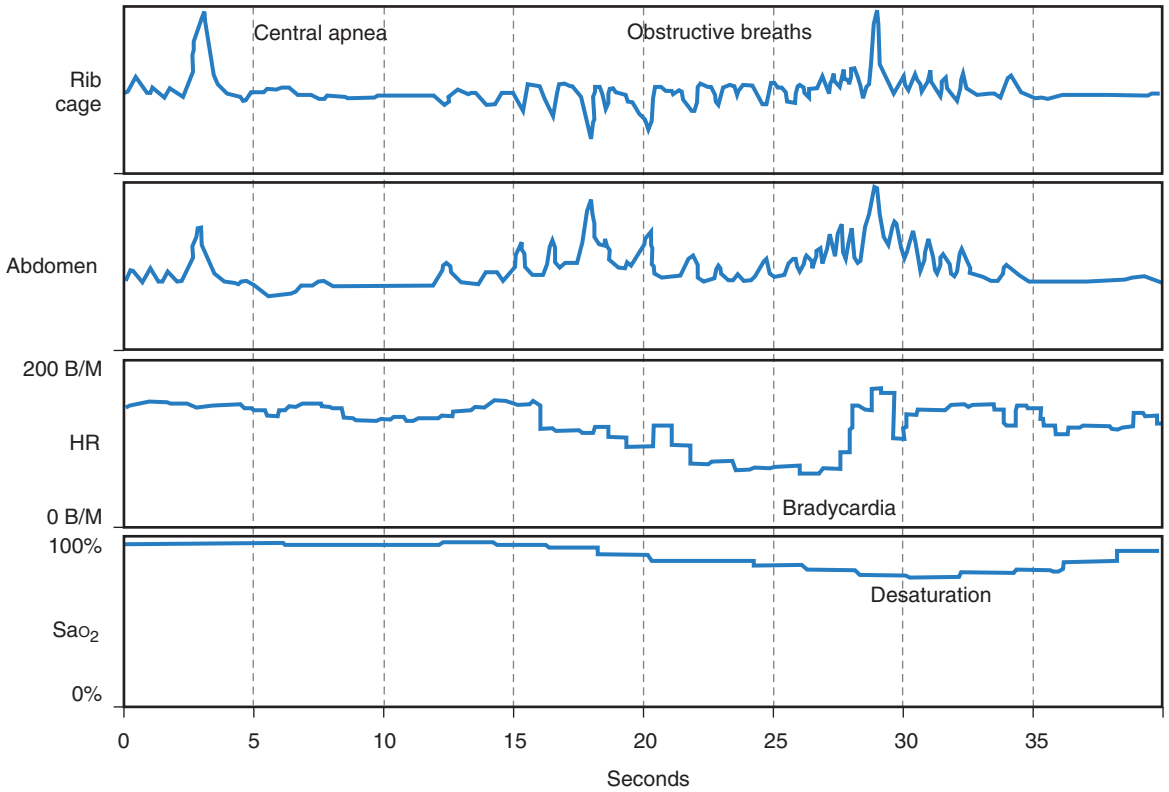
Apnea has traditionally been defined as the cessation of breathing for greater than 15-20 seconds. Shorter events (<15 seconds) may also be identified as apnea if accompanied by oxygen desaturation and bradycardia. Types of apnea include central, obstructive, and mixed (demonstrating both central and obstructive components). Central apnea is characterized by total cessation of respiratory effort with no evidence of obstruction. In obstructive apnea, the infant tries to breathe against an obstructed upper airway, resulting in chest wall motion without air flow. Mixed apnea consists of obstructed respiratory effort usually following a central pause (Fig. 67.3) and is the most common type of apnea in preterm infants. The site of upper airway obstruction is mostly in the pharynx; however, it may also occur at the larynx and possibly at both sites. It should be emphasized that these three patterns of apnea appear to form a continuum in which airway obstruction may also be involved in purely central events and vice versa.[41]

Standard bedside monitoring or impedance monitoring in the neonatal intensive care unit (NICU) detects central apnea and bradycardia but is unable to detect obstructive and mixed apnea. An automated computer algorithm to analyze ECG, chest wall impedance, and pulse oximetry from NICU bedside monitors was developed by investigators from the University of Virginia. The recognition of apnea, bradycardia, and desaturation (ABD) events require that all three components be present. Apnea was defined as >10 seconds if accompanied by bradycardia (HR <100 beats/minute) and desaturation (SpO_2 <80%).[51] The automated computer algorithm was found to be far more reliable at detecting ABD events than bedside nursing documentation. Although there is consensus that nursing observations do not correlate with electronically recorded events, it is still the practice in most centers to rely on nursing documentation as a measure of apnea, bradycardia, and oxygen desaturation frequency and severity.

Bradycardia may be defined as a HR <100 or <70-80 in the convalescing preterm infant approaching discharge. There is no consensus in the definition of a HR threshold or duration to identify a clinically significant bradycardia event.

More recently, hypoxia, especially intermittent hypoxia (IH), often associated with periodic breathing, has become a focus of research and ongoing debate about its significance and consequences. In animal models, chronic IH increases activation of the sympathetic nervous system with cardiovascular and metabolic consequences, including type 2 diabetes, hypertension, and heart failure.[11] Cardiovascular morbidity may be related to sensitization of the carotid body from free radical injury. Prolonged desaturation episodes in the absence of apnea or bradycardia, both in healthy preterm infants and more frequently in infants

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• **Fig. 67.3** Characteristic mixed apnea of approximately 20 seconds' duration commencing with a central component and prolonged by obstructed inspiratory efforts. In the absence of simultaneous measurement of rib cage and abdominal motion, as occurs during routine impedance monitoring, the inspiratory efforts are not recognized as obstructed. As noted in this tracing, bradycardia and desaturation are secondary to the cessation of effective ventilation during the mixed apnea. B/M, Beats per minute; HR, heart rate; Sao_2, arterial oxygen saturation.

TABLE 67.1 Factors Implicated in the Pathogenesis of Apnea of Prematurity

Central Mechanisms	Peripheral Reflex Pathways	Others
Decreased central chemosensitivity	Decreased carotid body activity	Genetic predisposition
Hypoxic ventilatory depression	Increased carotid body activity	Sepsis and cytokines
Upregulated inhibitory neurotransmitters, e.g., GABA, adenosine	Laryngeal chemoreflex Excessive bradycardic response to hypoxia	Bilirubin

GABA, γ-aminobutyric acid.

with bronchopulmonary dysplasia, could represent obstructive apnea, hypoventilation, or intrapulmonary right-to-left shunting. Like bradycardia, the definition and duration of hypoxemia also lacks consensus and may be defined as SpO_2 <90%, <85%, or <80%. The long-term consequences of apnea, but perhaps especially bradycardia, and hypoxemia remain a concern. Recurrent or intermittent hypoxia has been associated with retinopathy of prematurity, necrotizing enterocolitis (NEC), and periventricular leukomalacia.

Pathogenesis

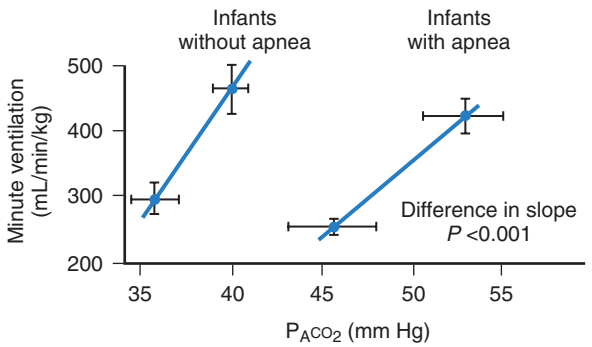
Apnea of prematurity is a developmental disorder that reflects physiologic rather than pathologic immaturity of respiratory control (Table 67.1). However, despite major advances in the understanding of the control of breathing, the exact mechanisms responsible for apnea in premature infants have not been clearly identified. This is understandable in view of the limitations of studying human infants and the lack of an animal model that exhibits spontaneous

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apnea. Therefore, most of our knowledge is derived from both physiologic studies in preterm infants and studies in immature animals. Immaturity of respiratory responses in preterm infants affects all levels of respiratory control, including central and peripheral chemosensitivity, as well as inhibitory pulmonary afferents. This immaturity is manifested by impaired ventilatory responses to hypoxia and hypercapnia and an exaggerated inhibitory response to stimulation of airway receptors. Although a direct relationship has not been demonstrated between a disturbed respiratory control mechanism and the occurrence of apnea in preterm infants, strong associations are very well established. Histologically, immaturity of the preterm brain is manifested by a decreased number of synaptic connections, dendritic arborizations, and paucity of myelin. Functionally, auditory-evoked responses are impaired in infants with apnea when compared with matched preterm control subjects, indicating a delay in brainstem conduction time. Interestingly, this delay improves after treatment with aminophylline, signifying a functional rather than an anatomic immaturity.

The impairment of central chemosensitivity in preterm neonates is evident by the flat ventilatory response to CO_2 when compared with that in term neonates or adults. This impairment of hypercapneic ventilatory response is more pronounced in preterm neonates with apnea when compared with their controls without apnea. In other words, at the same level of CO_2 and for the same degree of change in alveolar CO_2, minute ventilation in babies with apnea is decreased (Fig. 67.4). Whereas exposure to hyperoxia silences the carotid body and may induce apnea, hypoxic ventilatory depression does not seem to contribute to the initiation of apnea, because most infants are not hypoxic before apnea occurs. However, once apnea occurs it might prolong apnea and delay its recovery.

The peripheral chemoreceptors are located primarily in the carotid body and are responsible for stimulating breathing in response to hypoxia. Both enhanced and reduced peripheral chemoreceptor function may lead to apnea, bradycardia, or desaturation in the premature infant. In utero, the carotid chemoreceptor O_2 sensitivity is adapted to the normally low PaO_2 of the mammalian fetal environment



• **Fig. 67.4** The ventilatory response to carbon dioxide has a decreased slope in infants with apnea.

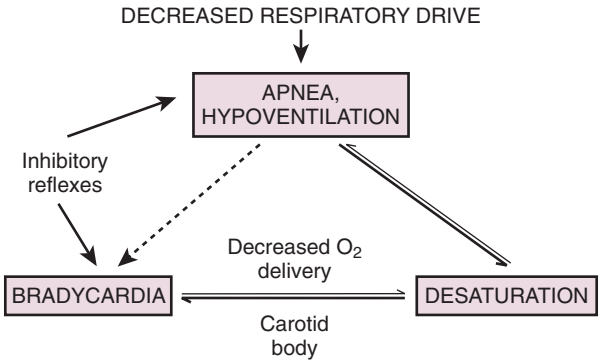
(23-27 mm Hg). In response to the fourfold increase in PaO_2 with the establishment of air breathing, the peripheral chemoreceptors are silenced. This is followed by gradual increase in hypoxic chemosensitivity, although the mechanisms underlying this maturation are not completely understood.[35] A similar developmental profile has been described for both preterm and term infants. However, the contribution of immaturity of the peripheral chemoreceptors to apnea of prematurity is not clear. Apnea can persist for many weeks to months in premature infants despite maturation of peripheral chemosensitivity. Excessive peripheral chemoreceptor sensitivity in response to repeated hypoxia as seen in babies with bronchopulmonary dysplasia may also destabilize breathing patterns in the face of significant fluctuations in oxygenation. Data in rat pups indicate that conditioning with intermittent hypoxic exposures results in facilitation of carotid body sensory discharge in response to subsequent hypoxic exposure. Furthermore, preterm infants with high frequency of apnea were found to have increased carotid body activity.[35] Hypoxia can also inhibit metabolism in the preterm infant and decrease CO_2 levels, thereby narrowing the difference between baseline CO_2 and the apneic threshold CO_2 (CO_2 level below which apnea occurs). The baseline $PaCO_2$ in both preterm and term infants was found to be only 1-1.3 mm Hg above the apneic threshold.[26] The closeness of the apneic threshold to baseline CO_2 together with excessive activation of the carotid body might allow small oscillations of CO_2 in response to mild hyperventilation, startles, or stimulation to cause apnea. Much remains to be learned about both the short- and long-term consequences of intermittent hypoxic episodes during early development.

Although LCR is thought to be an important contributor to apnea, bradycardia, and desaturation episodes associated with feeding and gastroesophageal reflux in preterm babies, the relationship of LCR to apnea of prematurity is less clear. The association of both apnea of prematurity and LCR with swallowing movements, as well as the observation of glottic closure and swallowing in fetal lambs during spontaneous apnea, points to the possibility of a common neural network controlling both functions. Furthermore, similar to apnea of prematurity, LCR matures with advancing gestational age and is thought to be exaggerated in immature newborns and animals secondary to decreased central neural output or a dominance of inhibitory pathways.[4]

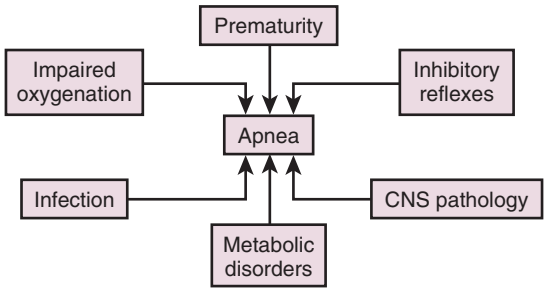
Rapid eye movement (REM) or active sleep is the predominant sleep state in preterm infants. It has long been recognized that respiratory control is disturbed during REM sleep. The primary mechanism appears to be a loss of upper airway muscle tone, resulting in pharyngeal collapse and airway obstruction. Paradoxical breathing during active sleep may also lead to hypoxemia and apnea.

The mechanism underlying bradycardia associated with apnea is not clear; although, it has been postulated that bradycardia during apnea might be related to hypoxic stimulation of the carotid body chemoreceptors, especially in the absence of lung inflation (Fig. 67.5). On the other hand,

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• **Fig. 67.5** Proposed physiologic mechanisms whereby apnea induces reflex bradycardia. This can occur secondary to hypoxemia in the absence of lung inflation or by stimulation of upper airway inhibitory afferents.



• **Fig. 67.6** Specific contributory causes of apnea. CNS, central nervous system.

bradycardia occurs simultaneously with apnea during stimulation of laryngeal receptors, suggesting a central mechanism for the production of both apnea and bradycardia. The interaction between central respiratory and cardiovascular centers in the production of bradycardia in association with apnea of prematurity needs further investigation.

The impact of genetic variability on regulation of breathing and apnea is suggested by the finding of a mutation in the *PHOX2B* gene in patients with congenital central hypoventilation. Similar to preterm infants with apnea, these children are characteristically symptomatic during the initial months of life and demonstrate absent or extremely reduced ventilatory responses to CO_2 and hypoxia even though no obvious brain, muscular, cardiac, or pulmonary lesions are apparent.[20] Tamim and colleagues found a higher incidence of apnea of prematurity in infants born to first-degree consanguineous parents than in other infants.[48] These findings raise the possibility of a role for developmentally regulated genes that might contribute to the vulnerability of preterm neonates to apnea. It has also been demonstrated that specific polymorphisms in the A2A adenosine receptor gene are associated with apnea of prematurity, BPD, and response to caffeine therapy.[27] Further studies are clearly needed to explore the role of genetics in the pathogenesis of apnea of prematurity.

Clinical Associations

Apnea can be physiologic, the presenting sign of a change in status, or may accompany other conditions that adversely affect the preterm infant. With the current and widespread early use of caffeine and broad application of noninvasive respiratory support strategies in the NICU, the severity of clinical apnea and accompanying bradycardia in the 21st century has substantially decreased. When apnea does become a concern, a thorough investigation of possible etiologies is always warranted, especially when an escalation in respiratory support is required (Fig. 67.6). Sepsis and other causes of inflammation and central nervous system disorders, particularly intracranial hemorrhage, hypoxic ischemic encephalopathy, and brain malformations, can precipitate apnea in both preterm and term infants. Term infants presenting with apnea require a thorough history and physical examination, monitoring, and evaluation for central nervous system abnormalities (especially seizures) and infectious, genetic, and metabolic disorders.[39]

Sepsis is a known trigger of apnea and is routinely investigated as a potential cause, especially when associated with other symptoms. In rat pups, systemic administration of cytokine IL-1β–inhibited respiratory activity, both at rest and in response to hypoxia, and this respiratory inhibition was diminished by prior blockade of prostaglandin synthesis with indomethacin. In subsequent work from the same group of investigators, evidence was presented for IL-1β binding to IL-1 receptors on vascular endothelial cells of the blood–brain barrier during a systemic immune response. Activation of the IL-1 receptor, in turn, induces synthesis of prostaglandin E2, which, when released into respiratory-related regions of the brainstem, results in respiratory depression.[22] Intrapulmonary inflammation has also been shown to increase cytokine expression in the brainstem and decrease hypoxic ventilatory response.[24] New-onset apnea or an increase in the baseline incidence of apnea should prompt an appropriate workup for sepsis or necrotizing enterocolitis. In the older infant, the presentation of respiratory syncytial virus (RSV) and other viral infections is sometimes heralded by apnea.

Episodes of hypoxemia often occur in infants with bronchopulmonary dysplasia. Immature respiratory control superimposed on abnormal lung function and pulmonary vasoconstriction may all play a role in the occurrence of these events.[31]

Anemia, whether iatrogenic, physiologic, or a result of acute blood loss, is also common in preterm infants and may contribute to an increase in apnea frequency or severity. The decision to transfuse an infant with apnea is often debated. The potential benefits from a packed red blood cell transfusion could be either from an improvement in oxygen-carrying capacity, elimination of hypoxic respiratory depression, or an increase in intravascular volume. Zagol and colleagues demonstrated the relationship between hematocrit and apnea in two ways. They found that not only were transfusions associated with fewer computer-detected apneic events, but that an inverse relationship

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existed between admission hematocrit values and the probability of future apnea. These findings suggest that decreased oxygen-carrying capacity is a major trigger for apnea of prematurity.[56] Other conditions that may precipitate apnea include common metabolic disorders such as hypoglycemia, hypocalcemia and electrolyte imbalances, temperature instability, and metabolic acidosis perhaps associated with inborn error of metabolism. Medications including opiates, benzodiazepines, magnesium sulfate, and prostaglandin E1 can all cause apnea.

Periodic breathing is an immature respiratory pattern with short cycles of a few breaths alternating with respiratory pauses. Periodic breathing is absent in the first few days of life and becomes more frequent at 2-4 weeks of age (much like intermittent hypoxia). Even in term infants, periodic breathing may persist for up to 6 months of age and is related to progressive myelination and maturation of the central nervous system.[16] Patel and colleagues used an automated periodic breathing detection system to analyze bedside monitors on all infants <35 weeks' gestation. They concluded that on average, infants spend <6% of the time in periodic breathing and that an acute increase may reflect illness or physiologic stressors. Extreme periodic breathing was defined as periodic breathing for >10% of a 12-hour period and >6 standard deviations above the mean for GA and postmenstrual age. In 45% of infants with extreme periodic breathing, a temporal relationship was found between infection or NEC.[38]

Gastroesophageal Reflux and Neonatal Apnea

Gastroesophageal reflux (GER) is often implicated as a cause of neonatal apnea (also see Chapter 82). While it is true that both GER and apnea are common in preterm infants, investigations of the timing of reflux in relation to apneic events demonstrate that they are rarely temporally linked. Furthermore, when apnea and reflux coincide, there is no evidence that GER prolongs the apnea or worsens its severity.[10] Although physiologic experiments in animal models reveal that reflux of gastric contents to the larynx induces reflex apnea, there is no clear evidence that the treatment of reflux will treat apnea in most preterm infants. There are, however, two publications that challenge this premise and present conflicting evidence. Corvaglia and colleagues studied infants less than or equal to 33 weeks' gestation to characterize the features of reflux (acidity, duration, and height) that influence apnea. They found that the frequency of apnea detected after non–acid reflux episodes was significantly higher than before the reflux event.[8] In another study examining the temporal association between recorded cardiorespiratory events and GER identified by multichannel intraluminal impedance-pH probe, a subject-specific association was found in three of seven infants. These infants, born between 24 and 29 weeks' gestation, underwent polysomnography at 39-48 weeks postconceptional age because of persistent cardiorespiratory events and as part of a presurgical evaluation for fundoplication. Two of the infants improved following a fundoplication procedure.[36] Although a relationship between cardiorespiratory events and GER was identified in this select group of infants, the management of reflux with agents that decrease gastric acidity or enhance gastrointestinal motility should not be used routinely for the treatment of apnea and bradycardia of prematurity. Moreover, antacid therapy is not benign. Several studies have shown that the use of H_2 blockers and proton pump inhibitors pose an increased risk for infection and NEC. A safety study from Italy examined the association between ranitidine therapy and infections, NEC, and death in very-low-birth-weight infants. The ranitidine-exposed patients had a significant increase in all three adverse outcomes.[49]

Brief Resolved Unexplained Events (BRUE) (Formerly Known as Apparent Life-Threatening Events or ALTE)

Apparent life-threating events are often interpreted as apnea, which is rarely the case. In 2016, the American Academy of Pediatrics (AAP) issued a new clinical practice guideline that provides significant enhancements to the management of patients with an ALTE (apparent life-threatening event). One of the major contributions of the BRUE guidelines is the removal of the caregiver's perception that the event was life-threatening. Instead, it is the provider who is tasked with obtaining a thorough history and performing a detailed physical examination. In addition, the initiation of CPR is only relevant when performed by a health care provider. Choking or gagging is not included in the definition of a BRUE, thereby eliminating an event likely related to gastroesophageal reflux. Finally, criteria are listed that define an infant as low or high risk (Box 67.1). Low-risk infants should *not* be hospitalized, but instead, parents should be educated, shared decision making should occur between the parents and provider, and CPR training should be offered. Short-term observation with pulse oximetry, an ECG, and pertussis testing are options that may be considered.[50]

• BOX 67.1 BRUE Definition

An Event Occurring in an Infant <1 Year of Age That Is Not Resolved With ≥1 of the Following:

- Cyanosis or pallor
- Absent, decreased, or irregular breathing
- Marked change in tone (hyper- or hypotonia)
- Altered level of responsiveness

Low-Risk Criteria

- >60 days of age
- Gestational age ≥32 weeks; postconceptional age ≥45 weeks
- First BRUE
- Event duration <1 minute
- No CPR required by trained medical provider
- Benign history and physical exam findings

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Because of the high incidence of GER in infancy, symptoms of GER do not qualify as a BRUE, although GER may contribute to low-risk BRUE.

Treatment

Continuous Positive Airway Pressure

Various forms of noninvasive and invasive respiratory support are used to treat clinically significant apnea, usually in conjunction with caffeine. Because apnea, bradycardia, and intermittent hypoxia rarely occur in isolation, the noninvasive support that is selected should consider other common comorbidities such as RDS, pneumonia, and BPD. Continuous positive airway pressure (CPAP) at 4-6 cm H_2O has been used safely and effectively for more than 35 years. CPAP treats the obstructive component of apnea by splinting the upper airway with positive pressure, thereby reducing the risk of pharyngeal or laryngeal collapse. Continuous positive airway pressure also increases FRC and improves oxygenation. At a higher FRC, time from cessation of breathing to hypoxemia and resultant bradycardia is prolonged. Other noninvasive support strategies include BiPAP (bilevel CPAP), noninvasive positive pressure ventilation (NIPPV), and high-flow nasal cannula (HFNC) (or nasal high-flow therapy, nHFT). HFNC, defined as flows >1-2 LPM, is a popular alternative to CPAP largely because of its more comfortable and less traumatic patient interface, especially in more mature infants. A 2016 clinical report from the Committee on the Fetus and Newborn concludes that there is no evidence for the benefit of NIPPV or BiPAP in the treatment of apnea of prematurity and that safety concerns persist for the use of HFNC.[9] An experienced group of clinical researchers in the field of nHFT recently published a consensus approach with guidelines that include the need for adequate heating and humidification, prongs that are sized to prevent occlusion of the nares (to avoid extremely elevated airway pressures), and initial flow rates of 4-6 LPM with a maximum flow of 8 LPM. The assessment of FiO_2 or work of breathing should be used to determine flow escalation or weaning.[55]

Xanthine Therapy

Methylxanthines have been the mainstay of pharmacologic treatment for apnea of prematurity for more than 30 years. Both theophylline and caffeine are used, and both have multiple physiologic and pharmacologic mechanisms of action. Xanthine therapy increases minute ventilation, improves CO_2 sensitivity, decreases hypoxic depression of breathing, promotes bronchodilation, enhances diaphragmatic activity, and decreases periodic breathing. The precise way in which xanthines improve respiratory mechanics via an increase in respiratory neural output is still under investigation; however, competitive antagonism of adenosine receptors is well documented. Although adenosine acts as an inhibitory neuroregulator in the CNS via activation of adenosine A1 receptors, an effect on adenosine A2A receptors' activation of GABAergic neurons might also play a role. The methylxanthines, especially aminophylline, have some well-documented acute adverse effects. Toxic levels may produce tachycardia, cardiac dysrhythmias, feeding intolerance, and, infrequently, seizures. These effects are rarely seen with caffeine at the usual therapeutic doses. Mild diuresis is caused by all methylxanthines. The observation that xanthine therapy causes an increase in metabolic rate and oxygen consumption of approximately 20% suggests that caloric demands may be increased at a time when an infant's nutritional status is already compromised. Another positive attribute of caffeine is its direct anti-inflammatory effect on the lung.[54] The Caffeine Therapy for Apnea of Prematurity (CAP) trial randomized infants with birth weights between 500 and 1250 g to caffeine versus placebo therapy. This study was designed to test both the short- and long-term safety of caffeine, and although initial findings revealed a significant reduction in the rate of bronchopulmonary dysplasia (BPD),[46] the 5-year outcome data demonstrated no difference in the combined outcome of death or disability in the caffeine versus placebo groups.[45,47] Caffeine therapy for apnea of prematurity did not significantly reduce the combined rate of academic, motor, and behavioral impairments but was associated with a reduced risk of motor impairment in 11-year-old children with very low birth weight. At the doses used in this trial, neonatal caffeine therapy is effective and safe into middle school age. Most recent outcome data from this trial are very encouraging.[45,47] Importantly, Schmidt and colleagues confirmed that caffeine therapy was not only effective in treating apnea of prematurity but was also safe.

Perhaps because of the evidence of caffeine safety, investigators in Egypt compared high (40 mg/kg loading dose and maintenance of 20 mg/kg) with standard dosing (20 mg/kg loading dose and 5–10 mg/kg maintenance) in an effort to determine an optimal dose. Although there was a significant reduction in extubation failure and frequency and duration of apnea, there was a significant increase in tachycardia (not considered a significant side effect). No change was found in the incidence of BPD or length of stay.[33] At this time, many questions remain concerning optimization of the timing of caffeine therapy and its dose despite the success of this therapy (Box 67.2).[15a]

Other Therapeutic Approaches

Doxapram is an agent that stimulates peripheral and central chemoreceptors and for many years has been advocated by some as adjunctive therapy for persistent apnea of prematurity. A recent systematic review confirms previous reports that based on limited evidence, adverse effects of the drug, and no benefit over theophylline, routine use cannot be recommended.[52]

Any approach to nursing care that optimizes the infant's well-being is clearly desirable. Kangaroo care, or skin-to-skin nursing, has achieved widespread acceptance for high-risk infants and provides an opportunity for greater parental involvement. Although the advocates of this approach have suggested a decrease in apnea rates, the evidence does not

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• BOX 67.2 Neonatal Caffeine Therapy: Unresolved Issues

	Pro	Con
Optimal dosage	Higher doses more strongly enhance respiratory neural output	• Adenosine receptor subtype inhibition of inflammation is variable and dose dependent, raising safety concerns • Preliminary report of cerebellar injury • Proposed need for postnatal dose adjustments
When to start	Early onset of therapy improves various morbidities	• Available data are largely based on associations rather than randomized trials
When to stop	Prolonged therapy decreases duration of intermittent hypoxic episodes	• May prolong hospitalization and potentially increase home monitor use

support this impression. Meanwhile, research on the biologic basis of sleep and awake states needs to be translated into preventive strategies for apnea.[28] Supplemental oxygen to avoid hypoxic respiratory depression is another treatment for apnea; however, the ideal SaO_2 target range remains elusive (currently in the 90%-95% range) and is likely on a continuum associated with gestational and postnatal age. The frequency and severity of oxygen desaturation accompanying apnea would be decreased at higher baseline SaO_2. A low O_2 saturation target is associated with an increased rate of intermittent hypoxemia.[14] A novel, alternative approach to apnea therapy is the supplementation of inspired air with a very low concentration of CO_2 to increase respiratory drive.[6,7] Although logical from a physiologic perspective, CO_2 was compared with theophylline in both trials, and the response to CO_2 was inconsistent, likely from fluctuations in gas delivery. Recently, investigators from UCLA published data using neuromodulation of limb proprioceptive afferents by means of a noninvasive vibratory device placed on one hand and one foot. Significantly fewer respiratory pauses, bradycardia, and intermittent hypoxia events occurred during vibration periods.[25]

Resolution and Consequences of Apnea, Bradycardia, and Intermittent Hypoxia

Apnea of prematurity generally resolves by 36-40 weeks' postconceptional age. Cardiorespiratory events in most preterm infants return to baseline "normal full-term" levels by 43-44 weeks' postconceptional age.[43] In infants ≤26 weeks' gestation, resolution may take longer. For a subset of infants, the persistence of cardiorespiratory events can delay hospital discharge despite having achieved other physiologic developmental milestones. In these infants, apnea longer than 20 seconds is rare; rather, these infants exhibit frequent bradycardia to less than 70 or 80 beats per minute with short respiratory pauses.[13] As mentioned earlier, bedside nursing observations are known to be an unreliable measure of apnea and bradycardia and do not correlate with electronic recordings of events; however, they may be beneficial when trying to determine which episodes are clinically significant. A 2016 Clinical Report from the Committee on Fetus and Newborn emphasizes the lack of consistent definitions for apnea, bradycardia, and desaturation and recognizes that monitoring practices vary among NICUs. These inconsistencies have major implications on length of stay (Box 67.3).[17] To assess the maturation of respiratory control in premature infants and better inform discharge planning, Lorch and colleagues examined the success rates (the percentage of infants who had no additional events) following various event-free intervals. They found that the risk of recurrence of apnea or bradycardia depends on both the gestational age and postmenstrual age at the time of the last event. For the entire cohort in this retrospective study, a 95% success rate was achieved with a 7-day apnea- or bradycardia-free interval.[29]

Because of the growing concern over the consequences of intermittent hypoxia and recognition that intermittent hypoxia persists after discontinuation of caffeine for the treatment of apnea of prematurity, extended caffeine dosing until term-adjusted age has recently been proposed and is under investigation.[15,44]

• BOX 67.3 Key Elements From the Committee of Fetus and Newborn: Clinical Report and Guidance for Hospital Discharge of Preterm Infants With Apnea

- Individual NICUs are encouraged to develop monitoring policies.
- Lower heart rate alarm settings in convalescing infants >33-34 weeks may be reasonable.
- A trial off caffeine may be considered when an infant has been free of clinically significant apnea or bradycardia events off positive pressure support for 5-7 days or at 33-34 weeks' postmenstrual age, whichever comes first.
- Brief, isolated bradycardias that spontaneously resolve and feeding events that resolve with interruption of feeding are common and generally need not delay discharge.
- Individual units are encouraged to develop policies and procedures for assessment, intervention, and documentation of bradycardia/desaturation events.
- Electronically archived monitoring data may reveal events of uncertain clinical significance that do not predict outcomes.

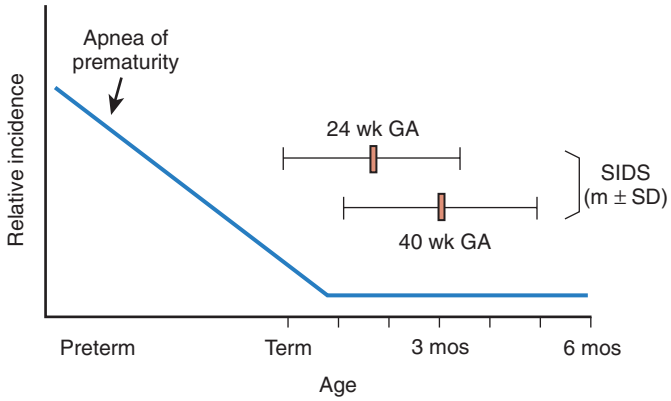
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Correlating apnea and its consequences with an unfavorable neurologic outcome is problematic, because apnea and brain injury may coexist in premature infants, making it challenging to determine causality. However, evidence is mounting and there are data that suggest a link between delayed apnea resolution and the severity of the apnea course with impaired neurodevelopmental outcome.[40] A high number of cardiorespiratory events recorded after discharge via home cardiorespiratory monitoring also appear to correlate with a less favorable neurodevelopmental outcome.[23] A 2014 retrospective chart review in extremely low birth weight infants found an association between a greater frequency and severity of bradycardia and worse language development in the first 2 years of life after adjusting for neonatal and social variables.[21] And finally, in a post hoc analysis of the Canadian Oxygen Trial, prolonged hypoxemic episodes in the first 2-3 months of life were associated with adverse 18-month outcomes.[42] Former preterm infants appear to be at greater risk of later sleep-disordered breathing. Recurrent episodes of desaturation during early life and resultant effects on neuronal plasticity related to peripheral or central respiratory control mechanisms may serve as the underlying mechanisms for such a putative relationship.

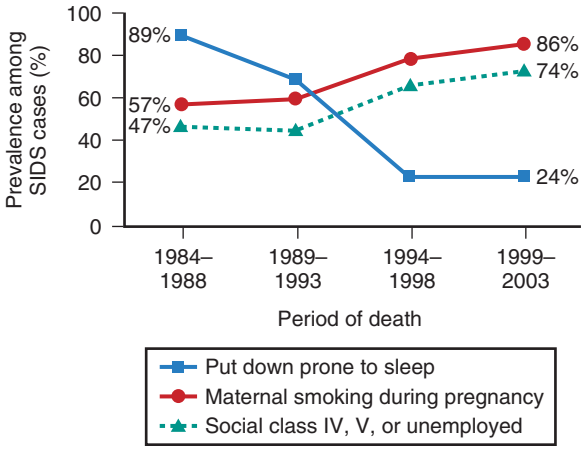
Apnea and Sudden Infant Death Syndrome

Apnea of prematurity and sudden infant death syndrome (SIDS) are separate conditions. However, prematurity is known to be a significant risk factor for SIDS. Malloy and associates have shown that the mean postconceptional age at which SIDS occurs in preterm infants is younger than that of term infants and that clinically significant apnea of prematurity resolves by that postnatal age (Fig. 67.7).[30] The incidence of SIDS has decreased by more than half with the introduction of the international campaign to avoid all sleep positions except supine. However, the relative contribution of other risk factors, including maternal smoking and socioeconomic factors, to the incidence of SIDS increased during the same period (Fig. 67.8),[18] emphasizing the need for targeting these factors to further decrease the risk of SIDS.

In the 2016 AAP policy statement from the Task Force on Sudden Infant Death Syndrome, SIDS is considered a subcategory of sudden unexpected infant death (SUID). Ill-defined and unspecified causes of mortality and accidental suffocation and strangulation in bed are other recognized causes of SUID. As with SIDS, all other causes of SUID are inversely related to gestational age and the biologic, environmental, and sociodemographic vulnerabilities associated with prematurity.[1,37] Hospital discharge practices that include modeling a safe sleep environment and parent education that emphasizes safe sleep practices are paramount in the effort to prevent SUIDs post discharge.



• **Fig. 67.7** Schematic representation of the timing of sudden infant death syndrome (SIDS) in term (40 weeks' gestation) and very preterm (24 weeks' gestation) infants in relation to the decline in incidence of apnea of prematurity. It appears that apnea has largely resolved by 44 weeks' postconceptional age, which is before the peak incidence of SIDS at all gestational ages (GA).



• **Fig. 67.8** The prevalence of risk factors among victims of sudden infant death syndrome with the Back to Sleep campaign. Social class IV, Semi-skilled occupation; Social class V, unskilled occupation. (Adapted from Fleming P, Blair PS. Sudden infant death syndrome and parental smoking. *Early Hum Dev.* 2007;83:721, with permission.) Current practice remains to target these high-risk groups, including co-sleeping.[19]

Key Points

- Apnea of prematurity is a developmental disorder inversely associated with gestational age.
- Consensus is lacking regarding a clinically significant apnea, bradycardia, or desaturation event.
- The severity and duration of bradycardia and hypoxemia are likely of greater consequence than apnea to long-term neurodevelopmental outcome.

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68

Upper Airway Lesions in the Neonate

TODD D. OTTESON AND TAMMY WANG

A spectrum of pathologic conditions can affect the neonatal upper airway, resulting in respiratory distress at birth or within the first few weeks of life. The clinical presentations of these disorders, however, are often quite similar. The most common symptom is stridor; other signs and symptoms include cyanosis, apnea, dyspnea, retractions, hypercapnia, difficulty feeding, abnormal cry, and cough. The physician's ability to arrive at a diagnosis and treatment plan in the neonate with respiratory distress requires an understanding of the unique anatomic and physiologic factors that affect neonatal upper airway physiology. Of primary importance in evaluating the neonatal airway is determining the degree of emergency and the need to establish an artificial airway (endotracheal intubation or tracheostomy).

The evaluation of an infant with a suspected airway problem should encompass the entire upper airway, from the anterior nasal vestibule to the tracheal bifurcation. Obstruction at any level can lead to respiratory distress. The duration and severity of the infant's symptoms and the progressive nature of the airway distress direct the examiner to either a congenital or acquired disorder. Division of the neonatal upper airway into four primary physiologic components—nasal, oral, laryngeal, and tracheal—allows orderly discussion of the pathologic conditions that could afflict the newborn infant's airway.

Nasal and Nasopharyngeal Lesions

Pyriform Aperture Stenosis

The pyriform aperture is defined as the bony inlet of the nose formed by the nasal bones superiorly, frontal process of the maxilla laterally, and the premaxilla and anterior nasal spine inferiorly.[15] Pyriform aperture stenosis is hypothesized to occur from bony overgrowth of the medial process of the maxilla, causing unilateral or bilateral nasal airflow restriction. Clinical presentation may include tachypnea, difficulty passing a nasogastric tube, apneic events, or cyclic cyanosis improved with crying. While the etiology remains uncertain, there is correlation with holoprosencephaly, absent maxillary frenulum, pituitary dysfunction, and central maxillary megaincisor. The diagnosis of pyriform aperture stenosis can be confirmed with computed tomography (CT) scanning; while various radiographic criteria have been proposed, a pyriform aperture width of less than 11 mm in a full-term infant is commonly considered diagnostic.[35] However, pyriform aperture dimensions do not correlate directly with symptoms, thus each infant should be evaluated based on specific symptoms and ability to compensate for the relative obstruction. In most patients, conservative therapy with judicious use of topical decongestants and topical steroids will reduce mucosal edema and provide symptomatic relief. A McGovern nipple or continuous positive airway pressure may also be helpful. The long-term prognosis of pyriform aperture stenosis is excellent, as the pyriform aperture will enlarge along with the craniofacial skeleton during normal development. However, in refractory cases, especially in infants with sleep apnea, growth restriction, and feeding difficulties, or failure to extubate, surgical intervention is indicated.[27] Surgical techniques typically include a sublabial approach and drillout of the stenosis with or without nasal stenting.

Nasolacrimal Duct Cysts

Nasolacrimal duct cysts (dacryocystoceles) are congenital mucoceles of the nasolacrimal duct system, which include a proximal and distal obstruction. Clinical exam is notable for a cystic swelling of the lower medial canthus, associated epiphora and mucopurulent discharge, and a submucosal nasal cyst that appears as a smooth, mucosa-covered mass under the inferior turbinate.[33] The diagnosis is confirmed with CT or MRI scanning. On CT, a cystic mass at the medial canthus and below the inferior turbinate is often noted (Fig. 68.1). Conservative therapy includes topical decongestants and/or antibiotics, warm compresses, and local massage. However, in the event of local infection, mass effect, or respiratory compromise, surgical intervention is recommended, usually with a combined endoscopic approach as well as via dacryocystorhinostomy to marsupialize the cyst[5] (Fig. 68.2). While the external approach is more commonly performed, the endoscopic approach has gained popularity and has demonstrated similar rates of success in the pediatric population.[28]

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Abstract

Neonatal airway obstruction can result from a variety of processes and can vary in severity. A methodical but timely evaluation, including examination from the nasal vestibule to the tracheal bifurcation, will help direct any appropriate interventions.

Keywords

neonatal respiratory distress
airway obstruction
choanal atresia
laryngomalacia
subglottic stenosis

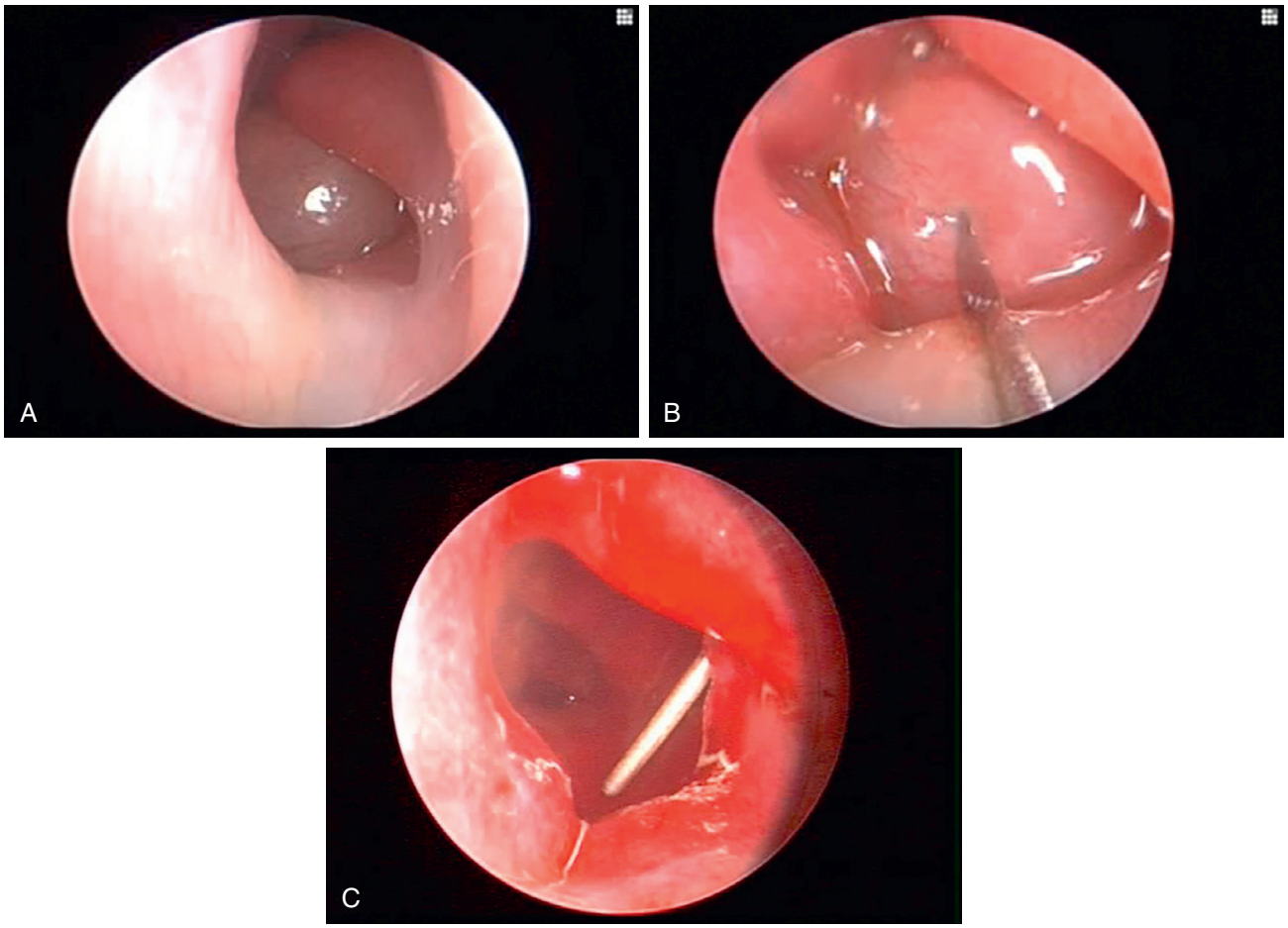
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• **Fig. 68.1** Axial CT demonstrating bilateral nasolacrimal duct cysts causing complete anterior nasal obstruction.

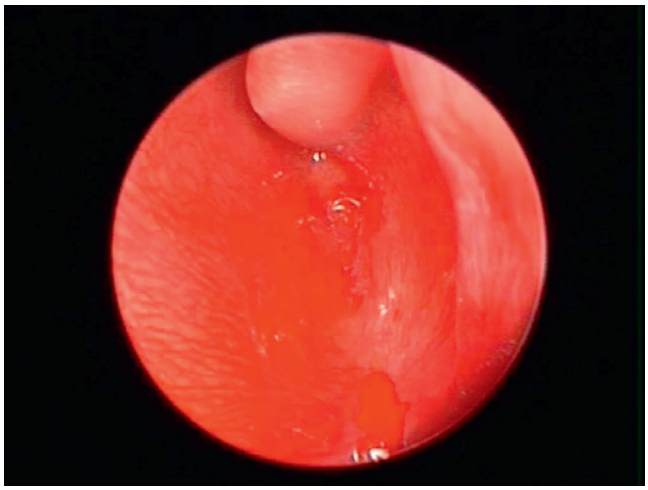
Choanal Atresia

Neonates are preferential nasal breathers for the first 4-6 weeks of life. The entire length of the neonate's tongue is in close proximity to the hard and soft palate, which creates a vacuum and resultant respiratory distress when nasal obstruction is present. The posterior choanae are the bony outlet of the nose, formed by the undersurface of the sphenoid bones, the medial pterygoid plates, the vomer, and the horizontal portion of the palatal bone. Bony overgrowth of any of these structures may cause choanal atresia, defined as closure of the posterior choanae of the nasal cavity, eliminating communication between the posterior nasal cavity and the nasopharynx. The estimated incidence is 1 in 5000-7000 live births, with up to two-thirds of cases being unilateral, affecting the right side, and occurring in females.[23] Congenital anomalies are seen in about 50% of patients with choanal atresia, characteristically CHARGE syndrome. Other congenital anomalies include polydactyly, cleft palate, hypertelorism, laryngomalacia, and Treacher Collins and Crouzon syndromes. CHARGE syndrome is a clinical diagnosis that includes *c*oloboma or other ophthalmic anomalies, *h*eart defect, *a*tresia choanae, *r*estriction of growth and development, *g*enital hypoplasia, and *e*ar



• **Fig. 68.2 A,** Endoscopic view of a nasolacrimal duct cyst causing nasal obstruction. **B**, Endoscopic marsupialization of nasolacrimal duct cyst using a sickle knife. **C**, Endoscopic view of lacrimal probe visible after marsupialization of nasolacrimal duct cyst.

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• **Fig. 68.3** Endoscopic view of right choanal atresia.

anomalies with hearing loss. Heterozygous mutations in the *CHD7* gene (chromodomain helicase DNA-binding protein) located on chromosome 8q12 have been identified in 90%-95% of neonates meeting diagnostic criteria for CHARGE syndrome.[18] Although there is phenotypic overlap between CHARGE and 22q11 deletion syndromes, including lymphopenia and hypocalcemia, no specific immune defects have been clearly linked with CHARGE syndrome.[19] Children with CHARGE syndrome require intensive medical management and multidisciplinary care. A complete evaluation to rule out associated anomalies is, therefore, mandatory in all infants with bilateral choanal atresia.

Although bilateral obstruction always produces symptoms in the neonatal period, the degree of distress and cyanosis varies from severe asphyxia with a history of multiple failed extubations to choking during feeding. Typically, the infant has a history of distress when resting that is relieved with agitation and crying. In contrast, unilateral choanal atresia is typically diagnosed later in life and may present with chronic nasal obstruction, rhinorrhea, or sinusitis.

In a suspected case of choanal atresia, an attempt should be made to pass a 6-French catheter into the nasopharynx. Failure of the catheter to pass suggests choanal atresia. Flexible nasal endoscopy has also become invaluable in assessing the presence and character of the atresia (Fig. 68.3). Definitive evaluation is obtained with a computed tomography scan to characterize the exact thickness and width of the atretic plate (Fig. 68.4).

Treatment of choanal atresia depends on the severity of the obstruction and the clinical presentation of the infant. Unilateral atresia rarely requires surgical intervention during infancy and is usually corrected before the child begins school (4-5 years of age). Bilateral atresia is usually repaired within the first few days of life. Historically, this was performed via a transpalatal approach using a posteriorly based mucosal flap and drilling of the atretic plate. Today, transnasal endoscopic repair is the predominant technique employed by pediatric otolaryngologists (Fig. 68.5). A 2.9 or 4.0 mm Hopkins rod is used while the



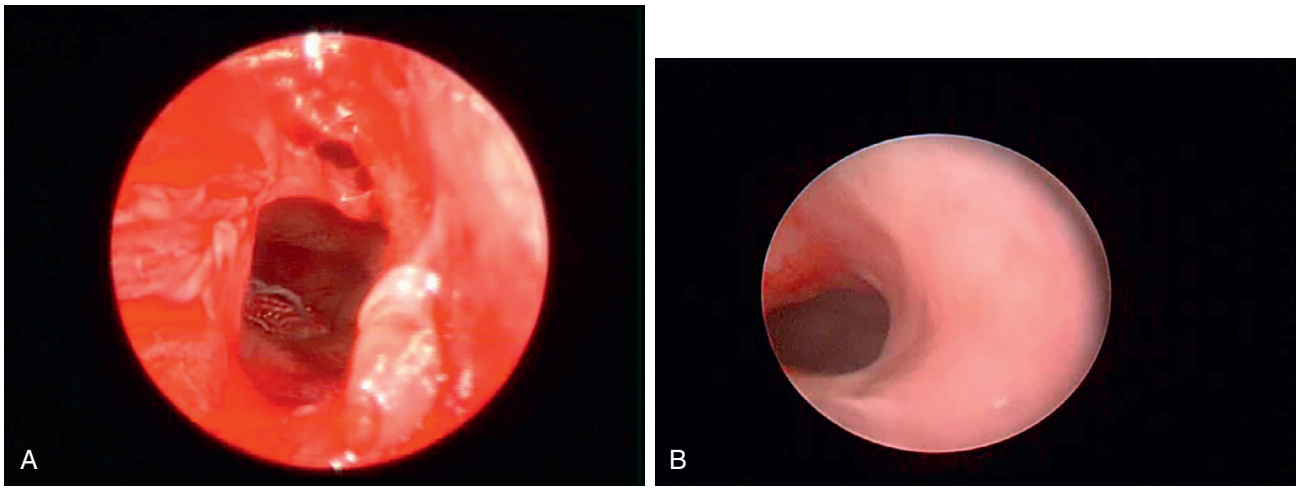
• **Fig. 68.4** Axial CT demonstrating unilateral right choanal atresia.

atretic plate is opened with a urethral sound or microdrill, then progressively dilated, and a backbiter may then be used to remove the posterior vomer.[29] Postoperative stenting remains a controversial topic and has not been shown to produce significant improvement in surgical outcomes while increasing rates of local infection, synechiae, and granulation tissue.[23] Topical application of mitomycin C, an antineoplastic agent inhibiting fibroblast proliferation, has been described in multiple studies but has not shown a difference in the restenosis rate for choanal atresia repair.[8] Regardless of the technique, recurrence rates following endoscopic techniques remain high, with risk factors including reflux, age less than 10 days, pure bony atresia, and associated malformations. Meanwhile CHARGE patients may require tracheostomy upfront due to multilevel airway obstruction or cardiopulmonary issues; surgical repair is also less likely to be successful in these patients because of more contracted anatomy and poor pharyngeal muscular control.[23]

Congenital Nasal Masses

Nasal obstruction with airway distress can result from congenital midline masses such as dermoids, epidermoids, cerebral heterotopia, and encephaloceles. Any infant with a midline nasal mass should be fully evaluated, generally with both CT and magnetic resonance imaging (MRI) to assess for skull base involvement and intracranial extension before intervention is undertaken. Biopsy of an unsuspected nasal

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• **Fig. 68.5** **A,** Endoscopic view during repair of right choanal atresia. **B,** Postoperative view after right choanal atresia repair, 8 weeks.

encephalocele can lead to cerebrospinal fluid leak, meningitis, and death.

Congenital midline nasal masses are theorized to arise from failed retraction of a dural diverticulum, and tissue extension through the fonticulus frontalis or foramen cecum may produce an extranasal or intranasal mass, respectively. Dermoids contain ectodermal and mesodermal tissue, while epidermoids contain only ectodermal tissue. These lesions are often grouped together due to their similar embryologic origin and may present as cystic or solid masses located anywhere between the columella and the glabella. Dermoids may also present with sinus tracts and pits secreting sebaceous material, classically with a dimple at the rhinion and protruding hair. Intracranial communication should be suspected in the case of recurrent meningitis, and imaging revealing an enlarged foramen cecum, bifid nasal septum, or bifid crista galli.[36] Treatment consists of complete surgical excision, including associated tracts, and collaboration with neurosurgical teams as indicated.

Cerebral heterotopia (previously known as nasal glioma) represents sequestra of glial tissue following incomplete retraction of the dural diverticulum, and neonates may present with nasal obstruction and an intranasal mass. Up to 15% of lesions retain a dural connection, and 10%-30% retain a fibrous stalk.[36] Failure to recognize the fibrous stalk can lead to incomplete resection and tumor recurrence. Encephaloceles maintain their intracranial communication with the subarachnoid space, with herniated brain tissue, dura, and cerebrospinal fluid constituting the tumor. These masses are pulsatile, transilluminate with light, and demonstrate a positive Furstenberg test (expansion following jugular vein compression). Early surgical resection with multidisciplinary coordination is generally recommended to alleviate the risk of meningitis that accompanies these tumors. In addition, progressive growth of the lesion can result in marked nasal deformity. Recently, transnasal endoscopic approaches have been described for the surgical resection of these lesions while shortening operative time and decreasing complication rates.[1]

Nasopharyngeal Teratoma

Teratomas are benign tumors composed of all three germ layers with recognizable early organ differentiation. Females are disproportionately affected (6:1 ratio), and associated fetal conditions include hydrops and pulmonary hypoplasia. While these lesions are most commonly found in the sacrococygeal region, teratomas of the head and neck carry a notable risk of airway obstruction. In the nasopharynx, they may appear in the midline or lateral pharyngeal wall and appear heterogeneous on MRI with fat and bone. A persistently high alpha-fetoprotein (AFP) level may be suggestive of teratoma and may be used to monitor for disease progression or response to treatment.[30] Prenatal diagnosis with ultrasound and MRI, along with multidisciplinary prenatal care, is critical to evaluate the degree and extent of airway obstruction, and an EXIT procedure may be indicated in severe cases.[6]

Mucosal Obstruction

Neonatal rhinitis is a common cause of nasal obstruction that may present with stertor, difficulty feeding, and increased work of breathing.[39] Generalized mucosal hypertrophy or edema can result in significant anterior nasal congestion and symptomatic obstruction in the neonate until oral breathing becomes reflexive. Treatment of these patients is generally conservative and includes humidification, saline drops, and judicious suctioning. Excessive attempts at suctioning can result in increased edema and exacerbation of the infant's symptoms. Gastroesophageal reflux may reach the level of the nasopharynx and can exacerbate nasal obstruction as well. Appropriate treatment of reflux may improve the nasal airway. Intranasal steroid drops might be helpful during periods of increased congestion such as that associated with viral rhinitis. Prolonged use of intranasal decongestants can lead to rhinitis medicamentosa (paradoxical mucosal swelling) and should be avoided.

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Continuous Positive Airway Pressure Trauma

Care must be taken with the use of continuous positive airway pressure (CPAP) nasal prongs and masks in the neonate, because nasal trauma can occur. Cosmetic and functional sequelae of nasal injury from nasal CPAP have been described not only in neonates but also in adolescents and adults with a history of nasal CPAP administration as a neonate.[26] Thus, if nasal injury is imminent and discontinuation of nasal CPAP is not possible, then changing to a different style of delivery (e.g., nasal mask) may be useful. Nasal cannulas cause significantly less nasal trauma than CPAP.

Oral and Oropharyngeal Lesions

Normal oral cavity and oropharyngeal development is critical in establishing a patent upper airway. A variety of congenital anomalies have a known association with micrognathia, glossoptosis, and posterior tongue displacement and subsequent airway obstruction. Pierre Robin sequence, Treacher Collins syndrome, Goldenhar syndrome (oculoauriculovertebral dysplasia), Crouzon disease, and Down syndrome are the most common congenital anomalies that have oropharyngeal airway obstruction as an important clinical feature.

In most of these patients, normal growth and development results in an increase in oropharyngeal space and a decrease in obstructive symptoms. Any treatment plan for these patients must take into consideration the knowledge that normal growth alleviates much of the obstructive pathology. Often, placing the infant in a prone position with slight head elevation during sleep dramatically decreases the degree of symptomatic obstruction. A McGovern nipple that maintains oral patency or a soft nasal trumpet may be sufficient to achieve adequate airway patency until growth of the mandible occurs. For patients with severe micrognathia and respiratory distress that does not respond to conservative therapy, multidisciplinary care should be coordinated with pulmonology and genetics, as well as a swallow evaluation, polysomnogram, airway evaluation, and computed tomography imaging. Those with craniofacial-microsomia-Goldenhar syndrome, persistent aspiration, poor neuromuscular tone, ventilator dependence, or other source of airway obstruction should receive tracheostomy as an initial procedure prior to mandibular distraction osteogenesis (MDO).[25] Otherwise, MDO represents an effective surgical technique to relieve the airway obstruction from severe micrognathia and may obviate the need for a tracheostomy or increase the likelihood of successful decannulation in those with pre-existing tracheostomies.

Lymphatic Malformations

Lesions of the floor of the mouth or base of the tongue that cause posterior tongue displacement also can be associated with secondary airway obstruction. Lymphatic malformations are benign congenital vascular anomalies with a predilection for the head and neck region and may infiltrate the soft tissue of the floor of the mouth and cause significant upper airway obstruction. Prenatal diagnosis of cervical lymphatic malformation with airway obstruction or floor of mouth involvement may necessitate an EXIT (ex utero intrapartum treatment) procedure to secure a safe airway.[24] Local infection of vascular anomalies is also an important entity to recognize, as localized swelling may compromise an existing airway, and long-term antibiotics have been proposed to prevent recurrent cycles of infection.[42] An increased incidence of sleep-disordered breathing has also been noted in this population[14] and may warrant formal evaluation with polysomnography.

In addition to airway compromise, lymphatic malformations may also cause dysphagia, dysarthria, and dental problems. Treatment should be tailored to the specific functional and cosmetic impact of each lesion, as well as the pathologic type (macrocystic versus microcystic). Surgery and sclerotherapy represent the mainstays of treatment, although radiofrequency ablation, lasers, propranolol, and sirolimus have also been described, albeit with limited data on objective efficacy. At present, multimodality and sequential treatment with surgery and sclerotherapy is most commonly used for extensive lesions. Isolated neck disease also holds an improved prognosis for resolution compared to lesions in the larynx, parotid, or oral cavity.[4]

Oral Cavity Cysts

Cysts of the base of the tongue are a rare but serious cause of airway obstruction in the newborn infant. An acute airway crisis could appear shortly after birth or several months later. These cysts may represent lingual thyroglossal duct remnants at the foramen cecum.[37]

Dermoid cysts of the oral cavity are benign, slow-growing tumors that may cause progressive symptoms of dysphagia or airway obstruction in the pediatric population.[32] In contrast with the infant with a thyroglossal duct cyst at the base of the tongue, a more insidious onset of symptoms may be noted. Airway obstruction may be worsened by the mass effect in the hypopharynx and inferoposterior displacement of the epiglottis, which causes supraglottic obstruction.

Surgical excision is the treatment of choice in these patients. Marsupialization may be an option for the large cyst that is not amenable to complete resection. Significant tongue swelling can develop postoperatively, and temporary intubation may be necessary to ensure a protected upper airway.

Laryngeal Lesions

Embryologically, the larynx has three primary functions: airway protection, respiratory modulation, and voice production. The neonatal larynx has unique features, compared with that of an adult, that affect its ability to perform

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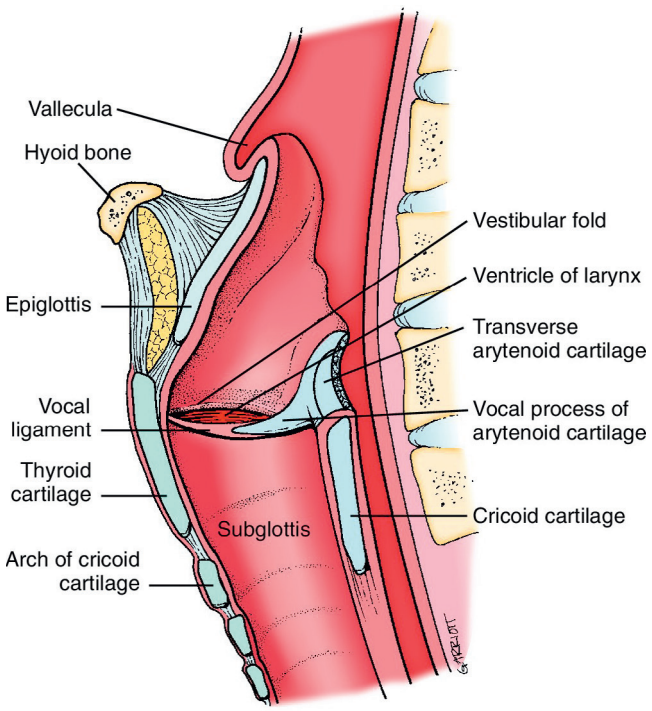
these three primary functions both in the normal and the diseased state.

Although the neonatal larynx is less than one-third the size of the adult larynx, the arytenoid cartilages are adult size at birth. This relationship between the supraglottic structures and the laryngeal inlet can contribute to the development of laryngomalacia in some infants. The subglottis is the smallest component of the pediatric larynx, whereas in the adult, the glottic aperture is the size-limiting factor. The development of subglottic stenosis in the infant following endotracheal intubation is directly related to the small size of the subglottic opening.

In addition to differences in size, the infant larynx differs in its position in the neck relative to the cervical and facial skeleton. At birth, the larynx may be found at approximately the level of the C4 vertebra. As the child grows, the larynx begins its inferior descent, ultimately resting at the level of C7. The high location of the larynx in the infant provides some protection against external trauma.

The cephalad location of the larynx also provides additional protection to the lower airway of the neonate, who has not yet fully developed the necessary protective reflexes to prevent aspiration during swallowing. In the young infant, the epiglottis rests on the nasopharyngeal surface of the soft palate. This position allows the infant to suckle without danger of aspiration and to breathe with the mouth closed.

Anatomically, the larynx may be subdivided into three components: supraglottis, glottis, and subglottis (Fig. 68.6). Disorders in one of these components produce a unique set of symptoms that allows narrowing of the field of possible causes of airway distress in the infant. An attempt should be made to characterize stridor, when present, as inspiratory, expiratory, or biphasic.



• **Fig. 68.6** Parasagittal view of infant larynx demonstrating cartilaginous relationships.

Although not uniformly true, the level of obstruction is often reflected in the character of the stridor. Supraglottic lesions tend to produce a coarse, inspiratory stridor, whereas glottic and subglottic disorders are more "musical" in quality and often biphasic in nature. Pure tracheal lesions often manifest with a prolonged expiratory phase and expiratory stridor. Changes in the quality of the stridor with the level of activity and position of the infant are also a crucial aspect of the history. The quality of the child's cry (normal, weak, or aphonic) can direct one to a glottic lesion, although severe subglottic narrowing could produce an abnormal cry because of limited air movement.

The presence or absence of cough should be documented. A feeding history is critical. Symptoms of aspiration or cyanosis with feeds can signal a specific disorder. Failure to thrive or other signs of systemic illness could indicate a more chronic disorder. The infant's prenatal and perinatal history could reveal an unsuspected history of traumatic delivery or neonatal intubation.

If the infant is in extremis, or there are signs to suggest significant airway compromise, extreme caution should be exercised. Manipulation of the infant should be minimized until the airway can be secured. The infant can be observed for tachypnea, tachycardia, retractions (supraclavicular, subcostal, intercostal), nasal flaring, cyanosis, drooling, cough, and level of consciousness (restless, agitated, stuporous) without increasing the level of the infant's anxiety.

Laryngeal examination should not be performed in the infant with an unstable airway unless the appropriate personnel and equipment are available for urgent airway access when necessary. Flexible fiberoptic nasolaryngoscopy is widely available and allows direct inspection of the larynx in the stable neonate.

Evaluation of the awake child has several distinct advantages. The larynx can be viewed in a dynamic fashion so that the degree of laryngeal collapse during active respiration is appreciated. In addition, vocal cord motion can be assessed. Flexible bronchoscopy allows further dynamic evaluation of the subglottic airway and lower tracheobronchial tree.

For more controlled laryngeal evaluation, direct laryngoscopy and rigid bronchoscopy under general anesthesia are necessary. If a deep inhalational anesthetic technique is used, dynamic laryngeal and tracheal function can be assessed using this method as well. Direct laryngoscopy with rigid bronchoscopy is the method of choice in evaluating an infant with air hunger, cyanosis, or any critical symptoms that may necessitate intubation.

Ancillary testing in the infant with a stable airway is useful in further identifying the site of the lesion before possible endoscopy and surgical intervention. Radiographic evaluation of the upper airway (usually with a CT scan with contrast) is useful in suspected subglottic stenosis (either congenital or iatrogenic), soft tissue laryngeal tumors (hemangiomas, papillomas), or congenital laryngeal or esophageal

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cysts. Less commonly, anteroposterior and lateral soft tissue radiographs of the neck can be obtained. Ballooning of the hypopharynx is often seen on the lateral neck radiograph in an infant with significant airway obstruction. Reversal of the cervical lordotic curvature is suggestive of a retropharyngeal process. Airway fluoroscopy allows a dynamic assessment of the airway and can be done in conjunction with a modified barium swallow to evaluate for vascular anomalies or tracheoesophageal fistula or to better define the contribution of a swallowing disorder to the airway symptoms. Computed tomography scan is also useful for evaluating the infant with a laryngeal tumor for a severe laryngotracheal anomaly not fully delineated by endoscopy or for the evaluation of laryngeal trauma. Computed tomography scanning is also useful for virtual bronchoscopy to map extensive tracheal or bronchial stenosis. Magnetic resonance imaging is useful for defining mediastinal anatomy in the infant with a suspected vascular anomaly.

Disorders of the neonatal larynx are best subdivided into congenital and acquired lesions. Severe congenital laryngeal anomalies are quite rare and in general manifest themselves within the first few minutes of life. These include complete atresia, severe stenosis, or near-total laryngeal webs. If these disorders are recognized, tracheostomy may be a life-saving procedure. Often, these severe laryngeal anomalies are found in conjunction with other life-threatening neurologic, cardiac, gastrointestinal, and lower airway lesions. In the neonate, the acquired laryngeal injury is usually the result of endotracheal intubation (see Chapter 65). The overall prognosis for these neonates depends not only on the laryngeal problem but also on the infant's overall development and the impact of other concomitant lesions.

Laryngomalacia

Laryngomalacia (congenital flaccid larynx, congenital laryngeal stridor) is the most common cause of stridor in the infant. The etiology of laryngomalacia remains elusive, although generalized neurologic immaturity of the infant's airway and digestive tract is believed to play a role. Clinically, stridor develops between the second and fourth weeks of life, although it occasionally may be present at birth. The stridor is typically characterized as coarse inspiratory noise.

The infant is generally better in the prone position, because this serves to decrease the degree of supraglottic collapse on inspiration, although this must be weighed against the Safe to Sleep campaign advocating the supine sleeping position to reduce the risk of sudden infant death syndrome. Agitation tends to exacerbate the stridor, which tends to disappear completely during rest, and the cry is usually normal. The natural history of the disease is one of progression until 8-12 months of age, with complete resolution in most children by 2 years of age. However, in cases of severe laryngomalacia, infants may have constant stridor, increased work of breathing, periodic apneas, failure to thrive, cor pulmonale, or pectus excavatum.

Symptoms of swallowing or feeding difficulty have been reported in 50% of infants with laryngomalacia regardless of comorbidities,[38] and dysphagia evaluation should be included in standard workups in the form of clinical swallow evaluation (CSE), modified barium swallow (MBS), or functional endoscopic evaluation of swallowing (FEES). Gastroesophageal reflux often coexists with laryngomalacia and may exacerbate symptoms,[17] thus infants with signs and symptoms of reflux should be treated with acid suppression therapy. Concomitant neurologic disease is also described more frequently in infants with moderate or severe laryngomalacia. Concomitant obstructive or central sleep apneas also warrant formal evaluation with polysomnography.

Up to 50% of infants with laryngomalacia have a synchronous airway lesion such as congenital subglottic stenosis.[2] Direct laryngoscopy with rigid bronchoscopy is indicated in the atypical patient to confirm the suspected diagnosis of laryngomalacia and evaluate for the possible existence of a secondary lesion below the level of the glottis.

Diagnosis in the more typical patient begins with fiberoptic office nasolaryngoscopy. During inspiration, the supraglottic structures collapse into the laryngeal inlet, narrowing the air passage and creating the classic coarse stridor. Visualization of the vocal cords may be limited by shortened aryepiglottic folds, a curled omega-shaped or retroflexed epiglottis, and arytenoid collapse (Fig. 68.7). Each of these sites may contribute to airway collapse laterally, anteriorly, or posteriorly, respectively; description of the exact site and degree of collapse is critical in surgical planning.[41]

Surgical intervention is indicated for patients with respiratory or feeding difficulties not responsive to conservative therapy or for severe laryngomalacia characterized by cyanosis, apnea, failure to thrive, or aspiration. Supraglottoplasty may include division of aryepiglottic folds and trimming of redundant supra-arytenoid or epiglottic tissue, using CO_2 laser, cold instruments, or microdebrider. This procedure not only produces excellent success rates for symptoms of laryngomalacia but also improves concurrent obstructive sleep apnea.[16] Tracheostomy is reserved for severe laryngomalacia that results in significant airway obstruction despite supraglottoplasty.

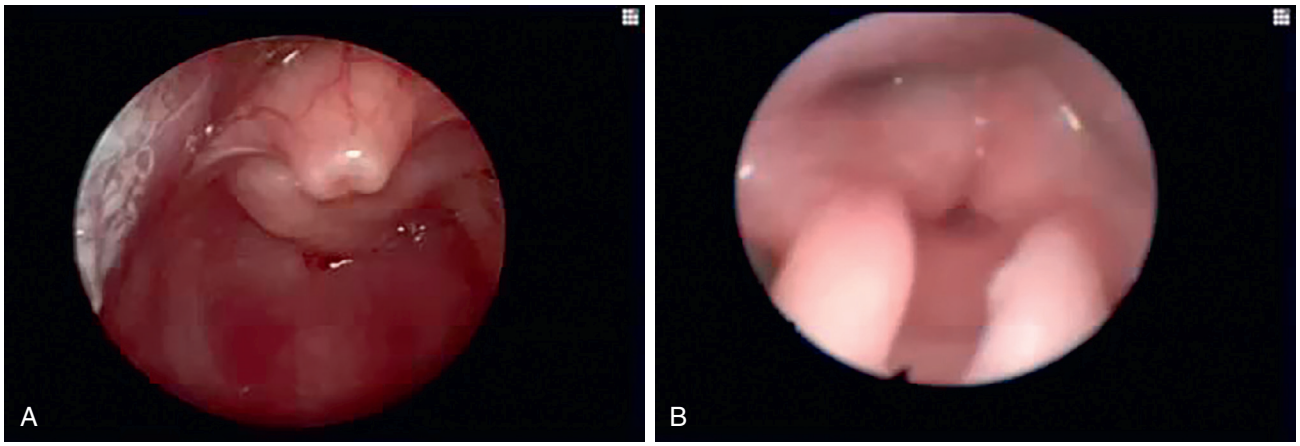
Bifid or Absent Epiglottis

Both the bifid epiglottis and the absent epiglottis are extremely rare. Severe subglottic stenosis is usually seen with these unusual supraglottic anomalies. Tracheostomy is necessary because of the associated subglottic lesion. Aspiration is variable.

Laryngeal Cysts

Most cysts of the larynx develop in the supraglottic location (aryepiglottic fold, epiglottis, vallecula) and gradually increase in size during the first few months of life. Ductal obstruction may lead to accumulation of mucous within

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• **Fig. 68.7** **A,** Infant supraglottis with laryngomalacia. Coiled epiglottis and tightened aryepiglottic folds. **B,** Infant supraglottis with laryngomalacia. Arytenoid edema and prolapse preventing visualization of vocal cords.

a saccular cyst. Owing to the location of these lesions as well as their slowly progressive course, they may be indistinguishable clinically from laryngomalacia. Patients may present with stridor and respiratory distress and require early intubation; others only exhibit inspiratory stridor that worsens with agitation and when in the supine position. In older children, the voice can become muffled as the cyst enlarges.

If undetected and untreated, these cysts can become quite large and cause complete laryngeal obstruction. Fiberoptic evaluation confirms the presence of a saccular cyst and is the minimum requirement for all infants with new-onset, progressive inspiratory stridor. Formal evaluation with rigid endoscopy under general anesthesia, as well as magnetic resonance imaging, may be needed in more extensive lesions. The treatment involves either endoscopic marsupialization or complete excision (either endoscopically or externally) of the cyst. Attempts to aspirate the cyst inevitably lead to cyst recurrence. Subglottic cysts can form just below the vocal cords and are caused by obstruction of mucosal glands related to intubation. Endoscopic marsupialization with a carbon dioxide laser or cold instrumentation is usually curative.

Vocal Cord Paralysis

Vocal cord paralysis is the second most common laryngeal anomaly of infancy. Bilateral vocal cord paralysis typically produces inspiratory stridor that worsens with agitation or infection, a weak voice, and airway obstruction. In contrast, unilateral vocal cord paralysis may be initially asymptomatic, with dysphonia or stridor that worsens with agitation. The child may have a history of choking, coughing, or brief cyanotic spells during feeds, which is indicative of aspiration. Concomitant airway disease such as laryngomalacia, tracheomalacia, and subglottic stenosis may also be present.[34]

Radiographic evaluation remains an important step in the management of these patients. Unilateral paralysis may be associated with cardiac atrial enlargement or anomalous great vessels, which can be detected on chest radiographs and barium swallow or echocardiogram. In the absence of a history of infection (syphilis, Guillain-Barre), traumatic delivery, prolonged intubation, or cardiothoracic surgery (e.g., ligation of patent ductus arteriosus [PDA], repair of tracheoesophageal fistula), the course of the vagus nerve should be investigated radiographically. An MRI of the brain, neck, and chest may reveal a Chiari malformation or mass effect from a mediastinal or cervical mass. Awake fiberoptic laryngoscopy is often necessary to confirm the diagnosis of vocal cord paralysis, and video recording may be helpful to examine findings in more detail.

The treatment of unilateral vocal cord paralysis depends on the severity of the child's symptoms. While many symptoms of difficulty feeding or dysphonia may resolve spontaneously, 20%-40% remain symptomatic after 8-12 months.[21] Thus, for the first few years after diagnosis of unilateral vocal cord paralysis, conservative measures and temporary injection laryngoplasty may be offered. Medialization thyroplasty is typically reserved for older patients who are able to tolerate an awake procedure under local anesthesia to fine tune exact placement of the implant. Reinnervation using ansa cervicalis to the recurrent laryngeal nerve has been shown to be effective in improving voice and vocal cord tone (but not mobility) without foreign material or alteration of the laryngeal framework.[7]

Bilateral vocal cord paralysis creates more severe respiratory symptoms because of significant encroachment on the glottic aperture. Often there are associated neurologic abnormalities, such as Chiari malformation and hydrocephalus. Unlike unilateral paralysis, bilateral vocal cord paralysis often necessitates tracheostomy.

Laryngeal Web

A laryngeal web is the result of a failure to recanalize the laryngeal inlet at approximately 10 weeks' gestation. A commonly referenced classification system was proposed by Cohen in 1985, with type 1 less than 35% glottic length

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involvement; type 2 35%-50%; type 3 50%-75%; and type 4 thick web up to 99% and with associated subglottic stenosis.[10] Infants with type 1 webs may not be symptomatic at birth but then develop biphasic stridor between 4 and 6 weeks of age after activity levels begin to increase. For more severe glottic webs, respiratory distress and aphonia may be present. Frequent association with velocardiofacial syndrome (VCFS) and 22q11 deletion warrants fluorescence in-situ hybridization or genetic sequencing in patients with anterior glottic webs.[31] Treatment of a laryngeal web depends on the thickness of the web itself and the degree of subglottic extension. Type 1 and 2 glottic webs can often be treated endoscopically with web excision using cold instruments or lasers, sometimes with stent or keel placement to prevent scarring and web recurrence anteriorly. Type 3 and 4 glottic webs may require tracheostomy and an open approach with laryngotracheal reconstruction and cartilage grafts.[11]

Congenital Subglottic Stenosis

The normal subglottis measures between 5 and 7 mm in the neonate. Congenital subglottic stenosis occurs when the subglottic diameter of a full-term infant is less than 4 mm at birth and may be associated with 22q11 deletion, Down syndrome, and CHARGE syndrome. Congenital stenosis often results from an abnormally shaped cricoid ring, elliptical rather than circular, or from excessive thickening of the subglottic tissue. Rarely, the first tracheal ring may be displaced superiorly and come to lie within the cricoid itself.

In mild forms, the stenosis can go undetected until the child is 2-3 years of age, at which point recurrent croup-like episodes prompt endoscopic evaluation. In more severe cases, biphasic stridor is present with a classic croupy cough in the absence of any systemic signs of a viral illness. The cry is usually normal, and feeding is only an issue in cases of significant shortness of breath resulting from airway compromise. In general, congenital subglottic stenosis is concentric. Radiographic evaluation usually demonstrates symmetric subglottic narrowing.

Formal evaluation with direct laryngoscopy and rigid bronchoscopy is necessary to evaluate the full extent of the stenosis. A cuffless endotracheal tube is placed past the stenosis, and the largest size that allows a leak pressure of 10-25 cm H_2O is used to determine the Cotton-Meyer grade of stenosis: grade 1 (0%-50%), grade 2 (51%-70%), grade 3 (71%-99%), and grade 4 (no discernable airway).[31]

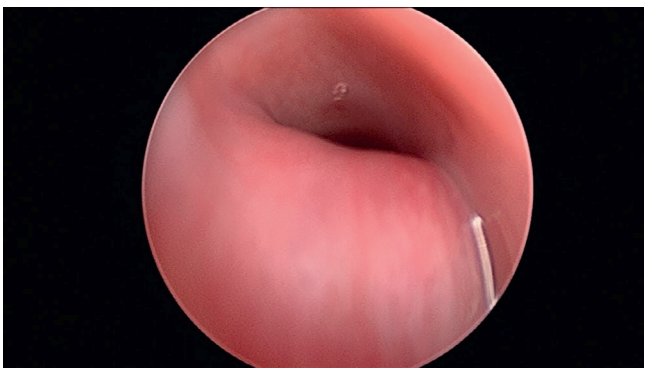
Management of these lesions depends on the severity of the infant's symptoms and the age at presentation. Congenital subglottic stenosis is usually less severe than the iatrogenic form following endotracheal intubation. In select cases, an anterior cricoid split can prevent the need for tracheostomy in infants up to 18 months of age. In more severe cases of stenosis or in the older child, laryngotracheal reconstruction using rib for augmentation is the treatment of choice.

Subglottic Hemangioma

Subglottic infantile hemangioma is the most common neoplasm of the infant airway and can lead to significant airway compromise if left untreated. These benign vascular growths are characterized by disorganized endothelial proliferation and stain positively for GLUT-1 and are more prevalent in infants from in vitro fertilization, premature births, and females.[20] In the larynx, the lesion generally appears as a smooth, eccentric, compressible mass in the subglottis, most commonly located in the left posterior subglottic space. Subglottic hemangioma is associated with a segmental beard distribution hemangioma, and any patient with a large cervicofacial hemangioma should be evaluated for PHACES (*p*osterior fossa anomalies, *h*emangioma, *a*rterial lesions, *c*ardiac/aortic anomalies, *e*ye abnormalities, *s*ternal defects) and undergo further imaging to evaluate for associated anomalies.

The clinical presentation of a subglottic hemangioma is similar to that of subglottic stenosis. The infant typically has progressive biphasic stridor beginning at 4-6 weeks of age. Unlike with the static subglottic lesion, the symptoms associated with a hemangioma can fluctuate in severity from day to day. The fluctuating character of symptoms is strongly diagnostic of subglottic hemangioma. The stridor is worse with crying or agitation owing to vascular engorgement of the hemangioma. Feeding difficulties are unusual unless severe airway obstruction exists. The cry is generally normal. Radiographic evaluation (CT scan with contrast or anteroposterior soft tissue neck film) may show an asymmetric narrowing of the subglottis. The diagnosis of a subglottic hemangioma is confirmed at the time of direct laryngoscopy with rigid bronchoscopy (Fig. 68.8).

The treatment of subglottic hemangiomas must take into account the natural history of the neoplasm. Initially, the lesion undergoes rapid postnatal growth for 8-18 months (proliferative phase) followed by slow but inevitable regression for the next 5-8 years (involutive phase). Since the serendipitous discovery of the efficacy of propranolol in the treatment of infantile hemangiomas in 2008, and its formal approval by the Food and Drug Administration in 2014, treatment with propranolol for hemangiomas causing airway symptoms has rapidly become a first-line therapy,



• **Fig. 68.8** Subglottic hemangioma before treatment.

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although the exact mechanism of therapeutic reduction is not well understood. A consensus statement released in 2013 proposes a dosing protocol starting with 2 mg/kg/day in three divided doses, with titration customized to severity of side effects ranging from hypotension, bradycardia, and hypoglycemia.[13] Systemic steroids on a daily or every-other-day schedule may control the proliferative phase of the hemangioma in patients with minimal airway or feeding compromise. Surgical debulking or resection, lasers (CO_2, Nd:YAG, and pulsed dye lasers), and pharmacologic therapies (interferons, vincristine) are typically reserved for hemangiomas with airway symptoms refractory to beta blocker therapy.[9] In cases of extensive airway involvement, a tracheostomy provides a secure airway until the tumor involutes.

Laryngeal Cleft

Failure of fusion of the tracheo-esophageal septum results in a posterior laryngeal cleft. The Benjamin-Inglis classification is commonly used to describe these clefts,[3] with type 1 extending to the level of the true vocal cords, type 2 involving part of the posterior cricoid plate, type 3 involving the cervical trachea, and type 4 extending to the thoracic trachea. Presentation may vary from dysphagia and recurrent aspiration pneumonia to cyanosis and respiratory distress. While most cases are sporadic, associated syndromes include CHARGE, VACTERL, Optiz-Frias, and Pallister Hall. Evaluation should include a swallow evaluation (modified barium swallow or functional evaluation of swallowing) and flexible laryngoscopy; however, definitive diagnosis requires formal evaluation in the operating room with palpation of the interarytenoid area. For type 1 clefts, dietary changes (thickened feeds), close coordination with speech-language pathology, and antireflux medications are sufficient in about one-third of cases, while the remaining two-thirds do need surgical repair.[40] Surgical repair may be performed via open or endoscopic approaches, with the latter being more common, especially for types 1-3 laryngeal clefts. Cold instrumentation or laser may be used to de-epithelialize the mucosa lining the cleft, and vicryl sutures are placed from an inferior to superior direct to close the defect. Open approaches may require a cartilage or muscle graft, laryngofissure, pharyngotomy, cardiopulmonary bypass, or extracorporeal membrane oxygenation.

Congenital High Airway Obstruction Syndrome

Congenital high airway obstruction syndrome (CHAOS) was defined by Hedrick and colleagues in 1994 as prenatally diagnosed upper airway obstruction with concomitant findings of large echogenic lungs, dilated airways, flattened or inverted diaphragms with associated fetal ascites, or nonimmune hydrops. These hallmark findings are found consistently only when there is complete high upper airway obstruction with no tracheoesophageal connection because of laryngeal atresia, severe subglottic stenosis, glottis web, obstructive laryngeal cysts, or a double aortic arch. This leads to trapping of the fluid secreted by the fetal lung tissue. If the lung fields expand to the point of producing esophageal compression, then polyhydramnios may occur as a result of impaired swallowing of amniotic fluid. These findings necessitate a more detailed scan for other abnormalities, because CHAOS may be one fetal presentation of Fraser syndrome, characterized by variable expression of laryngeal atresia, cryptophthalmos, syndactyly, renal agenesis, and abnormalities of the ears and external genitalia.[12]

This life-threatening condition was previously thought to be rare and uniformly fatal. Advances in prenatal imaging techniques have enabled this syndrome to be recognized more readily. Planning for the EXIT (ex utero intrapartum treatment) procedure can then be made to maximize survival.

If there is incomplete airway obstruction or a tracheoesophageal fistula, the degree of fluid trapping is lessened, and the diagnosis is less obvious on prenatal ultrasound imaging. In these cases, with the diagnosis less obvious, survival depends on the degree of upper airway obstruction, the ability to tracheally intubate the child past the tracheoesophageal fistula, or the ability to expeditiously perform a tracheostomy.

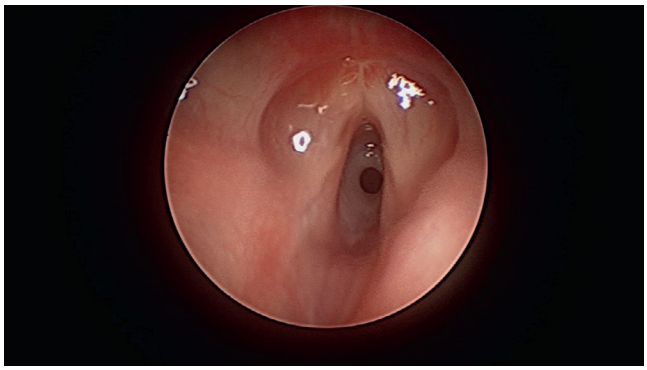
Intubation Trauma

The use of endotracheal intubation to secure the airway in the neonate for mechanical ventilation has become the standard of care for the critically ill newborn. Despite recent efforts to reduce the risk of iatrogenic injury, however, granuloma formation, arytenoid dislocation with true vocal cord fixation, and subglottic stenosis continue to occur.

Granuloma formation can follow endotracheal intubation. The infant is often hoarse following extubation, with progression rather than improvement of the symptoms with time. Evaluation of the larynx reveals a yellow-red pedunculated mass arising from the vocal process of the arytenoid. Subglottic cysts or mucoceles may develop when the opening of submucosal glands is interrupted by tissue reaction from an endotracheal tube. Microlaryngoscopy and removal of these lesions often result in resolution of the infant's symptoms. Repeat evaluation is recommended at 2-3 weeks to ensure that the granuloma has not reformed, which can be lessened by aggressive treatment of gastroesophageal reflux.

Several factors in the pediatric airway predispose the intubated neonate to subglottic stenosis (Fig. 68.9). The subglottic lumen is the narrowest aspect of the pediatric larynx. Premature infants and children with Down syndrome tend to have smaller cricoid rings than normal, thus increasing the overall risk of subglottic stenosis. Gastroesophageal reflux and infection at the time of intubation have been proposed as potential factors in the development of subglottic stenosis.[22] Difficulty in stabilizing the endotracheal tube in the neonate often results in repeated

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• **Fig. 68.9** Iatrogenic subglottic stenosis following prolonged endotracheal intubation in a neonate.

intubations and increased injury to the subglottis. Extreme immaturity requiring intubation periods of several months predisposes to subglottic injury. Hypoxia and sepsis are important variables in the development of subglottic tissue damage and are commonly seen in the neonatal intensive care setting. Injury to the subglottis may be reduced if the following steps are taken:

- Use smaller endotracheal tubes.
- Avoid cuffed endotracheal tubes in the infant and young child.
- Aggressively treat systemic infection.
- Minimize patient movement to prevent abrasions of the subglottic mucosa and resultant exposed cartilage as well as to prevent accidental extubation requiring further manipulation (sedate as necessary).
- Consider tracheostomy if prolonged intubation is anticipated. Neonates tolerate intubation for much longer periods than the child or young adult.
- Extubate under ideal conditions. In the difficult airway, high-dose systemic steroids for 24-48 hours before and after extubation may aid extubation. Use of inhaled epinephrine immediately following extubation can help reduce airway edema.

Treatment of iatrogenic subglottic stenosis depends on the severity of the stenosis, the age of the child, and concomitant medical problems. Tracheostomy remains the cornerstone of treatment, especially in the infant with multilevel airway involvement, multisystem failure, or significant pulmonary disease. The anterior cricoid split may be used in the neonate up to 18 months of age if mild stenosis exists. As in congenital subglottic stenosis, laryngotracheal reconstruction using rib cartilage is the method most commonly employed for treatment of significant pediatric subglottic stenosis. In selected patients, laryngotracheal reconstruction may be performed as a single-stage procedure, allowing immediate decannulation in the patient with a pre-existing tracheostomy or avoidance of a tracheostomy altogether in the virgin trachea.

Conclusion

Management of the neonate with upper airway obstruction requires that a rapid evaluation and diagnosis be made based on a complete understanding of the unique anatomic and physiologic characteristics of the neonatal airway. The airway should be assessed from nasal vestibule to tracheal bifurcation in a search for the etiology of acute or progressive respiratory distress. Treatment of the neonate with upper airway pathology is tailored to the specific abnormality as well as coexisting medical problems.

Key Points

- Dividing the neonatal upper airway into four primary physiologic components (nasal, oral, laryngeal, tracheal) helps frame the discussion of airway abnormalities in the newborn.
- Evaluation of an infant with a suspected airway abnormality should encompass the entire upper airway, from the anterior nasal vestibule to the tracheal bifurcation.
- Neonates are preferential (almost obligate) nasal breathers; any process that causes bilateral nasal obstruction (such as bilateral pyriform aperture stenosis, bilateral choanal atresia, or bilateral nasolacrimal duct cysts) will precipitate significant airway obstruction requiring acute intervention.
- Infants with choanal atresia as a component of CHARGE syndrome are more likely to require a tracheostomy, more likely to have concurrent airway lesions, and less likely to experience a successful atresia repair.
- The pathophysiology and behavior of congenital midline nasal masses depends on a defect in the fonticulus frontalis or foramen cecum.
- Neonates with retrognathia with or without a cleft palate may have feeding abnormalities or airway obstruction requiring intervention (such as prone positioning, nasopharyngeal airway, mandibular distraction osteogenesis, or tracheostomy).
- Cervicofacial teratomas or lymphatic malformations diagnosed in utero may necessitate an EXIT (ex utero intrapartum treatment) procedure if impending airway obstruction is suspected.
- Disorders of the neonatal larynx may be congenital (laryngeal atresia, laryngeal web) or acquired (glottic intubation granulomas).
- Laryngomalacia is the most common cause of stridor in an infant and can also cause feeding issues in up to half of patients; typically symptoms resolve over time with no surgical intervention required.
- Subglottic hemangiomas can cause airway obstruction during their proliferative phase; propranolol has demonstrated efficacy in treating these lesions.

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69

Bronchopulmonary Dysplasia in the Neonate

EDUARDO H. BANCALARI AND DEEPAK JAIN

The introduction of mechanical ventilation for the management of premature infants with severe respiratory distress syndrome (RDS) in the 1960s changed the natural course of the disease, resulting in increased survival of smaller and sicker infants, many of whom had severe chronic lung damage. Northway and associates were the first to describe this condition in 1967 and introduced the term *bronchopulmonary dysplasia* (BPD).[49] All these infants had severe respiratory failure and received prolonged mechanical ventilation with high airway pressures and fraction of inspired oxygen (FiO_2). Since then, the advancements in the field of neonatal and perinatal medicine have resulted in increasing survival of extremely preterm infants and evolution in the clinical presentation of BPD to a milder form of chronic lung disease.

Epidemiology of BPD

BPD continues to be the most important respiratory complication of preterm birth, and it is associated with long-term respiratory morbidities. Prematurity is the most important risk factor for BPD, with infants born at less than 28 weeks' gestation being at greatest risk (Fig. 69.1). According to the data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN), the incidence of BPD in this group decreased from 45% in 2000 to 40% in 2008, with some increase in incidence of BPD over the last few years.[64] The stable or increasing incidence of BPD is likely due to increasing survival of extremely preterm infants, with more infants surviving with milder forms of BPD as compared to before (Fig. 69.2).[61] The incidence of BPD varies widely among different centers[36] not only due to differences in clinical practices and population characteristics but also according to the definition used.[53]

Definition of BPD

Since Northway's first description of BPD for the clinical and radiographic course of a group of preterm infants with severe respiratory failure, the definition of BPD has been modified multiple times to reflect changes in patient population and to better predict pulmonary outcomes. Initial definitions of BPD consisted of oxygen use along with radiographic pictures consistent with BPD at 28 days.[4] With increasing survival of more immature infants over time, the implication of oxygen use at 28 days was questioned, and oxygen requirement at 36 weeks was shown to be more accurate predictor of long-term pulmonary outcomes.[59] In 2001, a workshop conducted by the National Institutes of Health (NIH) proposed a severity-based definition of BPD into three categories based on the duration and level of oxygen therapy required (Table 69.1). The assessment of severity of BPD adds richness to the outcome measure and identifies a spectrum of adverse pulmonary and neurodevelopmental outcomes. As the severity of BPD increases, the incidence of adverse events also increases. The use of supplemental oxygen as a criterion to define severity of BPD has some limitations. The use of supplemental oxygen in these infants is often inconsistent and is not based on a physiologic assessment, which can greatly affect the reported incidence of BPD. To overcome this inconsistency, a physiologic test to standardize the need for supplemental oxygen has been used.[71] Some of the other limitations of the current definition of BPD include failure to classify infants with nonpulmonary causes such as central apnea or airway complications for need for respiratory support, inability to classify infant dying secondary to severe respiratory failure prior to 36 weeks, or failure to appropriately categorize infants on more contemporary modes of respiratory support like high flow nasal cannula.[53] Definitions of BPD are currently evolving in an attempt to categorize infants by severity of disease based on level of support.[24a]

Pathogenesis

BPD, as described originally by Northway and colleagues, resulted from injury to developing lung secondary to prolonged mechanical ventilation with high airway pressures and inspired oxygen concentration. In contrast, BPD

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Abstract

Bronchopulmonary dysplasia (BPD) is the most important respiratory complication of preterm birth, and it is associated with long-term respiratory morbidities. Since its first description by Northway half a century ago, the clinical presentation of BPD has evolved from a severe respiratory failure in relatively bigger preterm infants to a more common milder disease presenting in extremely premature infants today. The advancements in obstetric and neonatal care on one hand have resulted in survival of extremely preterm infants at earlier stages of lung development, while on the other have modified some of the risk factors associated with development of BPD. This has presented unique challenges in understanding the pathogenic factors and defining or devising strategies for prevention and management of BPD. It is quite clear that BPD is the end result of a complex interplay of altered alveolar and vascular development, injury, and reparative processes in a premature lung. With increasing knowledge of the mechanisms involved in the pathogenesis of BPD, various innovative strategies like stem cells and growth factors are being evaluated for prevention of BPD. In addition, the role of some established strategies such as patent ductus arteriosus management and postnatal steroids are being reevaluated. There is increasing evidence of the adverse impact of BPD on long-term pulmonary function and respiratory health. There is increasing realization that prevention and management of BPD will require a multipronged approach with novel therapeutic agents acting at different stages of the disease process.

Keywords

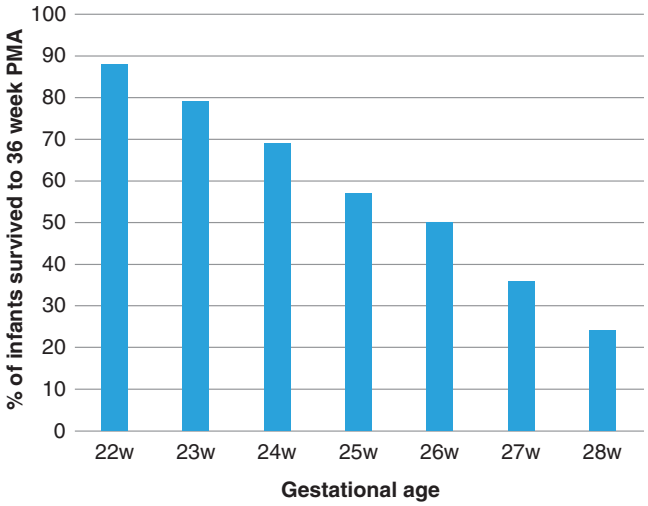
bronchopulmonary dysplasia
preterm
lung
prevention
respiratory support
oxygen

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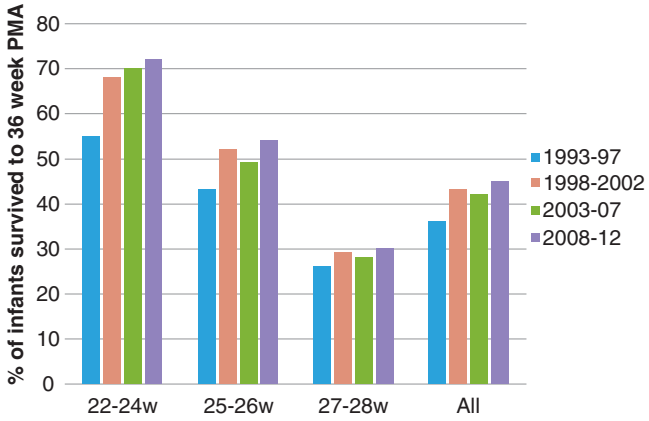
TABLE 69.1 Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria

Gestational Age	<32 Weeks	≥32 Weeks
Time point of assessment	36 weeks' PMA or discharge to home, whichever comes first	>28 days but <56 days' postnatal age or discharge to home, whichever comes first
Treatment With >21% Oxygen for at Least 28 Days PLUS		
Mild BPD	Breathing room air by 36 weeks' PMA or discharge, whichever comes first	Breathing room air by 56 days' postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 weeks' PMA or discharge, whichever comes first	Need for <30% oxygen at 56 days' postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks' PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days' postnatal age or discharge, whichever comes first

BPD, Bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; PMA, postmenstrual age; PPV, positive pressure ventilation.
Adapted from Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723.



• **Fig. 69.1** Incidence of bronchopulmonary dysplasia (BPD) defined as oxygen at 36 weeks' postmenstrual age (PMA) in infants born at GA 22-28 weeks in the Neonatal Research Network between January 1, 2008, and December 31, 2012. (Data from Stoll BJ, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA.* 2015;314(10):1039-1051.)



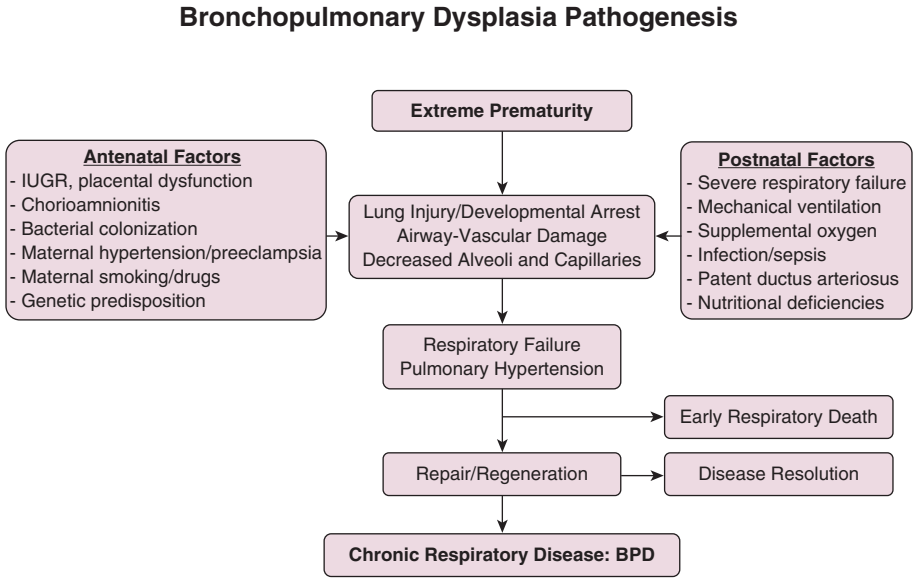
• **Fig. 69.2** Trends in the incidence of bronchopulmonary dysplasia (BPD) defined as oxygen at 36 weeks' postmenstrual age (PMA) in infants born at GA 22-28 weeks and alive at 36 weeks' PMA in the Neonatal Research Network between January 1, 1993, and December 31, 2012. (Data from Stoll BJ, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039-1051.)

currently is mostly seen in extremely preterm infants in late canalicular or early saccular stage of lung development at birth. Multiple pathogenic factors including pre- and postnatal infections, mechanical trauma from positive pressure ventilation, oxygen toxicity, and pulmonary edema secondary to increased pulmonary blood flow from patent ductus arteriosus (PDA) acts on the immature alveolar and vascular structure of the immature lung. The complex interplay of lung development, injury by pathogenic factors, and reparative processes results in the morphologic and functional lung alterations characteristic of BPD (Fig. 69.3).

Prenatal Factors

Prematurity is the most important risk factor for development of BPD. The prevalence of BPD is inversely related to gestational age and birth weight, strongly suggesting that incomplete development of the lungs plays a critical role in the pathogenesis of BPD.[30] Epidemiologic studies have identified male gender, white race, and maternal smoking and hypertension as risk factors associated with increased risk for BPD.[34,44] Intrauterine growth restriction is also associated with increased risk for BPD, likely secondary to impaired alveolar and vascular growth.[38,57] The role of maternal chorioamnionitis on the risk for BPD has been unclear, with multiple studies showing increased risk for BPD in infants born to mothers with evidence for chorioamnionitis; others, however, have failed to show such association.[24,67] The effect of chorioamnionitis on fetal lung varies from inflammation and lung injury to enhanced lung maturation depending on fetal inflammatory response, the organism causing the infection, and the severity or duration of infection.[29]

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• **Fig. 69.3** Algorithm for pathogenesis of bronchopulmonary dysplasia. IUGR, Intrauterine growth restriction. (Modified from Abman S, Bancalari E, Jobe A. *Am J Respir Crit Care Med.* 2017;195(4):421.)

Postnatal Factors

Mechanical Trauma

Although high-peak inspiratory pressure is one of the factors implicated as a cause of BPD, it is difficult to separate the role of the high pressures from the underlying lung disease on the chronic lung damage. The damaging effect of high airway pressure and tidal volume on the surfactant-deficient lung was demonstrated in preterm lambs. Lung compliance was decreased after only a few breaths, with excessive tidal volumes given before surfactant replacement.[8] Experimental evidence strongly suggests that excessive tidal volumes can damage the lung, initiate an inflammatory cascade, and interfere with normal lung development.[25] The effect of prolonged ventilation was shown in newborn mice where ventilation for 24 hours resulted in increased apoptosis, inhibition of alveolarization, and angiogenesis in the lung.[43]

Although injury from the mechanical ventilation continues to be an important factor in the pathogenesis of BPD, today most premature infants who require prolonged ventilation due to milder respiratory failure or poor respiratory effort receive lower airway pressures. Therefore, mechanical trauma appears to play a lesser role among the multiple factors acting concurrently on a premature lung to result in milder BPD.

Oxygen Toxicity

Clinical and experimental evidence suggested that pulmonary oxygen toxicity was a major factor in the pathogenesis of the severe original BPD. Although many tissues can be injured by high oxygen concentrations, the lung is exposed directly to the highest partial pressure of oxygen. The precise concentration of oxygen that is toxic to the immature lung probably depends on a large number of variables, including gestational age, nutritional and endocrine status, and duration of exposure to oxygen and other oxidants. Although a safe level of inspired oxygen has not been established, any concentration in excess of room air might increase the risk of lung damage when administered over a long period of time.

The pulmonary changes of oxygen toxicity are nonspecific and consist of atelectasis, edema, alveolar hemorrhage, inflammation, fibrin deposition, and thickening of alveolar membranes. There is early damage to capillary endothelium in animals, and plasma leaks into interstitial and alveolar spaces. Pulmonary surfactant can be inactivated by protein in the airspaces, adding to the risk of atelectasis. Type 1 alveolar lining cells can be injured early, and bronchiolar and tracheal ciliated cells can also be damaged by oxygen. Total resolution after oxygen toxicity is possible if the initial exposure is not overwhelming.

Continued exposure to high inspired oxygen levels is accompanied by influx of polymorphonuclear leukocytes containing proteolytic enzymes. In addition, the antiprotease defense system is significantly impaired in infants exposed to prolonged high inspired oxygen levels, favoring proteolytic damage of structural elements in alveolar walls. This could be an important pathogenic factor in oxygen toxicity and BPD. High inspired oxygen concentration can also inhibit the normal process of alveolar and capillary formation in immature animals.

Although the cellular basis for oxygen toxicity has not been completely elucidated, the principal mechanisms involve the univalent reduction of molecular oxygen and formation of free radical intermediates. The latter can react with intracellular constituents and membrane lipids, thus initiating chain reactions that can cause tissue destruction.

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To resist the detrimental effects of oxygen, the organism has evolved a number of antioxidant systems. Antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase seem to play an important role in preventing the toxic effects of oxygen. Other elements, such as vitamin E, glutathione, and selenium, are also part of the endogenous antioxidant mechanisms. The capacity for synthesizing these enzymes in some animal species follows a maturational trend similar to the production of surfactant; therefore, animals born prematurely have lower concentrations of antioxidant enzymes than those born at term.

Loss of mucociliary function may be an additional pathogenic factor in BPD, because exposure to high oxygen concentrations results in a reduction of ciliary movements.

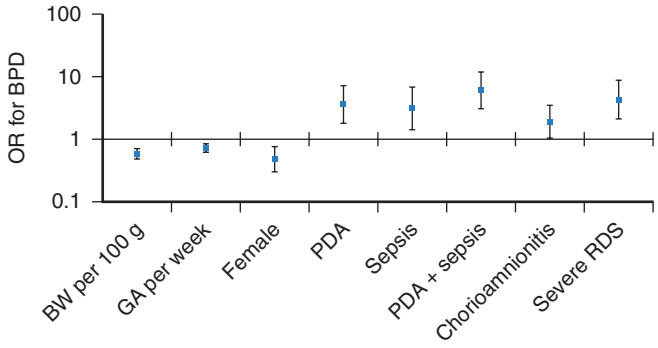
Postnatal Infection

There is ample evidence supporting the role of infections in the development of BPD, especially in very small infants in whom nosocomial infections are associated with a marked increase in the risk of BPD.[56] Evidence suggests that postnatal adenovirus and cytomegalovirus infection might also increase the risk for BPD.[31] Pulmonary colonization with ureaplasma has been evaluated as one of the possible risk factors for BPD. Experimental studies in animal models have shown that colonization of fetal lung with ureaplasma resulted in increased inflammation, fibrosis, and impaired alveolar development.[12,69] Several studies have suggested an association between *Ureaplasma urealyticum* tracheal colonization and the development of BPD in infants with very low birth weight. Surprisingly, trials evaluating treatment with macrolide antibiotics have so far shown inconsistent effect on BPD.[11,47,68]

Patent Ductus Arteriosus and Pulmonary Edema

There is an association between the presence of a PDA and an increased risk for BPD (Fig. 69.4).[23,56] This may be secondary to increased pulmonary blood flow producing an increase in interstitial fluid and a decrease in pulmonary compliance and increased airway resistance. This can prolong the need for mechanical ventilation with higher ventilatory pressures and oxygen concentrations, increasing the risk for BPD. Moreover, the increased pulmonary blood flow can damage the pulmonary capillary endothelium and induce neutrophil margination and activation in the lung, contributing to the progression of the inflammatory cascade. Data from studies in preterm baboons also showed decreased alveolarization in animals that remained for a longer time with an open ductus arteriosus, supporting the role of a persistent ductus arteriosus in the pathogenesis of BPD.[41] Despite epidemiologic and experimental evidence of association between PDA and BPD, prospective clinical trials to evaluate early closure of the PDA have failed to show a decrease in the incidence of BPD.[62]

Infants with BPD have a predisposition to fluid accumulation in their lungs. Possible causes are an increase in pulmonary vascular resistance, low plasma oncotic pressure, and increased capillary permeability that favor the extravascular accumulation of fluid. Pulmonary vascular pressure can be increased because of remodeling of the pulmonary vessels aggravated by hypoxemia and hypercapnia. Fluid accumulation can also be secondary to left ventricular dysfunction that has been described in patients with chronic respiratory failure. Capillary permeability might be increased secondary to the effects of high inspired oxygen concentration, mechanical trauma, increased flow caused by a PDA, and infection on the capillary endothelium. The abnormal accumulation of lung fluid in infants with BPD further compromises lung function, perpetuating a cycle in which more aggressive respiratory assistance is required, which produces further lung damage.



• **Fig. 69.4** Perinatal and postnatal risk factors for bronchopulmonary dysplasia (BPD) defined as 28 days' duration of oxygen dependency during hospitalization. Obtained by logistic regression analysis from all extremely premature infants born at University of Miami Jackson Memorial Medical Center during the period 1995-2000. (*N* = 505 alive at 28 days; birth weight [BW], 500-1000 g; gestational age [GA], 23-32 weeks). OR, Odds ratio; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome. (From Bancalari E, et al. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. *Semin Neonatol.* 2003;8:63.)

Other Factors

The possibility of a genetic predisposition to BPD has been evaluated in recent years. Studies evaluating twin pairs have shown that genetic factors contributed to a significant proportion of the variance in risk for BPD. The efforts to identify specific candidate genes using genome-wide association studies have so far not been successful.[35]

There is also evidence that vitamin A deficiency could increase the risk for BPD in preterm infants. Vitamin A levels are lower in infants who develop BPD when compared to those who recovered without lung sequelae. This possible association is supported by the similarities between some of the airway epithelial changes observed in severe BPD and vitamin A deficiency and by the clinical evidence that vitamin A administration during the weeks after birth reduces the risk of BPD.[14]

Early adrenal insufficiency has also been suggested as a contributing factor in the development of BPD in the smallest infants. Infants with lower cortisol levels in the first week of life have an increased incidence of PDA, more lung inflammation, and increased incidence of BPD.[72]

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Final Common Pathway

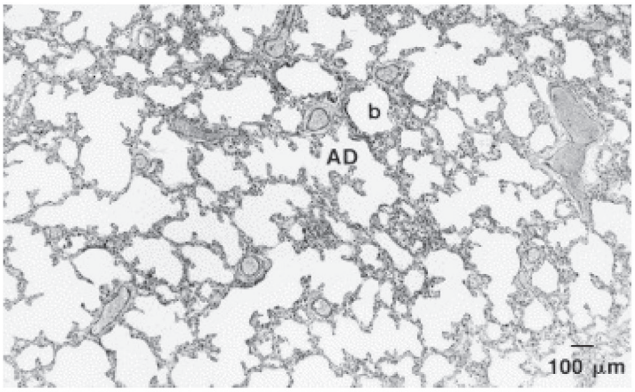
Inflammation plays a crucial role in the development of BPD and can be triggered by multiple factors such as oxygen, mechanical ventilation, PDA, and infections. Multiple studies have shown the presence of inflammatory cells, pro-inflammatory cytokines such as chemokines, interleukin, leukotrienes, and platelet-activating factor and other mediators in infants with BPD. Increased desmosine excretion in the urine during the first week of life has been described in infants who subsequently develop BPD, indicating increased elastin degradation resulting from lung inflammation and injury. Increased concentration of inflammatory mediators could contribute to the bronchoconstriction and vasoconstriction and the increased vascular permeability characteristic of these infants.

The inflammatory reaction might also be responsible for the decreased alveolar and capillary formation characteristic of infants with BPD.[30,74] This is a key component in the pathogenesis of BPD and results in a reduction in alveolar number and gas exchange surface area, as well as a decrease in lung capillaries. In experimental models of BPD, these findings have been accompanied by decrease in lung angiogenic growth factors, such as vascular endothelial growth factor and nitric oxide, and decreased expression of endothelial markers, such as platelet/endothelial cell adhesion molecule-1 suggesting impaired angiogenesis. In addition, reduced expression or impaired function of other growth factors associated with lung development, including connective tissue growth factor, fibroblast growth factor, and platelet-derived growth factor have been associated with BPD.[1,54]

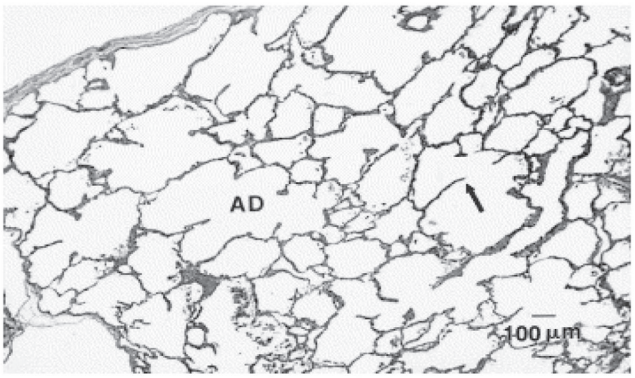
Pathology

The pathologic picture of BPD has evolved significantly over the last few decades. Most of the infants with BPD nowadays are extremely premature and have milder forms of BPD. These infants have diffuse injury with little emphysema or fibrosis. The characteristic morphologic changes in lungs with mild BPD are reduced number and simplified alveoli, decreased and dysmorphic capillaries, and a reduction in the gas exchange surface area (Figs. 69.5 and 69.6).[10,26]

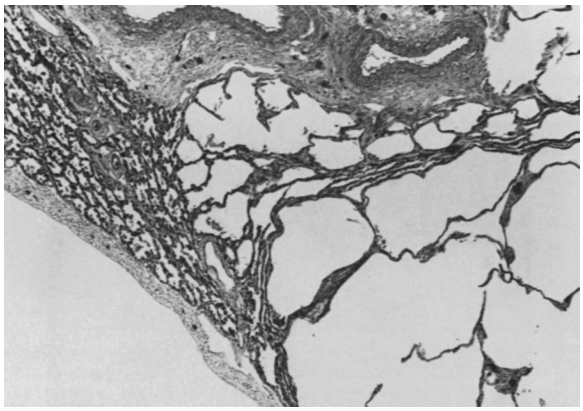
A small number of these infants still go on to require prolonged mechanical ventilation and high oxygen and end up with severe BPD. Macroscopically, the lungs of these infants are firm and heavy and have a darker color than normal. The surface is irregular, often showing emphysematous areas alternating with areas of collapse. On histologic examination, the lungs are characterized by areas of emphysema, sometimes coalescing into larger cystic areas, surrounded by areas of atelectasis, interstitial edema and increase in fibrous tissue, and widespread bronchial and bronchiolar mucosal hyperplasia and metaplasia (Fig. 69.7). Often, there are vascular changes of pulmonary hypertension, such as medial muscle hypertrophy and elastic degeneration. There also



• **Fig. 69.5** Lung tissue section (autopsy) from a term + 5 months child. This specimen shows numerous secondary crests and alveolar structures within the airspaces and alveolar ducts (*AD*), yielding a pattern of increased acinar complexity. b, bronchiole. (From Coalson JJ. Pathology of new bronchopulmonary dysplasia. *Semin Neonatol.* 2003; 8(1):73-81.)

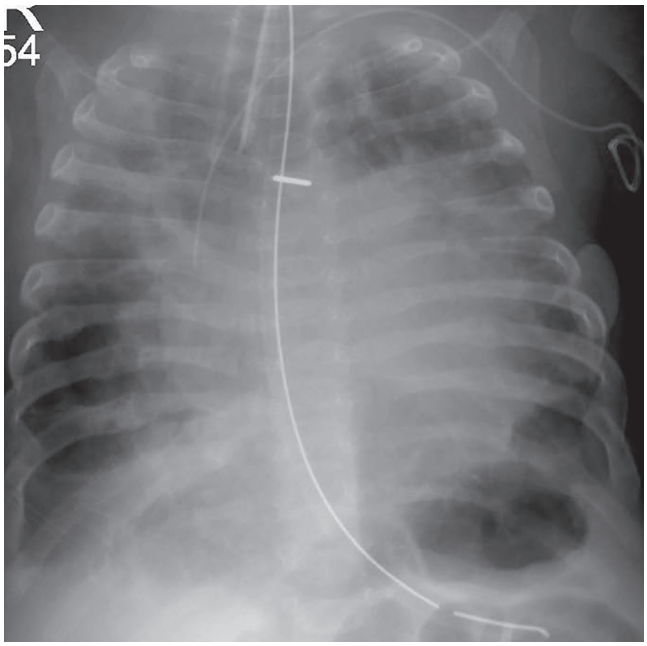


• **Fig. 69.6** Lung tissue section (biopsy) from an infant with new BPD showing enlarged airspaces including alveolar ducts (*AD*) and scattered alveolar structures (*arrow*) lacking additional branching, resulting in acinar simplification. (From Coalson JJ. Pathology of new bronchopulmonary dysplasia. *Semin Neonatol.* 2003;8(1):73-81.)

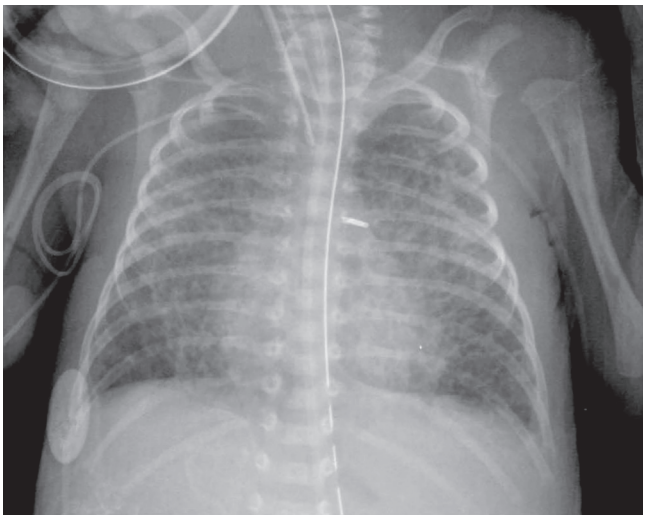


• **Fig. 69.7** Low-magnification view showing areas of emphysema alternating with areas of partial collapse. (From Bancalari E, et al. Barotrauma to the lung. In Milunsky A, et al., eds. *Advances in perinatal medicine.* New York: Plenum; 1982:181, with permission of Springer Science and Business Media.)

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• **Fig. 69.8** Chest radiograph shows areas of hyperinflation and emphysema with adjacent dense areas of atelectasis. This picture is characteristic of old BPD.



• **Fig. 69.9** Chest radiograph from an infant with new BPD showing generalized homogenous opacities with an interstitial pattern.

may be evidence of right ventricular hypertrophy and, in some cases, left ventricular hypertrophy as well.

Clinical Presentation

In their original description of BPD, also often called *old BPD*, Northway and colleagues described the clinical, radiographic, and pathologic course of a group of infants with severe respiratory distress syndrome (RDS) requiring mechanical ventilation with high airway pressures and oxygen concentration. The respiratory course of these infants evolved from the initial severe RDS to final stage of chronic lung disease with high incidence of cor pulmonale and mortality. The radiographic picture of these infants with severe chronic lung disease was characterized by increased densities secondary to areas of collapse and fibrosis, with adjacent large emphysematous areas (Fig. 69.8).

The clinical picture of BPD has evolved significantly in the last few decades due to increasing survival of extremely premature infants and improvements in the care of these infants. The majority of these infants initially have mild respiratory disease requiring continuous positive airway pressure or ventilation with low pressures and oxygen concentration. During the subsequent days or weeks, a large proportion of these infants show progressive deterioration in lung function possibly triggered by pulmonary or systemic infections or increased pulmonary blood flow secondary to left to right shunting through a large PDA.[23] In these cases, the functional and radiographic changes are usually milder, revealing more diffuse haziness without the marked changes observed in the severe forms of BPD (Fig. 69.9). This entity has been termed *new BPD*.[30] Most of these infants show a slow but steady improvement in their lung function and radiographic changes and, after variable periods, can be weaned from respiratory support and supplemental oxygen prior to discharge.

A small group of preterm infants have atypical respiratory course with inadequate response to surfactant and continued severe respiratory failure requiring mechanical ventilation with high airway pressures and oxygen concentration. Their respiratory course is often complicated by pulmonary air leaks, secondary pulmonary infections, and recurrent pulmonary edema likely due to PDA or inflammation, progressing to severe BPD. The radiographic picture of these infants commonly resembles that of old BPD. These infants commonly develop pulmonary hypertension and signs of right heart failure. In these infants, severe airway damage with bronchomalacia can lead to severe airway obstruction, especially during episodes of agitation and increased intrathoracic pressure.[40] Furthermore, anastomoses between the systemic and pulmonary circulations can aggravate their pulmonary hypertension.

Because of the respiratory failure, infants with BPD take oral feedings with difficulty and often require nasogastric or orogastric feeding. Weight gain is usually less than the expected normal even when they receive an amount of calories appropriate for their age. This lower weight gain can be a result of chronic hypoxia and the higher energy expenditure required by the increased work of breathing.

The diagnosis of BPD is based on the clinical and radiographic course described earlier, but these signs are not specific for any given etiology. For this reason, specific etiologies that could lead or contribute to the lung damage must be considered before concluding that the infant has BPD. Among these, one must rule out congenital heart disease, congenital pulmonary anomalies, chemical pneumonitis resulting from recurrent aspiration, cystic fibrosis, or disorders of surfactant homeostasis.

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Prediction of Bronchopulmonary Dysplasia

A number of studies have been performed to develop scores that can predict the risk for BPD in ventilated preterm infants. Most of these scores include the state of maturation of the infant and factors that reflect the severity of the initial respiratory failure. These scores are helpful in identifying patients for clinical trials and could become more useful in the future if effective preventive therapies become available.

Pulmonary Function

The disruption of pulmonary function in BPD reflects the structural alterations of the lungs with degree of pulmonary function abnormalities varying depending on age and the severity of lung injury. The early clinical course of infants who later develop severe BPD is marked by low compliance, low to normal functional residual capacity (FRC), and high airway resistance. These alterations in pulmonary function during the first weeks of life have been used with some success to improve accuracy of BPD prediction models.[39]

In infants with severe BPD, FRC increases to above normal range with age reflecting gas trapping secondary to small airway obstruction.[28] These infants have abnormal distribution of ventilation, reflecting involvement of the small airways, but in infants with milder forms of BPD, the distribution of the inspired gas is usually normal as measured by nitrogen clearance delay.

Infants with severe BPD characteristically have increased airway resistance and airway hyperreactivity. Multiple factors contribute to airway changes, including bronchiolar epithelial hyperplasia and metaplasia, mucosal edema secondary to trauma, oxygen toxicity, pulmonary edema secondary to PDA, and infection. These infants can also have bronchoconstriction resulting from smooth muscle hypertrophy. In some infants, tracheobronchomalacia develops, which is responsible for marked airway obstruction, especially during periods of agitation and increased intrathoracic pressure. Increased airway resistance can alter the time constant of different regions of the lung and impair the distribution of the inspired gas, favoring uneven lung expansion.

The lung compliance in BPD is decreased because of fibrosis, edema, overdistention, and collapse of lung parenchyma. It is also possible that some of these infants have a decreased concentration or inactivation of surfactant on the alveolar surface. In addition, the airway obstruction results in frequency dependence of dynamic compliance, thereby compliance decreases at higher respiratory rates.

The high resistance and decreased compliance result in a markedly increased work of breathing that contributes to the hypoventilation and hypercapnia frequently observed in these infants. Minute ventilation is usually increased, but because of the lower lung compliance, this is accomplished with a smaller tidal volume and a higher respiratory rate than normal. Thus, there is an increase in dead space ventilation that also contributes to alveolar hypoventilation and CO_2 retention. The increased $PaCO_2$ is also secondary to an increased alveolar-arterial CO_2 gradient produced by ventilation-perfusion mismatch and increased alveolar dead space. Chronic hypercapnia often results in an increased serum bicarbonate concentration that tends to compensate for the respiratory acidosis. This increase in base is often exaggerated by the use of loop diuretics.

Most infants with severe BPD have hypoxemia and require supplemental oxygen to maintain acceptable oxygenation levels. The hypoxemia results from a combination of ventilation-perfusion mismatch and alveolar hypoventilation. The oxygen requirement decreases gradually as the disease process improves, but it can increase during feedings, physical activity, or episodes of pulmonary infection or edema.

Prevention of BPD

There is a wide variation in the incidence of BPD among different centers, suggesting that certain steps in the management of preterm infants can influence the risk of BPD.[36] Since BPD is a multifactorial disease, effective prevention requires a combination of strategies to limit lung and vascular injury and promote normal development (Table 69.2).

Since BPD is exclusively seen in preterm infants, any strategy that can prolong pregnancy will reduce the incidence of BPD. Attempts to develop these strategies have not been very successful, but recent studies to evaluate use of progesterone prophylaxis in pregnant women at risk of preterm delivery have shown some effectiveness in reducing the incidence of preterm birth. Administration of antenatal steroids to promote maturation of surfactant system has been shown to reduce the incidence and severity of RDS, but the effect on the incidence of BPD has been less consistent partly due to improved survival of infants at increased risk for BPD.[9]

There is significant evidence from animal studies suggesting that injudicious use of respiratory support at birth, even for short duration, may result in lung injury[25]; therefore, the effort should be directed to reduce the infant's exposure to high airway pressures, tidal volumes, and oxygen, as much as possible. Surfactant replacement therapy after endotracheal intubation has been shown to decrease mortality, incidence of severe RDS, and the need for aggressive ventilation but has failed to show reduction in the incidence of BPD. To decrease the risk of lung injury associated with positive pressure ventilation during surfactant replacement, multiple less-invasive methods of surfactant instillation like nebulization or less-invasive surfactant administration (LISA) are currently being evaluated, showing some reduction in the incidence of BPD.[27]

Although the use of early CPAP to reduce the use of mechanical ventilation has been shown to have a small effect on reducing the incidence of death or BPD,[22] a large proportion of the more premature infants fail CPAP and require invasive ventilation. Nasal positive pressure ventilation (NIPPV) has been evaluated as an alternative mode of

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TABLE 69.2 Strategies for Prevention of BPD

Strategies From Randomized Clinical Trials/Meta Analyses	
Vitamin A[14]	RR: 0.87 (CI 0.77-0.99)**
Noninvasive respiratory support[22]	OR: 0.83 (CI 0.71-0.96)**#
Lower oxygen target[2]	RR: 0.87 (CI 0.81-0.94)**ᵗ
High-frequency oscillatory ventilation[13]	RR: 0.86 (CI 0.78-0.96)**
Postnatal dexamethasone	
Early[16]	RR 0.79 (CI 0.71-0.88)**
Late[17]	RR 0.76 (CI 0.66-0.88)**
Postnatal hydrocortisone[6]	OR: 1·48 (1·02 to 2·16)*##
Postnatal surfactant + budesonide[76]	RR: 0.58 (0.44-0.77)*#
Strategies With Inconclusive Evidence	
Antenatal steroids	
Exogenous surfactant	
Caffeine for apnea or extubation[€]	
Volume-targeted ventilation[€]	
Inhaled nitric oxide	
Early PDA closure	
Stem cell treatment	

BPD, Bronchopulmonary dysplasia; OR, Odds ratio; PDA, patent ductus arteriosus; RR, risk ratio.
*Randomized controlled trial
**Meta-analysis
#BPD or death
##Survival without BPD
ᵗBPD: oxygen at 36 weeks
€Lacking data from trials with BPD as primary outcome

noninvasive ventilation to avoid endotracheal intubation. The effect of NIPPV on the incidence of BPD has been inconsistent among trials with recent large RCTs failing to show a reduction in the incidence of BPD with its use.[32,51] High-flow nasal cannula (HFNC) is another mode of noninvasive respiratory support that has been evaluated because of its ease of use and less risk of injury to nares when compared to CPAP. There is increasing evidence that the HFNC is inferior to CPAP as primary mode of respiratory support after birth with increased risk of treatment failure and a trend toward increased incidence of BPD.[55,73] These data suggest the type of respiratory support for each infant should be individualized, with close monitoring of the respiratory status over time.

Since a large number of preterm infants require invasive mechanical ventilation, it is crucial to limit the exposure to excessive tidal volume. The use of volume-targeted ventilation has been shown to reduce the duration of mechanical ventilation and the combined outcome of death or BPD.[33] Although there is some data suggesting that high-frequency ventilation can reduce lung injury, it has not been shown to be consistently effective in reducing the incidence of BPD.[13]

Oxygen is one of the important factors in the pathogenesis of BPD, and continuous monitoring of arterial oxygen saturation by pulse oximetry (SpO_2) is a standard practice to titrate oxygen supplementation. To find the optimum target SpO_2 range, three large trials in extremely preterm neonates have compared the effect of lower (85%-89%) and higher (91%-95%) target SpO_2 range on mortality and neonatal morbidities. A recent meta-analysis of these trials showed a significant reduction in the incidence of BPD in the lower target group. However, the lower target was associated with a higher incidence of necrotizing enterocolitis (NEC) and mortality, suggesting a need to strike a critical balance when targeting SpO_2.[2]

Presently, there is no agreement among clinicians regarding the role of different PDA management strategies in the development of BPD. Although some epidemiologic data suggest that the persistence of a hemodynamically significant PDA is associated with an increased incidence of BPD,[37] the results of prospective clinical trials to evaluate whether early closure of the PDA would improve pulmonary outcome have not confirmed this hypothesis.[62] Postnatal growth failure is common in infants at high risk for BPD, and undernutrition has been associated with impaired lung growth in animal models. Despite paucity of clinical evidence, a nutritional strategy consisting of judicious fluid restriction while providing adequate macro and micronutrients and preventing growth failure is recommended. There is some evidence that exclusive breast-milk feeding is associated with lower incidence of BPD.[63]

Administration of postnatal systemic corticosteroids during the early stages of the respiratory failure to prevent its progression to BPD has been well studied, with several reports showing rapid improvement in lung function, facilitating weaning from the ventilator and decreasing the risk of BPD.[16,17] Many potential mechanisms for these beneficial effects include enhanced production of surfactant and antioxidant enzymes, decreased bronchospasm, decreased pulmonary and bronchial edema and fibrosis, improved vitamin A status, and decreased responses of inflammatory cells and mediators in the injured lung. Potential complications of prolonged steroid therapy include masking signs of infection, arterial hypertension, hyperglycemia, increased proteolysis, adrenocortical suppression, somatic and lung growth suppression, and hypertrophic cardiomyopathy. In addition, long-term follow-up studies suggest that infants who received early high-dose postnatal dexamethasone therapy have worse neurologic outcome than control infants.[75]

It appears that treatment with shorter courses and lower doses beyond the first week of life offers significant advantage and fewer side effects than the previous more aggressive treatment strategy, confirming the potential role of low-dose dexamethasone therapy specifically for infants at high risk for BPD.[19] Furthermore, a meta-regression analysis reported a significant effect modification by risk for BPD. With a risk

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for BPD less than 35%, corticosteroid treatment increased the chance of death or cerebral palsy, whereas when the risk for BPD exceeded 65%, corticosteroid treatment reduced this risk.[18] Although the avoidance of steroids may in fact be detrimental to a class of infants at high risk for BPD, the optimal age of treatment, dose schedule, and duration of therapy still needs to be established.[52]

In an attempt to avoid the potential neurotoxic effect of dexamethasone, systemic hydrocortisone treatment has been evaluated as an alternative for prevention of BPD due to lower neurotoxic effects.[21] Earlier trials evaluating the use of hydrocortisone soon after birth in extremely preterm infants showed improvement in respiratory outcomes but with increased risk of gastrointestinal perforation. There is some recent evidence suggesting that a lower dose may improve respiratory outcomes without increasing the risk of gastrointestinal perforation or neurodevelopmental impairment in early childhood.[6,7] Most recent available data demonstrate that among mechanically ventilated very preterm infants, administration of a 22-day course of systemic hydrocortisone between 7 and 14 days after birth, compared with placebo, did not improve the composite outcome of death or BPD at 36 weeks' postmenstrual age. These findings do not support the use of hydrocortisone for this indication.[52a] To induce the beneficial effects on the lung but minimize the systemic side effects, steroids have been administered locally either alone by nebulization or by direct tracheal instillation with exogenous surfactant. Both of these therapies have been recently shown to significantly reduce the incidence of BPD, but concerns for long-term safety and neurodevelopmental effect need to be evaluated in large trials.[5,76]

The administration of caffeine to wean infants from mechanical ventilation and to treat apnea of prematurity has been associated with a significant reduction in the incidence of BPD.[58] Some of the possible mechanisms of this beneficial effect are shorter duration of mechanical ventilation and the anti-inflammatory or diuretic effects of caffeine. Vitamin A supplementation has been shown to result in small reduction in the incidence of BPD, likely because of its role in lung development and repair of respiratory epithelium after injury.[14]

Since endogenous nitric oxide is required for alveolar and vascular development, and the low-dose inhaled nitric oxide supplementation in animal models of BPD inhibits inflammation and reduces lung injury,[66] clinical trials have evaluated low-dose inhaled nitric oxide supplementation for the prevention of BPD. These studies have provided inconsistent results with a systematic review showing no significant effect of inhaled nitric oxide on BPD.[15]

Increasing knowledge of molecular pathways of alveolar and vascular development has resulted in the development of innovative strategies for prevention of BPD. Mesenchymal stem cells are among the most promising of these, with multiple reports of their effectiveness in prevention as well as treatment of hyperoxia-induced lung injury in animal models.[42,65] The results from a preliminary phase-1 clinical study have been promising, but additional work is needed to better understand its mechanism of action, safety and efficacy in preterm infants. Some of the other promising therapies currently being evaluated for the prevention of BPD include Clara cell protein (CC10), a protein secreted by nonciliated respiratory epithelial cells with anti-inflammatory and immunomodulatory properties, and growth factors involved in alveolar and vascular development such as insulin like growth factor (IGF-1).

Management of Established BPD

Prevention of further lung damage is the cornerstone of management by avoiding, as much as possible, all factors that predispose to more injury. There is a lack of good quality evidence base for managing infants with BPD, resulting in significant variation in treatment practices.

Respiratory Support

During the initial phase of respiratory failure, the goal is to avoid unnecessary intubation and mechanical ventilation-associated lung injury. When mechanical ventilation is used, the lowest peak airway pressure necessary to obtain adequate ventilation must be applied. The expiratory tidal volume (Vt) measured using a flow sensor at the endotracheal tube (proximal flow sensor) should be closely monitored with avoidance of excessively low (Vt <3 mL/kg) or excessively high tidal volumes (Vt >7 mL/kg) during acute phase of illness. Short inspiratory times between 0.3-0.5 seconds are used, as shorter inspiratory times exaggerate the maldistribution of the inspired gas while longer inspiratory times may increase the risk of airspace rupture and cardiovascular side effects. An end-expiratory pressure between 4 and 8 cm H_2O is usually applied to achieve lung recruitment without causing overdistension.

Adequacy of gas exchange should be monitored closely to avoid large fluctuation in ventilation and oxygenation status. The arterial oxygen tension (PaO_2) and arterial carbon dioxide tension ($PaCO_2$) measured in arterial blood are considered the reference standards, but the results from the samples obtained by arterial puncture should be interpreted carefully, because the infant responds to pain with crying or apnea. Pulse oximeters offer the most reliable estimate of arterial oxygenation and have the advantage of simplicity of use and the possibility of assessing oxygenation during feeding and crying. Although there are no conclusive data in the literature on the optimal level of oxygenation for these infants, in general, it is recommended to maintain the oxygen saturation in the range of 90%-95% to minimize the risk of oxygen exposure and toxicity and prevent hypoxemia with associated risk of morbidities.[2] The ideal range of $PaCO_2$ for infants with BPD is not established, but avoidance of values higher than 55 and less than 35 mm Hg during the initial period after birth is warranted to limit changes in cerebral perfusion.

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Weaning these patients from the ventilator is often difficult and must be accomplished gradually. When the patient can maintain an acceptable SpO_2 and $PaCO_2$ with low peak pressures (15-18 cm H_2O) and FiO_2 lower than 0.3-0.4, the ventilator rate is gradually reduced to allow the infant to perform an increasing proportion of the respiratory work. During the process of weaning, it may be necessary to increase the FiO_2. Concurrently, the $PaCO_2$ can rise, but as long as the pH is within acceptable limits, some degree of hypercapnia must be tolerated to wean the patient from the ventilator. In small infants, caffeine is used as a respiratory stimulant during the weaning phase.[58] The use of nasal continuous positive airway pressure (CPAP) or nasal ventilation (NIPPV) after extubation can stabilize respiratory function and reduce the need to reinstitute mechanical ventilation.

Infants with chronic respiratory failure commonly have increased dead space, heterogeneous areas of different lung compliance, and airway resistance necessitating longer inspiratory times and higher tidal volumes than those used during early stages of illness. In some of the infants with severe airway obstruction, especially those with bronchomalacia, the use of high positive end-expiratory pressure levels of 5-8 cm H_2O may help reduce expiratory airway resistance and improve alveolar ventilation.

Although it is necessary to reduce the FiO_2 as quickly as possible to prevent oxygen toxicity, it is important to maintain the SpO_2 above 90% to ensure adequate tissue oxygenation and prevent the pulmonary hypertension and cor pulmonale that can result from chronic hypoxemia. Furthermore, infants with BPD might respond to episodes of acute hypoxemia with increased airway and vascular resistance. Because oxygen consumption increases and PaO_2 may decrease during feedings, it might be necessary to provide a higher FiO_2 to prevent hypoxemia. Oxygen therapy could be required for several weeks or months. Some of these patients are discharged with oxygen therapy at home. This practice offers significant advantages, such as a better environment for the patient and cost savings, but it requires a supportive family and home environment to be accomplished safely and successfully.

Bronchodilator Therapy

Infants with severe BPD can have airway smooth muscle hypertrophy and airway hyperreactivity. Because hypoxia can increase airway resistance in these patients, maintenance of adequate oxygenation is important to avoid bronchoconstriction. Bronchodilators, most of them β-agonists, administered by inhalation have been shown to reduce airway resistance in infants with BPD. However, their safety and efficacy have not been evaluated in randomized clinical trials. Their effect is usually short lived, and many of these drugs have cardiovascular side effects such as tachycardia, hypertension, and possible arrhythmias. Because of this, it is preferred to limit their use to the management of acute exacerbations of airway obstruction.

Corticosteroid Therapy

Systemic or inhaled steroids are commonly used in infants with BPD, both as short-term therapy for acute exacerbation as well as chronic therapy. The potential short-term benefits include decrease in inflammation, airway edema, capillary leakage, and lung fibrosis. The effects of steroids in infants with established BPD on long-term respiratory outcomes have not been evaluated. As described previously, chronic use of steroids is associated with significant side effects; therefore, their use should be limited with clearly defined goals after due consideration of risks and benefits of this therapy.

Management of Pulmonary Hypertension in BPD

The clinical course of infants with severe BPD is frequently complicated by pulmonary hypertension,[46] thereby necessitating the need for close monitoring and early diagnosis by echocardiogram. Oxygen therapy to prevent hypoxemia is probably the most important first step to reduce pulmonary hypertension in these infants. Because pulmonary vascular resistance is extremely sensitive to changes in alveolar Po_2 in infants with BPD, it is important to ensure normal oxygenation, not only when the infant is quiet or asleep but also when the infant is performing physical activity such as feeding and crying.

Despite increasing use of pulmonary vasodilators, the evidence for their efficacy in infants with pulmonary hypertension with BPD is very limited. These therapies include inhaled nitric oxide (iNO), phosphodiesterase inhibitors (sildenafil), endothelin receptor antagonists, and calcium channel blockers (nifedipine). Inhaled nitric oxide is commonly used as a pulmonary vasodilator in acute onset pulmonary hypertension and has been shown to decrease pulmonary vascular resistance, although its effect on long-term outcomes has not been evaluated. The potential role of iNO in the prevention of BPD has been evaluated in multiple trials with no clear long-term benefits so far. Sildenafil, a phosphodiesterase-5 inhibitor, is mostly used as long-term therapy for pulmonary hypertension in infants with BPD. There are limited data on safety or effectiveness of this drug in this population, but some clinical reports suggest that the therapy is safe and may be effective.[45] Nifedipine, a calcium channel blocker, decreases pulmonary vascular resistance but is also a systemic vasodilator and can produce depression of myocardial contractility. Other agents like endothelin receptor antagonists and prostacyclin analogs have been tried in infants who fail to respond to initial treatment, but their efficacy and safety have not been established.

Fluid Management

Infants with BPD do not tolerate excessive or even normal amounts of fluid intake and have a marked tendency to accumulate excessive interstitial fluid in the lung. This

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excess can lead to a deterioration of pulmonary function, with exaggeration of hypoxemia and hypercapnia and longer ventilator dependency.

To reduce lung fluid in infants with BPD, water and salt intake should be limited to provide the calories necessary for metabolic needs and growth. When increased lung water persists despite fluid restriction, diuretic therapy can be used successfully. The use of diuretics in infants with BPD can be associated with an acute improvement in lung compliance and decrease in resistance, but blood gases do not always show improvement. Complications of chronic diuretic therapy include potential ototoxicity, hypokalemia, hyponatremia, metabolic alkalosis, hypercalciuria with nephrocalcinosis, and hypochloremia.

Because increased metabolic demands in infants with BPD are associated in severe cases with low arterial oxygen tension, it is important to maintain a relatively normal blood hemoglobin concentration. This may be accomplished with blood transfusions or by the administration of recombinant erythropoietin.

Nutrition

Infants with BPD frequently have impaired growth due to increased metabolic demand partially caused by increased work of breathing, growth suppression from frequent postnatal steroid and diuretic use, and frequent interruptions in oral feedings due to exacerbation of respiratory failure. Malnutrition can delay somatic growth and the development of new alveoli, making successful weaning from mechanical ventilation less likely. The malnourished patient may also be more prone to infection and oxygen toxicity. Decreased caloric intake potentiates oxygen-induced lung damage and can interfere with cell multiplication and lung growth. For these reasons, an aggressive approach should be taken toward supplying a parenteral or oral caloric intake that is adequate for growth. High-calorie formulas and supplements of protein, calcium, phosphorus, and zinc can be used to maximize the intake of calories while restricting fluid intake to prevent congestive heart failure and pulmonary edema.

Adequacy of nutrition should be closely monitored, and growth charts for weight, head circumference, and length must be kept. Rib fractures noted on routine chest radiographs, together with generalized bone demineralization, are often observed in infants with BPD and are usually a manifestation of rickets. The cause could relate to dietary or parenteral deficiency of calcium or vitamin D or to the calciuria resulting from long-term diuretic therapy. Administration of extra calcium and vitamin D is necessary to prevent rickets in these infants.

Infants who receive exclusively parenteral nutrition for prolonged periods are more susceptible to developing deficiency of specific nutrients, such as vitamins A and E, and trace elements such as iron, copper, zinc, and selenium, all of which play a role in antioxidant function, protection against infection, and lung repair.

Gastroesophageal reflux is often observed in infants with BPD, and when severe, may contribute to the chronic inflammatory process and lung damage. When severe reflux is documented, antireflux management might be indicated to alleviate respiratory symptoms.

Control of Infection

Any infection can have serious consequences for the child with BPD, and bacterial, viral, or fungal infection generally results in a profound setback. As a result, the child must be closely watched for early evidence of infection. Tracheal secretions are collected for culture and Gram stain, and a change in the quality and quantity of secretions indicates possible infection. A complete blood count, blood culture, and chest radiograph are obtained if pneumonia is suspected.

Although it is difficult to distinguish between colonization of the airway and true infection, this distinction is important because overtreatment with antibiotics can result in the emergence of resistant and more virulent organisms. Selection of antibiotics is based on the sensitivity of the implicated organism, and treatment is continued until the infection has been controlled. Measures to prevent pulmonary nosocomial infection are important. These include careful hand washing before handling the airway, maintenance of sterility of the respiratory equipment, and isolation from individuals with respiratory infections.

Infant Stimulation

The infant with severe BPD could be ventilator dependent for many months and thus deprived of normal parental stimulation. Developmental delays are common and are compounded if any gross neurologic disability exists. A well-organized program of infant stimulation can help the infant achieve maximum potential. Such a program instructs the caretakers in helping the infant with various social, language, cognitive, and motor skills. As a child grows, speech therapy is useful in teaching communication skills, which are especially important for children with a tracheostomy. Beanbag chairs, strollers, and other adaptive tools are employed to mobilize the child and teach gross motor skills. Progress is monitored by periodic developmental evaluations, and emphasis is placed on areas in which delay is evident.

Parental Support

The parents of an infant with severe BPD lose considerable control of their child to the hospital staff, particularly in areas related to medical care. Parental participation is critical for the child's development and for establishment of normal relationships. Therefore, parents are encouraged to visit as frequently as possible and to participate in the day-to-day care of their child. They are educated about relevant medical equipment and procedures. In time, many are able

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to assume complete responsibility for procedures such as chest physiotherapy and tracheal suctioning, in addition to holding and playing with their child. During the prolonged hospitalization, every effort must be made to assign a permanent physician and nursing team to oversee the child's care and be available for continuing parental support. Parental support groups may also be a valuable resource for these families.

Outcome

The outcome of infants with BPD has improved in part because of better management but mainly because of the milder presentation of the disease. The mortality rate for infants with BPD is low. When death occurs, it is usually a result of respiratory failure, intercurrent infections, or intractable pulmonary hypertension and cor pulmonale. With adequate nutrition, somatic growth, and control of infection and heart failure, gradual improvement in pulmonary function may be accompanied by resolution of cor pulmonale and radiographic evidence of healing.

Lower respiratory tract infections are common during childhood in patients with BPD. Among survivors of BPD, hospitalizations for episodes of wheezing suggestive of bronchiolitis or asthma are common during the first 2 years of life, and infection with respiratory syncytial virus (RSV) can be life threatening. The American Academy of Pediatrics has recommended that all infants with BPD receive palivizumab during RSV season. Acute radiographic evidence of hyperinflation can be difficult to appreciate in infants with severe BPD who generally are already in a state of pulmonary hyperinflation. Such episodes of bronchiolitis are often accompanied by focal, transient areas of atelectasis.

Pulmonary function studies of children with a history of severe BPD indicate that pulmonary function may be impaired for many years even though the infants may be asymptomatic.[20,70] Northway and associates have reevaluated pulmonary function in their original cohort of infants with severe BPD reported in 1967.[50] At a mean age of 18 years, these adolescents and young adults still exhibited some evidence of pulmonary dysfunction, including airway obstruction and hyper-activity as well as hyperinflation. Infants and toddlers with severe BPD also have decreased pulmonary diffusing capacity consistent with decreased alveolar capillary surface area.[3] The ultimate clinical consequences of these findings remain to be determined, but most long-term studies suggest that with growth, pulmonary function tends to improve. In a study using 3He magnetic resonance, it was found that infants with BPD evaluated at 10-14 years of age had similar alveolar dimensions as term controls or preterm infants without BPD.[48] These interesting findings suggest that infants with BPD can have catch-up alveolarization.

Infants with severe BPD also have more neurodevelopmental sequelae when compared with similar control groups, and they exhibit transiently impaired growth curves. These neurodevelopmental and pulmonary impairments persist at 8 years of age, with 54% requiring special education classes compared with 37% of survivors born at very low birth weight without BPD.[60] Neurodevelopmental prognosis also depends on the severity of the BPD and on other associated risk factors that could be present in these infants.

Key Points

- Since its first description half a century ago, bronchopulmonary dysplasia continues to be the most important respiratory complication of preterm birth.
- Advancements in obstetric and neonatal care over time have altered the patient population at risk, thereby modifying the pathogenic factors and clinical course of BPD.
- The new BPD is the end result of a complex interplay of altered alveolar and vascular development, injury, and reparative processes in a premature lung.
- With increasing knowledge of the pathophysiology of BPD, the role of many of the proposed prevention strategies, such as different respiratory support modalities, PDA management, or postnatal steroids, is being reevaluated. New promising prevention strategies such as stem cells are being investigated.
- Management of infants with BPD requires a multidisciplinary approach to optimize lung and other organ development.
- Future prevention and management of BPD is likely to involve therapeutic agents tailored to different BPD genotypes and phenotypes and acting at different stages of disease process.

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70

Therapy for Cardiorespiratory Failure in the Neonate

EILEEN K. STORK

Assisted ventilation and oxygen therapy remain the standard of care for neonatal respiratory failure. A few term and late preterm infants with a wide range of diagnoses develop intractable cardiorespiratory failure despite maximal ventilatory support. In these patients, severe pulmonary hypertension often contributes to persistent hypoxemia.

Two unique therapies for such patients are presented in this section: extracorporeal membrane oxygenation (ECMO), which is now well established as a rescue therapy for intractable respiratory failure in term and late-preterm neonates, and inhaled nitric oxide (iNO), a noninvasive inhalational therapy that can elicit selective pulmonary vasodilation.

Extracorporeal Membrane Oxygenation

In ECMO, techniques of cardiopulmonary bypass, modified from those originally developed for open heart surgery, are used over a prolonged period to support heart and lung function. In newborns with hypoxic respiratory failure, this allows the lungs to rest and recover and prevents the often damaging effects of aggressive mechanical ventilation and 100% Fio_2.

The use of ECMO offers support for mature neonates with life-threatening cardiopulmonary disease. Because of serious inherent risks, such as systemic and intracranial hemorrhage, the procedure is currently reserved for neonates with reversible pulmonary disease in whom trials of conventional or high-frequency ventilation as well as inhaled nitric oxide have failed (see next section on inhaled NO).

Several randomized trials have demonstrated improved survival in infants supported with ECMO. The most rigorous prospective, randomized trial was conducted in the United Kingdom, where 185 infants with severe respiratory failure were randomized to ECMO or conventional ventilatory management.[30] Survival in the ECMO-treated patients was 68% compared to 41% survival in the control arm ($p = .0005$), equivalent to one extra survivor for every three or four infants allocated to ECMO. Neurologic outcome was similar among survivors of either treatment arm, making it unlikely that ECMO contributed any added morbidity to this cohort of critically ill newborns.

Respiratory disease in the newborn is often complicated by persistent pulmonary hypertension of the neonate (PPHN), previously called persistent fetal circulation. In this circumstance, the pulmonary vascular resistance approaches or exceeds systemic vascular resistance, offering significant impedance to pulmonary blood flow. Desaturated blood returning to the right heart is shunted to the systemic circulation (following the path of least resistance) across one or both persistent fetal channels, the patent ductus arteriosus (PDA) and the foramen ovale, resulting in marked cyanosis.

The clinical course of such infants is variable, depending on the severity of the underlying disease process and the degree to which PPHN contributes to the cyanosis. Common diagnoses associated with severe hypoxic respiratory failure in neonates include congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), sepsis, and pneumonia. Idiopathic pulmonary hypertension is sometimes seen in patients who exhibit minimal or no lung disease and have clear chest radiographs. There is a large "other" category, which includes less common diagnoses but also includes infants with hypoxic respiratory failure (HRF) of unknown origin. Among these "unknown" diagnoses are some of the rarer causes of HRF associated with pulmonary hypertension, many of which carry serious or lethal outcomes. These include alveolar capillary dysplasia, surfactant protein abnormalities, pulmonary hypoplasia other than CDH, pulmonary interstitial glycogenosis, alveolar proteinosis, pulmonary lymphangiectasia, and pulmonary venous occlusive disease.[40] These diagnoses, if complicated by pulmonary hypertension, can seldom be determined in the first few days of life, and several require lung biopsies for confirmation. The International Extracorporeal Life Support Organization (ELSO) Registry reports a 5-year distribution of primary diagnoses and survival for patients undergoing ECMO support in the United States (Fig. 70.1).[28]

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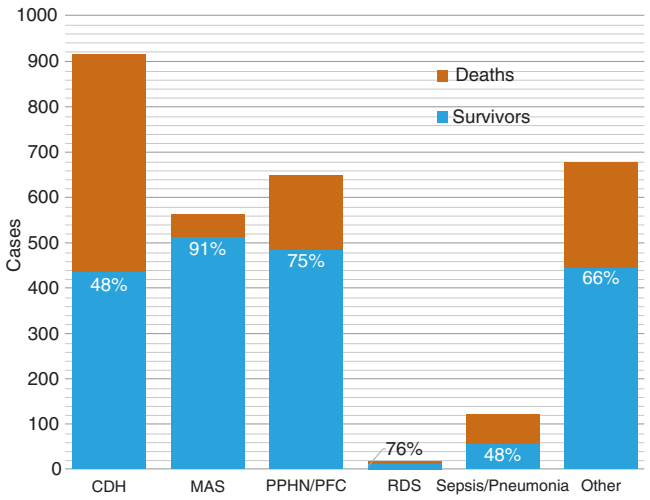
Abstract

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass support for term and late preterm infants with severe, life threatening, hypoxic respiratory failure. Affected infants present within the first 2 weeks of life, and the majority of these also have persistent pulmonary hypertension of the neonate (PPHN). For newborns who fail to improve with oxygen therapy, ventilator assistance, and judicious fluid/pressor support of systemic blood pressure, ECMO can improve oxygenation over a period of days to weeks, allowing the lung to rest and recover until pulmonary arterial pressures decline and blood flow to the lung is restored. Common diagnoses requiring ECMO support, details on the two types of bypass support commonly used, and patient eligibility criteria for ECMO are described in this chapter. Benefits and risks of the procedure are also addressed. The number of neonatal ECMO cases has declined significantly over the past 20 years since the introduction of inhaled nitric oxide (iNO), a potent vasodilator that can improve pulmonary blood flow and thus reverse PPHN. For the iNO-resistant newborn, however, there are a number of newer pulmonary vasodilators that are being studied, such as sildenafil, milrinone, inhaled prostacyclin derivatives, and bosentan. Unfortunately, nitric oxide has not been shown to improve survival or BPD in preterm infants, but subgroups within the preterm population, such as the ELBW infants with PPROM, oligohydramnios, and suspected pulmonary hypoplasia, may still benefit from iNO. Lastly, the emergence of pulmonary hypertension in infants with BPD as they approach term-corrected age and beyond remains a serious therapeutic challenge.

Keywords

extracorporeal membrane oxygenation (ECMO)
venovenous vs. venoarterial ECMO
persistent pulmonary hypertension of the neonate (PPHN)
inhaled nitric oxide (iNO)
oxygenation index (OI)
sildenafil

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• **Fig. 70.1** International ECMO experience (through July 2018). CDH, Congenital diaphragmatic hernia; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the neonate; RDS, respiratory distress syndrome. (Data are derived from the Extracorporeal Life Support Organization Registry.)

Traditional therapy for hypoxic respiratory failure complicated by PPHN consists of the use of oxygen, mechanical ventilation to minimize V-Q mismatch, and pharmacologic vasodilators to decrease pulmonary vascular resistance and increase blood flow to the lungs. Surfactant treatment should be considered if the infant has parenchymal lung disease such as MAS, RDS, or pneumonia, as this treatment has been shown to decrease the need for ECMO.[52,60] Surfactant is of no benefit in term or late preterm newborns with CDH and HRF, nor in infants with isolated PPHN.[60] Inhaled nitric oxide (iNO) is a well-studied, selective pulmonary vasodilator that enhances pulmonary blood flow and improves oxygenation in PPHN (see next section). It is for infants who do not respond to these measures that ECMO can be a life-saving therapy.

Basic Techniques

The standard ECMO procedure used most frequently in newborns with HRF today is venoarterial (VA) bypass, which provides both pulmonary and cardiac support. The right atrium is cannulated via the right internal jugular vein with a Silastic or polyvinyl chloride catheter (8- to 14-French diameter). Whether a roller head pump or centrifugal pump is utilized, blood is siphoned from the right atrium and circulated through the artificial lung. These pumps are servoregulated to slow or shut down if venous return is not adequate to meet circuit flow demands. As the blood circulates through the artificial lung, gas exchange occurs against a filtered mixture of oxygen, CO_2, and nitrogen in ambient air. The artificial lung commonly used in neonates in the United States is a hydrophobic, pediatric-specific, polymethylpentene hollow fiber membrane (Quadrox iD [diffusion membrane oxygenator]) that serves as a blood-gas interface, similar to the alveolar capillary membrane. Gas flows through the hollow fibers and venous blood flows around the outside of these fibers. Oxygen and carbon dioxide flow down their diffusion gradients, and gas exchange occurs across the hollow fiber membrane. Similar to the native lung, blood leaving the membrane lung has a normal to low CO_2 and a high Pao_2, with oxygen saturation of 100%. Depending on the size of the infant, CO_2 may need to be added to the gas mixture in order for the blood leaving the membrane lung to have a normal pH and pCO_2. Advantages of this newer artificial lung include a low priming volume and reduced blood/foreign surface area contact. This new generation of artificial lung also incorporates a heat exchanger to rewarm the oxygenated blood returning to the patient.

Oxygenation can be regulated by varying blood flow through the ECMO circuit. The higher the volume of cardiac output diverted through the membrane lung, the better the oxygen delivery from the ECMO circuit. Oxygenated blood exiting the artificial lung is returned to the infant via an 8- to 12-French catheter positioned in the ascending aortic arch through a right common carotid artery cannulation.

Blood flow through the ECMO circuit, at a rate of 80 to 100 mL/kg per minute, is usually adequate to provide excellent cardiac and respiratory support with maintenance of adequate blood pressure and oxygenation. Arterial wave dampening with narrowed pulse pressure is noticeable at flow rates approaching the infant's cardiac output, because the ECMO circuit provides relatively nonpulsatile blood flow. Pressor support and vasodilators can usually be stopped while the infant is on venoarterial ECMO support, because perfusion pressure from the pump largely replaces cardiac output. Only mild sedation—allowing the babies to breathe spontaneously, open their eyes, and move their extremities—is recommended on bypass support.

Systemic anticoagulation therapy with unfractionated heparin is administered for the duration of the bypass procedure to prevent clotting in the circuit and possible thromboembolization. Activated clotting times (ACTs) are measured at bedside every 1-2 hours and are maintained within a range of 180-240 seconds. Lower ACT targets are chosen in patients with elevated risk for bleeding (such as preterm infants or postoperative cases), although this increases the risk of thrombus formation in the ECMO circuit. Some centers monitor anticoagulation with anti-factor Xa assays, maintaining values between 0.3 and 0.7 unit/mL. Thromboelastography (TEG) can also be used to monitor coagulation status during an ECMO run.

Bivalrudin, a reversible direct thrombin inhibitor, is used instead of heparin for anticoagulation in some centers. Bivalrudin is particularly useful as an anticoagulant in cases where heparin-induced thrombocytopenia (HIT) is suspected. This complication, although not common, can occur in infants as well as adults, particularly in infants who have had cardiac surgery.[78]

Once the infant is placed on ECMO, ventilation and airway oxygen support are reduced to avoid further

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ventilator-induced lung injury (VILI) while maintaining functional residual capacity (FRC). Wide practice variation exists with regard to ventilator settings used for "lung rest" during bypass support. A study was published detailing ventilator practices during ECMO, derived from more than 3000 neonatal cases submitted to the ELSO database between 2008 and 2013.[4] Conventional mechanical ventilation (CMV) was used in 88% of cases while 12% used high-frequency ventilation (HFV) during ECMO. Most practitioners who used CMV for lung rest used a rate of 10 cycles/minute and peak inspiratory pressures (PIP) of 15-20 cm H_2O. Fio_2 use ranged from 21%-40%. There was far more variation in the use of positive end expiratory pressure (PEEP) than in other parameters: 32% used low PEEP (4-6 cm H_2O), 43% used high PEEP (10-12 cm H_2O), and 22% used a mid-PEEP range (7-9 cm H_2O). The mean time on ECMO was reduced by 22 and 21 hours in the high and median PEEP groups, respectively. This confirms an older report where high PEEP shortened ECMO duration by 32 hours.[47] Lower PEEP may be used if the patient has a pneumothorax or pneumomediastinum. Use of HFV compared to CMV was associated with longer ECMO duration, although these were sicker patients with increased oxygenation indices (OIs), lower pH, and lower blood pressure prior to ECMO initiation. If volume ventilation is preferred, 4-6 mL/kg tidal volume can be used to achieve mild chest rise with each delivered breath. The goal is to maintain FRC and to allow for continued pulmonary toilet. The respiratory status of the infant can be monitored with intermittent arterial blood gases obtained from the umbilical or peripheral arterial line. An oxygen saturation electrode inserted on the venous side of the circuit allows continuous monitoring of the mixed venous saturation at the level of the right atrium. A mixed venous saturation of 70% or greater reflects adequate oxygen delivery. The efficiency of the membrane lungs in use today allows most neonates to have normal mixed venous saturations throughout the ECMO course.

As lung function improves and pulmonary hypertension abates, the mixed venous saturation and partial pressure of arterial oxygen (Pao_2) rise above the baseline oxygenation provided through the artificial lung. Blood flow through the artificial circuit can then be decreased in small increments (10-20 mL) while mixed venous and arterial oxygenation remain adequate. When ECMO flow has been reduced to 10-20 mL/kg per minute, the infant can usually be weaned from extracorporeal support.

Increased Fio_2 and ventilator settings are provided as the patient approaches decannulation, although the support required is usually far less than needed prior to ECMO. The duration of bypass support may be anywhere from 2-60 days with an average need for 9.2 days of support.[28] Two decades ago, the average time on ECMO support was only 5 days. The significant increase in ECMO-run duration and marginal increase in mortality rate among neonatal ECMO patients compared to years past likely reflects a sicker cohort of patients now requiring ECMO consideration. In 1992, 1345 neonates with HRF were placed on ECMO in the United States whereas, in 2017, only 533 infants required ECMO among cases reported to the ELSO Registry.[28] Over the same time period, the number of neonatal cardiac cases increased substantially to 275 in 2017. Continued ventilator support following ECMO can be quite variable (days to weeks) depending on the underlying cause of respiratory/cardiac failure, as well as the degree of barotrauma incurred before initiation of ECMO.

In most ECMO centers, the right carotid artery and internal jugular vein are permanently ligated at decannulation. This approach is technically easier and prevents any concern about acute embolic complications associated with vascular reconstruction. However, some surgeons reanastomose these vessels if the patient has been on bypass less than 7-10 days to prevent future ischemic risks to the developing newborn brain as well as during later adult life. Studies show no disadvantage to this approach. Magnetic resonance angiograms (MRAs) and Doppler flow studies confirm good antegrade flow through the reconstructed carotid artery in the majority of these infants with no embolic sequelae reported.[23] Neurodevelopmental outcome and neuroimaging were equally favorable. However, one study in 2006 reported a 72% occlusion or stenosis of the right common carotid artery (RCCA) at 2 years of age in a select cohort of 18 survivors with CDH. There was no difference in neurologic impairment compared to ligated controls in this study, however.[17] In 2015, a single center retrospective study of 51 ECMO survivors with varying diagnoses who underwent right common carotid reconstruction (RCCR) (at <7 days ECMO support) had Doppler ultrasound or MRA assessment of carotid patency at a median age of 63 days. Thirty-seven of 51 (73%) survivors who underwent carotid repair had follow-up imaging to determine carotid artery patency as well as auditory brainstem evoked response (ABR) testing prior to hospital discharge. Thirty-one of 37 (83%) patients showed good antegrade blood flow through the RCCA. Compared to ligated infants, there was no difference in right-sided brain lesions or failed ABR at discharge among infants with carotid reconstruction.[25]

Longer term follow-up of this cohort is of interest to pediatric surgeons and neonatologists alike. Unfortunately, carotid reconstruction is time sensitive and the longer ECMO runs reported over the past 5 years may preclude arterial reanastomosis in most. Beyond 7-10 days, scar tissue encasing the carotid artery at the cannulation site, a part of the natural healing process, often makes reanastomosis impossible.

Venovenous Extracorporeal Membrane Oxygenation

A growing experience supports the ability of venovenous ECMO to provide adequate oxygen delivery in patients with serious respiratory failure but adequate heart function. In adults, this technique usually involves draining desaturated blood from the right atrium and returning oxygenated

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blood through the femoral vein. Similarly, the majority of pediatric ECMO patients with HRF are supported with venovenous (VV) ECMO, utilizing a double lumen catheter in the right atrium or a two-vein cannulation.

VV bypass in newborn infants has been greatly improved by the development of double-lumen catheters of varying sizes (13, 16, 19 French) that allow bypass support with cannulation of the right atrium alone. The 13 French catheter is appropriate for term newborns >2.5 kg birth weight. Desaturated blood is withdrawn from the right atrium through the outer fenestrated venous catheter wall. Oxygenated blood from the ECMO circuit is returned to the inner arterial, single lumen catheter, which is positioned to direct blood across the tricuspid valve. Higher flow rates are required to maintain adequate oxygen delivery with VV bypass, owing to the obligatory mixing of fully saturated blood returning from the ECMO circuit with desaturated systemic venous return within the right atrium.

Advantages of VV bypass include avoidance of carotid artery cannulation, which is highly desirable, and maintenance of normal pulmonary blood flow. The major disadvantage is that, unlike VA bypass, VV ECMO does not provide cardiac support. Oxygen delivery in VV bypass remains entirely dependent on adequate native cardiac output. The severity of cardiac dysfunction in ECMO-sick patients is highly variable, and often the heart function will improve once adequate oxygen content is restored on VV ECMO. Out of 3052 neonatal ECMO cases reported to the U.S. ELSO Registry between January 2013 and January 2018, 1010/3052 (33%) were supported on VV bypass with 75% survival; survival among infants supported on VA bypass, in comparison, was 61%.[28] VV ECMO complication rate and length of bypass support also compare favorably with VA bypass. Only 10%-12% of VV cases require conversion from VV to VA support should the patient's cardiac output prove to be subpar. Therefore, VV bypass should always be the first consideration in infants whose primary diagnosis is pulmonary disease.

Personnel Needs

ECMO is the most labor-intensive procedure in the neonatal intensive care unit (NICU). Specialists trained in managing patients on ECMO must remain at the patient's bedside for the duration of bypass. In addition to monitoring the infant's respiratory status, specialists must regulate the rates of blood and gas flow through the extracorporeal circuit to meet the infant's metabolic and respiratory demands. They must adjust anticoagulation by frequently measuring the activated clotting time or antifactor Xa assays in the blood and titrate the heparin infusion accordingly. Additionally, they must evaluate the patient for bleeding and replace losses appropriately. The specialists can be physicians, nurses, perfusionists, or respiratory therapists who have completed extensive training in ECMO support.

An ECMO physician trained in the clinical management of bypass patients must always be readily available for consultation, especially in case of mechanical failure or acute clinical decompensation. Additional support services required include 24-hour availability of personnel trained in radiology and ultrasonography, pediatric surgery, neurology, genetics, cardiology, and cardiothoracic surgery. The expertise and personnel needed to support these patients are extensive and costly.

• BOX 70.1 Patient Selection Criteria for Neonatal Extracorporeal Membrane Oxygenation

- Gestational age of 34 weeks or older
- Normal cranial ultrasound or stable grade I or II intraventricular hemorrhage
- Absence of complex congenital heart disease
- Less than 10-14 days of mechanical ventilation
- Reversible lung disease, including congenital diaphragmatic hernia
- Failure of maximum medical therapy
- No lethal congenital anomalies or evidence of irreversible brain damage

Criteria for Patient Selection

The cumulative experience of many ECMO centers has resulted in the establishment of guidelines that are currently used to decide whether ECMO support is appropriate.[89] These are described in Box 70.1.

Gestational Age of 34 Weeks or Older

Preterm newborns with respiratory failure carry a higher risk for intracranial hemorrhage (ICH) compared with term infants at baseline, and this risk is heightened with systemic anticoagulation required during ECMO support. Furthermore, changes in cerebral blood flow patterns associated with cardiopulmonary bypass can also place the immature brain at increased risk for bleeding.

In the early ECMO trials, premature infants less than 35 weeks' gestation had an 89% incidence of spontaneous ICH associated with heparinization.[15] Subsequent studies (all retrospective) revisiting this issue reported improvement in outcome but confirmed increasing rates of ICH as gestational age decreases.

ECMO management has changed over time, and technical refinements in bypass support have made this mechanical support possible for infants weighing as little as 1800 grams. However, even with improvements in management, gestational age remains a strong predictor of ICH risk. Late preterm infants who are recommended for ECMO (34 0/7 to 36 6/7 weeks' gestation at birth) experience higher mortality and morbidity on bypass compared to their term counterparts. In a review of 21,218 neonatal ECMO cases in the ELSO Registry (excluding CDH) from 1986-2006, late preterm infants (34 0/7 to 36 6/7 weeks' gestation) experienced the highest mortality on ECMO (26.2%) compared to early-term (37 0/7 to 38 6/7), 8% mortality,

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and full-term ($39^{0/7}$ to $42^{6/7}$), 11.2% mortality (p<.001), infants. Higher rates of intracranial hemorrhage (ICH) were also noted in late preterms (12.3%) compared to full terms (3.6%). Late preterm infants also experienced longer ECMO runs and higher rates of serious complication.[28,79]

Looking at a large cohort of preterm infants ≤34 weeks who were treated with ECMO prior to 1993, Hirschl reported a peak ICH incidence of nearly 50% at 33 weeks and a decrease to 30% by 34 weeks.[42] In 2004, Hardart reported that postconceptional age, rather than gestation at birth (corrected gestational age at initiation of ECMO), proved to be the highest predictor for ICH risk in preterm neonates. Out of 1524 neonates less than 37 weeks' gestation treated with ECMO between 1992 and 2000, ICH developed in 25% of infants at 32 weeks' estimated gestational age with linear decrease to 18% at 34 weeks.[35]

A study in 2018 comparing ECMO outcome at 34 weeks ($N = 509$) to that of preterms between 29 and 33 weeks' gestation ($N = 243$) reported survival was greater at 34 weeks' gestation (58%) compared to 48% survival in the <34-week cohort, $p = 0.05$. The rate of ICH peaked at 44% at 31 weeks and decreased incrementally to 17% by 34 weeks. A higher rate of cerebral infarction was also reported in the <34-week cohort. The authors suggest that while the risk of poor outcome in <34-week preterms is higher than seen at 34 weeks' gestation, the rate of ICH and cerebral infarction is not so high that ECMO should be completely contraindicated.[19]

No Major Intracranial Hemorrhage

The catastrophic extension of ICH, along with the attendant neurologic sequelae, is the primary risk reported in the early series of Bartlett and associates.[15] There is little argument that patients with grade III or IV ICH should not be offered ECMO, because these bleeds are likely to expand with exposure to anticoagulation, further augmenting poor long-term prognoses. Some centers have successfully managed infants with stable grade II intraventricular hemorrhage on bypass using minimal heparin dosage and high ECMO flow rates to prevent clotting in the extracorporeal circuit. This is not universal, however, as some centers exclude grade II hemorrhage cases due to concern for ICH extension.

Uncontrolled bleeding from surgical wounds, chest tubes, or other sites also worsens with heparin therapy and is a contraindication to ECMO. The septic infant is of concern in this regard because of the commonly associated coagulopathy. Although these infants have a higher risk of bleeding complications on ECMO, meticulous correction of their coagulopathy and careful heparin management have allowed them to be successfully treated without sequelae.

Absence of Complex Congenital Heart Disease

Infants in severe respiratory failure must have an echocardiogram to rule out congenital heart disease as the underlying cause for refractory hypoxemia. In some instances, the degree of hypoxemia is not easily explained based on the heart lesion alone (e.g., in a newborn with an atrioventricular canal complicated by meconium aspiration or sepsis). Use of ECMO can provide cardiovascular support to stabilize such a patient until the reversible component of the lung disease is no longer an issue, rendering the baby a more viable surgical candidate at some later date.

Similarly, an infant with suspected cyanotic congenital heart disease may present to an ECMO center with profound cyanosis and cardiogenic shock despite the use of prostaglandins and inotropes. Preoperative ECMO can stabilize such infants who are believed to have reparable cardiac defects but who are deemed to be poor surgical candidates by virtue of their clinical instability. Both venovenous and venoarterial ECMO have been used preoperatively in infants with cyanotic congenital heart disease and cardiovascular instability. Indications for ECMO include arterial saturations of 60% or less accompanied by hypotension and metabolic acidosis unresponsive to mechanical ventilation and pharmacologic support with inotropes and vasodilators. For most infants presenting with isolated cyanotic congenital heart disease, however, prompt surgical intervention, not ECMO, is the obvious treatment of choice.

Less Than 14 Days of Assisted Ventilation

Although ECMO can support cardiovascular function for days to weeks, it does not reverse serious pre-existing pulmonary damage. In early studies, infants subjected to prolonged mechanical ventilation with high pressures and Fio_2 before ECMO suffered extensive barotrauma and did not recover despite prolonged support (more than 2 weeks) on bypass. Severe bronchopulmonary dysplasia (BPD), or inability to wean from ECMO support, was the result.[15] Infants who have recovered from BPD, however, are eligible for ECMO later in life. Survivors of BPD have been placed on ECMO in later infancy or toddlerhood for life-threatening respiratory infections with good survival results: 59 of 76 (78%) patients from the ELSO registry.

Changes in ventilatory management with lower pressure and volume settings to avoid barotrauma (permissive hypercapnea or gentle ventilation) may protect the neonatal lung from irreversible damage for longer periods than earlier studies suggested. Use of surfactant and iNO may also blunt ventilator-induced lung injury. Nevertheless, the longer an infant is ventilated with high Fio_2 before initiating ECMO, the longer that infant will take to recover, owing to the barotrauma and oxygen toxicity superimposed upon the infant's underlying lung disease. Therefore, if a patient fails to respond favorably to available respiratory measures, ECMO support should be considered expeditiously. However, given the improvements in respiratory support used today, prolonged ventilation is considered only a relative contraindication to ECMO.

Reversible Lung Disease

Using reversible lung disease as a criterion to determine whether to offer ECMO is intended to exclude infants with severe lung hypoplasia incompatible with life. Patients with marked renal dysplasia and prolonged oligohydramnios,

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large CDH presenting in extremis at birth with unfavorable lung to head (L:H) ratio in utero, and hydrops fetalis fall into this category. However, infants with respiratory failure in all these categories have survived with ECMO support, making the judgment of irreversible lung disease in the newborn extremely problematic.

Failure of Maximal Medical Therapy

Because ECMO is an invasive procedure, it is currently reserved for infants with HRF unresponsive to optimal conventional therapy. In the early days of ECMO (1975-1995), those with an 80% mortality risk based on retrospective data at the time were considered candidates for ECMO. In well-intentioned attempts to keep newborns with HRF/PPHN alive, neonatologists would increase ventilator settings to extreme levels in hopes to reverse life-threatening hypoxemia. Tolazoline, which often caused serious systemic vasodilation, was the only vasodilator available. Sometimes it worked, oftentimes it did not.

Over the past 25 years, however, much has changed in the ventilator and NICU management of HRF in the newborn, including our choice of blood gas parameters in ventilated patients. Hyperventilation, alkali therapy, and muscle paralysis are no longer recommended, as serious side effects are associated with each of these interventions. It is, therefore, difficult to know what might constitute an 80% mortality risk in the ECMO-sick newborn today. Box 70.2 offers guidelines utilized by ECMO intensivists for deciding when bypass is likely needed.

A screening echocardiogram should be obtained in all infants with severe HRF to rule out serious congenital heart disease and to assess cardiac function. Hyperoxia should be avoided because of adverse effects of the reactive oxygen species (ROS) generated in the lung with prolonged exposure to high oxygen levels. Lakshminrusimha reports that oxygen-induced pulmonary vasodilation is maximized at a Pao_2 of 60-70 torr, arguing against "maintaining a margin of safety" with pO_2s over 100 torr.[55] Although CDH infants may be an exception, utilizing conventional mechanical ventilation (CMV) or HFV to achieve a normal pH should be the goal in respiratory support. Maintenance of normal blood pressure with judicious use of fluid infusions and pressors may also be required.

Early surfactant therapy has been shown to decrease the need for ECMO when administered to infants with HRF associated with parenchymal disease such as MAS, RDS, or pneumonia.[52,60] Inhaled nitric oxide has proven to decrease the need for ECMO in term and late preterm infants by 40% in multiple prospective randomized trials[13,74] (see next section on inhaled nitric oxide).

The use of other potent vasodilators commonly used in adults with pulmonary hypertension, such as sildenafil, epoprostenol, and bosentan, is not recommended in newborns with HRF/PPHN until these agents are proven safe and efficacious alone or in combination with iNO. Systemic hypotension is the main concern. Milrinone, a PD3 inhibitor that enhances pulmonary vasodilation and improves cardiac output, is presently under study.[56]

• BOX 70.2 Formulas and Criteria for Neonatal Extracorporeal Membrane Oxygenation

Oxygenation Index (OI)

- $OI = (MAP \times Fio_2 \times 100)/Pao_2$
- Usual criterion is OI of 35-60 for 0.5-6 hours.

Alveolar-Arterial Oxygen ($Aado_2$) Gradient (at Sea Level)

- $AaDo_2 = Fio_2 (P - 47) - Pao_2 - Paco_2 (Fio_2 + (1 - Fio_2)/R)$
- Usual criterion is $AaDo_2 > 605$-620 mm Hg for 4-12 hours.

Partial Pressure of Arterial Oxygen

- Usual criterion is $Pao_2 < 60$ mm Hg for 2-12 hours.

Acidosis and Shock

- Usual criterion is pH < 7.25 for longer than 2 hours or with hypotension.

From Suttner DM, Short BL. Neonatal respiratory ECLS. In Annich GM, et al., eds. *ECMO: extracorporeal cardiopulmonary support in critical care*. 4th ed. Ann Arbor, MI: ELSO; 2012:226.

The Dilemma of Congenital Diaphragmatic Hernia (CDH)

Congenital diaphragmatic hernia (CDH) is an anatomic defect of the diaphragm resulting in herniation of abdominal contents into the thoracic cavity. The majority (85%) of CDHs are left-sided lesions. Pulmonary hypoplasia of variable severity results on the ipsilateral side of the defect (see Chapter 66 for more on CDH).

CDH is often associated with intractable PPHN/HRF. A combination of pulmonary arterial hypertension, right ventricular hypertrophy, and in some cases, left ventricular hypoplasia results in severe PPHN. Often these infants prove unresponsive to conventional management, including oxygen, ventilation (including HFV), and pulmonary vasodilators like inhaled nitric oxide. Pulmonary hypoplasia and decreased cross-sectional area of the pulmonary vascular bed contribute to the hypoxic respiratory failure in newborns with CDH. In large diaphragmatic defects, the stomach, intestines, and liver can herniate into the chest, causing displacement of the heart, which restricts the growth of the contralateral lung as well as the ipsilateral lung.

ECMO is reserved for CDH patients who are failing optimal medical treatment, including a strategy of pressure-limited (gentle) ventilation to minimize ventilator-associated lung injury. Criteria that predict high mortality prior to initiation of ECMO have not been universally established. Published indications for initiating ECMO in infants with CDH include the following: severe hypoxia and HRF with preductal oxygen saturations <80%-85%, metabolic acidosis (lactate >5) or respiratory acidosis with pH persistently <7.20, or hypotension with poor tissue perfusion and/or

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oliguria unresponsive to intravenous fluid and inotropic support.[36]

The survival among CDH infants treated with ECMO over the last 5 years has declined to 47% within the United States, which reflects the highest mortality among neonatal etiologies of respiratory failure reported in the ELSO Registry.[28] In 1991, survival in this cohort was 64%. The reason for this decline is not entirely clear. A recent publication commenting on the decline in survival notes that over the past 10 years the prevalence of respiratory acidosis in this cohort has more than doubled ($p < .0001$), and the length of ECMO support has increased ($p < .001$), pointing either to a sicker population receiving bypass support or an unrecognized risk of permissive hypercapnea, a ventilator technique commonly used now in CDH infants to avoid serious lung barotrauma.[90] Stevens and colleagues suggest that improvements in ventilator management postdelivery have resulted in early survival of a sicker cohort of CDH patients who might otherwise have died but now are stabilized on ECMO.[88] In all, 25%-35% of infants with CDH require ECMO support, usually VA bypass, and the majority of these are cannulated prior to surgical repair of the hernia because of the infants' clinical instability.

Echocardiographic findings in a cohort of 44 CDH infants revealed no difference in the severity of pulmonary hypertension between ECMO ($N = 15$) and non-ECMO CDH patients ($N = 29$). However, compared to non-ECMO patients, those who required ECMO had significantly decreased left and right ventricular function with diminished cardiac output. The authors proposed that abnormal cardiac function may explain the lack of sustained response to pulmonary vasodilators in newborns with CDH. Focusing attention on support of cardiac function in these fragile infants may prove critical to outcome.[6]

Pre- and postnatal respiratory therapies that have improved survival in preterm infants have also been studied in term and late preterm CDH infants. An observational study of antenatal steroids administered at 34 weeks' gestation did not benefit survival in CDH patients.[58] Surfactant replacement therapy has also been investigated because of earlier evidence, mostly from animal data, suggesting surfactant deficiency in CDH. However, a large prospective observational study conducted by the CDH Study Group involving 424 preterm infants with CDH <37 weeks' gestation showed worse survival and increased complications associated with surfactant replacement.[59] Neither the length of bypass support, number of days of mechanical ventilation, nor the length of oxygen requirement were improved among those given surfactant therapy in this cohort.

Ventilatory management of infants with symptomatic CDH begins in the delivery room with early intubation and placement of a nasogastric (NG) tube to decompress the bowel in the chest.[7] Most ECMO centers focus on strategies to minimize ventilator-associated lung injury utilizing low distending pressure, minimal sedation, and avoidance of muscle paralysis. Hyperventilation and attempts to normalize pCO_2 for infants with CDH have largely been abandoned with this adoption of gentle ventilation. There is no particular mode of ventilation that has been shown to be superior in the management of CDH. A multicenter randomized trial of HFV versus conventional ventilation in CDH infants showed no advantage to HFOV with regard to survival or avoidance of ECMO.[84]

Currently, ECMO is used in CDH newborns largely for preoperative stabilization in sicker infants. The optimum timing for repair of the hernia in ECMO-sick patients remains unclear, however, because of variability among centers and lack of convincing data on how best to proceed. The CDH Study Group found that surgical repair of CDH on ECMO was associated with decreased survival, relative to repair after ECMO therapy (48.2% vs. 77.1%, hazard ratio, 1.41, 95% CI 1.03-1.92). Kays et al., who consistently publish one of the highest survival rates in CDH, reported a 92% survival in left-sided, liver-up CDH newborns (a higher risk cohort) who were repaired early, that is, before going on ECMO, compared to 65% survival among those placed on ECMO unrepaired.[45] Other reports reviewed by McHoney favor decannulation after CDH repair.[65]

A multidisciplinary CDH management team at the Children's Hospital, Colorado, choose to delay surgical repair of CDH infants until echocardiogram-estimated pulmonary artery pressure decreases to <80% systemic blood pressure. In a retrospective study of 77 infants with Bochdalek herniae managed between 2008 and 2015, they reported fewer postoperative decompensations and a trend toward improved survival to 30 days postoperatively among the infants repaired after improvement in pulmonary pressures (94% vs. 80%; $p = 0.06$).[22] This manuscript provides a detailed description of this group's management protocol for CDH patients, starting with initial stabilization in the delivery room, respiratory management in the ICU, timing of hernia repair on or off ECMO, and postoperative management.

The true impact of ECMO on survival and long-term outcome in newborns with CDH is difficult to ascertain. Infants with CDH who received ECMO support appear to have a higher risk and greater severity of neurologic morbidity compared to those who did not receive ECMO, or those who received ECMO for other causes of HRF.[36,64] Among neonatal ECMO patients who survived to hospital discharge, CDH patients had a 74% 5-year survival compared to 98% survival in MAS patients.[92] Most deaths in the CDH cohort were caused by chronic lung disease.[44] Neurodevelopmental morbidity and growth failure among children with CDH have been confirmed in several studies. Madderom assessed 35 CDH survivors at 8 years of age, ECMO-treated (N = 16) and non-ECMO-treated (N = 19). The mean intelligence quota for the ECMO group was 91.7 versus 111.6 for the non-ECMO group ($p = 0.015$). Both were within normal developmental quotient (DQ) range but significantly lower in the CDH-ECMO cohort. Motor problems were noted in 16% of all participants as were problems with concentration (68%) and behavioral attention (33%), compared to a normal Danish

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reference group, but not different between ECMO-treated and non-ECMO-treated CDH groups.[61]

Because the sicker newborns with CDH were placed on ECMO for intractable HRF, it is hard to know what degree of their later morbidity is intrinsic to their underlying condition and greater severity of illness versus ECMO exposure. These issues should be discussed with parents before birth in the case of prenatal diagnosis of CDH and early in the NICU course of all CDH infants.

Extracorporeal Membrane Oxygenation Referral

One of the hardest decisions faced by neonatologists in tertiary care is when to refer a newborn in respiratory failure to an ECMO center. Because of the volatile nature of PPHN, the risk of sudden cardiorespiratory decompensation and death remains high in any infant not responding favorably to conventional supportive measures. Likewise, transporting these unstable babies is problematic, with one series reporting 25% mortality among ECMO transports before inhaled NO was available.[16] In 2016 in New South Wales, Australia, the use of inhaled nitric oxide improved oxygenation in a cohort of 57 out of 130 consecutive transports of high-risk newborns with HRF. The majority of these transports were over large distances, and all infants arrived at the referral hospitals safely.[8]

It is essential that ECMO referrals be made as expeditiously as possible, certainly before the infant is moribund and preferably before the baby reaches ECMO-eligible respiratory criteria. Early and frequent telephone contact with an ECMO physician to discuss the details of each case can help establish transport criteria agreeable to both parties.

The parameters most often used to predict poor outcome in infants failing conventional or high-frequency ventilator support and regarded as entry criteria for ECMO are listed in Box 70.2. These criteria are applied when the infant has reached optimal ventilatory support on 100% oxygen. Expert opinion has stated that when the oxygenation index (OI), described below, is greater than 25, a non-ECMO center should at least be in discussion with an ECMO center to determine the optimal time to transport the infant.

One criterion is the oxygenation index:

$$\text{OI} = \text{mean airway pressure} \times \text{Fio}_2 \times 100 / \text{postductal Pao}_2$$

This equation has a certain appeal in that it reflects the ventilator support being used to achieve any given Pao_2. The oxygenation index is the parameter used in most ECMO centers today to gauge the severity of respiratory insufficiency.

Another criterion is the alveolar-arterial oxygen gradient (AaDO_2):

$$\text{AaDO}_2 = \text{Fio}_2(\text{P} - 47) - \text{Pao}_2 - \text{Paco}_2(\text{Fio}_2 + (1 - \text{Fio}_2)/\text{R})$$

where P is the barometric pressure, 47 is the partial pressure of water vapor, R is the respiratory quotient (0.8), Fio_2 is the fractional inspired oxygen concentration, Pao_2 is the partial pressure of arterial oxygen, and Paco_2 is the partial pressure of arterial carbon dioxide. When Fio_2 is 100% and assuming PAo_2 (partial pressure of alveolar oxygen) is equivalent to Pao_2, the equation reduces to: $\text{AaDO}_2 = \text{P} - 47 - \text{Pao}_2 - \text{Paco}_2$, where P is 760 mm Hg at sea level.

An OI of 40 or greater or an AaDO_2 gradient of 605-620 or greater served as a baseline criterion for ECMO eligibility in the original UK randomized trial of ECMO versus conventional management alone. Assessment of respiratory failure parameters begins after infants have received surfactant or iNO, or both, when clinically relevant. Supporting cardiac output with judicious use of volume loading and pressor infusion is crucial to maintaining adequate oxygen delivery in newborns with borderline blood pressure and respiratory insufficiency. In the ventilatory management of these infants, equal attention must be paid to providing optimal ventilation without overdistending the lung, which compromises venous return and hence adversely affects cardiac output. Hyperventilation (to induce respiratory alkalosis) is no longer recommended in the ventilatory management of PPHN.

For the infant who remains severely hypoxic and/or hypotensive despite every supportive measure offered, the choice for ECMO is easily made. However, for the infant whose blood gases and systemic blood pressure are marginally stable on maximal support, including iNO, but who is unable to wean from these supports, the choice between invasive bypass support (ECMO) and the risk for extended volutrauma to the lungs remains difficult.

One large study in newborns with respiratory failure and PPHN confirmed that aggressive weaning of iNO over 96 hours can be accomplished without increasing the risk for ECMO.[20] Judicious but steady weaning of both Fio_2 and ventilator settings is recommended to avoid serious lung injury. If the infant's respiratory status fails to stabilize and improve over a number of days, then ECMO is an alternative.

Extracorporeal Membrane Oxygenation Follow-Up

More than 27,000 infants have been treated for respiratory failure in more than 200 ECMO centers worldwide for an overall survival to discharge of 74%.[28] The outcome of these children compares favorably with that of term and near-term infants surviving severe respiratory compromise and PPHN with conventional management.

A valid criticism of early ECMO follow-up studies was the lack of proper control data, that is, the outcome of infants with severe respiratory compromise who were managed during the ECMO era with conventional treatment alone. Such control data are essential for distinguishing morbid outcome caused by the underlying disease process and NICU management of respiratory failure, or both, from the morbidity that is secondary to the ECMO procedure itself.

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To address this issue, Walsh-Sukys and associates were the first to report on the neurodevelopmental outcome of 74 consecutive neonates older than 34 weeks' gestation admitted to Rainbow Babies and Children's Hospital with severe respiratory failure.[96] Eighteen of 24 (75%) infants treated conventionally survived, whereas 43 of 48 (90%) treated with ECMO survived. Patients were evaluated at 8 and 20 months. Sixty-two of 72 (91%) survivors were seen in follow-up. Four of 17 (24%) conventionally treated survivors and 10 of 38 (26%) ECMO-treated survivors had neurodevelopmental impairment defined as either Mental Developmental Index Score lower than 80 or neurosensory impairment. The conventionally treated group had significantly more chronic lung disease, longer duration of oxygen therapy, more chronic reactive airway disease, and more rehospitalizations than those treated with ECMO. Macrocephaly was noted in 24% of ECMO survivors, all treated with VA bypass, but in none of the conventional group. This study concluded that ECMO survivors did not suffer increased neurologic morbidity compared with similarly ill neonates managed conventionally and that they may have fewer pulmonary sequelae.

Vaucher and colleagues prospectively assessed growth and neurodevelopmental outcome in a cohort of 190 infants surviving neonatal respiratory failure who met institutional criteria for the use of ECMO.[94] Fifty-two were managed with conventional or high-frequency ventilation, and 138 required ECMO. At 12-30 months of age, the mean developmental scores of ECMO survivors were similar to those for infants who survived without ECMO. Neuroimaging abnormalities or diagnosis of bronchopulmonary dysplasia each independently predicted adverse neurodevelopmental outcome regardless of treatment strategies used in the NICU. This observation mirrors the same predictors of poor outcome described in another high-risk cohort familiar to neonatologists, namely, infants with very low birth weight (less than 1000 g).

In 2006, the UK Collaborative ECMO Trial Group published the 7-year follow-up of their surviving patients from the largest prospective randomized ECMO trial carried out so far.[67] In this study, a single psychologist assessed 90 of the 100 children available for follow-up without prior knowledge of treatment allocation (ECMO versus conventional management). At age 7 years, there was no difference in cognitive function between the 56 patients randomized to ECMO versus the 34 controls; 68 (76%) children recorded a cognitive level within the normal range. Learning problems were similar in the two groups. There were notable difficulties with spatial and processing tasks; the children also had particular difficulty completing tasks of reading comprehension with 35 (39%) scoring below the 10th percentile. There was no difference in laterality of neuromotor disability between the two groups, which is important because VA ECMO is usually performed on the right-sided common carotid and internal jugular vessels; thus, no side preference would imply that there were no injuries related to complications from cannula placement. A higher respiratory morbidity and increased risk of behavioral problems among children treated conventionally (first reported in the 4-year follow-up) persisted. In the conventionally treated group, 11 of 30 (32%) children continued to have wheezing attacks and 14 of 32 (41%) regularly used an inhaler over the 12 months before study assessment. In comparison, 6 of 43 (11%) ECMO children wheezed and 14 of 48 (25%) used an inhaler. In behavioral assessment, the total deviant score was higher in the conventionally treated group—38% versus 18% in ECMO survivors. The most commonly described difficulty reported by parents and teachers in both groups was hyperactivity; overall, 22 of 85 (26%) children had difficulty with hyperactivity. In 1996, the primary outcome of death or severe disability in this UK trial occurred in 37% of the ECMO group compared with 59% in the conventional group (relative risk 0.64; $p = .004$), leading the authors to reaffirm that ECMO remains a beneficial treatment. These results, which have not changed between the 4- and 7-year follow-up, are equivalent to one additional child surviving without severe disability for every four to five children referred for ECMO. Overall, 31 of 56 (55%) ECMO survivors and 17 of 34 (50%) conventionally treated survivors were assessed with no disability at 7 years. The authors concluded that the data collected at 1, 4, and now 7 years' follow-up of the UK ECMO trial participants suggest that the underlying disease process (and associated physiologic instability) appears to be the major influence in long-term outcome. Their findings confirm significant long-term morbidity in many surviving children who had life-threatening respiratory failure soon after birth, regardless of their subsequent medical treatment. Furthermore, although both groups had problems, the beneficial influence of ECMO persists to 7 years.

Neurodevelopmental follow-up of ECMO survivors in the Netherlands was reported at 5, 8, and 12 years of age. There was no control group in this study of ECMO survivors, however. By 8 years (n = 135), intelligence was normal with 91% attending regular education, albeit with increased special education supports, compared to a normal Dutch reference cohort. Increased behavior and attention issues were also cited. CDH survivors scored at the lower end of normal in IQ testing compared to those with other newborn diagnoses. All children in this cohort received VA ECMO as infants.[61]

Two hundred and fifty-four children treated with ECMO in the neonatal period were also evaluated longitudinally for motor performance utilizing the Movement Assessment Battery for Children (MAB-C). At 5 (n = 78), 8 (n = 126), and 12 (n = 36) years, motor performance was normal in 73.7%, 74.8%, and 40.5%, respectively, compared to 85% expected based on Danish reference values, $p < 0.001$. In the 36 children evaluated at all three ages, Z scores were similar at 5 and 8 years but significantly lower at 12 years. The significant decline in motor scores at 12 years was most pronounced in children with chronic lung disease and CDH. Exercise capacity (based on the Bruce treadmill

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protocol) also worsened significantly over time, that is, from assessment at 5, 8, and 12 years.[91]

The significance in such decline in motor performance and exercise capacity is troublesome and points to a serious need for long-term follow-up of these children into adulthood. In the United States, unfortunately, we do not have neurodevelopmental follow-up to compare to the UK and Netherlands programs. In 2016, a survey assessment of a cohort of 142 adult (>18 years, born before 1994) survivors of neonatal ECMO in the United States was published. While this self-reported outcome was largely favorable, this study represented only a small fraction (<2%) of neonatal ECMO survivors who have reached adulthood.[27] Finding these patients, particularly those not receiving routine medical care, will prove formidable.

ECMO and Hypothermia Therapy

Induced hypothermia for 72 hours to a depth of 33-34°C is now standard of care for newborns suffering moderate or severe encephalopathy, as this therapy has been shown in large, prospective, randomized trials to decrease death or disability in these infants.[82] In a study of 303 infants with HIE who were cooled, 67 (22%) had PPHN. The incidence of PPHN in the general newborn population is 1.9/1000 live births. Mortality was higher in the subset of cooled infants (27% vs. 16%), and the hospital length of stay was prolonged in PPHN/HIE survivors (26 vs. 10 days).[57] In the Optimizing Cooling Trial, among the infants with PPHN who were cooled to 32°C for 72 or 102 hours, 67% required iNO and 12% needed ECMO support, compared to 3% iNO and zero ECMO use in HIE infants without PPHN who were cooled in standard fashion (i.e., 33.5°C). Worsening PPHN at the lower temperature was an unexpected adverse outcome in this study. For this reason, deeper hypothermia (i.e., <33°C) is not recommended for infants with HIE.[83]

In a multicenter prospective study of 267 neonates (<30 days old) undergoing ECMO at eight clinical sites, 20 infants also received therapeutic hypothermia. Eighty percent of neonates who were cooled during ECMO had a primary respiratory diagnosis, and 65% had PPHN. Infants receiving therapeutic hypothermia were more likely to have ICH during the first 7 days on ECMO, compared to noncooled ECMO patients: 40% versus 15%. Not all infants had pre-ECMO head ultrasound screens, however, so it is not certain whether some of these bleeds might have occurred prior to the initiation of ECMO. The authors point out that hypothermia and rewarming have been associated with fluctuations of cerebral blood flow and that in combination with abnormal coagulation profiles and low platelets could offer an explanation for the association between therapeutic hypothermia and ICH on ECMO.[18]

Massaro and colleagues reported the use of ECMO in 5/117 patients who required hypothermia for moderate to severe encephalopathy. All five patients demonstrated prolonged coagulation studies and thrombocytopenia during hypothermia. Three of the five developed ICH while on ECMO. The authors posed a cautionary note that, while both ECMO for refractory HRF and cooling for HIE independently demonstrate improved outcome, the combination of the two therapies is less certain and needs further study. This uncertainty should be conveyed to parents before pursuing both therapies in tandem, especially in cases of severe encephalopathy.[63]

The Neonatal ECMO Study of Temperature (NEST) Trial randomized 111 neonates on ECMO to receive therapeutic hypothermia (34°C) for 48-72 hours after bypass initiation or ECMO alone. These children did not have HIE as a primary diagnosis. The hypothesis of this study was that therapeutic hypothermia during ECMO would reduce the proportion of infants with brain injury and, thus, later impairment. CDH and postoperative cardiac infants were excluded. The primary outcome was the cognitive composite score of the Bayley Scales of Infant and Toddler Development (3rd edition) at 2 years of age. The mean cognitive score of the hypothermic cohort was 88 (SD 16.2) compared to 90.6 (SD 13.1) for the noncooled infants, confirming no advantage in cognitive outcome at 2 years of age among survivors treated with moderate hypothermia while on ECMO. Indeed, a pattern of small differences favoring standard ECMO was observed across the health and neurologic outcomes investigated. No significant increase in ICH was found in the infants who were cooled, however, compared to noncooled ECMO patients. The proportion of infants who survived without impairment was, nonetheless, similar in both groups: 27/52 infants (52%) in the ECMO with cooling group versus 28/49 infants (57%) in the standard ECMO group.[29]

Cost Analysis

Although ECMO saves lives, it does cost more than conventional management of neonatal respiratory failure. A cost-effectiveness analysis of neonatal ECMO was published based on 7-year results from the UK Collaborative ECMO Trial.[77] Mean health service costs during the first 7 years of life were £30,270 in the ECMO group compared with £10,229 in the conventional management group. Data for this analysis included air and ground transport costs, initial and all subsequent hospitalizations, outpatient hospital care, and community health care, as well as other health care services. These combined costs over 7 years translated into a cost of £13,385 per life-year gained. The incremental cost per disability-free life-year gained was estimated at £23,566. These incremental costs should decrease as the surviving children grow older. The authors concluded that ECMO was not only clinically effective but also as cost-effective as other intensive care technologies in common use.

Alternative Uses for Extracorporeal Membrane Oxygenation

Support by ECMO has been extended to a broader array of high-risk candidates. A small number (5%) of infants

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undergoing surgical repair of their heart defects cannot be successfully weaned from cardiopulmonary bypass or they develop low cardiac output syndrome several hours after repair. VA ECMO can provide circulatory support for these patients until their cardiac function improves. However, survival in postcardiac surgery infants requiring ECMO is low (41%) compared to respiratory case survival (74%).[28,41]

In a single-center retrospective study of 671 patients undergoing open-heart surgery between January 2001 and October 2003, 36 (5.4%) infants received extracorporeal life support within 1 day after surgery (age younger than 30 days, $N = 34$). Overall, 28 patients (78%) were weaned from extracorporeal support successfully, and 24 (67%) survived to hospital discharge. These infants had a variety of disorders, including single ventricle anatomy as well as failed hemodynamics postcardiotomy. The authors concluded that expanded use of extracorporeal support may improve outcome in some of the highest risk neonates, especially those with univentricular anatomy.[5] In another single-center review from Vanderbilt University Medical Center, 84 children with congenital heart disease required postcardiotomy ECMO between January 2001 and September 2004. The median age of the patients was 128 days (1 day-5 years), and median weight was 4.5 kg (2-18 kg). Fifty-two (61.9%) survived for more than 24 hours after decannulation, but only 31 (36.9%) survived to discharge. High arterial lactate levels at the time of ECMO initiation were strongly correlated with poor outcome. Inability to wean off ECMO by 6 days correlated with high mortality.[81]

ECMO has been used as a bridge to cardiac transplantation in infants with myocarditis or complex congenital heart disease, as well as support for early graft failure following heart transplantation in infancy. It has also been used to stabilize infants with refractory supraventricular tachycardia until antiarrhythmic drugs could be maximized or radioablation of the aberrant pathway accomplished.[95] Tracheal reconstruction in infants with serious congenital defects of the upper airway has also been successfully accomplished while on ECMO.[38]

Extracorporeal Membrane Oxygenation Present and Future

ECMO has become an established treatment for cases of hypoxic respiratory failure refractory to conventional management. Because of advances in neonatal respiratory care, the number of annual neonatal respiratory ECMO cases has declined from a peak of 1345 in 1992 to 533 infants in 2017.[28] Surfactant treatment, gentle ventilation, permissive hypercapnea, high-frequency ventilation, and inhaled nitric oxide have all contributed to the welcomed decline in the need for ECMO rescue in neonatal respiratory failure.

Research efforts continue to focus on PPHN treatment that could preclude the need for bypass altogether. Randomized controlled trials over the past decade have proven the efficacy of iNO as the selective pulmonary vasodilator that decreases the need for ECMO (see the next section). Other drugs used extensively in the treatment of adult and pediatric pulmonary hypertension have been reported, so far in small case series, and hold promise in the future treatment of PPHN. As the number of neonatal pulmonary cases declines, the use of ECMO support for cardiac low-output syndrome, as in myocarditis or postcardiotomy, has increased. Time is needed to determine whether this use of extracorporeal support will translate into increased survival or improve neurodevelopmental outcome in this high-risk cohort.

Nitric Oxide Therapy

Persistent pulmonary hypertension in the neonate (PPHN) is a serious and sometimes lethal cardiorespiratory complication of the transition to extrauterine life. The incidence ranges from 0.43-6.8 per 1000 live births.[97] It is well recognized that in the absence of congenital malformations of the lung, this condition improves if the patient can be supported through the period when pulmonary vascular resistance is most volatile, often exceeding systemic vascular resistance. Support is required for a matter of only days, usually less than 2 weeks.

Potent vasodilators such as tolazoline, nitroprusside, prostaglandin E_1 (PGE_1), and prostaglandin D (PGD) have been shown in small trials to reverse the severe pulmonary vasoconstriction that causes profound hypoxemia in PPHN. Although all these medications are efficacious in lowering pulmonary vascular resistance, their use is severely limited by a lack of pulmonary selectivity. Systemic vasodilation invariably occurs, leading to hypotension, compromised tissue perfusion, and inadequate oxygen delivery to vital organs.

In 1980, Furchgott and associates described an endogenous vasodilator called *endothelium-derived relaxing factor* (EDRF).[33] In 1987, NO was identified as the molecule responsible for the biologic activity of EDRF. Previously recognized as a toxic component in cigarette smoke and atmospheric pollution, NO has proved to be an important endogenous mediator of multiple physiologic processes in the human body, including regulation of vascular tone. When delivered by inhalation, NO can selectively decrease pulmonary vascular resistance and improve pulmonary blood flow without compromising systemic blood pressure or worsening $\dot{V}/\dot{Q}$ mismatch. At present, NO is the most selective pulmonary vasodilator available for clinical use in neonatal patients.

Physiology and Pharmacology

Nitric oxide (NO) is a short-lived (seconds) reactive molecule, with an unpaired electron cleaved from the terminal nitrogen of L-arginine by the enzyme nitric oxide synthase (NOS). Three distinct isoforms of NOS have been described. Neuronal NOS (NOS I, nNOS) is produced in central and peripheral nerves and is pivotal in neuronal transmission and cell-to-cell communication in the

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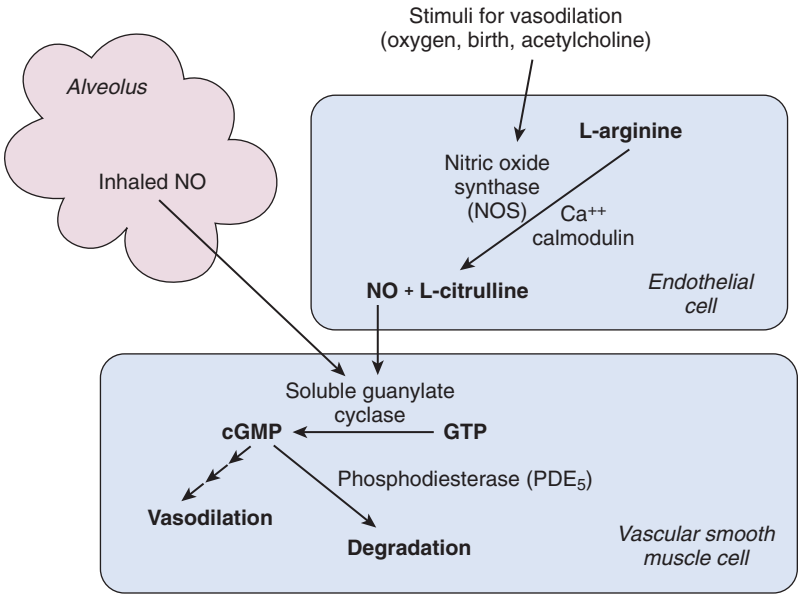
central nervous system. Inducible NOS (NOS II, iNOS) is upregulated in the face of inflammatory stimuli such as infection. While NOS II is expressed by immune cells such as neutrophils and macrophages, it is also found in other cell lines, including hepatocytes. Endothelial NOS (NOS III or eNOS) is expressed by endothelial cells and is critical for the regulation of vascular tone, the subject of this section.[43]

In the classical mechanism of NO signaling, NOS converts arginine to citrulline and NO as follows. Pulmonary endothelial and epithelial cells are active sites of NOS activity in both fetal and newborn lungs. Nitric oxide generated in the endothelium enters the adjacent smooth muscle cell where it binds to the heme protein of soluble guanylate cyclase. This induces a conformational change and upregulation of this enzyme, promoting synthesis of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP) (Fig. 70.2). Activation of a cascade of cGMP-dependent protein kinases results in calcium efflux from the adjacent muscle cells and sequestering of intracellular calcium within the sarcoplasmic reticulum. With less cytoplasmic calcium available for depolarization and contraction, smooth muscle relaxation follows, resulting in pulmonary vasodilation.[43] Intracellular cGMP is, therefore, a significant modulator of vascular smooth muscle tone. Its biologic half life is short, however. A family of phosphodiesterases hydrolyze and inactivate cGMP, regulating the concentration and duration of action of cGMP within the smooth muscle cell.

Lung endothelial NOS mRNA and protein are present in the early fetus and increase with advancing gestation in utero in the rat model. In the fetal lamb, intrapulmonary infusion of NOS inhibitors increases basal pulmonary vascular resistance by 35% as early as the second trimester.[1] Endogenous NO plays a pivotal role in the acute decrease in pulmonary vascular resistance at birth along with other vasodilators such as adenosine and prostacyclin. NOS expression is largely responsible for postnatal adaptation of the lung circulation following newborn delivery. Other nitrovasodilators, such as sodium nitroprusside, nitroglycerin, and the organic nitrates, donate NO through the NO-cGMP pathway to promote vasodilation. When administered by inhalation, NO rapidly diffuses across the alveolar membrane of ventilated portions of the lung to relax the pulmonary vascular bed through upregulation of cGMP production. In contrast to intravenous vasodilators, inhaled NO has minimal effect on systemic vascular tone because of rapid binding by reduced hemoglobin within the pulmonary circulation.

Nitric Oxide Toxicity

Clinicians should be aware of toxicity issues when using inhaled nitric oxide (iNO) in human subjects. Nitric oxide reacts with oxygen to form nitrogen dioxide (NO_2). Both NO and NO_2 are toxic in higher concentrations, causing death in dogs at concentrations between 0.1% and 2% because of methemoglobinemia and pulmonary edema. This concentration is much higher than the inhaled dose of NO used therapeutically in newborns (5-20 ppm) or the endogenous levels of NO produced in the endothelium (ppb). When NO reacts with superoxide in the lungs, peroxynitrite ($ONOO^-$) is formed, which can cause membrane lipid peroxidation. Furthermore, at levels used in clinical trials, NO can inhibit platelet aggregation and adhesion. In one study, prolonged bleeding time was noted in healthy adults breathing 30 ppm iNO. However, no studies to date have reported issues of systemic bleeding with iNO treatment. Occupational safety guidelines limit exposure to NO in the workplace to 8 hours a day at levels of 25 ppm, while 3 ppm is the upper limit for NO_2. Scavenging devices on most iNO delivery systems remove excess NO sufficiently enough to lower bedside workers' exposure to far below these limits.



• **Fig. 70.2** Nitric oxide (NO) is produced in the vascular endothelium during the conversion of L-arginine to L-citrulline by the enzyme NO synthase (NOS). Endogenous NO from the endothelium or exogenous NO inhaled into the alveolus diffuses to the vascular smooth muscle cell, stimulating soluble guanylate cyclase, which increases cyclic guanosine monophosphate (cGMP) production. Phosphodiesterase, specifically PDE_5, hydrolyzes cGMP, reversing smooth muscle relaxation. GTP, Guanosine triphosphate.

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Patients treated with iNO must have methemoglobin levels monitored daily to ensure they do not exceed 5%-7%. Methemoglobin is a source of potential toxicity with exposure to high doses of NO (≥80 ppm), especially with prolonged use.

NO has multiple effects on cell signaling, inflammation, growth, differentiation, and metabolism throughout the human body. While NO-based signaling via soluble guanylate cyclase explains much of the activity, parallel studies suggest that NO elicits much of its physiologic effects through cGMP independent mechanisms. S-nitrosylation, a covalent post-translational modification of protein cysteins, has emerged as a paradigm of nonclassical NO signaling in which the reaction of NO with protein thiols forms S-nitrosothiols (SNOs). Hemoglobin (Hb) is the prototypical S-nitrosylated protein in that it can deploy NO bioactivity as the red blood cells (RBCs) transit the circulatory system.

NO binds to heme iron of deoxy tension (T) state Hb in the venous circulation to generate HbFeNO. In response to oxygenation within the lungs, the Hb molecule undergoes a conformational change from the T state to a relaxed (R) state, and the NO group is transferred to the cysteine residue on the β chain to form SNO-Hb. The transition from high to low oxygen tension in the distal circulation promotes the release of SNO-based vasodilatory activity from the RBCs, thereby improving oxygen delivery where it is needed most. The binding and release of NO bioactivity in the form of SNOs is thought to be a central component of the physiologic response to local hypoxia at the tissue level.[24,62]

Neonatal Studies of Inhaled Nitric Oxide

Term Infants

Inhaled nitric oxide has proven to be an effective pulmonary vasodilator in term and near-term neonates with hypoxic respiratory failure (HRF) and PPHN. Seventeen prospective, randomized trials have been published on the use of iNO in this cohort.[13] One of the largest of these was the NINOS Trial sponsored by the National Institute of Child Health and Human Development (NICHD), in which 235 infants older than 34 weeks' gestation who had a diagnosis of HRF were randomized to iNO at 20-80 ppm versus standard ventilation management with 100% Fio_2. Nearly all infants enrolled had echocardiogram confirmation of pulmonary hypertension, although this was not required for study eligibility. The primary outcome was death or need for ECMO. Although the mortality rate was no different in either treatment arm, there was a 40% reduction in need for ECMO among the babies treated with iNO: 54% of infants required ECMO in the control arm while 39% required ECMO in the iNO treatment arm.[75] Follow-up of survivors at 2 years showed no difference in neurodevelopmental outcome between treated and control patients, although abnormal outcome occurred in 25% of all newborns evaluated.[74]

In a later multicenter trial of iNO in term and late preterm newborns, Clark and coworkers reported a 38% reduction in ECMO use but no difference in mortality among 248 infants with PPHN randomized to low-dose, short-duration (96 hr or less) iNO treatment versus control.[20] This study, unlike previous trials, showed a significant decrease in chronic lung disease in infants treated with iNO. These two studies led to the eventual FDA approval for the use of iNO in term and preterm infants.

Following the success of the NINOS Trial in reducing the need for ECMO in infants with severe HRF, Konduri et al. in 2004 conducted a blinded, prospective, randomized study of 299 infants comparing the use of iNO in HRF of moderate severity defined as an OI between 15 and 25 and Fio_2 requirement ≥80%.[53] Infants randomized to the iNO arm started at 5 ppm, increasing to 20 ppm if only a partial response was noted. Control infants received simulated iNO with nitrogen gas alone, but if their OIs exceeded 25, they, too, were given iNO at 20 ppm. Unfortunately, the trial was terminated for slow enrollment (34 months) and an interim analysis, which confirmed that early iNO therapy, as defined in this study, did not reduce the combined incidence of ECMO/mortality from 35%-20% as the initial hypothesis proposed. In fact, only 12 infants in either arm of the study required ECMO, less than 10% of enrolled infants with HRF.

In 2013, Konduri published a post hoc analysis of this same cohort of 299 infants with moderate HRF and reported that early administration of surfactant and iNO therapy at a lower acuity of illness (OI < 20) was associated with decreased risk of ECMO/death, worsening progression of HRF, and decreased hospital stay.[52] Early use of surfactant for infants diagnosed with parenchymal lung disease (i.e., respiratory distress syndrome, meconium aspiration syndrome, and pneumonia/sepsis but not PPHN alone) was associated with lower risk of death/ECMO ($P = 0.002$). These data were consistent with the finding reported earlier by Lotze et al. in which the need for ECMO was significantly reduced among infants with severe HRF and parenchymal lung disease who were treated with surfactant alone. Again, infants with "black lung" (i.e., isolated PPHN) did not benefit from surfactant therapy.[60]

A meta-analysis of the results from 17 randomized trials (including the three studies detailed earlier) of iNO use in term and late preterm newborns with PPHN demonstrated that 50% of hypoxic late preterm and term infants responded to iNO within 30-60 minutes. The Pao_2 in the patients treated with iNO was 53 mm Hg higher (weighted mean difference) than in controls, and the OI was 15 units lower than in control patients. Mortality was not reduced in any study of iNO, perhaps because ECMO was used as a rescue therapy in nonresponders in whom severe hypoxic respiratory failure persisted.[13]

Unfortunately, iNO has not been shown to benefit newborns with congenital diaphragmatic hernia (CDH) in the first 2 weeks of life (see Chapter 66). In a prospective, masked trial of 52 infants with CDH who were randomized

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separately in the NINOS Trial, iNO neither reduced mortality nor decreased the need for ECMO. In fact, the need for ECMO was higher in the CDH infants treated with iNO in this trial.[31] Clark et al. also reported lack of efficacy for iNO treatment in a similar cohort of 35 CDH infants randomized to iNO or standard therapy in the first 4 days of life.[20] In contrast, Kinsella's group reported iNO to be useful in treating a subset of older CDH patients after surgical repair, whose pulmonary hypertension by echocardiographic measurements remained severe at the time of elective extubation (26 ± 3 days). Although their respiratory status was much improved (OI average 4 ± 1) after surgical repair, 10 of 47 CDH infants were found to have late pulmonary hypertension and were successfully treated with iNO administered through nasal cannulae until subsystemic pulmonary artery pressures were achieved. The infants received iNO in this fashion for a median of 17 days (range 5-60 days).[50]

The toxicity of NO and its metabolites in the newborn lung warrant careful monitoring, particularly with regard to long-term exposure. Concern for methemoglobinemia (metHgb) is rare in newborns treated with 20 ppm iNO. In the NINOS Trial, infants who did not respond to 20 ppm of iNO did not derive additional benefit from 80 ppm, and a small number of infants exposed to the higher dose had elevated metHgb levels. For this reason, 20 ppm iNO is recommended as the starting dose for the treatment of PPHN in term/late preterm infants. Despite its known antiplatelet activity, there have been no increased bleeding complications reported among term or late preterm neonates treated with iNO in randomized clinical trials.

Given the available evidence, including the neurodevelopmental and general medical outcome information, term and late preterm infants with HRF unresponsive to oxygen, ventilator support, and inotrope/volume support of systemic blood pressure should be offered a trial of iNO. This therapy significantly reduces the need for ECMO in non-CDH infants with the number needed to treat (NNT) of 5.3.[13] Infants with CDH complicated by severe HRF and PPHN are unlikely to avoid ECMO with early iNO use.

Transient improvement in oxygenation can be seen with iNO, however, which may stabilize a CDH infant's clinical status prior to the initiation of ECMO or facilitate early surgical repair before ECMO.

Nitric Oxide in Premature Infants

In preterm infants, survival and outcome are limited by RDS and its sequelae, BPD. Findings from a substantial body of experimental work in developing animals suggested that nitric oxide may enhance lung growth and reduce lung inflammation independently of its effects on pulmonary vascular resistance. Improved outcome in term infants with HRF who were treated with iNO furthered the interest that iNO might substantially improve pulmonary outcomes in low birth weight infants, particularly those below 1500 g birth weight. However, the use of iNO was approached with trepidation because of the increased risk of intracranial hemorrhage in this high-risk cohort and nitric oxide's known antiplatelet effect. Early pilot trials confirmed acute improvement in oxygenation in preterm infants with severe HRF treated with iNO. However, survival was not improved, and the rate of intracranial bleeding was alarmingly high.

Several large randomized trials of iNO use in preterms have now been completed in which the primary outcome focused on survival without BPD[37] as well as incidence of intraventricular hemorrhage (IVH). In a single-center trial, Schreiber and colleagues randomized 207 infants with low birth weight (<1500 gm) to treatment with a 7-day course of iNO or placebo starting on the first day of life. The authors reported a 24% reduction in the incidence of BPD and death in the iNO group, largely accrued in the subset of infants with milder respiratory disease (OI < 6.94). A 47% reduction in severe ICH and periventricular leukomalacia (PVL) was also noted.[80] At 2-year follow-up, 24% of the iNO-treated patients had abnormal neurodevelopment compared with 46% of the control group (NNT = 5).[70]

Van Meurs and colleagues enrolled 420 newborns (401-1500 g birth weight) in a multicenter, randomized controlled trial through the NICHD.[93] Only responders (i.e., infants showing improved Pao_2) continued on iNO; the average treatment duration was 76 hours. They found no difference in the incidence of death or BPD at 36 weeks' postmenstrual age between the iNO and control groups. Post hoc analysis revealed that NO reduced these rates in neonates weighing more than 1000 g. However, a higher rate of ICH and PVL, noted in the infants weighing less than 1000 g (43% iNO vs. 33% control), was concerning. An editorial accompanying this manuscript, however, pointed out that Van Meurs and colleagues' patients were smaller, more immature, and had more severe respiratory failure at study entry compared with Schreiber's study, making comparisons between the trials problematic.

In 2006, two large, prospective, randomized trials of iNO in preterm babies were published in the United States. Kinsella and colleagues randomized 793 newborns less than 34 weeks' gestation within 48 hours of birth to 5 ppm iNO versus placebo gas for 21 days or until extubation. OI at study entry was 5.4-5.8. There was no difference in the incidence of death or BPD between groups. However, iNO reduced the incidence of BPD by 50% for infants with birth weights greater than 1000 g ($p = .001$, NNT 3). Low-dose iNO reduced the combined incidence of ICH, PVL, and ventriculomegaly for the entire study population receiving iNO ($p = .032$, NNT 16).[51]

Ballard and colleagues, also in 2006, reported on the outcome of their prospective, randomized, placebo controlled, and masked trial of iNO treatment in preterm infants at risk for BPD (NO CLD Study).[12] Five hundred eighty-two infants who required ventilatory support between 7 and 21 days of age were randomized (birth weight 500-1250 g). Infants were enrolled in the study with an estimated OI between 5 and 9; treatment with iNO versus placebo gas (nitrogen) lasted a minimum of 24 days. The incidence of

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survival without BPD was increased in the iNO treatment group (43.9%) compared with controls (36.8%, $p = .04$, NNT 14). This effect was largely noted in those starting treatment between 7 and 14 days of life, suggesting that early treatment is important to prevent BPD. One-year follow-up of study survivors was notable for decreased pulmonary sequelae in the iNO cohort, reflected in decreased medication requirement at 1 year of age.[39]

In 2010, Mercier reported the results of a large, multicenter, masked, placebo-controlled trial of inhaled nitric oxide (iNO) for the prevention of BPD in preterm infants. Eight hundred infants between 24 0/7 and 28 6/7 weeks' gestation were randomized from 36 centers in 9 countries in the European Union. Infants were enrolled within 24 hours of birth and received either low-dose iNO (5 ppm) or placebo (nitrogen gas) for 7-21 days. In this industry-sponsored study, neither survival nor the incidence of BPD at 36 weeks' postmenstrual age was improved with iNO treatment.[69]

Differences in study design, entry criteria, dose, and duration of iNO therapy across 14 prospective randomized trials of iNO therapy in preterm infants make it difficult to understand why this treatment appears efficacious in some studies but not in the majority of infants studied. To address this issue, an individual patient data analysis was performed on the outcomes in 96% of the 3430 individual infants enrolled in these prospective randomized iNO studies. This analysis concluded no statistically significant effect of iNO on death or CLD (59% vs. 61%; relative risk 0.96, confidence interval 0.92-1.01), or severe neurologic events on head imaging (25% vs. 23%; relative risk 1.12, 95% confidence interval 0.98-1.28, $p = .09$). Inclusion or exclusion of the NO CLD study (enrollment after 1 week of life) did not affect the results of this meta-analysis. The authors concluded that use of iNO for treatment of mild to moderate respiratory failure in preterm infants cannot be recommended.[9] Neurodevelopmental outcome reported from six of the 14 trials has shown no adverse effects in iNO-treated preterm infants compared to controls up to 5 years of age. Interestingly, in 2018 Askie reported racial differences in outcome among randomized iNO trials where more than 15% of enrollees were African American. This select cohort appeared to derive considerable benefit from inhaled nitric oxide compared to other races, a factor that had not been previously evaluated. African Americans had a significant reduction in the composite outcome of death or BPD with iNO treatment: 49% treated versus 63% controls, $p = .003$. While mortality was not different between racial groups, African-American infants had a significant reduction in the incidence of BPD: NNT of 7.[10]

Two meta-analyses, including an individual patient analysis of more than 3000 preterm infants enrolled in iNO trials, together with the 2011 NIH Consensus Statement and 2014 AAP Report, all recommending against the use of iNO in premature infants, should have laid to rest the hypothesis that inhaled nitric oxide improves outcomes of preterm infants with mild to moderate respiratory failure.[9,13,21,54] While the common practice of iNO use to prevent BPD has declined substantially, its use in premature infants is far from eliminated.

In fact, the rate of off-label iNO treatment in preterm infants has increased in the years following the NIH Statement discouraging the use of iNO in this population. A query of the Pediatrix Medical Group Data Workhouse on the rate of iNO utilization among 23-29 week preterm infants between 2009 to 2013 revealed an increase in the use of iNO from 5.03%-6.19%, a relative increase of 23%, $p = .003$.[26] Of all neonates who received iNO therapy, nearly half were less than 34 weeks' gestation. With preterm infants accounting for more than half of all "first exposure iNO days" each year of the study period, the authors describe this increased use of iNO in a manner contrary to clinical evidence and expert opinion as "fascinating and provocative." The Canadian Neonatal Network also reported that 4.2% of preterms less than 34 weeks received iNO between 2010 and 2013, with the highest use in the most immature infants. Sixteen percent of infants between 22 and 25 6/7 weeks' gestation received iNO within the first 2 weeks of life.[85] Why is this happening?

The prevailing thought is that there exist subsets of premature infants who, in fact, benefit from the use of iNO but were not addressed in the multiple trials described previously. Small case series of preterm infants, usually <1250 g, who share a history of HRF following premature prolonged rupture of membranes (PPROM) and oligohydramnios, is one such cohort. In a 12-year prospective study from Finland, 2.2% of infants <32 weeks' gestation met criteria for acute HRF with echocardiographic evidence of pulmonary hypertension. All 17 infants had a prenatal diagnosis of PPROM for >7 days; all received iNO following confirmation of PPHN at a median age of 4 hours with good response to iNO reflected in decreased OI and decreased oxygen requirement and ventilator settings. The median duration of iNO treatment was 35 hours; survival was 15/17.[3] The incidence of BPD was high (65%) but was not different between extremely low birth weight (ELBW) infants receiving iNO and well-chosen comparison groups. It would appear, then, that the response to iNO in premature infants associated with PPROM, oligohydramnios, and presumed pulmonary hypoplasia is pathophysiologically similar to classic PPHN in term infants. However, unlike their term counterparts with PPHN, these immature infants are not eligible for ECMO and the majority carry the extra burden of BPD should they survive.

In a retrospective cohort study conducted over a 6 year period, Baczynski reported the short- and long-term outcomes of 89 preterm neonates with acute severe pulmonary hypertension receiving rescue treatment with iNO. The primary outcome was survival without moderate to severe disability at 18 months of age. Forty-six percent of this cohort, with a mean gestational age of 27.7 weeks and 1077 g birth weight, responded to iNO with a decrease in Fio_2 ≥20% within one hour of iNO treatment initiation.

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Responders showed improved survival without disability: 51% versus 15%, $p < 0.01$ and lower mortality; 34% versus 71%, $p < 0.01$ compared to nonresponders.[11] The authors reported that preterm infants presenting with acute pulmonary hypertension after 3 days of age rarely responded to iNO therapy, however, particularly when associated with culture positive sepsis.

Nakanishi et al. investigated the characteristics of PPHN in ELBWs and its impact on neurodevelopmental outcome at 3 years of age. Among 12,954 preterm infants born in Japan between 2003 and 2012, the prevalence of PPHN was 8.1% (95%, CI 7.7%-8.6%) with a higher proportion as gestational age decreased: 18.5% for infants born at 22 weeks compared to 4.4% for those born at 27 weeks. The diagnosis of PPHN was determined during the peripartum period, utilizing echocardiographic assessment of pulmonary pressures, and/or greater than 10% difference in the pre- and postductal saturations. Among ELBW survivors seen at 3 years, those who had both BPD and PPHN had the lowest weights and head circumferences, as well as lower developmental quotient (DQ) scores, compared to those with BPD alone or those without BPD or PPHN. Of note, PPHN in this cohort was found to be an independent risk factor for visual impairment, even after adjustment for severe retinopathy of prematurity ≥ stage III. Greater than 60% of ELBWs with PPHN received nitric oxide treatment.[73]

Unfortunately, given the rarity of this finding of acute pulmonary hypertension in infants <32 weeks' gestation, the pursuit of a randomized trial of iNO therapy in this cohort seems unlikely.[32,49,52] Experts in the field of PPHN are particularly concerned about anecdotal reports of third-party payers refusing payment for any use of iNO in any preterm infants following the 2014 AAP statement reporting lack of efficacy of iNO in infants <34 weeks of gestation. The Pediatric Pulmonary Hypertension Network has proposed a prospective registry be established to identify preterms with HRF and PPHN, confirmed by echocardiographic assessment, who are treated with iNO or any other vasodilator as pulmonary hypertension therapy.[49] Although not a randomized control trial, this registry could provide outcome comparisons in premature infants who present with the diagnosis of HRF complicated by PPHN, a sicker cohort not addressed in the 14 randomized trials previously described.

In summary, the available evidence from randomized trials in low birth weight infants with mild to moderate lung disease demonstrates apparent lack of efficacy with iNO therapy. This is disappointing, especially in light of animal data that suggests that NO plays a vital role in lung morphogenesis. An NIH consensus statement on the use of iNO in preterm infants does not endorse the routine use of iNO, given the lack of consistent evidence. However, it does state that in rare clinical situations (i.e., pulmonary hypertension or pulmonary hypoplasia), iNO may be of benefit to preterm infants, but the risks and benefits as well as long-term uncertainties of use of this therapy in infants less than 34 weeks' gestation must be communicated with the parents.[21]

Alternative Treatments and Avenues for Future Research

Future clinical trials of nitric oxide will better define the neonatal subgroups for whom this inhalational treatment is efficacious. The optimum dose, when to start treatment, and how long to continue therapy require further refinement. For the 40%-50% of term and late preterm newborns with PPHN who fail to respond to iNO, or who do not sustain improvement in oxygenation, other drugs are now available for study. Particularly in countries with limited medical resources, alternative treatment to costly iNO or ECMO would be most welcome.

An alternate approach to the treatment of PPHN is to augment endogenous vasodilator therapy by inhibiting the rapid degradation of cyclic nucleotide second messengers, cGMP and cAMP, which play a central role in modulating smooth muscle relaxation in the pulmonary vascular bed. Phosphodiesterases (PDEs) have a wide distribution in normal mammalian tissues, with more than 11 distinct families based on substrate specificity and sensitivity. The neonatal lung is particularly rich in PDE5 and PDE3. PDE5 inhibitors block the degradation of cyclic GMP (NO pathway), and PDE3 blocks the degradation of cyclic AMP (prostacyclin pathway), both of which potentiate vasodilation.

Sildenafil is a specific PDE5 inhibitor marketed as Revatio for pulmonary hypertension and as Viagra for erectile dysfunction. In a double-blind, randomized, placebo-controlled study in 278 adults with primary pulmonary hypertension, sildenafil reduced mean pulmonary artery pressure and improved functional class of disease severity over 12 weeks of treatment. Sustained improvement over 1 year of treatment with sildenafil in adults with pulmonary arterial hypertension (PAH) was also confirmed, leading to U.S. Food and Drug Administration (FDA) approval for this drug in adults with PAH.[34] However, safety and efficacy of sildenafil to treat pulmonary hypertension in the pediatric and neonatal populations has not yet been established. Barst and colleagues studied the use of sildenafil in pediatric patients with pulmonary hypertension.[14] They randomized 235 children (ages 1-17 years old) who were treatment naïve to receive either a low, moderate, or high dose of sildenafil. All doses were well tolerated by their subjects. There was no difference in those treated with low-dose when compared to placebo, but improved outcomes were found in those treated with a moderate or high dose. However, in long-term follow-up at 3 years, those who were treated with high-dose sildenafil had a higher risk of death, although mortality rate was lower than that of the natural history of the disease. Based on the increased risk of death in the high-dose group and ineffectiveness of the low-dose group, the FDA published a warning on the use of oral sildenafil in pediatric patients, particularly for long-term use.

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There have been several small studies on the use of sildenafil in neonates with PPHN.[76] Four of these trials, including 137 patients, evaluated the use of sildenafil versus placebo in term or near term infants with PPHN. The trials reported that sildenafil improved oxygenation and decreased mortality in the treatment group, 5.9% versus 44% in controls.[46] These studies were conducted in resource-limited countries where HFV, iNO, and ECMO were not available.

In 2009, Steinhorn et al. published a study on the kinetics of intravenous sildenafil in 36 newborn infants with PPHN.[87] Affected infants were treated within 72 hours of birth for a mean duration of 77 hours. Sildenafil clearance increased rapidly over the first 7 days of life, presumably because of increased hepatic clearance. Adverse side effects were mild to moderate in severity and included hypotension (three subjects), labile blood pressure (one subject), and PDA (one subject). These data will pave the way for future clinical trials of this drug in newborns who are particularly sensitive to systemic vasodilation and $\dot{V}/\dot{Q}$ mismatch.

Large, prospective, randomized studies investigating the safety and efficacy of sildenafil as a single treatment agent or in combination with iNO for refractory PPHN have yet to be reported. Fortunately, a multicenter randomized clinical trial to test the efficacy of sildenafil in iNO-resistant PPHN is nearing completion (NCT01720524). For the time being, however, the benefit and safety of sildenafil remain uncertain in term and premature infants in settings where HFV and iNO are available for treatment of PPHN.

Milrinone, a PDE3 inhibitor, is widely used in intensive care as an inotrope and afterload-reducing agent. It has been described in case series to be useful in the treatment of PPHN, particularly in the face of left ventricular dysfunction.[55] Infants with PPHN refractory to iNO therapy have responded favorably to IV milrinone.[68] Prostacyclin (PGI_2) (Flolan, epoprostenol sodium), which causes pulmonary vascular relaxation through upregulation of cyclic AMP levels, has emerged as one of the primary chronic treatments of idiopathic pulmonary hypertension in adults and children, wherein the drug is delivered by continuous intravenous infusion in nanogram doses.[66] Systemic hypotension has been a limiting factor in neonatal use. All PGI_2 analogs have the limitation of an extremely short half-life and variable effects on systemic blood pressure. Prostacyclin analogs currently approved for adult use include the following[56]:

- Epoprostenol (intravenous)
- Iloprost (intravenous and inhaled)
- Treprostinil (oral, intravenous, and subcutaneous)
- Beraprost (oral)

Randomized trials of IV prostacyclin in PPHN have not been done as hypotension is a major concern. Iloprost has proven efficacious in adults with pulmonary hypertension and has been successful in small case series of PPHN. Its drawback is the requirement for aerosol treatments 8-10 times per day. In the NICU, given the time frame of PPHN, this could be achievable for short-term use. Blood pressure instability remains an issue with iloprost, as with any prostanoid; therefore, its use should be confined to investigational pilot trials for the time being.[2] Randomized trials, especially with inhalational prostanoids, would be most welcome.

Endothelin is a potent vasoconstrictor and a smooth muscle mitogen that may contribute to the development of PPHN. Increased endothelin levels have been measured in newborns with PPHN. Medications are available that block the endothelin receptors on vascular smooth muscle cells in the lung and ameliorate pulmonary vasoconstriction in adults with pulmonary hypertension. Bosentan is the most widely studied of these and is approved by the FDA for the treatment of pulmonary hypertension in adults. Bosentan improved cardiac index and reduced mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR); functional class also improved in adult patients treated with bosentan. Liver toxicity, which appears to be dose dependent, is seen in 25% of bosentan-treated adults.[2]

There have been two small, randomized, placebo-controlled trials of oral bosentan in PPHN. In a study of 47 infants with PPHN comparing bosentan to placebo in iNO naïve newborns, oxygenation improved in the treatment group and ventilator days were fewer in those receiving bosentan (4.3 days vs. 11.5 days). Survival was no different between the groups.[71] A multicenter trial (FUTURE 4 study) conducted over 2 years enrolled 21 infants with hypoxic respiratory failure and PPHN to receive bosentan ($n = 13$) versus placebo ($n = 8$). All infants were already receiving nitric oxide. The time to weaning from nitric oxide or the ventilator was not improved in the treatment group. Furthermore, it took 5 days for the blood concentration of bosentan to reach study state in the treated infants, which may have contributed to its lack of efficacy in acute PPHN.[86]

As with many new therapies, early reports of treatment response to iNO were almost euphoric. Randomized controlled trials have proven the efficacy of this inhaled vasodilator in mature infants with PPHN, but they have also tempered our enthusiasm with the reality that up to 40% of affected newborns with severe respiratory failure will not respond to iNO, many of whom still require ECMO support.

Last, the treatment of late-onset pulmonary hypertension in surviving infants with very low birth weight and BPD has emerged as a serious therapeutic challenge. Mortality in this cohort is high, and treatment with a variety of pulmonary vasodilators is being used with little evidence for which drug combinations are efficacious.[2,40] A study of patients with BPD and pulmonary hypertension reported survival rates of 64% at 6 months and 52% at 2 years after the diagnosis of pulmonary hypertension.[48] Mourani and coworkers reported the effects of long-term sildenafil use for the treatment of pulmonary hypertension in infants younger than 2 years with chronic lung disease stemming from the neonatal period.[72] Eighteen of 25 were infants with low birth weight and BPD. The drug was judged to be well tolerated and effective in treated patients; median treatment duration was 241 days (range 28-950 days). However, 28%

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of treated patients also received other drugs for pulmonary vasodilation, including iNO, calcium channel blockers, milrinone, and bosentan. Five of the 25 (20%) died during the 8-month follow-up period, emphasizing the vulnerability of this uniquely fragile cohort of NICU graduates.

Adjunctive therapies, such as those discussed above, appear promising and may enhance the benefit of iNO or replace this inhalational agent altogether. Within the relatively short period of neonatal intensive care, the discovery and use of one selective pulmonary vasodilator, namely iNO, represents a significant advance in the management of PPHN. Hopefully, we can look forward to several treatment options for pulmonary hypertension in newborns once the therapeutic efficacy of these agents has been rigorously tested.

Key Points

- ECMO is a heart/lung mechanical support for mature neonates with severe hypoxic respiratory failure/PPHN who have not responded to ventilatory support or inhaled nitric oxide.
- Venovenous bypass is the preferred mode of ECMO support, but venoarterial bypass is required if the infant's cardiac output is not sufficient to meet oxygen delivery needs.
- Survival of ECMO patients in the NICU is tied to their underlying diagnosis, for example, 50% survival in CDH infants versus 90% survival in meconium aspiration syndrome infants.
- The number of infants requiring ECMO support for hypoxic respiratory failure in the United States has declined more than 50% over the past 25 years.
- In mature newborns with respiratory failure, the use of inhaled nitric oxide has been shown in multiple prospective randomized trials to significantly reduce the need for ECMO.
- Inhaled nitric oxide in premature infants with mild to moderate lung disease does not improve survival or prevent BPD.
- Pulmonary hypertension develops in up to 20% of infants with BPD, worsening survival in this high-risk cohort.

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71

Cardiac Embryology

STEPHANIE M. FORD, MICHIKO WATANABE, AND ERIC J. DEVANEY

Introduction

Congenital heart defects (CHDs) affect about 1% of all live births around the world, with variations in reporting depending on birth rates and access to medical care.[73] The care of children with CHDs has increasingly become a neonatal specialty, aided by prenatal detection. The fetal diagnosis of critical CHDs decreases postsurgical morbidity and mortality,[27] and reparative or palliative cardiovascular surgery is commonplace in the first months of life. This success has led to a larger population of adults with CHDs and an expansion of a subspecialty for the care of these individuals. In parallel with these clinical advances, there has been exciting progress in understanding the cellular and molecular basis of normal and abnormal cardiogenesis and the relationship of heart defects to other congenital defects. The global incidence of CHDs has not decreased and has in fact increased as prenatal detection becomes more common worldwide.[73] Yet our knowledge of the pathogenesis of CHDs is far from complete. Understanding normal and abnormal cardiac embryology is critical to understanding the pathology underlying CHDs and ultimately their prevention.

The mature heart is the product of gene expression driven by endogenous and exogenous influences. The developing heart manifests its morphologic and physiologic plasticity under environmental stimuli. A detailed understanding of the factors that drive normal cardiogenesis is necessary for understanding the causes and consequences of abnormal development. Errors in cardiac morphogenesis involved with septation, valve formation, and proper patterning of the great vessels are responsible for most forms of CHDs. Normal heart development requires precise timing for coordination of the complex three-dimensional contortions of tissues; but paradoxically, these tissues also have a remarkable capacity for modification that compensate for mistakes. These adjustments allow abnormal heart structures and resultant function to be compatible with life up to and even after birth, but they complicate identification of the primary causes of cardiac anomalies. This chapter will focus on clinically relevant aspects of cardiac embryology and how disruptions of this process may lead to CHDs.

Overview of Normal Heart Development

The following description of human heart development, especially the earlier events, is synthesized from information provided by studies of animal models and human embryonic and fetal tissues. A timetable of selected events in human heart development is presented in Fig. 71.1,[63] which depicts the major transitions in early mammalian heart development.

The primordia of the heart are formed by bilaterally symmetric heart fields derived from the lateral plate mesoderm. These primordia migrate through the primitive streak, between the ectoderm and endoderm layers, to become symmetric mesoderm regions on either side of the primitive streak. During body folding, the primary heart fields fuse cranially and ventrally to form a tubular structure comprising an inner layer of endocardium, a thick layer of extracellular matrix, and an outer layer of myocardium. This apparently "simple" tube begins to contract rhythmically and grows differentially so that dilations (primordia of the heart chambers) and constrictions (primordia of the partitions between chambers) appear along its length. Later additions from the second heart field to the distal ends of the tubular heart form the outflow tract (OFT) and the sinus venosus. Dextral looping of the tube brings the venous caudal portion to a more dorsal position and to the left of the arterial cranial portion as septation of the tubular heart begins. The epicardium arises from tissue dorsal to the heart at the level of the atrioventricular (AV) junction and spreads over the outer surface of the myocardium as a layer of squamous epithelial cells and associated connective tissue during the early phase of septation.

The atrial chamber divides into two chambers by the growth of the septum primum, which forms perforations to create the foramen secundum. A second atrial septum subsequently grows to the right of the primary atrial septum and forms a one-way valve (right-to-left blood flow) between the two atria in the fetus. This avenue of blood flow, the foramen ovale, is permanently closed shortly after birth to functionally complete atrial septation. Ventricular septation is not complete at the time the primary atrial septum is formed. The ventricular septum results from the growth and remodeling of trabecular sheets, continues with

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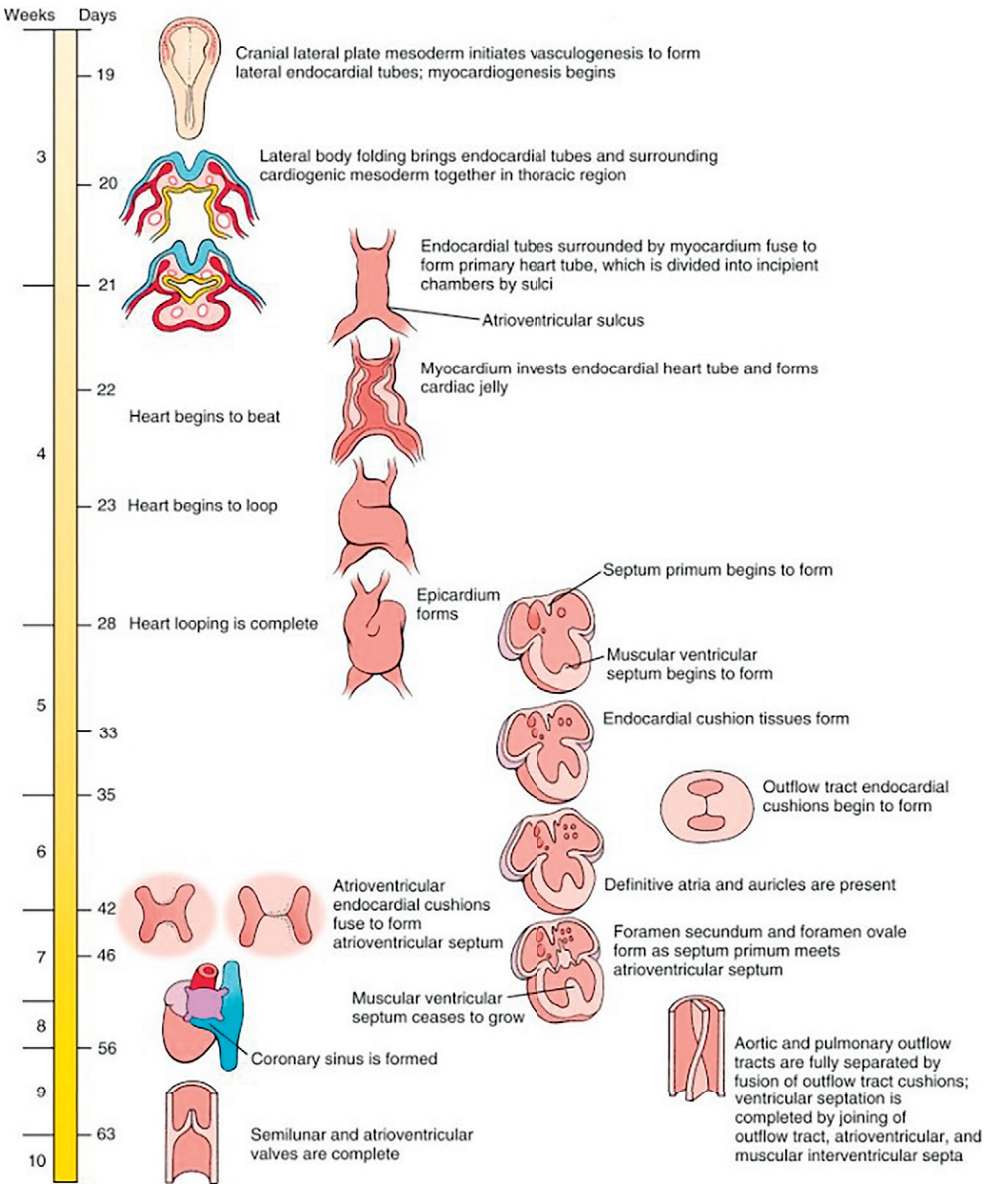
Abstract

Congenital heart defects (CHDs) affect about 1% of all live births worldwide, with variations in reporting depending on birth rates and access to medical care. The fetal diagnosis of critical CHDs decreases postsurgical morbidity and mortality, and reparative or palliative cardiovascular surgery is commonplace in the first months of life. This success has led to a larger population of adults with CHDs and an expansion of a subspecialty for the care of these individuals. Along with these clinical advances, there has been exciting progress in understanding the basis of normal and abnormal cardiogenesis. The global incidence of CHDs has not decreased and has, in fact, increased as prenatal detection becomes more common worldwide. Yet our knowledge of the pathogenesis of CHDs is far from complete. Understanding normal and abnormal cardiac embryology is critical to understanding the pathology underlying CHDs and ultimately their prevention. The mature heart is the product of gene expression driven by endogenous and exogenous influences. Understanding the effects of the factors that drive normal cardiogenesis is necessary for understanding the causes of abnormal development. Errors in cardiac morphogenesis involved with septation, valve formation, and proper patterning of the great vessels are responsible for most forms of CHDs. This chapter will focus on clinically relevant aspects of cardiac embryology that when disrupted lead to CHDs and touches on the efforts to predict, alleviate, and prevent CHDs.

Keywords

cardiovascular development
cardiac embryology
septation
congenital heart defects
congenital heart disease
neural crest cells

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• **Fig. 71.1** Overview of cardiac embryology in human gestation. (From Schoenwolf G, Bleyl S, Brauer P, Francis-West P. *Larsen's human embryology.* 5th ed. Churchill Livingstone; 2014.[63])

expansion of the ventricular chambers, and ends with the fusion of several tissues, including endocardial cushions from several sources and the muscular septum, to form the membranous and muscular interventricular septum. The outflow tract septation is the result of growth and fusion of spiraling ridges that eventually divide the truncus into aortic and pulmonary tracts. The venous and arterial vessels (aortic arches) undergo partial incorporation into cardiac chambers, differential degeneration, fusion, and growth to attain the mature structures.

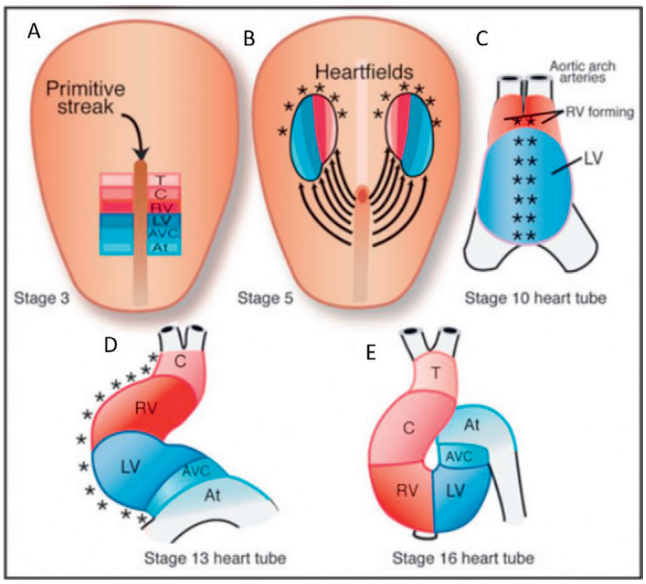
The human heart has completed the major morphogenetic processes 8 weeks after fertilization. What follows is the completion of maturation of structures, growth, accumulation of cellular junctions at the intercalated discs, biochemical and metabolic adjustments, and compensation for the abrupt changes in patterns of blood flow at birth, such as permanent closure of the foramen ovale of the atrial septum and closure and fibrosis of the ductus arteriosus and ductus venosus.

Scientific Basis of Cardiogenesis

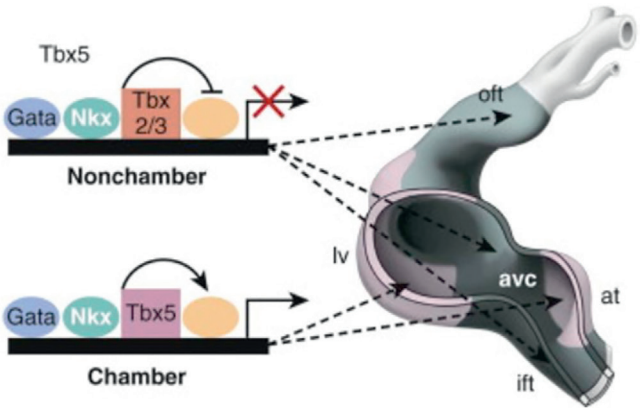
Precardiac to Cardiac Tissues: Commitment and Formation of Primary Axes

The tissue regions giving rise to the heart have been mapped by the application of dyes, particles, and radiolabels at stages when the vertebrate embryo comprises two layers: the epiblast (or primitive ectoderm) and the hypoblast (or primitive endoderm). The process of gastrulation, the movement of precardiac epiblast cells through the primitive streak, appears to be important in specification (Fig. 71.2*A*).[37]

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• **Fig. 71.2** Myocardial progenitors in the chick primitive streak and their fates in the heart tube **(A-E)**. The craniocaudal organization of progenitor cells **(A)** transitions as they migrate and assume a mediolateral orientation **(B)**. Cranial sections marked by asterisks **(B)** become the ventral portion of the heart tube **(C)** and later the right-most border of the looping heart **(D)**. At, Atrium; AVC, atrioventricular canal; C, conus; LV, left ventricle; RV, right ventricle; T, truncus. (Adapted from Kirby M. *Cardiac development.* Oxford University Press; 2007.[37])



• **Fig. 71.3** Model of transcription regulation of cardiac chamber and nonchamber genes. *NKX2.5, GATA4*, and *TBX5* are widely expressed in the developing heart and promote chamber-specific gene expression (chamber), whereas *TBX2* and *TBX3* are differentially expressed and inhibit chamber-specific gene expression by competing with *TBX5* binding (nonchamber). Chambers are the left ventricle (*lv*) and the atrium (*at*). Nonchamber regions include the outflow tract (*oft*), atrioventricular canal (*avc*), and inflow tract (*ift*). These proteins bind to DNA at specific sequences that are involved in controlling gene expression. The combinatorial effect of the binding of these proteins depresses or stimulates the transcription of cardiac-specific genes. (Modified from Christoffels VM, Burch JBE, Moorman AFM. Architectural plan for the heart: early patterning and delineation of the chambers and the nodes. *Trends Cardiovasc Med.* 2004;14(8):301-307.[12])

These cells migrate laterally to form the left and right heart fields (see Fig. 71.2*B*), which then create the horseshoe-shaped first and second heart fields around the end of the primitive streak, the primitive node. The second heart fields are adjacent to and influenced by cardiac neural crest cells, a process critical to understanding how the later steps in cardiogenesis are affected by neural crest–associated genetic syndromes.

Transcription factors are proteins that bind as part of complexes to specific DNA sequences and influence the expression of genes (Fig. 71.3).[12,18] Such factors influence many aspects of cardiogenesis[18] and include members of the following families: the helix-loop-helix proteins (dHand and eHand), zinc finger proteins (GATAs), homeobox gene proteins (NKX2.5), and MADS box proteins related to serum response factor. Of the zinc finger proteins, GATA4, 5, and 6 are much-studied members of the evolutionarily conserved transcription factor subfamily that recognizes a "GATA" DNA sequence motif. These have been implicated in the early specification of embryonic tissue destined to become heart.

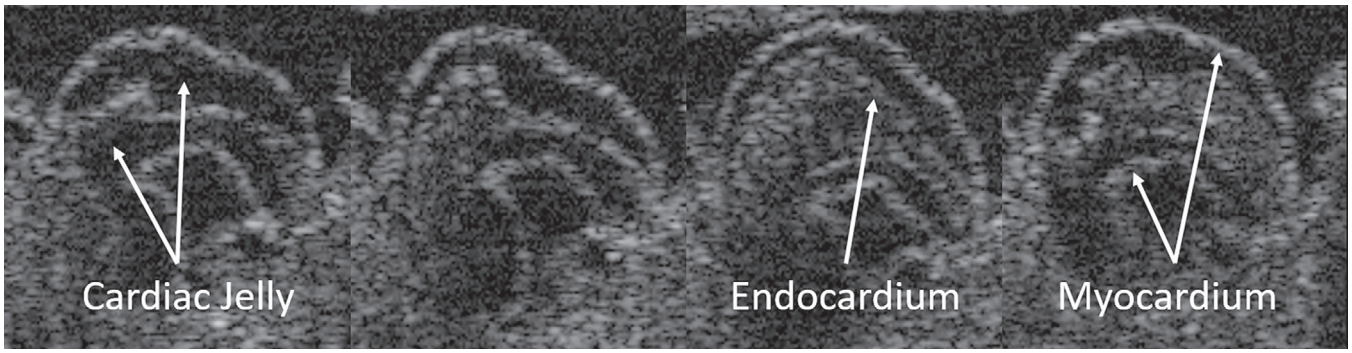
An example from the homeobox gene family demonstrates how the study of fruit flies has advanced our understanding of human heart development. The dorsal vessel pumps hemolymph (insect blood) and is considered the insect heart. It is derived from mesoderm under the influence of homeobox genes. The mutation of one of these genes, *tinman*, results in absence of the dorsal vessel. Frog and mouse homologues of these homeobox genes were identified and localized in expression to the developing heart. Transgenic mice lacking a *tinman* homologue (*NKX2.5*) do not lack hearts but die at 9 days of development with severely abnormal hearts.[44] Humans in whom the *tinman* homologue *NKX2.5* is mutated suffer atrial septal defects with associated AV conduction delay and other complications.[56,67,68] The fruit fly findings led to the study of a set of genes critically important to many aspects of human heart development.

The Tubular and Looping Heart

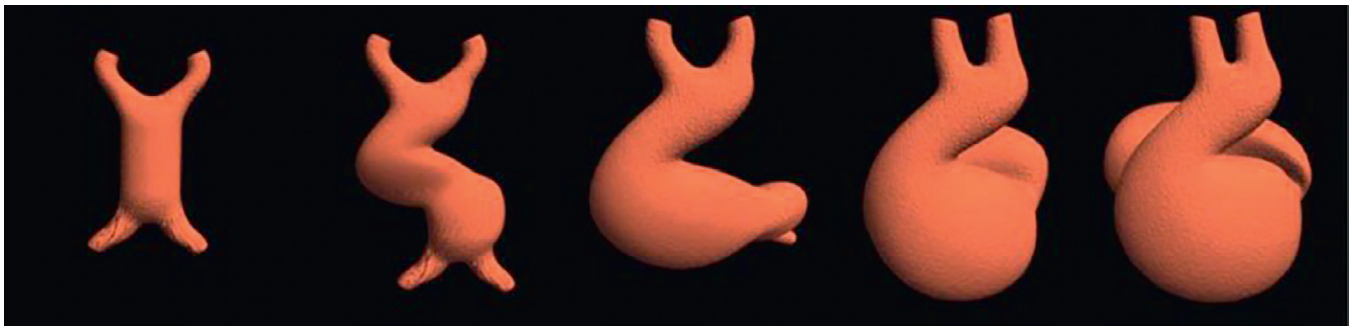
Within each side of the first heart fields primitive endocardial tubes form, come together, and fuse as the lateral body portions fold to create the primitive heart tube. The most caudal cells of the right and left heart fields will form the most ventral portion of the primitive heart tube (asterisks in Fig. 71.2). The inflow portion of the heart quickly gains pacemaker activity and initiates slow, unidirectional contractions along the tube. Concurrent with this process, endocardial and myocardial cells—which form the layers of the developing heart—emerge from a common precursor.[41] The myocardium secretes a thick layer of acellular extracellular matrix, also known as cardiac jelly, which creates a distinct layer between the myocardium and the endocardium (Fig. 71.4). This tissue progression requires cell differentiation, sorting, and polarization. Evidence supports both negative and positive influences from the surrounding neural tissue and endoderm on these processes.

The primitive heart tube undergoes three connected steps, looping, convergence, and wedging, all of which are

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• **Fig. 71.4** In vivo images of a quail heart. The images demonstrate portions of the cardiac cycle in a stage 14 quail embryo. The cardiac jelly is an acellular (black) layer between the myocardium and the endocardium.



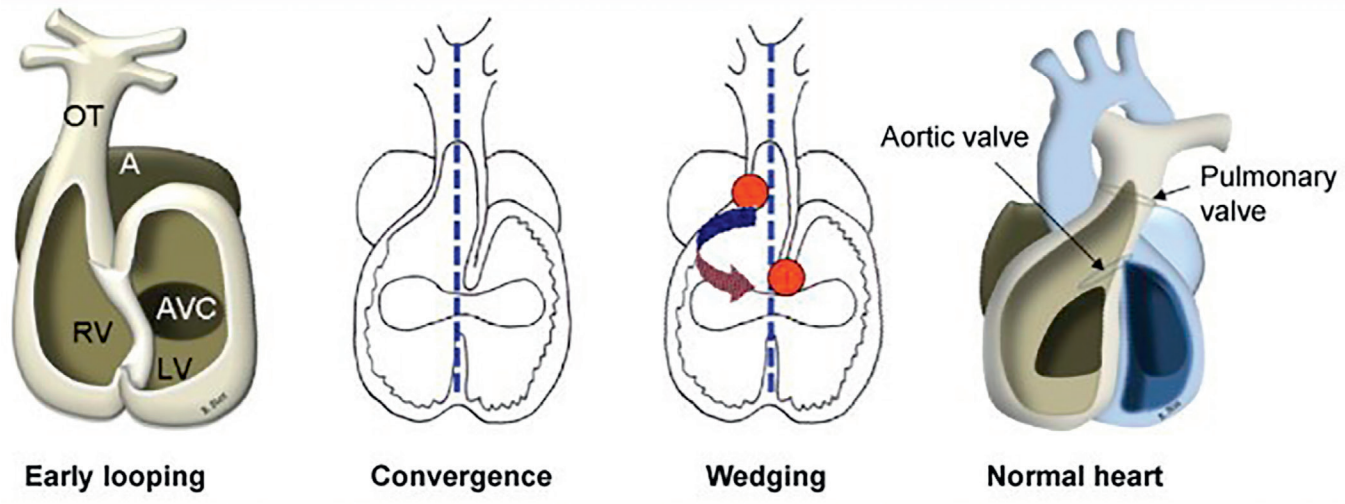
• **Fig. 71.5** The progression of looping in the tubular heart. (Modified from Schleich J-M, Abdulla T, Summers R, Houyel L. An overview of cardiac morphogenesis. *Arch Cardiovasc Dis*. 2013;106(11): 612-623.[62])

crucial to normal cardiac septation. Looping is the first obvious structural left–right lateralization in the developing embryo (Fig. 71.5). The heart tube elongates and folds into an "S" shape to the right. The direction of looping will determine the ultimate ventricular positions. Looping to the right will give the normal Dextro, or "D," looping. If the primitive tube loops to the left, this will result in Levo, or "L," looping and result in the left ventricle on the right side and the right ventricle on the left side. The left–right handedness of looping is directed by monocilia in the primitive node many stages before looping starts. These cilia are angled 40 degrees posterior and rotate in a clockwise direction, resulting in a leftward laminar flow of fluid containing key signaling molecules. Mutations in genes responsible for ciliary ultrastructure result in syndromes such as Kartagener syndrome.[28] Importantly, the primitive atrium is not involved in this portion of looping, so atrial position is not severely disturbed by abnormal looping. Atrial positions are affected by situs abnormalities as seen in heterotaxy syndromes. Left–right embryologic abnormalities have a wide range of known genetic causes in which mutations interfere with early breaking of left–right symmetry, abnormal signal transduction or gene expression in the lateral plate mesoderm, and abnormal morphogenesis of internal organs.[16]

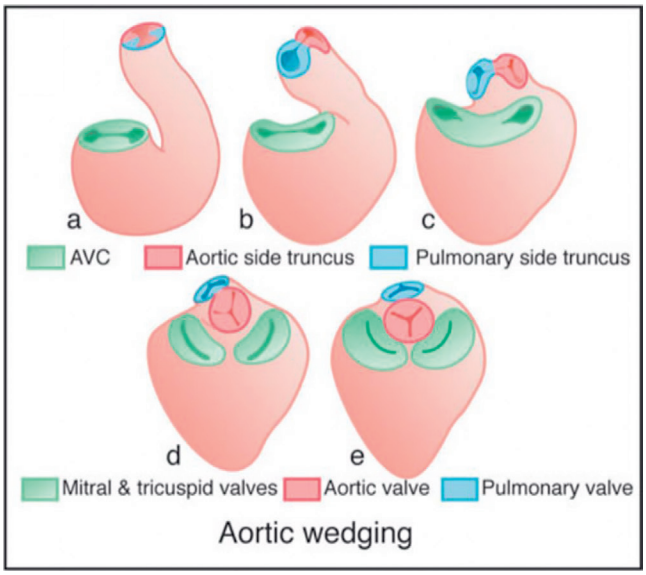
Convergence is the process of proper orientation of the inflow and outflow tracts (Fig. 71.6). The inflow tract rises cranially behind the outflow tract such that the inflow and outflow tracts are aligned, with the outflow tract ventral to the inflow tract. Abnormalities can lead to irregularities in atrial and ventricular septa and outflow tracts. Convergence and looping are dependent on lengthening of the polar ends of the heart tube, which is achieved by the addition of cells from the second heart field. The original primitive heart tube will grow to become the left ventricle and portions of the atrioventricular canal, and additions from the second heat field will direct formation of the outflow tracts, right ventricle, and atria. As cardiac neural crest cells influence the second heart field, it becomes easier to understand how neural crest cell–associated disease such as DiGeorge syndrome, 22q11 deletion syndromes, and velocardiofacial syndromes result in abnormalities of these cardiovascular structures.

Occurring in parallel with convergence and septation (see Figs. 71.5 and 71.6) is wedging (Fig. 71.7). Here, the outflow tract rotates counterclockwise approximately 45 degrees, resulting in the future aorta residing behind the future pulmonary artery (see Fig. 71.7). The aortic portion shortens, and the future site of the aortic valve "wedges" between the future tricuspid and mitral valves. This separates the mitral valve from the septum, which is why the mitral valve has no connections to the septal wall. Irregularities in wedging result in conotruncal defects such as tetralogy of Fallot and double outlet right ventricle.

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• **Fig. 71.6** The early stages of cardiac development while in the tubular phase include looping, convergence, and wedging. The red circles indicate the changing positions of the future aortic valve. A, Atrium; AVC, atrioventricular canal; LV, left ventricle; OT, outflow tract; RV, right ventricle. (Modified from Schleich J-M, Abdulla T, Summers R, Houyel L. An overview of cardiac morphogenesis. *Arch Cardiovasc Dis.* 2013;106(11):612-623.[62])



• **Fig. 71.7** Process of aortic wedging. The outflow tract descends and rotates **(a-c)**, aligning it with the center of the atrioventricular valves and canal. The area of the future aortic valve then migrates between the future tricuspid and mitral valves **(d-e)**. (Adapted from Kirby M. *Cardiac development.* Oxford University Press; 2007.[37])

How is the program for cardiac muscle differentiation turned on and regulated? This question has been approached by studying the transcription factors that bind to promoter regions of the cardiac-specific cytoskeletal genes coding for molecules that appear in the early tubular heart. The discovery of MyoD, a helix-loop-helix DNA-binding protein that controls skeletal muscle expression, led investigators to search for similar factors in cardiac muscle. Current findings support the idea that both positive and negative regulators of cardiac genes exist and that they work in complexes that define the spatiotemporal pattern of expression of cardiac genes (see Fig. 71.3).

Closely related to the question of cardiac-specific gene regulation is the question of regional specification of the heart tube. Segmentation, although not as obvious in the vertebrate heart as it is in the insect body plan, is important in cardiogenesis. Chamber-specific expression of a number of endogenous genes and promoter-driven reporter genes suggests that the outflow tract, the left and right ventricles, the atria, and the sinus venosus can in some cases be considered separate cardiac segments. However, many of the endogenous cardiac genes do not strictly follow chamber-specific expression but rather appear to be modularly controlled based on their position along the anteroposterior axis[25] (see Fig. 71.2).

An understanding of segment specification has been greatly advanced by the study of the homeobox genes in the fruit fly.[1] The identity and differentiation of segments are determined by interactions among homeobox and other genes. These interactions occur in the mesoderm, which gives rise to the heart tissues and the tissues adjacent to the mesoderm.

The vertebrate heart tube normally loops to the right side of the embryo. Sidedness appears to be influenced by factors acting at a time when the heart is not recognizable as a distinct organ structure.[58] Transplantation studies using the early chicken embryo suggest that left and right sidedness are already determined in the precardiac mesoderm stages. Sidedness can also be regulated in part by retinoids. Retinoic acid–soaked bead implants in chicken embryos or application of all-*trans* retinoic acid in mouse embryos cause transposition of the great arteries.[32] Abnormalities in the direction of cardiac looping also occur in humans.[8] These abnormalities are linked to an autosomal recessive gene defect that has been detected in the Amish population and

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another gene defect in the X chromosome (Xq24-q27.1) in the general population.[9] Interestingly, abnormalities in genes associated with left–right asymmetry may also be responsible for apparently isolated cases of congenital heart defects. Mutations in the laterality *CFC1* gene have manifested as transposition of the great arteries in humans without other obvious laterality defects.

Two mouse mutants have abnormalities in sidedness. The iv/iv mutant mouse develops L-looping and dextrocardia 50% of the time.[29] A large percentage of these mice have a combination of cardiac defects, including persistent sinus venosus, atrial and ventricular septal defects, common AV canal, double-outlet right ventricle, tetralogy of Fallot, and transposition of the great arteries. This gene has been mapped to mouse chromosome 12, which is homologous to human chromosome 14. The *inv/inv* mutant mouse develops *situs inversus* close to 100% of the time.[75] Mutation screens using the zebrafish have uncovered a number of genes involved in laterality specification and indicate that there are organ-specific laterality regulators.[11] Identification of the genes involved in these human, mouse, and zebrafish mutations could provide valuable insight into the mechanisms of normal dextral looping of the heart.[4]

Septation

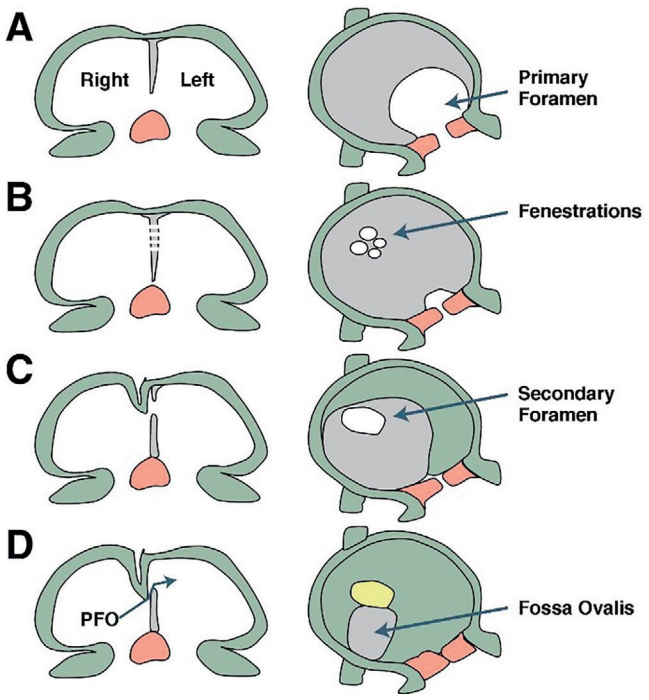
Endocardial Development: Formation of Cushion Tissue

Septation of the heart begins with the swelling of the extracellular matrix between the endocardium and the myocardium at specific regions of the heart tube. These regions include the AV junction, the outflow tract, the leading edge of the primary atrial septum, and the ridge of the interventricular septum. A complex set of inductive events has been elucidated by studying cushion formation of the AV junction and the outflow tract.[54] These events include signaling between the specialized myocardium and a subset of competent endocardial cells through growth factors (e.g., transforming growth factor-βs [TGFβs], vascular endothelial growth factor [VEGFs], bone morphogenetic proteins [BMPs]) and extracellular matrix molecules. Various proteases and homeobox genes are also involved.

The subsequent cascade of events includes release and migration of cells from the endocardial epithelium (termed *endothelial-mesenchymal transition*, EMT) into the previously acellular cardiac jelly and proliferation, death, and differentiation of these endocardial mesenchyme cells within a complex matrix. In the outflow tract, the cushions are also populated by cardiac neural crest cells. The endocardial cushions of the AV junction are also invaded by cells originating from the embryonic epicardium. The cushions eventually give rise to, or at least greatly influence, the subsequent development of septa and valves of the heart. Because a number of factors, cell types, and tissues are involved in this process at multiple levels and at different stages, there are many sites where mistakes can occur. It is, therefore, not surprising that septation defects are so common. The differentiation of resilient valves requires remodeling of the extracellular matrix, an aspect that is poorly understood. However, it has been revealed that steps in cardiac valve differentiation and maturation share mechanisms with those of cartilage, tendon, and bone development.[42]

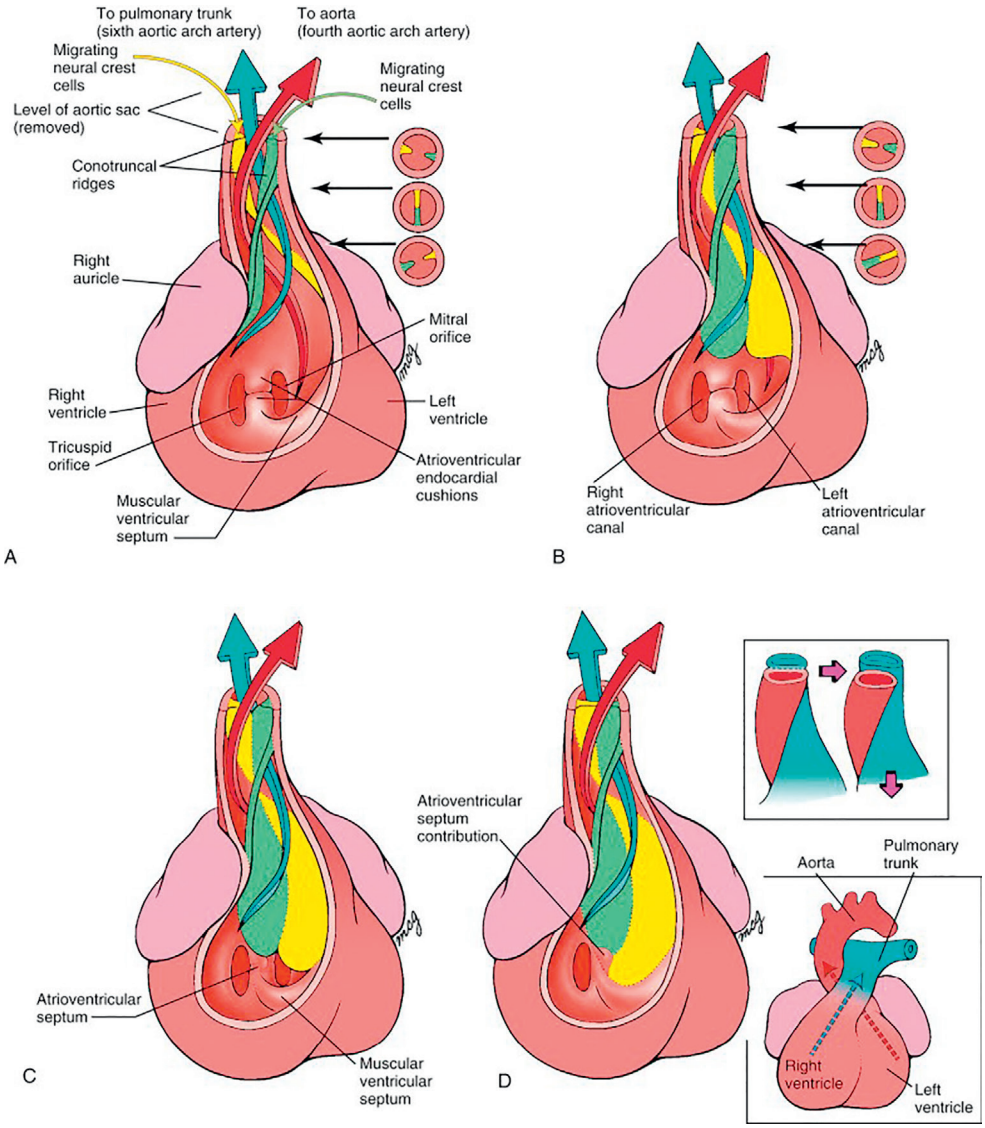
In the primitive atrium, a ring of tissue, the septum primum, grows toward the endocardial cushions near the AV junction (Fig. 71.8). Through apoptosis, fenestrations form in this tissue, creating the osteum secundum. The osteum primum, between the tip of this outgrowth of the septum primum and the endocardial cushion, closes as the tissue advances. The atrial roof folds inward, and the septum secundum begins to grow down on the right of the septum primum and continues in a crescent shape to form to the right of the base of the septum primum. This makes the septum primum a flap over the foramen ovale, allowing only right-to-left flow across the atria.

Ventricular and outflow tract septation occur in tandem, and aberrations in one may have structural consequences for the other. The myocardium from the outer curvature of the ventricle invaginates, growing cranially. AV canal endocardial cushions grow toward the myocardium, completing the ventricular septum. Outflow tract endocardial cushions form ridges that spiral along the conotruncus (Fig. 71.9).



• **Fig. 71.8** Atrial septation. The septum primum extends from the roof of the common atrium toward the endocardial cushion **(A)**. Fenestrations appear, creating the osteum primum **(B)**, and then the septum secundum descends from the roof of the atrium to the right of the septum primum **(C)**, covering the osteum primum. This creates the patent foramen ovale (*PFO*) through which blood can flow in a right-to-left direction but not in the reverse **(D)**. (Modified from Rana BS, Thomas MR, Calvert PA, et al. Echocardiographic evaluation of patent foramen ovale prior to device closure. *JACC Cardiovasc Imaging.* 2010;3(7):749-760.[59])

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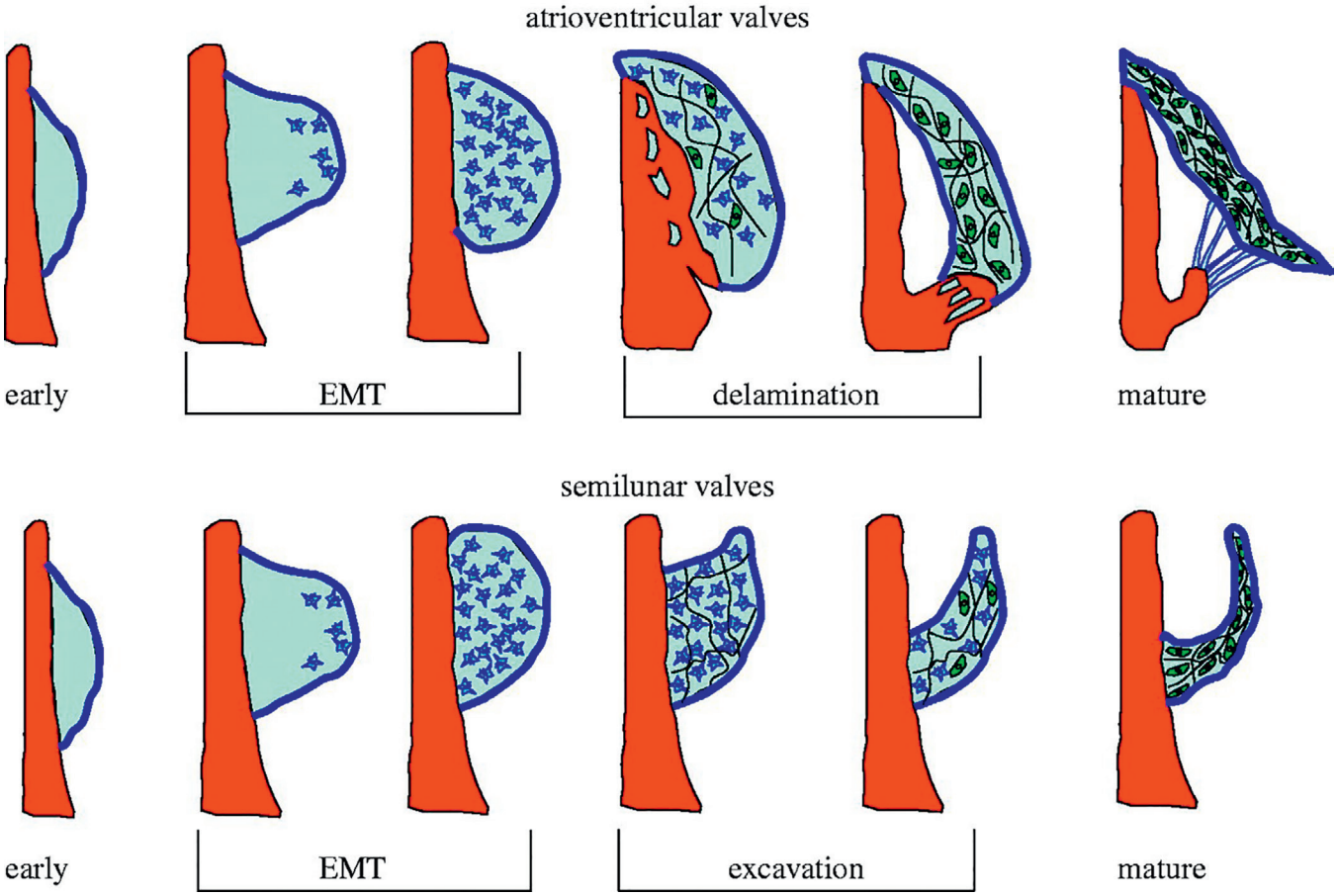
• **Fig. 71.9** Septation of the ventricles and conotruncus. A portion of the right ventricle has been removed to show the positions of the outflow tracts. Conotruncal ridges (*yellow and green*) grow from the outflow tract, creating a spiral septum represented here at multiples levels in **(A-B)**. This septum separates the aortic and pulmonary outflow tracts. The conotruncal septum then extends to the muscular portion of the ventricular and atrial septa, completing the ventricular septum **(C-D)**. (Adapted from Schoenwolf G, Bleyl S, Brauer P, Francis-West P. *Larsen's human embryology.* 5th ed. Churchill Livingstone; 2014.[63])

These ridges grow together to divide the conotruncus into the trunks of the aorta and pulmonary arteries. The AV canal and outflow tract endocardial cushions join, completing ventricular septation.

Endocardial cushions act as primitive valves and include the precursor cells of mature valves. During EMT, TGF-B and Notch signaling induce endothelial cells to adopt an invasive phenotype, and cells invade the previously acellular cardiac jelly. These cells adopt a mesenchymal phenotype to create fibrous tissue and collagen (Fig. 71.10). As the cushions grow, they delaminate from the myocardium, forming thin strands (chordae tendineae) that attach to outgrowths of myocardium (papillary muscles). The tricuspid valve attaches to papillary muscles on the interventricular septum as well as the free wall of the right ventricle. The mitral valve, however, has attachments only to the apex and the free wall of the left ventricle. Septal attachments do not form because the aortic valve displaces the primitive mitral valve from the septum during wedging. These early valve differences help identify ventricles during fetal and neonatal echocardiography.

Semilunar valve formation is similar to that of the AV valves. However, the apical surfaces of the valve leaflets develop depressions, eventually molding the leaflets into cusps (see Fig. 71.10). The arterial surface of the cusps become a more condensed fibrous tissue. Rather than chordae tendineae and papillary muscles, the leaflets extend attachments into the vessel walls to anchor them.

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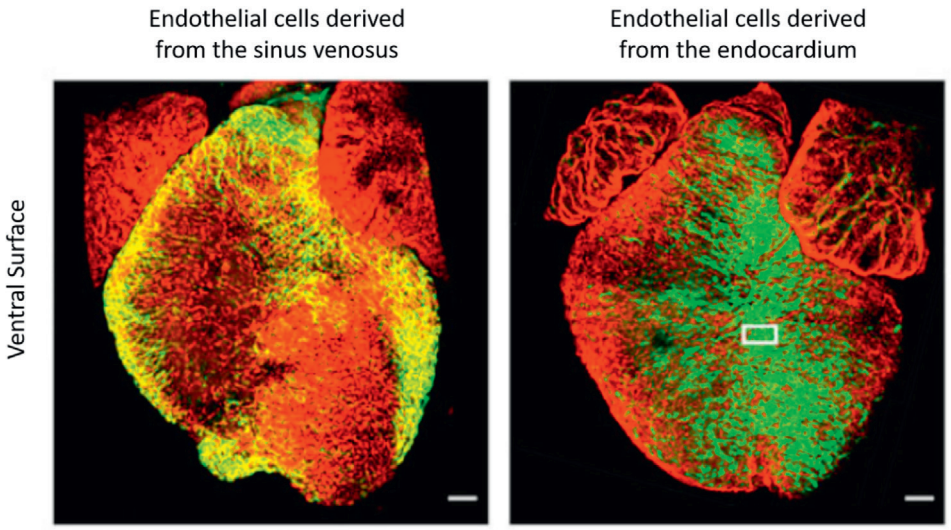
• **Fig. 71.10** Atrioventricular (AV) and semilunar valve formation. During looping, the myocardium secretes cardiac jelly, which is a gelatinous matrix rich in hyaluronan. Some of the myocardial cells lining these regions release factors that activate a subset of the overlaying endocardium, resulting in select endocardial cells that invade the cardiac jelly and assume a mesenchymal phenotype. This process is known as endothelial-mesenchymal transition (EMT). These cells proliferate, migrate, and differentiate. In AV valves, the portion of the cushions adjacent to the underlying myocardium differentiates onto a fibroblastic phenotype. Fenestrations develop and coalesce beneath this layer, resulting in delamination of the tissue from the developing cushion. Fenestrations also develop in the residual mesenchymal tissue strands, and these will develop into the tendinous cords of the AV valves. Semilunar valves form similarly, but instead of delaminating, they form conical depressions facing the myocardium in a process called excavation. Fibrous tissue radiates from the primitive valve cusps into the myocardial wall, anchoring the valve leaflets. (From Butcher JT, Markwald RR. Valvulogenesis: the moving target. *Philos Trans R Soc Lond B Biol Sci.* 2007;362(1484):1489-1503.[6])

Neural Crest Contributions to Cardiogenesis

A subset of neural crest cells that originate and migrate from the dorsal region of the neural tube contributes significantly to the development of the heart and associated vessels (Fig. 71.11).[30,47] The role of the neural crest has been determined by the study of avian embryos using immunohistochemical neural crest markers, transplantation (quail-chicken chimeras), ablation, and genetic manipulation of mice. The neural crest cells from the cranial and trunk regions contribute to the walls of the aortic arch arteries, including the proximal aorta, the stems of the proximal coronary arteries, and the sympathetic and parasympathetic innervation of the heart (including the cardiac ganglia). A subset enters the heart within the endocardium and is involved in septation of the aortic and pulmonary trunk. A subset also appears to enter the heart and regulates the formation and maturation of the cardiac conduction system.[24]

Neural crest cells migrate from the cranial region of the neural folds through the pharyngeal arches and contribute to the aorticopulmonary septum and the tunica media of the great arteries that branch from the aorta. Removal of this subset of neural crest cells causes cardiac inflow anomalies, including double-inlet left ventricle, tricuspid atresia, and straddling tricuspid valve; cardiac outflow anomalies, including persistent truncus arteriosus; and abnormalities in the aortic arch arteries, including interruption of the aorta, double aortic arch, variable absence of the carotid arteries, and left aortic arch. In contrast, the systemic and pulmonary venous structures are not as affected by cardiac neural crest ablation.

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• **Fig. 71.11** Origins of the endothelium: The ventral surface of the mouse heart with the sinus venosus-derived endothelial cells is labeled yellow (*left panel*) and the endocardial-derived cells are in green (*right panel*). (Adapted from Chen HI, Sharma B, Akerberg BN, et al. The sinus venosus contributes to coronary vasculature through VEGFC-stimulated angiogenesis. *Development.* 2014;141(23):4500-4512.[10])

A more global role for the cardiac neural crest is now recognized after the findings that removal or disturbance of cardiac neural crest cells can influence the function and proliferation of cardiomyocytes before neural crest cells migrate into the heart.[14] Findings point to a role for cardiac neural crest–derived cells in influencing the mesenchyme of the secondary or anterior heart-forming field that produces late-forming cardiac structures, including the outflow tract.[66,76] Because disturbances of neural crest development have the potential to cause cardiovascular anomalies, factors controlling normal neural crest cell development are receiving much attention. DiGeorge and related syndromes that include craniofacial and outflow tract abnormalities are believed to result from disruption of neural crest cell development.[19] These syndromes are often associated with deletions in 22q11, a region of human chromosome 22 that has been under close scrutiny.

The search for "the DiGeorge syndrome gene" was confounded by the number of candidate genes in the DiGeorge critical region and by the differences between the phenotypes of mice and humans mutated in homologous genes. It is also puzzling that individuals without the deletion can closely resemble those with the DiGeorge region missing. *TBX1* and *CRKL* are currently described as the best candidate genes within the most common 22q11 deletion. However, researchers continue to propose that there is no single affected gene responsible for the defects associated with DiGeorge or the 22q11 deletion syndrome. Rather, a combination of affected genes within that region, as well as those outside that region, appears to regulate the same critical cellular processes. Data suggest that many of the mutations identified in individuals with a range of craniofacial and cardiac syndromes that include DiGeorge syndrome are in genes associated with the extracellular-signal-regulated kinase (ERK) pathway.[2,52] These genes include upstream genes such as *TBX1* and *CRKL* and downstream genes such as *SRF*. A broader hypothesis is emerging that anything that dysregulates the activity of the ERK pathway up or down in developing neural crest cells results in craniofacial and cardiac syndromes.

Development of the Cardiac Conduction System

Primordia of the pulse-generating system function early in the caudal region of the tubular heart and allow unidirectional blood flow, but subsequent events in the development of the cardiac conduction system (CCS) are not well understood. Investigations of CCS embryogenesis in a variety of species, including the mouse, chicken, and zebrafish, have contributed to this understanding.[34] Classic histologic analyses are limited in the information they provide because the early CCS cannot be readily distinguished histologically or even ultrastructurally from the surrounding myocardium. Biochemical markers have been detected that transiently stain portions of the CCS and have been used to follow these tissues during the three-dimensionally complex morphogenesis of the heart. The rabbit model is unique in that there is a marker for it, NF-150, an antibody against neurofilament proteins, that delineates its cardiac conduction system throughout development and into the adult. These markers show that some of the tissues that give rise to the CCS can be distinguished from other cardiomyocytes as early as the tubular heart stages, because they have a different pattern of gene expression and cell proliferation.

The role of the differentially expressed CCS markers is still not completely understood; nevertheless, the markers have clarified issues about normal and abnormal morphogenesis. Marking the early CCS by using the markers' specific properties has allowed the CCS to be used as a point of reference to deduce which portion of the heart is growing and moving relative to others.[51]

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Lineage tracing of myocardial cells provided clues to the origin of the CCS. The clonal relationship between CCS cells and working cardiomyocytes suggests that these specialized myocardia can be recruited from unspecialized myocardial cells. Evidence from avian systems supports the hypothesis that the vasculature can be the source of factors that initiate such recruitment, with endothelin-1 being a strong candidate for signaling.[22]

Less is known about the physiology of the developing CCS primarily because of technical barriers to resolution. This barrier is, however, being overcome by advances in biomedical engineering technologies such as optical mapping using voltage-sensitive fluorescent dyes and optical coherence tomography that allow the capture of images of the tiny beating heart at high spatiotemporal resolution. Different strategies are used by the embryo at different stages of cardiogenesis for coordinating the contraction of the heart. The tubular heart has a peristaltic-type contraction pattern resulting from a pulse-generating focus of cells and a slow distribution of action potentials radiating evenly from that region in all directions.[36] In the septating heart, alternating regions of relatively slow and fast conduction allow pumping of blood in one direction, with the endocardial cushions acting as primitive valves. Slow regions, the sinus venosus, atrioventricular junction, and outflow tract, cause a delay of the impulse conduction between chambers.[15] The ventricular conduction system achieves its mature morphology simultaneous with the appearance of the mature sequence of activation.[13] Subsequent differentiation allows for increasing speed of action potential conduction through the fascicular portion of this system and compensation for the growth of the heart. Maturation of the fibrous ring that separates the atrial from ventricular muscle and the connective tissue sheath around the conduction system also follows serving as insulative barriers to inappropriate conduction to neighboring working myocardium.

Epicardium

The epicardium is a relatively late-forming cardiac tissue that does not appear until septation is under way. It provides the bulk of the non-cardiomyocyte cellular components, including smooth muscle cells, fibroblasts, and endothelial cells. The progression of epicardial development has been studied in detail using avian and mouse models. The epicardium, the outer layer of the heart, forms by the growth of epithelial tissue from the dorsal mesothelium of the sinus venosus region. This single-cell layer spreads in a stereotyped pattern over the myocardium. The squamous epithelium of the primitive epicardium and the myocardium are initially juxtaposed, but a rapid accumulation and differentiation of connective tissue components between these layers ensues to thicken the epicardium. The cells within the epicardium invade the myocardium and the endocardium, giving rise to valve cells, fibroblasts, smooth muscle cells, and other components of the coronary vasculature.[45] The controversy regarding the origin of the coronary endothelial cells is understandable because of the apparently conflicting findings from lineage tracing studies. Using retroviral lineage tracing, precursor cells labeled in the pro-epicardial were found to give rise to endothelial cells as well as smooth muscle cells.[48] However, cre-lox lineage tracing using what appeared to be epicardial-specific promoters identified only a small subset of labeled coronary endothelial cells.[7,77] Other investigators using a novel lineage tracing approach showed evidence that endothelial cells come from the endocardial lining of the sinus venosus.[60] More recently, it was proposed that coronary endothelial cells within the myocardium originate from endocardial cells within the ventricles.[74] Another investigation using another lineage tracing method now proposes that the bulk of coronary endothelial cells come from the cells within the epicardium (subepicardial cells) that originate from the endocardium lining the atrium or sinus venosus.[70] These findings are not necessarily in conflict; the endothelium lining the myriad of vessels within the myocardium is likely to come from several sources, depending on location within the heart and the types of vessel (see Fig. 71.11).

The epicardium is also the tissue in which cardiac ganglia develop, nerves travel, and fat cells accumulate. Evidence suggests that the embryonic epicardium may also include cells that can contribute a subset of cardiomyocytes.[7,77] This interesting tissue and its interaction with the myocardium are the focus of much current research.

Lymphatics

Although it is known that the adult vertebrate heart has an extensive lymphatic network, the lymphatic vasculature of the embryonic heart has not been investigated in detail. The mature heart is thought to have two plexuses: (1) the deep plexus immediately under the endocardium and (2) the superficial plexus subjacent to the visceral pericardium.[23,49] The deep plexus opens into the superficial plexus, whose efferent vessels will form right and left collecting trunks. The study of lymphatic development during cardiogenesis is now revived with the identification of lymphatic markers. This area of study is in its early stages. One of the many questions not yet answered in this field is, where do the lymphatic precursors originate? Lymphatic cells, whether or not they arise in the epicardium, do end up in the epicardium surrounding coronary vessels. An understanding of the mechanisms driving development of the lymphatic vasculature of the developing heart and of lymphangiogenesis may help in treating edema or similar conditions.[38]

Cell Division and Cell Death

Differential control of cell division and cell death can in part account for the enormous differences in morphologic features of the various regions of the heart. For example, the cells of the thin-walled atria divide less than the cells of the thick-walled ventricle. The central structures of the fascicular CCS slow their proliferation rate early compared with surrounding myocardium.[64] Apoptosis—programmed cell death—is a developmentally controlled strategy in the morphogenesis of many structures. It occurs during the

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pruning of the nervous system and the sculpting of digits of the hands and feet, and it occurs at many sites throughout cardiogenesis.[55] Endocardial cushion mesenchyme cells, which include cardiac neural crest cells, undergo a high level of apoptosis during septation. A high frequency of apoptosis of cardiomyocytes occurs coincident with outflow tract morphogenesis. Experimental manipulation to increase or decrease cell death at this stage results in conotruncal abnormalities.[61] Thus, regulated apoptosis of outflow tract cardiomyocytes is critical for the normal docking of the great arteries with the ventricles. Environmental and genetic factors that alter the level of apoptosis at these critical stages and sites in the developing heart may contribute to congenital heart defects.

Human Genetics

The entire human genome is sequenced, and efforts have been made to allow clinicians, basic scientists, industry scientists, and others to tap into the database and exchange information. Knowledge of the human genome helps in predicting potential problems, forming the basis for the growing field of genetic counseling. In addition, the study of human genetics allows identification of regions of the genome that might be adversely affected in patients with heart disease. Eventually, this information may be used in developing therapies for heart disease. Comparison of the human genome sequences with those of many other species has also provided important information. Sequences conserved across species often indicate regions of a gene that are critical for a particular function and that are worth focused scrutiny. The field of human genetics also provides information for the basic sciences, the "bedside-to-the-bench" links. Genetic analysis of individuals with certain syndromes can pinpoint genes and proteins that can be studied in detail in the laboratory to identify critical functions.

Epigenetics is the field investigating gene regulation that does not involve any changes in the sequence of DNA but rather the modifications to DNA and histones. These modifications, including methylation and acetylation, regulate transcription and translation. In addition to getting DNA sequence data, epigenetic data may become part of the diagnosis and assessment of therapeutic efficacy.

Cardiomyopathies are intrinsic disorders of heart muscle that are generally classified morphologically as hypertrophic, dilated, restrictive, and arrhythmogenic.[5,71] A genetic basis can be identified in a majority of these lesions, usually a mutation in a sarcomeric or structural gene that results in contractile abnormalities. Hundreds of mutations in dozens of genes have been identified as causative in familial and sporadic forms of cardiomyopathy.[71] The ultimate cardiac phenotype can develop at any age but occasionally presents in the neonatal period.[40] Left ventricular noncompaction is an increasingly recognized (particularly in neonates) form of cardiomyopathy characterized by dense trabeculation of the normally smooth-walled left ventricular cavity. This is a poorly understood defect that may be caused by abnormalities in the Notch signaling pathway or mutations in various sarcomeric genes.[40,43] Ongoing genetic studies will be focused not only on the identification of genetic abnormalities leading to cardiomyopathy but an investigation of the factors that lead to clinical disease progression.

Therapy

Strategies to repair heart tissue are relevant to both pediatric and adult cardiology and have been the focus of much effort. However, human myocardial cells lose their ability to divide soon after birth, and this terminal differentiation appears to be irreversible. It had been believed that, within adult heart tissue, no stem cells existed that could be activated to replace defective or damaged cardiomyocytes. To overcome this hurdle, investigators have been attempting to initiate cell division in cardiomyocytes[20,35] or stimulate myocardial differentiation in fibroblasts.[3,31] Fibroblasts are used because they continue to divide, are abundant in the postnatal and adult myocardium, and have been successfully transdifferentiated into myocardial muscle.[21,57]

Heart tissue appears amenable to such strategies. Myocardial cells (cell lines or embryonic myocytes) can integrate to some extent into the adult heart of animal models. Thus, they undergo some differentiation and integration in a foreign environment. Findings suggest that stem cells exist in the interstices of the adult heart and can be capable of differentiating into cardiomyocytes.[53] Endothelial cells, bone marrow cells, and umbilical cord cells are known to differentiate into cells with cardiac markers and are under study as potential candidates for use in cardiac tissue repair. Studies provide evidence, while controversial, that epicardial progenitor cells may have the capacity to contribute to the cardiomyocyte lineage in the developing heart.[7,77] Furthermore, investigators were able to induce the differentiation of adult epicardial cells into endothelial cells.[65] These findings suggest different strategies for therapy. The question remains whether any of these cells will be able to differentiate, integrate, and function appropriately in the adult heart as cardiomyocytes or endothelial cells without becoming malignant or causing malfunction. The potential for causing cancer or arrhythmias is possible with some of these therapies.

Commonly used graft materials offer no growth potential if used to correct tissue defects. However, the production of neo-vessels or neo-organ tissue from autologous cells using a biodegradable polymer scaffold is showing promise in the field of vascular tissue engineering. The autologous cells are seeded and produce an extracellular matrix with the inserted scaffolding eventually degenerating, leaving behind native-like tissue. Potential advantages of these tissue implants are that they will allow for growth, remodeling, and response to injury as the child ages, because these tissues resemble and act like original tissue.[39] Replacement heart valves are also being engineered using valvular interstitial cells seeded on a poly(glycerolsebacate) scaffold, and the mechanical properties of these valves have been retained or exceeded those of unseeded scaffolds.[46]

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A fairly new area of research is the study of micro-RNAs and their potential therapeutic value.[69,72] Micro-RNAs are single-stranded RNAs, about 22 noncoding nucleotides in length that are present endogenously. They act as specific regulators of gene expression in development and disease by interfering with translation of messenger RNAs or by enhancing the degradation of messenger RNAs. The ability of a particular micro-RNA to regulate RNAs from related sets of genes has raised the possibility that manipulating the levels of micro-RNAs may be a comprehensive strategy to prevent or reverse complex disease. The finding that sequences for micro-RNAs are found within the very genes they control is intriguing.

Gene therapy, in combination with intravascular stents, is being considered for treatment of coronary and peripheral vascular disease in adults. Exogenous genes can be introduced by a variety of means to the heart or vasculature. In vitro studies or those in animal models have also shown that physiologically significant genes (e.g., plasminogen activator) can be introduced and cause significant levels of protein expression for enough time to have therapeutic effects.

The most controversial approach for therapy involves manipulating the genome of the germ cells so that the entire embryo can go through development with the corrected gene. This approach requires that the manipulation result in little or no effect besides the desired effect. Introducing the gene into a genome can by itself cause inadvertent wide-ranging defects. Such methods also require a thorough understanding of the gene being manipulated so that all controlling elements, as well as the structural portion of the gene, are intact.

A recently discovered genetic editing method uses the strategy of the "immune system" of microbes.[50] Humans deploy a complex immune system to combat bacterial and viral intruders. Microbes like bacteria likewise have to combat viruses that can usurp bacterial cellular biochemistry for their own means. The bacteria do this by identifying and cutting up the foreign virus DNA, strategies adapted to the CRISPR/cas9 technique.[17,26,33] CRISPR is an acronym for clustered regularly interspaced short palindromic repeats, which is what is used to make a guide RNA that identifies the DNA sequence targeted for modification. Cas9 is the enzyme that cleaves double-stranded DNA at the identified site.

The previous DNA editing methods relied on using restriction enzymes that cut DNA at specific sites that would be close to, but not precisely, the site of interest. CRISPR/cas9, in contrast, allows more precise editing down to the nucleotide and is simpler and faster to complete. This has allowed rapid generation of genetic engineered mice and other model organisms. It also makes it feasible to precisely edit the human genome for therapeutic purposes. This technique is being rapidly optimized and will result in further breakthroughs in our understanding of molecular mechanisms of heart development and disease.

Another strategy in preventing congenital heart defects is to correct at a level farther along the pathway from the genome. This can be done by turning on alternative biochemical pathways or by boosting compensatory mechanisms. This approach requires a thorough understanding of the network of pathways and all of its interactions and feedback loops.

Finding the appropriate strategy for therapy is complicated, because defects involve a combination of genes and environmental factors and include direct and indirect effects that are difficult to control with current knowledge and techniques. However, with the great and often serendipitous advances in our understanding of cardiovascular development, certain defects might be preventable or reversed in our lifetime.

Key Points

- The majority of cardiac development is complete by 8 weeks' human gestation.
- Much of what is known about cardiac development is revealed by the use of animal and *in vitro* models.
- The primary heart field is responsible for the left ventricle and portions of the AV canal, whereas the second heart field, adjacent to neural crest cells, is responsible for outflow tract, right ventricle, and atrial formation.
- Looping of the primitive heart tube to the right (D) or left (L) will determine ventricular position, but not atrial position.
- Neural crest cells play multiple roles in the development of the function and structure of the heart and great vessels.
- The epicardium, the last heart layer to appear, plays roles in coronary vessel and valve development.
- As the web of genetic, epigenetic, and other molecular interactions is revealed by scientific inquiry, the apparent complexity of heart embryogenesis continues to expand.

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Pulmonary Vascular Development

ROBIN H. STEINHORN

Normal development of pulmonary vascular structure and function through prenatal and early postnatal life prepares the lung to perform its basic physiologic function of gas exchange across a thin blood–gas interface. Survival of the newborn is dependent upon rapid adaptation of the fetal cardiopulmonary system to the demands of extrauterine life. As development continues, normal lung function and growth depends on sustained low pulmonary vascular resistance. Abnormalities of vascular development can result in persistent pulmonary hypertension, which complicates the course and outcome of neonatal respiratory failure.

Fetal Pulmonary Vascular Development

Structural Development

Pulmonary vascular development begins during the embryonic phase of lung development and is highly coordinated with airway growth (Fig. 72.1). Endodermal lung buds arise from the ventral aspect of the foregut by the fifth week of gestation. The pulmonary trunk, derived from the truncus arteriosus, divides into the aorta and pulmonary trunks by 8 weeks of gestation by growth of the spiral aortopulmonary septum. The pulmonary trunk connects to the pulmonary arch arteries, which are derived from the sixth branchial arch arteries. The mesenchyme surrounding the lung bud then develops into the vascular network. In the human lung, the pre-acinar vascular branching pattern is present by the 20th week of fetal life. The intra-acinar arteries form later in fetal life and after birth during the alveolar phase of lung development. Development of the pulmonary veins parallels that of the arteries, but they arise separately from the loose mesenchyme of the lung septa and subsequently connect to the left atrium.

Angiogenesis and vasculogenesis are the two primary morphogenetic processes that form the pulmonary vasculature. Vasculogenesis is the de novo organization of blood vessels produced by the migration and differentiation of endothelial progenitor cells or angioblasts. These cells migrate, adhere, and form vascular tubes that become arteries, veins, or lymphatics depending on the local growth factors within the mesenchyme. Endothelial precursor cells, after differentiation into the endothelium, contribute either to the expression of smooth muscle phenotype in the surrounding mesenchyme or they recruit existing smooth muscle cells to the forming vessel. Angiogenesis refers to the budding, sprouting, and branching of existing vessels to form new ones. Vasculogenesis and angiogenesis are not necessarily sequential processes and both may occur early in lung development, perhaps giving rise to heterogeneous cell populations in the vasculature. In addition, a process of vascular fusion has been described that connects the angiogenic and vasculogenic vessels to allow for expansion of the vascular network.

Fetal lung septation and alveolarization begin at around 32-36 weeks' gestation in the human fetus and continue well into postnatal life. During this process, vascular growth and branching are tightly coupled with the growth and branching of the airway epithelium. The number of small pulmonary arteries increases, both in absolute terms and per unit volume of the lung. For example, in fetal lambs, lung weight increases by fourfold during the last trimester, while the number of small blood vessels in the lungs increases fortyfold. This dramatic increase in surface area of small blood vessels prepares the lungs to accept the tenfold increase in blood per unit of lung that occurs at birth. During the final stages of vascular development, the pulmonary capillaries surround the thinning alveolar walls, providing the increased alveolar and capillary surface areas necessary to support gas exchange at birth. Lung blood vessels actively promote alveolar growth during development and contribute to the maintenance of alveolar structures throughout postnatal life, and disrupted development of one system will have important consequences on the development of the other. Antenatal or postnatal events that affect the developmental program of the fetal or newborn lung may contribute to defective pulmonary vascular development.

The hypoxic conditions of fetal life support lung vascular growth. Hypoxia inducible factors (HIFs) are viewed as the "master regulators" of the transcriptional response to hypoxia and are involved in angiogenesis, survival, and metabolic pathways. HIFs are heterodimers consisting of oxygen-sensitive α-subunits (HIF-1α, HIF-2α) and constitutively expressed β-subunits. Hypoxia stabilizes the α-subunit, leading to nuclear accumulation and activation

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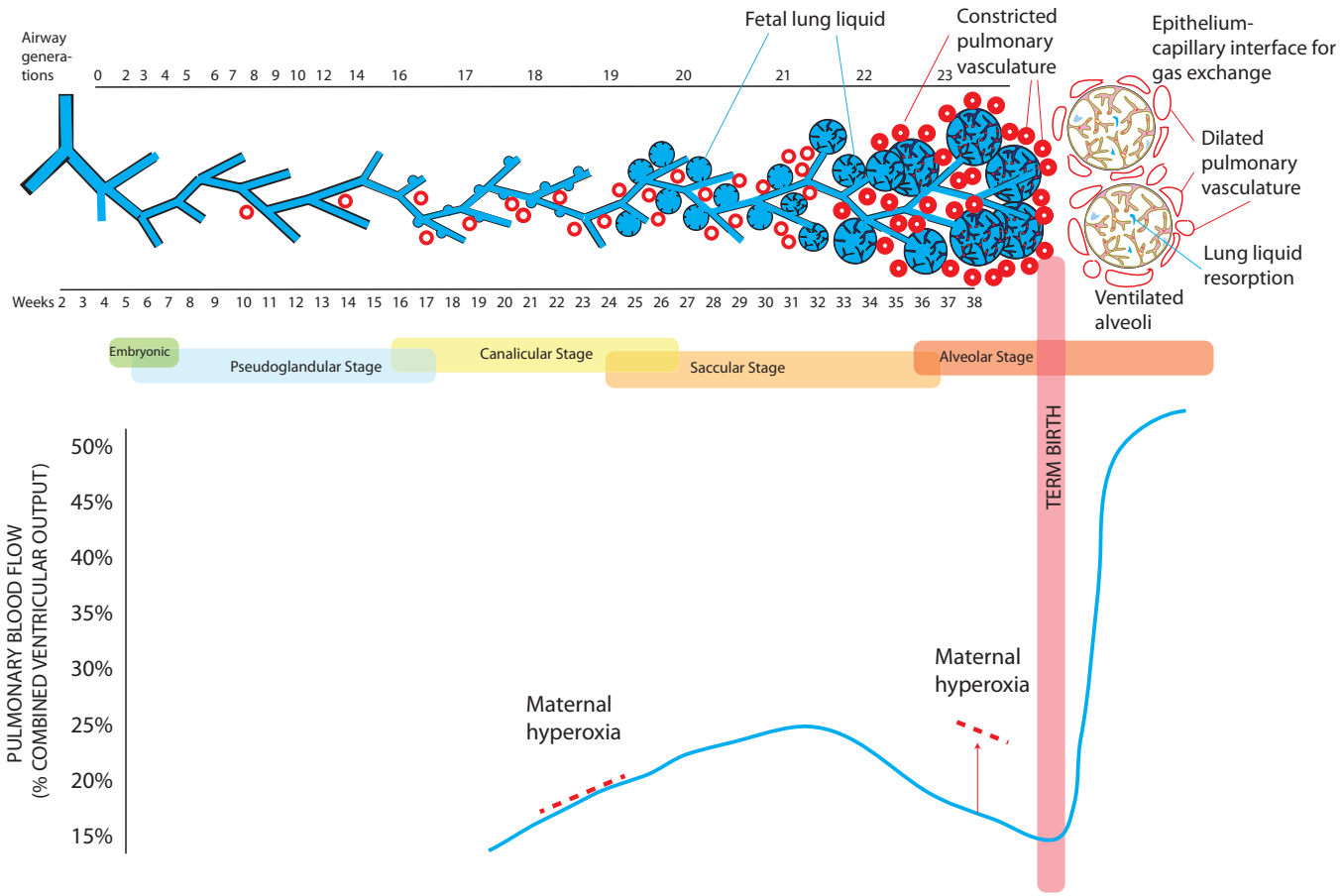
Abstract

Normal lung vascular development is supported by a hypoxic intrauterine environment, which promotes expression of hypoxia inducible factor (HIF) and vascular endothelial growth factor (VEGF). Maternal factors such as diabetes, high body mass index, smoking, use of SSRIs or NSAIDs, and caesarean section increase the risk of PPHN; postnatal factors include perinatal asphyxia, hyperoxia, hypoxia, infection, and lung inflammation. Medical management of PPHN requires lung recruitment, optimization of right and left ventricular function, and maintenance of PaO_2 between 60 and 80. Inhaled nitric oxide at 20 ppm improves oxygenation and reduces the need for ECMO support in term and near-term infants with PPHN. New therapies focused on downstream cGMP signaling, prostanoid signaling, and endothelin signaling are undergoing testing. ECMO support is indicated for term and near-term neonates with severe PH and/or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function. Infants that survive moderate to severe PPHN are at high risk for neurodevelopmental impairment and should receive neuroimaging and neurodevelopmental follow-up.

Keywords

pulmonary hypertension
pulmonary artery
nitric oxide
extracorporeal membrane oxygenation
endothelin

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• **Fig. 72.1** Changes in airway morphology and pulmonary vasculature during various stages of lung development and at birth. The cross-sectional area of pulmonary vasculature increases with gestation. However, pulmonary vasculature develops sensitivity to oxygen during later gestation, leading to hypoxic pulmonary vasoconstriction (thick red vessels). Pulmonary vasodilation secondary to ventilation and oxygenation at birth increases pulmonary blood flow. Changes in pulmonary blood flow (as a percentage of combined ventricular output) during the last half of human pregnancy and immediate postnatal life are shown in the bottom graph as a blue line. During early second trimester, pulmonary vasculature does not respond to changes in oxygen tension induced by maternal hyperoxia (*hyphenated red line*). During the third trimester, pulmonary blood flow increases with changes in oxygen tension (*hyphenated red line and red arrow*). After birth, following normal transition, the entire right ventricular output and left-to-right ductal shunt perfuses the lung, establishing this organ as the site of gas exchange during postnatal period. (Copyright Satyan Lakshminrusimha and Robin H. Steinhorn.)

of multiple target genes. HIF-1 regulates genes involved in angiogenesis (e.g., vascular endothelial growth factor), oxygen transport (e.g., erythropoietin), and energy metabolism (e.g., glycolytic enzymes), among others.[60] Deletion of HIF-1 or HIF-2 produces embryonic lethality, and knockout of HIF-1α in the smooth muscle cells of mice results in pulmonary hypertension.[38]

Vascular endothelial growth factor (VEGF) is expressed in vascular endothelial and smooth muscle cells and in airway epithelium in the fetal lung and is a key mediator of pulmonary vascular development. VEGF transcription is regulated by HIF, and VEGF signaling is transduced via two transmembrane tyrosine kinase receptors, VEGFR-2 and VEGFR-1 expressed on vascular endothelium. Experimental inactivation of VEGF or its receptors before birth results in embryonic lethality characterized by deficient organization of endothelial cells and vascularization; VEGFR-1 and VEGFR-2 inhibitors (e.g., SU5416) impair alveolar development in fetal and newborn rodent models, producing pathologic findings similar to those seen in clinical bronchopulmonary dysplasia (BPD).[27] In the clinical setting, decreased VEGF and VEGFR-1 mRNA and protein is observed in the lungs of premature neonates who died with bronchopulmonary dysplasia (BPD).[8] In adult rats, chronic VEGF receptor inhibition causes pulmonary hypertension and enlarges the air spaces, suggesting that normal VEGF function is required for the maintenance of the pulmonary vasculature and alveolar structures even after lung development is completed.[35]

VEGF-induced lung angiogenesis is in part mediated by nitric oxide (NO). Nitric oxide is best known for its role as a pulmonary vasodilator, but it also plays a key role in lung vascular growth during fetal and neonatal life. Lung endothelial nitric oxide synthase (eNOS) mRNA and

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protein are present in early fetal life in rats and sheep and increase with advancing gestation. The expression and activity of eNOS are regulated by multiple factors, including hemodynamic forces, hormonal stimuli (e.g., estradiol), paracrine factors (including VEGF), substrate and cofactor availability, oxygen tension, and others. The lungs of late fetal and neonatal eNOS-deficient mice have striking abnormalities of vascularization and are more susceptible to failed vascular growth following exposure to mild hypoxia.[5] Inhibition of VEGF receptors decreased lung eNOS protein expression and NO production, and lung vascular growth is restored by treatment with inhaled NO. However, in neonatal mice that are eNOS deficient, recombinant human VEGF protein treatment restores lung structure after exposure to mild hyperoxia, suggesting that VEGF operates in part through mechanisms independent of eNOS.

Numerous other transcription factors important to lung vascular development have been identified.[26] For example, the Forkhead Box (Fox) family of transcription factors regulate expression of genes involved in cellular proliferation and differentiation. Newborn mice with low *FOXF1* levels die with defects in lung vascularization and alveolarization, and endothelial-specific deletion of *FOXF1* produces embryonic lethality, growth restriction, and vascular abnormalities in the lung, placenta, and retina.[57] *FOXF1* haploinsufficiency is found in 40% of infants with alveolar capillary dysplasia, a lethal disorder of lung vascular development.[10]

Mediators of Fetal Pulmonary Vascular Tone

Pulmonary hypertension is a normal state during fetal life and a necessity for survival on placental support. In the fetal lamb, pulmonary arterial blood has a PO_2 of approximately 18 mm Hg and oxygen saturation of 50%.[59] Elevated pulmonary vascular resistance permits only ~16% of the combined ventricular output to be directed to the pulmonary vascular bed. Most of the fetal right ventricular output bypasses the lung via the foramen ovale and the ductus arteriosus and is directed to the descending aorta. The blood is then oxygenated in the placenta and returns to the body through the umbilical vein, with a PO_2 of ~32 to 35 mm Hg in lambs.

Multiple mechanisms maintain high PVR and low pulmonary blood flow in the fetus, including low oxygen tension, low basal production of vasodilator products (such as PgI_2 and NO), and increased production of vasoconstrictors. The fetal pulmonary circulation also exhibits a marked "myogenic response" as gestation progresses, meaning that the vasculature responds to vasodilatory stimuli with active vasoconstriction.

The low oxygen environment of the fetus plays a key role in maintaining high pulmonary vascular resistance. Maternal hyperoxygenation has no effect on human fetal pulmonary blood flow prior to 26 weeks' gestation but produces significant increases between 31 to 36 weeks of gestation, suggesting that the capacity of the pulmonary circulation to sense and respond to changes in oxygen tension is developmentally regulated. Because oxygen regulates activity of enzymes such as nitric oxide synthase, the low oxygen environment of the fetus may maintain low production of vasoactive mediators such as nitric oxide and prostacyclin. For example, maternal hyperoxygenation activates endothelial nitric oxide synthase and increases pulmonary blood flow to postnatal levels in fetal lambs.

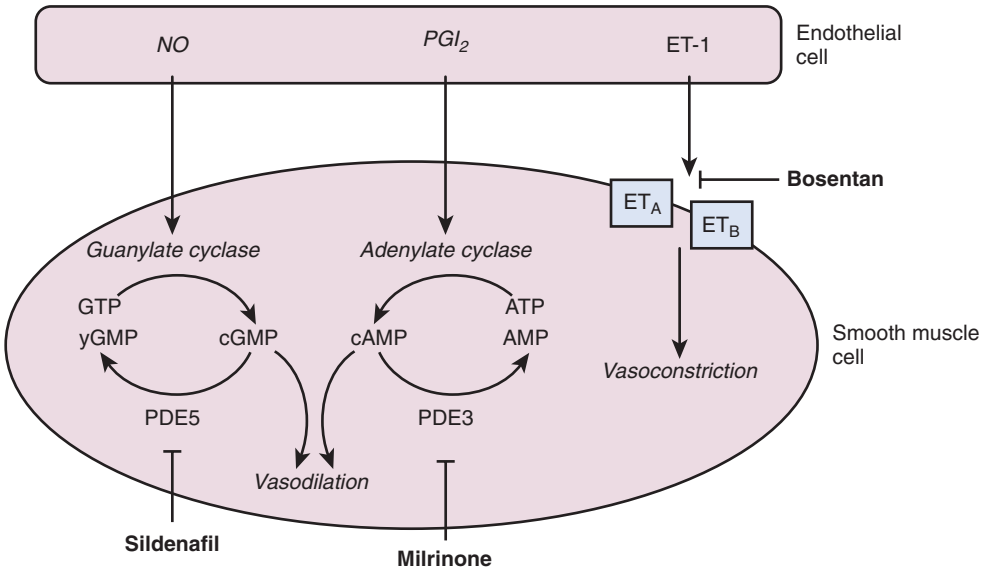
Pulmonary artery endothelial cells produce multiple vasoactive mediators that maintain the normal patterns of fetal pulmonary circulation. Proposed fetal pulmonary vasoconstrictors include endothelin-1 and lipid mediators, such as thromboxane and leukotrienes C_4 and D_4, and platelet-activating factor, but none have been shown to play a central regulatory role. Endothelin-1 (ET-1) is produced by vascular endothelium and acts on the ET-A receptors in the smooth muscle cell to induce vasoconstriction by increasing ionic calcium concentrations. A second endothelial receptor, ET-B, on the endothelial cell stimulates NO release and vasodilation. PreproET-1 mRNA (the precursor to ET-1) has been identified in fetal rat lung early in gestation, and high circulating ET-1 levels are present in umbilical cord blood. Although capable of both vasodilator and constrictor responses, ET-1 appears to primarily act as a pulmonary vasoconstrictor in the fetal pulmonary circulation.

Endogenous serotonin (5-HT) production also appears to contribute to the high PVR of the fetus. In fetal lambs, infusions of 5-HT increase PVR,[18,19] and infusions of ketanserin, a 5-HT 2A receptor antagonist, decrease fetal PVR. Conversely, brief infusions of selective serotonin reuptake inhibitors (SSRI), such as sertraline and fluoxetine, produce potent and sustained elevations of PVR. These findings suggest that 5-HT causes pulmonary vasoconstriction and contributes to maintenance of high PVR in the normal fetus through stimulation of 5-HT 2A receptors and Rho kinase activation. These findings have clinical implications for SSRI treatment for maternal depression.

Additional evidence suggests a critical role for the RhoA/Rho kinase signal transduction pathway, a central downstream pathway that promotes vasoconstriction through inactivation of myosin light chain phosphatase, thus increasing calcium sensitivity of the smooth muscle cell. Hypoxia activates RhoA, which increases Ca^{38+} sensitivity of the contractile myofilaments in the vascular smooth muscle. Rho kinase activity maintains high PVR in the fetal lung, and its inhibition dilates the perinatal circulation by a mechanism independent of NO.[3]

As gestation progresses, NO and cGMP become central to the emergence of pulmonary vascular reactivity. Chronic inhibition of VEGF receptors downregulates eNOS and induces pulmonary hypertension in the late gestation fetus,[30] indicating the importance of both in the development and function of the developing pulmonary vasculature. Inhibition of eNOS increases basal PVR as early as 0.75 gestation (112 days) in the fetal lamb, indicating that endogenous NOS activity contributes to vasoregulation during late gestation. The response to NO is dependent on

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• **Fig. 72.2** Schematic of the nitric oxide (NO), prostacyclin (PGI_2), and endothelin (ET)-1 signaling pathways. NO stimulates soluble guanylate cyclase to increase intracellular cGMP, and PGI_2 stimulates adenylate cyclase to increase intracellular cyclic AMP (cAMP). Both cGMP and cAMP indirectly decrease free cytosolic calcium, resulting in smooth muscle relaxation. Sildenafil inhibits PDE5 in vascular smooth muscle, and milrinone inhibits PDE3 in cardiomyocytes and vascular smooth muscle. ET-1 produced by endothelial cells binds endothelin A (ETA) and endothelin B (ETB) receptors on smooth muscle cells. The ET-1 receptor antagonist bosentan alleviates smooth muscle vasoconstriction by blocking ET-1 effects.

activity of its receptor molecule, soluble guanylate cyclase, in the smooth muscle cell (Fig. 72.2). In the fetal lamb, sGC mRNA levels are low through the second trimester and markedly increase toward the end of the third trimester. Intracellular cGMP levels are also tightly regulated by cGMP-specific phosphodiesterase (PDE5) activity. PDE5 expression and activity increase during late gestation, and it plays a critical role in pulmonary vasoregulation during the perinatal period. Overall, prostaglandins appear to play a less important role than NO in regulating fetal and transitional pulmonary vascular tone.

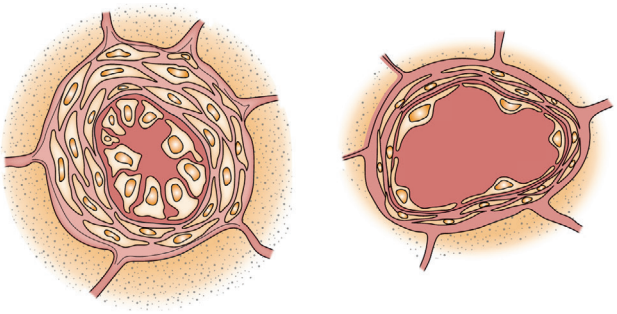
Pulmonary veins are now recognized to function as more than passive conduits; instead they are reactive vessels that contribute to the regulation of total pulmonary vascular tone and resistance. In perinatal sheep, both endogenous and exogenous NO increase intracellular cGMP content and relaxation to a greater degree in pulmonary veins than in arteries, effects that are oxygen dependent. Pulmonary veins are also the primary sites of action of certain vasoconstrictors such as endothelin-1 and thromboxane, and pulmonary venous constriction in turn increases microvascular pressures and promotes pulmonary edema.

Pulmonary Vascular Transition

At birth, the fetal pulmonary circulation must rapidly adapt to direct blood flow to the lungs as the organ of gas exchange. A rapid and dramatic decrease in pulmonary vascular resistance redirects half of the combined ventricular output from the placenta to the lung, leading to an eight- to tenfold increase in pulmonary blood flow. This increase in pulmonary blood flow will increase pulmonary venous return and left atrial pressure, promoting functional closure of the one-way valve of the foramen ovale. Systemic vascular resistance also increases at birth, in large part due to removal of the low resistance vascular bed of the placenta. The largest drop in pulmonary vascular resistance occurs shortly after birth, although resistance continues to drop over the first several months of life until it reaches the low levels normally found in the adult circulation. In preterm lambs, delayed cord clamping for 3-4 minutes until after ventilation is established improves cardiovascular function by increasing pulmonary venous return and left ventricular filling prior cessation of umbilical venous return.[9] As pulmonary vascular resistance drops and oxygen tension rises, blood flow through the patent ductus arteriosus reverses and the ductus arteriosus functionally closes. This effectively separates the pulmonary and systemic circulations and establishes the normal postnatal circulatory pattern.

The stimuli most important in decreasing PVR are lung inflation with a gas and an increase in oxygen tension. Each will independently decrease PVR and increase pulmonary blood flow, with the largest effects seen when the two events occur simultaneously. Mechanical distension of the lungs initiates the process of rapid structural adaptation of the pulmonary vessels. The external diameter of the nonmuscular arteries increases, and the prominent endothelial cells assume a flattened appearance (Fig. 72.3). There is an increase in cell length and surface-to-volume ratio as the cells "spread" within the vessel wall to increase lumen diameter and lower resistance. This process is likely facilitated by the paucity of interstitial connective tissue, allowing for

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• **Fig. 72.3** Changes in the small muscular pulmonary arteries during transition. Muscularized small pulmonary arteries from a near-term gestation fetus (*left*) demonstrate "swollen" endothelial cells and increased thickness of the muscular layer. Within 24 hours after birth (*right*), a considerable increase in luminal diameter is noted secondary to flattening of the endothelial cells, "spreading" of the smooth muscle cells, and an increase in external diameter caused by relaxation of the smooth muscle. These events contribute to the drop in pulmonary vascular resistance after birth. (From Lakshminrusimha S, et al. Pulmonary vascular biology during neonatal transition. *Clin Perinatol*. 1999;26:601-619).

greater plasticity of the vessel. In postmortem arterial-injected specimens, the number of nonmuscular arteries that fill with injection material increases rapidly during the first 24 hours, suggesting that there is a rapid increase in the number of precapillary arteries "recruited" into the pulmonary circulation after birth.

An increase in oxygen tension will reduce PVR independent of the effects of lung inflation. This oxygen response emerges at approximately 70% gestation in the fetal lamb and continues to develop as gestation progresses. The full vasodilatory effect of oxygen can be achieved with relatively modest increases in arterial concentrations: PaO_2 levels of ~50 mm Hg in the near-term fetal lamb will decrease pulmonary vascular resistance and increase pulmonary blood flow to levels comparable to postnatal lambs.[71] In addition to facilitating vasodilation, oxygen may also promote the rapid endothelial spreading and remodeling after birth.

Finally, the initial increase in pulmonary blood flow increases shear stress in the pulmonary vasculature, which further promotes rapid vasodilation in the pulmonary circulation of the newborn and late gestation fetus.[1] The mechanisms of shear stress-mediated responses are complex but involve stimulation of K^+ channels and activation of NO synthases.

Vasoactive Mediators of the Pulmonary Vascular Transition

Numerous vasoactive factors interact to facilitate the drop in pulmonary vascular resistance at birth, and increased vasodilator activity is probably more important than decreased vasoconstrictors. Of these, nitric oxide is a central mediator of pulmonary vascular tone at birth. NO stimulates soluble guanylate cyclase activity and increases cyclic guanosine monophosphate (cGMP) in vascular smooth muscle, producing smooth muscle relaxation via mechanisms involving decreased phosphorylation of myosin light chain (see Fig. 72.2). Pulmonary expression of all three isoforms of nitric oxide synthase (NOS) and its receptor molecule, soluble guanylate cyclase, increase late in gestation, preparing the lung for pulmonary vasodilation. Acute or chronic inhibition of NOS in fetal lambs produces pulmonary hypertension following delivery, illustrating the critical importance of the NO-cGMP pathway in facilitating normal transition. Expression of cGMP-specific phosphodiesterases also peaks at the time of birth, which maintains tight regulation of intracellular cGMP concentrations and signal transduction at birth.

Prostacyclin is a second central vasodilator that is upregulated in response to ventilation of the lung. Cyclooxygenase (COX) and prostacyclin synthase generate prostacyclin from arachidonic acid. COX-1 in particular is upregulated during late gestation, leading to an increase in prostacyclin production in late gestation and early postnatal life. Prostacyclin stimulates adenylate cyclase to increase intracellular cAMP levels, which, similar to cGMP, produces vasorelaxation through a decrease in intracellular calcium concentrations (see Fig. 72.2). Phosphodiesterase 3A (PDE3A) catalyzes the breakdown of cAMP. The decrease in PVR caused by PGI_2 at birth is modest in comparison to that induced by NO. Pharmacologic inhibition of cyclooxygenase does not prevent the drop in PVR after birth, indicating that while prostaglandin I_2 (PGI_2) is involved in the decrease in PVR at birth it is not absolutely required.

Abnormalities of Pulmonary Vascular Development

The most recent Nice classification of pulmonary hypertension was updated in 2013 and for the first time included a panel focused on pediatric disease.[64] Persistent pulmonary hypertension of the newborn (PPHN) is now included as a separate subcategory of pulmonary arterial hypertension (Group 1), recognizing its distinct anatomic and physiologic nature. The revised classification also recognizes the important role of abnormal lung vascular growth in the pathogenesis of pulmonary hypertension and impaired lung structure in developmental lung diseases. Conditions such as congenital diaphragmatic hernia, bronchopulmonary dysplasia, and other rare developmental disorders such as surfactant protein deficiencies and alveolar capillary dysplasia are listed in Group 3 (pulmonary hypertension caused by lung diseases and/or hypoxia).

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension (PPHN) describes the failure of normal pulmonary vascular adaptation at birth and is characterized by elevated pulmonary vascular

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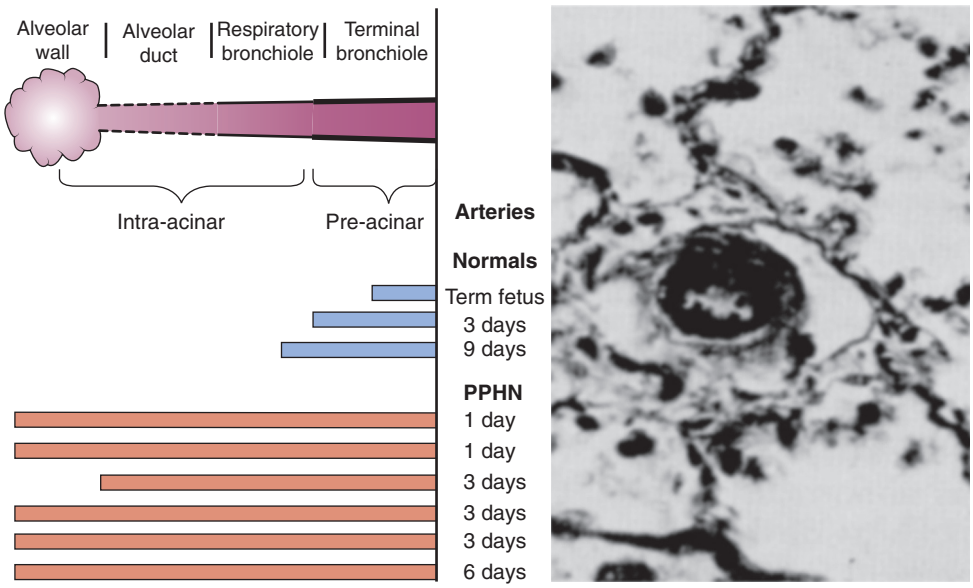
resistance and right-to-left extrapulmonary shunting of deoxygenated blood that produces severe hypoxemia. The PPHN syndrome complicates the course of approximately 10% of term and preterm infants with respiratory failure and carries a significant risk of death, pulmonary morbidity, and neurodevelopmental impairment. PPHN is often thought of as falling into one of three categories: 1) pulmonary vasoconstriction caused by lung parenchymal diseases such as meconium aspiration syndrome, respiratory distress syndrome, or pneumonia; 2) normal parenchyma and remodeled pulmonary vasculature, also referred to as idiopathic PPHN; or 3) hypoplastic vasculature as seen in congenital diaphragmatic hernia. While idiopathic pulmonary hypertension is responsible for only 10%-20% of all infants with PPHN, severe cases of PPHN associated with parenchymal disease are almost always complicated by a significant degree of vascular remodeling.

Significant pulmonary vascular remodeling occurs antenatally in infants presenting with early, severe PPHN, characterized by vessel wall thickening and smooth muscle hyperplasia. An important feature includes extension of the smooth muscle to the level of the intra-acinar arteries (Fig. 72.4), which does not normally occur until much later in postnatal development. Because it is difficult to gain sufficient mechanistic insights in the clinical setting, animal models have provided many of the insights into the antenatal and postnatal vascular abnormalities associated with PPHN.

Potential causes of antenatal remodeling of the pulmonary vasculature include environmental exposures or genetic risk factors. Maternal use of salicylates was one of the earliest triggers identified for PPHN, and earlier reports suggested a strong association between clinically significant PPHN and the maternal use of NSAIDs (aspirin, ibuprofen, naproxen). However, a recent large multicenter epidemiologic study found no significant association between PPHN risk and maternal use of nonaspirin NSAIDs or ibuprofen use during the third trimester.[73]

Conflicting evidence exists whether maternal selective serotonin reuptake inhibitor (SSRI) use during pregnancy increases the risk of PPHN. Exposure of pregnant rats to fluoxetine produces pulmonary hypertension, hypoxia, and increased mortality in the pups.[7,24] In human epidemiology studies, the use of SSRIs during the last half of pregnancy was associated with an increase in the incidence of PPHN, although recent reports indicate the risk is modest when controlling for maternal depression.[14,29,34,37,56] The severity of PPHN has also not been well described, and one recent report found that neonatal mortality rates were not higher in SSRI-exposed versus nonexposed neonates with PPHN (3.4% vs. 8.3%, p = NS).[53] The mechanism by which SSRIs induce PPHN remains poorly understood, although there is some evidence that SSRIs induce concentration-dependent constriction of the ductus arteriosus.[33] These findings are in agreement with a recent report from a large Swedish registry, which suggested that SSRI-exposed infants are more likely to have idiopathic PPHN without lung disease.[53] The FDA continues to recommend that health care professionals treat depression during pregnancy as clinically appropriate, indicating that neonatologists should be alert to signs of hypoxemia in neonates born to mothers who used SSRIs.

Unlike pulmonary hypertension in children or adults, PPHN is rarely familial, and few genetic risk factors have been identified. Endothelial cells generate NO from the precursor L-arginine, an amino acid supplied by the urea cycle. In term neonates with respiratory failure, with and without



• **Fig. 72.4** Vascular maldevelopment is a hallmark of PPHN. The pulmonary vessels show thickened walls with smooth muscle hyperplasia. Further, the smooth muscle extends to the level of the intra-acinar arteries, which does not normally occur until much later in the postnatal period. (From JD Murphy, et al. *J Pediatr.* 1981;98:962).

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PPHN, a polymorphism in the rate-limiting enzyme of the urea cycle, carbamoyl-phosphate synthetase-1, was associated with pulmonary hypertension, low plasma arginine concentrations, and low plasma nitric oxide metabolites.[54] Another single-center study reported the results of rigorous genotype analysis of 88 neonates with documented PPHN.[13] No differences were noted in most candidate genes, including BMPR2 and nitric oxide synthase. However, PPHN was significantly associated with genetic variants for corticotropin releasing hormone receptor-1 (*CRHR1*) and CRH-binding protein and with significantly increased levels of 17-hydroxyprogesterone. These data are supported by animal data indicating that antenatal and postnatal steroids reduce oxidant stress and normalize nitric oxide synthase and phosphodiesterase function in experimental PPHN.[15,55]

Children with Down syndrome (trisomy 21) commonly develop pulmonary hypertension in association with structural heart defects, and an elevated incidence of PPHN in the absence of cardiac disease has also been recognized.[16,61] In a Dutch cohort with excellent early ascertainment of Down syndrome, PPHN was documented in 5.2% of the infants.[77] Infants with Down syndrome are similarly overrepresented in the ECMO registry maintained by the Extracorporeal Life Support Organization, and their survival to discharge is significantly decreased compared to the general population.[65] Another recent study showed that 85% of autopsy specimens from Down syndrome children displayed pulmonary vascular remodeling.[12]

Delivery by elective cesarean section delays the decrease in pulmonary arterial pressure and increases the risk of PPHN,[48] and delivery before 39 weeks' gestation likely amplifies this effect. When compared to matched controls, infants with PPHN are more likely to have been delivered by cesarean section. Maternal diabetes, asthma, black or Asian race, and high body mass index are also important risk factors.[32,78]

Pulmonary hypertension complicates the course of 25% of infants with perinatal asphyxia. Fetal hypoxemia, ischemia, acidosis, meconium aspiration, and ventricular dysfunction delay the fall in PVR and increase the risk for PPHN. Acute asphyxia is associated with reversible pulmonary vasoconstriction, but chronic in utero asphyxia also induces vascular remodeling.[52] The adoption of therapeutic hypothermia for perinatal asphyxia raised concerns about its capacity to induce or aggravate PPHN in asphyxiated infants. Deep hypothermia (temperature decreased to 32°C) increased mean pulmonary arterial pressure by 30% in neonatal lambs and increased rates of PPHN and ECMO in human infants.[62] However, the effect of moderate hypothermia (33.5°C) on PVR appears to be modest, and analysis of randomized trials found that hypothermia does not significantly increase the incidence of PPHN.[70]

Disruptions in the production or function of vasoactive mediators in the perinatal period will also lead to pulmonary vasoconstriction and/or remodeling. Data from animal models and human infants indicate that disruptions of the NO-cGMP, prostacyclin-cAMP, and endothelin signaling pathways are among those that play an important role in the vascular dysfunction associated with PPHN. The NO-cGMP pathway has been a topic of particularly intense investigation, in part because of the ability to deliver inhaled nitric oxide gas as a therapeutic agent. Decreased expression and activity of eNOS have been documented in animal models, and decreased eNOS expression has been found in umbilical venous endothelial cell cultures from human infants with meconium staining who develop PPHN.[20] Furthermore, PPHN is associated with "uncoupling" of the eNOS enzyme, which reduces synthesis of nitric oxide and promotes production of reactive oxygen species, such as superoxide. Downstream vascular abnormalities include reduced levels of the critical second messenger, cGMP. For instance, in vascular smooth muscle from PPHN lambs, reduced cGMP concentrations are generated in response to NO, in part due to reduced activity of soluble guanylate cyclase and increased activity of cGMP-specific phosphodiesterase (PDE5). PDE5 activity is also elevated in fetal lambs with chronic intrauterine PH, and striking increases in PDE5 activity emerge in response to mechanical ventilation and oxygen therapy, further driving down cGMP levels.[21]

Less is known about the role of abnormal prostacyclin-cAMP signaling in PPHN. Some data suggest that abnormal prostacyclin synthesis and downstream adenylate cyclase signaling occur, analogous to the changes reported for NO-cGMP signaling. In addition, elevated production of the vasoconstrictor arachidonic acid metabolite, thromboxane, plays a role in pulmonary hypertension produced by chronic hypoxia.

Circulating levels of the potent vasoconstrictor endothelin (ET-1) are elevated in lambs and newborn infants with PPHN, and there is evidence that the balance of ET receptors is shifted to the vasoconstrictor (ET-A) pathways. In addition, endothelin may affect vascular tone by increasing production of reactive oxygen species such as superoxide and hydrogen peroxide, which also act as vasoconstrictors. Therefore, the elevated endothelin levels in PPHN may increase vasoconstriction through preferential stimulation of ET-A receptors and through increased production of superoxide.

Oxidant stress plays an important role in the pathogenesis of PPHN both antenatally and following birth. An increase in reactive oxygen species such as superoxide and hydrogen peroxide in the smooth muscle and adventitia of pulmonary arteries has been demonstrated in neonatal animal models of pulmonary hypertension.[11,23] Oxidant stress can be caused by immature or dysfunctional anti-oxidant defense mechanisms (e.g., superoxide dismutase, catalase) and/or increased activity of pro-oxidant enzymes such as NADPH oxidase, and reactive oxygen species can cause pulmonary vasoconstriction and trigger vascular remodeling as seen in PPHN.[11,40] Reactive oxygen species generated in response to hyperoxia can decrease eNOS expression and activity, decrease activity of soluble guanylate cyclase, and increase PDE5 activity, resulting in decreased cGMP levels.

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Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) represents ~8% of all major congenital anomalies and affects approximately 1 in 2500-3000 pregnancies when including patients identified by prenatal diagnosis. CDH includes abnormal diaphragm development, herniation of abdominal viscera into the chest, and a variable degree of lung hypoplasia. Herniation occurs most often in the posterolateral segments of the diaphragm, and 80% of the defects occur on the left side.

Severe CDH develops early in the course of lung development, and an arrest in the normal pattern of airway branching occurs in both lungs, resulting in reduced lung volume and impaired alveolarization. A similar developmental arrest occurs in pulmonary arterial branching, resulting in reduced cross-sectional area of the pulmonary vascular bed, thickened media and adventitia of small arterioles, and abnormal medial muscular hypertrophy extending distally to the level of the acinar arterioles. Although in utero lung compression by herniated viscera has been implicated as the primary mechanism responsible for producing the lung abnormalities of CDH, some evidence suggests that decreased pulmonary blood flow alone is sufficient to cause lung hypoplasia.[69]

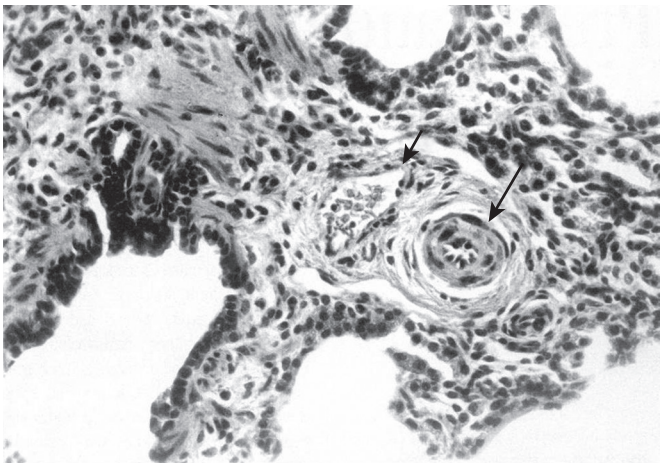
After birth, PVR often remains at suprasystemic levels, causing extra-pulmonary right-to-left shunting across the foramen ovale and ductus arteriosus and profound hypoxemia. High PVR in the newborn with CDH is related to multiple factors, including the small cross-sectional area of pulmonary arteries, structural vascular remodeling, vasoconstriction with altered reactivity, and LV dysfunction causing pulmonary venous hypertension. The mediators of altered pulmonary vascular reactivity in CDH are not well understood, although substantial evidence points to disruptions in NO-cGMP and endothelin signaling.[36] Chronic pulmonary hypertension is commonly seen in infants with severe disease and is associated with persistently high endothelin levels.[36]

Abnormalities of cardiac development and function also play an important role in the pathophysiology of CDH. The left ventricle, left atrium, and intraventricular septum are hypoplastic in infants that die of CDH relative to age-matched controls,[63] perhaps due to low fetal and postnatal pulmonary blood flow as well as compression by the hypertensive right ventricle. Left ventricular hypoplasia and dysfunction increase left atrial and pulmonary venous pressures, and the resulting pulmonary venous hypertension will diminish the clinical response to inhaled NO during the first few days of life. Some infants may have exceptionally severe left ventricular dysfunction that leads to dependence on the right ventricle for systemic perfusion; this subset may benefit from clinical strategies that maintain patency of the ductus arteriosus.

Alveolar Capillary Dysplasia

Alveolar capillary dysplasia (ACD, with or without misalignment of the pulmonary veins) is a rare form of interstitial lung disease that presents as severe PH and hypoxemia early in life. The etiology of ACD is believed to be caused by a genetic defect or early antenatal insult that prevents normal development of the pulmonary capillary bed. Findings include remodeling of the pulmonary arterioles, simplification of the alveolar architecture, and development of congested "misaligned pulmonary veins" residing in the same adventitial sheath (Fig. 72.5). These so-called veins have recently been recognized to be bronchopulmonary anastomoses that link the systemic and pulmonary circulations and bypass the alveolar capillary bed.[25] ACD remains universally fatal despite treatment with all known modalities, including extracorporeal support, although limited survival after lung transplantation was recently reported.[72] More than 50% of infants present with other anomalies, most commonly affecting the genitourinary, cardiovascular, and gastrointestinal systems. The diagnosis can only be made with certainty based on microscopic examination of the lung. Therefore, a complete postmortem evaluation should be recommended for all newborns that die as a result of unexplained pulmonary hypertension, and a lung biopsy should be considered in infants with prolonged, refractory PPHN. While ACD classically presents in the neonatal period, late presentation at several months of life has been reported. Approximately 10% of reported ACD cases have a familial association, indicating a probable genetic component. In 40% of infants with ACD, mutations or deletions in the *FOXF1* transcription factor gene or deletions upstream to *FOXF1* are identified.[66] A murine model of *FOXF1* deficiency produces defects in lung vascularization and alveolarization, further demonstrating the importance of the *FOXF1* protein in embryonic development of the pulmonary vasculature.

In addition to ACD and other developmental lung disorders, severe refractory PPHN may accompany respiratory



• **Fig. 72.5** Vascular abnormalities associated with alveolar capillary dysplasia. The lung parenchyma shows airspace simplification and widened alveolar walls. A central membranous bronchiole is accompanied by adjacent thick-walled arteries (*long arrow*) with associated dilated veins (*short arrow*). The prominently muscularized arteries extend into adjacent alveolar walls where they are also accompanied by dilated veins.

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failure caused by genetic abnormalities of surfactant deficiency. Surfactant protein B deficiency has been reported most commonly and is characterized by early presentation, radiographic findings of ground-glass opacities, progressive respiratory failure, and early death. The most common mutation is in codon 121 of the *SP-B* gene. Deficiencies in surfactant protein C also occur, but PPHN is not a known association. Mutations in the ATP-binding cassette (*ABC*) transporter 3 gene are now recognized to occur in neonates with severe neonatal lung disease and symptoms of surfactant deficiency and have been reported as a lethal cause of PPHN.

Pulmonary Hypertension in Premature Infants

Extremely preterm birth is associated with high rates of early pulmonary hypertension (PH), particularly when associated with oligohydramnios.[42] This disease should be considered when hypoxemia occurs out of proportion to the degree of parenchymal lung disease. Furthermore, echocardiographic findings consistent with early PH, such as ventricular septal wall flattening and right ventricle dilation, were found in ~40% of extremely low birth weight babies at 7 days of age and predicted BPD and late PH.[50]

Bronchopulmonary dysplasia is an important cause of chronic pulmonary hypertension, with an incidence of 16%-25% in infants with BPD and rates up to 40% in infants with severe BPD.[49] The pathogenesis of BPD-associated PH involves complex interactions between antenatal factors, such as growth restriction, preeclampsia, oligohydramnios, or fetal inflammation, and postnatal injury due to ventilator-induced lung injury, hyperoxia, hemodynamic stress, and infection. These injuries result in impaired angiogenesis, abnormal vascular signaling, and vascular pruning, culminating in a reduction in the alveolar-capillary surface area. The morphologic vascular alterations are accompanied by increased pulmonary vascular tone and heightened vasoconstrictor responses to acute hypoxia. Over time, reduced vascular growth limits vascular surface area and promotes high PVR, especially in response to high cardiac output at times of stress or exercise.

Pulmonary vein stenosis is a complication of severe bronchopulmonary dysplasia that can contribute to severe and progressive PH. The left-sided pulmonary veins (particularly the left upper vein) are most often affected, and severe PH can result after stenosis of only one vein. The true incidence and mechanisms producing pulmonary vein stenosis are not yet known. A number of findings, including a median age of diagnosis of 6 months, a lack of concordance in twins, and association with necrotizing enterocolitis indicate that the disease is postnatally acquired.[31,47] The disease tends to be progressive and is associated with high mortality (30%-50%) in the first 2 years after diagnosis.

Numerous preclinical and clinical studies are addressing the vascular signaling abnormalities in evolving and established BPD. In sheep and primate models of prematurity, lung endothelial nitric oxide synthase (eNOS) expression is decreased and nitric oxide inhalation normalizes patterns of lung growth and vascularization. However, clinical trials of inhaled nitric oxide have not demonstrated a convincing reduction in the severity of BPD.[4] Studies in preterm lambs indicate that deficient soluble guanylate cyclase activity could diminish vascular responses to nitric oxide and that elevated activity of the cGMP-specific phosphodiesterase (PDE5) may also disrupt the cGMP response to nitric oxide, but further study is needed to determine whether these findings will lead to new therapeutic insights.

Clinical Therapy of PPHN

PPHN presents with respiratory distress, labile oxygenation, differential saturation (higher Spo_2 in the right upper extremity compared to a lower extremity), or profound hypoxemia despite oxygen and mechanical ventilation. PPHN is most often recognized in the term or near-term neonate but should also be considered in premature neonates who have cyanosis out of proportion to their parenchymal lung disease.[39]

Echocardiography is mandatory to rule out congenital heart disease, establish an accurate diagnosis of PPHN, and identify extra pulmonary shunting. Findings that confirm PPHN include bidirectional or predominantly right-to-left shunting across the foramen ovale or ductus arteriosus, although other signs such as flattening or left deviation of the intraventricular velocity, tricuspid regurgitant velocity, and increased right ventricular dilation also suggest the diagnosis. Echocardiography also determines whether left ventricular insufficiency is present, which could trigger pulmonary venous hypertension that would only be aggravated by a pulmonary vasodilator. While levels of brain natriuretic peptide increase in the face of elevated right ventricular pressure, this biomarker does not have sufficient sensitivity and specificity to detect or monitor the severity of PPHN.

General Care

The American Heart Association (AHA) and American Thoracic Society (ATS) have published guidelines for management of pediatric pulmonary hypertension, including PPHN (Box 72.1).[2] General management principles for PPHN include maintenance of normal temperature (except for those undergoing therapeutic hypothermia), electrolytes (particularly calcium), glucose, and intravascular volume. Systemic blood pressure should be maintained at normal levels for age with volume and cardiotonic therapy, with the primary goal to optimize left and right ventricular function and enhance systemic O_2 transport. Maintaining normal left ventricular function is an important element of care. An "inodilator" such as milrinone may improve left ventricular function and reduce pulmonary venous hypertension, both of which may improve pulmonary blood flow and oxygenation in infants with refractory PPHN.[44] Increasing blood pressure to supraphysiologic levels for the sole purpose of

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• BOX 72.1 AHA/ATS Management Guidelines for Persistent Pulmonary Hypertension of the Newborn[2]

1. Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with PPHN or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I, Level A).
2. Lung recruitment strategies can improve the efficacy of iNO therapy and should be performed in patients with PPHN associated with parenchymal lung disease (Class 1, Level B).
3. ECMO support is indicated for term and near-term neonates with severe PH and/or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function (Class I, Level A).
4. Evaluation for disorders of lung development, such as alveolar capillary dysplasia and genetic surfactant protein diseases, is reasonable for infants with severe PPHN who fail to improve after vasodilator, lung recruitment, and/or ECMO therapy (Class IIa, Level B).
5. Sildenafil is a reasonable adjunctive therapy for infants with PPHN who are refractory to inhaled NO, especially with an oxygenation index that exceeds 25 (Class IIa, Level B).
6. Inhaled prostacyclin analogues may be considered as adjunctive therapy for infants with PPHN that are refractory to iNO and have an oxygenation index that exceeds 25 (Class IIb, Level B).
7. Intravenous milrinone is reasonable in infants with PPHN and signs of left ventricular dysfunction (Class IIa, Level B).
8. Inhaled NO can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease (Class IIa, Level B).
9. iNO and other PAH-targeted drug therapies should be used cautiously in subjects with CDH especially in those with confirmed or suspected left ventricular dysfunction (Class IIa, Level B).

CDH, Congenital diaphragmatic hernia; PAH, pulmonary arterial hypertension.

driving a left-to-right shunt across the PDA may transiently improve oxygenation but should be done with caution and combined with therapy to simultaneously reduce pulmonary vascular resistance.

Alveolar hypoxia and hypoxemia should be avoided, as they are pulmonary vasoconstrictors and contribute to the pathophysiology of PPHN. Oxygen is a mainstay of PPHN therapy to maintain oxygen delivery to the brain and other tissues and for its pulmonary vasodilator properties. High oxygen concentrations, frequently up to 100% oxygen, are commonly used to reverse hypoxemia and pulmonary vasoconstriction in infants with PPHN. However, hyperoxia may also exaggerate oxidative stress, increase pulmonary vascular contractility, and impair the pulmonary dilator response to nitric oxide. In normal lambs and lambs with PPHN, the vasodilatory effects of supplemental oxygen reach a plateau at about 60% oxygen or a PaO_2 of ~60 mm Hg.[45] The short-term pulmonary vascular benefits of hyperoxia should be carefully weighed against the risks of increased pulmonary vascular contractility, diminished vasodilator responses, as well as potential systemic risks. In patients undergoing therapeutic hypothermia, the oxygen dissociation curve is shifted to the left, which may influence PaO_2 levels at lower saturation levels. Factoring in this left shift when monitoring pulse oximetry and correcting blood gases to patient's actual body temperature help promote adequate oxygen delivery.

Lung recruitment should be optimized to 9-10 ribs expansion, and high-frequency ventilation and/or surfactant are often useful in infants with severe parenchymal lung disease. Surfactant deficiency (respiratory distress syndrome) or inactivation (e.g., from meconium aspiration syndrome or pneumonia) is commonly present. Surfactant improves oxygenation, reduces air leak, and reduces need for ECMO in infants with meconium aspiration, sepsis, and other parenchymal lung disease.[46] However, these strategies should be reserved for infants with parenchymal lung disease, as they are ineffective and run the risk of lung overdistension or acute airway obstruction in infants with idiopathic pulmonary hypertension. Registry studies indicate that surfactant does not benefit the infant with CDH.[74]

Acidosis is a pulmonary vasoconstrictor, particularly when combined with hypoxia, and pH should be maintained >7.3. Alkalosis induced by hyperventilation or infusion of sodium bicarbonate was frequently employed prior to the approval of inhaled nitric oxide.[76] While transient improvements in PaO_2 may be observed, there is no long-term benefit. Prolonged alkalosis may paradoxically worsen pulmonary vascular tone, reactivity, and permeability edema,[43] and may produce cerebral constriction, reduced cerebral blood flow, and worse neurodevelopmental outcomes.

Infants who fail to exhibit sustained improvement in oxygenation with good hemodynamic function should receive evaluation for treatment with extracorporeal membrane oxygenation (ECMO) in a center that is equipped with appropriate equipment and personnel. The oxygenation index (OI; calculated as [mean airway pressure x FiO_2 x 100]/PaO_2) is a useful gauge for the severity of disease, with OI >40 often used as an indication for referral to an ECMO center. Although ECMO is the only therapy that has been proven to reduce mortality for PPHN, it is also costly, labor intensive, and associated with potential adverse effects such as intracranial hemorrhage and ligation of the right common carotid artery. A registry maintained by the Extracorporeal Life Support Organization facilitates sharing of data and supports decision making for individual patients.

Pulmonary Vasodilator Therapy

The primary goal of PPHN therapy is selective pulmonary vasodilation. Pulmonary vasodilator therapies are based on abnormalities in the endogenous signaling pathways (see Fig. 72.2). Inhaled nitric oxide (iNO) is the only specific pulmonary vasodilator therapy approved by the FDA for PPHN. iNO acutely improves oxygenation and decreases the need for ECMO support in newborns with PPHN and an oxygenation index of >25. However, 30%-40% of infants fail to achieve a sustained improvement in oxygenation, and iNO has not reduced mortality or length of hospitalization in any study. Doses greater than 20 ppm

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provide no benefit and increase the risk of methemoglobinemia and other complications. The optimal window for introduction of therapy with iNO remains under investigation. The use of iNO for milder or earlier respiratory failure (i.e., oxygenation index of 15 to 25) does not decrease the incidence of ECMO or death, reduce chronic lung disease, or decrease the incidence of neurodevelopmental impairment. However, at least one study suggests that delaying iNO initiation until respiratory failure is advanced (oxygenation index of >40) may increase the length of time on oxygen.[28] Similar to term infants, preterm infants with early PPHN, particularly after prolonged rupture of membranes or oligohydramnios, will show marked improvement in oxygenation after treatment with iNO.[39]

Once oxygenation improves, iNO can usually be weaned relatively rapidly to 5 ppm without difficulty and discontinued within 5 days. Infants who remain hypoxemic with evidence of PPHN beyond that time are more likely to have an underlying cause of dysregulated pulmonary vascular tone, such as developmental lung abnormalities like alveolar capillary dysplasia, pulmonary vein stenosis, severe pulmonary hypoplasia, or progressive lung injury. When iNO is stopped abruptly, "rebound" PH sometimes develops, even if no improvement in oxygenation was observed at the onset of therapy.[17] This interesting phenomenon can be life-threatening and raises questions about whether vascular cells respond to iNO by upregulating vasoconstrictor pathways. However, from a practical standpoint, the clinical problem can usually be overcome by weaning iNO to 1 ppm prior to discontinuation.

Up to 40% of infants will not respond or sustain a response to iNO. PDE5 activity is elevated in PPHN, leading to interest in a role for PDE5 inhibitors as primary or adjunctive therapeutic agents. The use of enteral sildenafil was reported in a small, randomized controlled trial that showed a dramatic improvement in oxygenation and survival.[6] A subsequent open-label pilot trial of intravenous sildenafil demonstrated improved oxygenation in infants with PPHN, with low mortality and utilization of ECMO.[68] This study also showed that sildenafil clearance in neonates is initially low and increases rapidly through the first week of life, reflecting the relative immaturity of the hepatic cytochrome (P) system in the early neonatal period.[51] Hypotension was the most commonly reported adverse effect, although it can be avoided by delivering the loading dose over a longer 3-hour period. A clinical trial is underway to determine the benefit of sildenafil as an adjunct to iNO therapy (NCT01720524). Sildenafil can be delivered intravenously or as an enteral preparation. Enteral use makes the drug feasible for long-term therapy for infants with chronic pulmonary hypertension associated with congenital diaphragmatic hernia and BPD, although no randomized trials have yet been completed to confirm its efficacy.

Prostanoids

Intravenous prostacyclin (PGI_2) is commonly used for pulmonary hypertension in children and adults but is rarely considered in neonates because of concerns about systemic hypotension and/or ventilation-perfusion mismatch in infants with parenchymal lung disease. Aerosolized PGI_2 is commonly used in adults with pulmonary hypertension.[75] In case series reports of infants poorly responsive to iNO, inhaled PGI_2 produced transient pulmonary vasodilation and enhanced oxygenation. However, the alkaline solution needed to maintain drug stability could irritate the airway, and delivery of precise doses can be difficult because of loss of medication into the nebulization circuit. New, more stable preparations are emerging that are specifically designed for intermittent nebulization, such as iloprost or treprostinil. Treprostinil is particularly promising, because it is also suitable for systemic administration, including by the subcutaneous route.[22] A clinical trial is currently underway to determine the efficacy of treprostinil for PPHN (NCT02261883).

Milrinone

cAMP concentrations are regulated in part by cAMP-hydrolyzing phosphodiesterases such as PDE3 and PDE4. PDE3A expression and activity increases after birth and in response to iNO, which could promote vasoconstriction. In animal studies, the PDE3 inhibitor milrinone decreases PAP and resistance, acts additively with iNO, and prevents rebound PH. Clinical reports indicate that milrinone may enhance pulmonary vasodilation of infants with PPHN refractory to iNO. Milrinone may also reduce left ventricular dysfunction and pulmonary venous hypertension by lowering systemic vascular resistance.

Endothelin Receptor Antagonists

Endothelin-1 plays a role in experimental PPHN, and plasma endothelin-1 levels are increased in infants with PPHN and severe CDH and appear to correlate with the severity of illness. Bosentan, a nonspecific ET-1 receptor blocker, is established treatment for PH in adults and is approved for children over 3 years of age. Endothelin blockade enhances pulmonary vasodilation in experimental PPHN, and one single-center trial found that bosentan improved oxygenation in an iNO-naïve population of PPHN infants. In contrast, the FUTURE-4 multicenter trial found that bosentan as adjunctive therapy for iNO did not improve PPHN outcomes, time on iNO, or time to extubation, possibly in part due to inconsistent intestinal absorption.[67]

Outcome and Follow-Up

Prior to the introduction of ECMO in the late 1980s, the mortality rate for severe hypoxic respiratory failure was nearly 40%, and the prevalence of major neurologic disability in survivors was estimated at 25%-60%. ECMO produced remarkable reductions in the mortality rate of PPHN, and based on the recent iNO clinical trials, contemporary mortality rates for PPHN are approximately 7%-9%. Post-discharge medical problems for the first year

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of life include a >25% incidence of reactive airways disease and a 15%-20% incidence of significant feeding difficulty and/or poor weight gain (<5th percentile for age). The need for supplemental oxygen decreases substantially by 2 years of age, although the incidence of reactive airways disease and rehospitalization remains high through school age. Adult pulmonary outcomes are not yet known.

Approximately 25% of survivors of PPHN will display significant neurodevelopmental impairment when tested at 12-24 months of age. Neurodevelopmental disability rates are similar in infants with moderate versus severe disease, and no therapy to date has been demonstrated to improve developmental outcomes. Neuroimaging is suggested before discharge for all children with moderate to severe PPHN (OI >25), even when ECMO or therapeutic hypothermia are not required.

It is not clear that any therapy, including iNO, improves neurodevelopmental outcomes. In numerous clinical trials, a trend toward higher motor impairment was observed after iNO versus placebo. In the early iNO trial reported by Konduri et al., the decrease in the Bayley PDI was statistically significant.[41] The reasons for these findings remain unknown, but it is possible that other factors, such as antenatal injury and/or commonly used therapies such as hyperventilation, hyperoxia, or drugs such as pancuronium, play a significant role in adverse outcomes. Serial screening for late sensorineural hearing loss is mandatory, as its prevalence is 6%-10% and will continue to emerge through school age. Comprehensive follow-up of a large PPHN cohort through school age found a 9% incidence of severe intellectual disability (FSIQ <70) and a 7% incidence of moderate intellectual disability (IQ of 70 to 84).[58] Comprehensive screening is recommended for all HRF survivors before they enter school to determine if any subtle deficits may predispose them to learning disabilities.

Key Points

- Normal lung vascular development is supported by a hypoxic intrauterine environment, which promotes expression of hypoxia inducible factor (HIF) and vascular endothelial growth factor (VEGF).
- Maternal factors such as diabetes, high body mass index, smoking, use of SSRIs or NSAIDs, and caesarean section increase the risk of PPHN; postnatal factors include perinatal asphyxia, hyperoxia, hypoxia, infection, and lung inflammation.
- Medical management of PPHN requires lung recruitment, optimization of right and left ventricular function, and maintenance of Pao_2 between 60 and 80.
- Inhaled nitric oxide at 20 ppm improves oxygenation and reduces the need for ECMO support in term and near-term infants with PPHN.
- New therapies focused on downstream cGMP signaling, prostanoid signaling, and endothelin signaling are undergoing testing.
- ECMO support is indicated for term and near-term neonates with severe PH and/or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function.
- Infants that survive moderate to severe PPHN are at high risk for neurodevelopmental impairment and should receive neuroimaging and neurodevelopmental follow-up.

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73

Prenatal Diagnosis of Congenital Heart Disease

JAMES STRAINIC, COREY STIVER, AND SARAH PLUMMER

Introduction

Congenital heart disease (CHD) affects 6-8 per 1000 live births. However, only 20% of babies with congenital heart disease would be identified if the examination of the fetal heart were confined to traditional high-risk groups such as increased nuchal translucency, family history of CHD, and teratogen exposure.[25]

The current American Society of Echocardiography guidelines suggest the optimal timing for performance of a comprehensive transabdominal fetal echocardiogram is between 18-22 weeks' gestation.[44] Repeat fetal echocardiograms are suggested for those fetuses identified with diseases that can be progressive, a suboptimal scan, or any patient with fetal arrhythmia. The interpreting physician must be able to recognize the full spectrum of simple and complex acquired and congenital heart disease and its manifestations and natural history throughout gestation. This includes knowledge of the principles of biologic ultrasound instrumentation; understanding of maternal–fetal physiology; familiarity with the latest developments in obstetric diagnostics; and knowledge of the growing field of invasive fetal intervention. It is important to recognize the limitations of fetal echocardiography in detecting important associated lesions and to have the skill to apply all modalities of echocardiography including two-dimensional, M-mode, pulsed-wave, continuous wave, and Doppler color flow mapping in recognizing and evaluating both the normal and abnormal fetal anatomy and physiology throughout the stages of human heart development. There should also be a thorough understanding of fetal arrhythmias and a team readily available to further aid in the diagnosis and treatment of dysrhythmias.[44]

Historical Perspective

The first real-time cardiac heart images and quantitative data were published by the Lange, Sahn, and Reed group in Tucson, Arizona, in 1980. Lindsey Allan published echocardiogram/anatomical correlates in the same year describing systematically real-time normal and abnormal ultrasonic anatomy of the fetal heart, laying the foundation for the field of fetal echocardiography. Using ultrasonic equipment available at the time, real-time, cross-sectional study and diagnosis of fetal cardiac anomalies in utero in the second trimester was possible.

Improvements in diagnostic capabilities over the past 40 years have had tremendous impact on fetal cardiac diagnosis. The use of direct Doppler interrogation of fetal intracardiac flow was first demonstrated in 1985. Use of Doppler color flow mapping in the assessment of fetal cardiac malformations and particularly in a screening situation was started shortly after. The use of color Doppler has become indispensable in the diagnosis of more complicated cardiac malformations. By the late 1990s, the diagnostic accuracy of the nature of complex cardiac malformations in utero was as high as 95%.[4,7,25,45]

Overview of Fetal Circulation and Cardiac Adaptation at Birth

One must not assume that the fully developed fetal heart is analogous to the infant or child heart. This section discusses the difference between the fetal myocardium and the postnatal myocardium and unique fetal blood flow through naturally occurring shunts, blood flow to the placenta, and pulmonary blood flow.

The fetal myocardium has significant differences from the pediatric and adult myocardium. It is composed of a greater proportion of noncontractile elements (60% versus 30%), and fetal cardiomyocytes can divide, whereas adult cardiomyocytes can only hypertrophy. In addition, the removal of calcium from troponin C is slower in the fetus, resulting in slower muscle relaxation. The right ventricle handles more volume, its radius is greater, the radius-to-wall thickness is greater, and it hypertrophies to maintain appropriate wall tension. As a result, the wall thickness of the right ventricle is approximately equal to that of the left in fetal life.

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Abstract

Congenital heart disease (CHD) is one of the most common congenital defects in the fetus. Prenatal diagnosis has been shown to improve outcomes for infants born with CHD. The goals and objectives of this chapter are to discuss the historical perspective of fetal echocardiography and fetal cardiology, describe the fetal circulation and the effects of parturition on postnatal circulation, discuss indications for fetal echocardiogram, discuss assessment of fetal cardiovascular performance, discuss impact of prenatal diagnosis on outcome, discuss diagnosis and therapy of fetal arrhythmias, discuss the limitations of fetal echocardiograms, discuss fetal interventions, and discuss novel approaches to prenatal diagnosis and interventions of congenital heart disease. The field of fetal cardiology has experienced rapid growth in the last 40 years. Advances in image quality allow for the diagnosis of a wide array of cardiac pathology. This allows for well-coordinated, postdelivery care of complex congenital heart defects, preparation of the parents through prenatal counseling, and management of evolving fetal pathology. Potentially, we may be able to alter the natural history of certain congenital heart defects through invasive fetal cardiac interventions. However, even with advances in echocardiography, one must be aware of limitations of fetal ultrasound when evaluating acutely ill neonates in the delivery room.

Keywords

fetal echocardiogram
prenatal cardiology
fetus
perinatal cardiology

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These differences result in increased stiffness and impaired relaxation of the fetal heart as demonstrated in the Doppler pattern across the atrioventricular (AV) valves. In the fetus, passive ventricular filling is impaired, and active atrial filling is responsible for emptying the atria. As a result, the right ventricle is more sensitive to changes in preload and shows signs of dysfunction before the left ventricle. Increased preload, as seen in anemia, viral illness, and significant arterial to venous malformations (AVMs) results in fetal hydrops. There is a gradual change from the "fetal heart" to an "adult heart" that progresses throughout the neonatal period to adulthood. These changes can be easily demonstrated by echocardiography.

The fetus has a unique physiology consisting of various shunts to promote oxygenated blood to the brain and deoxygenated blood to the placenta. The foramen ovale is designed to allow higher oxygenated blood from the placental veins preferentially to the left atrium. The increased oxygenated blood from the placenta travels through the umbilical vein to the ductus venosus. The blood then travels to the inferior vena cava (IVC) and is directed across the foramen ovale by the Eustachian valve. Lower oxygenated blood flow from the fetal brain is preferentially directed from the superior vena cava (SVC) to the right ventricle and eventually across the ductus arteriosus to the placenta. The ductus arteriosus is responsible for carrying most of the cardiac output from the "pulmonary circulation" to the descending aorta and the placenta. The flow pattern is typically a predominant systolic peak with continuous low-velocity diastolic flow. Continuous diastolic flow toward the descending aorta is a result of low-resistance placental circulation. Elevated diastolic flow in the ductus arteriosus is a sign of ductal constriction or lower body arteriovenous malformations. The aortic isthmus has a distinctive wave form in the fetus. The aortic isthmus is located between the left subclavian artery and the insertion of the ductus arteriosus. It is unique in that it straddles two different output systems (the "systemic" output of the left ventricle and the "pulmonic" output of the right ventricle that is directed toward the placenta). Flow is normally toward the placenta in both systole and diastole at the level of the aortic isthmus. Decreased flow in the aortic isthmus from inappropriate shunting can result in isthmus hypoplasia and eventually coarctation of the aorta. Left ventricular outflow tract obstruction or significant left ventricular dysfunction results in reversal of flow toward the head in systole. Reversal of flow may also be seen in decreased upper body vascular resistance (AVMs or stressed fetus).

The circulation to the fetal lungs is uniquely different than the blood flow in the adult. The size and number of pulmonary arteries and veins increase as gestation advances. From 20-30 weeks' gestation, blood flow to the lung increases from 15%-25% of the combined cardiac output, accompanied with a significant decrease in weight-indexed pulmonary vascular resistance (PVR). In the animal lab, increasing oxygen tension from 24-46 mm Hg increases pulmonary blood flow by tenfold in term lambs.[43] This suggests that a substantial portion of the high PVR in the mature fetus is maintained by vasoconstriction in an oxygen tension-sensitive manner. Increased oxygen tension in lesions such as transposition of the great arteries may explain development of foramen ovale restriction or closure in the neonatal period. Increased pulmonary blood flow results in increased venous return to the left atrium, resulting in increased left atrial pressure and potential restriction at the foramen ovale.

There is a transition between fetal life and infancy during the first few hours in which the pulmonary vascular resistance decreases, resulting in increased pulmonary blood flow. It results from various birth-related events that occur concurrently and sequentially, which include ventilation, oxygenation, increasing shear stress of blood flow, and changes in the activities of a number of vasoactive agents and their signaling pathways, such as EDNO, PGI2, endothelin-1 (ET-1), and PAF.[12,17,18,39] However, in certain cases, the maturation of the pulmonary vascular bed is delayed, which results in persistent pulmonary hypertension of the newborn (PPHN). Understanding the transition period between fetal circulation and infant circulation is critically important in certain types of congenital heart disease, especially ductal dependent lesions.

A major difference in the fetal circulation compared with the postnatal circulation is the inclusion of the placental circulation. Typically, the placenta is a low-resistance circuit. The umbilical arterial flow is in part dependent on the placental resistance. The placenta has the lowest vascular resistance of any structure in the fetal circulation and, therefore, is the major contributor to umbilical arterial flow. The two vessels that arise from the iliac artery and travel to the placenta carry a large amount of blood. The pulsatility is low and progressively decreases during pregnancy. Reversal of diastolic flow indicates flow toward other vascular regions in fetus where resistance is low, such as an AVM or severe elevation in placental resistance. The ductus venosus connects the umbilical vein with the inferior vena cava (IVC) as it enters the right atrium (RA). Flow is generally phasic in the IVC toward the heart. Phasic periods with absent forward flow or reversal of flow are markers of impaired relaxation of the right ventricle or right atrium secondary to decreased compliance. This can be the result of a cardiomyopathy, ductal restriction, and/or severe volume overload.

Indications for Fetal Echocardiogram

Indications for a fetal echocardiogram fall within three categories that are listed in Table 73.1 with examples from each category.[4,7,25,44,45] However, if all high-risk fetuses meeting the recommended indications have a fetal echocardiogram performed, only 20% of CHD will be detected. Recent data demonstrates that only 48%-60% of congenital heart defects are detected prenatally. Detection rates are poorest in rural communities.[13] This suggests that better screening mechanisms and indications must be determined to bring

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TABLE 73.1 Indications for a Fetal Echocardiogram

Fetal	Maternal	Genetic

• Extracardiac anomalies
  • Ompholocele
  • Duodenal atresia
  • Spina bifida
  • Vertebral anomalies
  • Limb anomalies
• Arrhythmia
• Hydrops
• Abnormal obstetrical ultrasound screen
• Increased nuchal translucency
	• Congenital heart disease
	• Teratogen exposure
	  • Lithium
	  • Antiseizure medications
	  • Cocaine
	• Metabolic disorder
	  • Diabetes
	• Phenylketonuria
		• History of familial CHD
		• Mendelian syndromes that include CHD
		  • Noonan
		  • Tuberous sclerosis
		  • DiGeorge
		• Chromosomal syndromes associated with CHD
		  • Trisomy 21
		  • Trisomy 13
		  • Trisomy 18
		• Turner syndrome

CHD, Congenital heart disease.



• **Fig. 73.1** Four-chamber view of the fetal heart at the level of the tricuspid and mitral valve. The arrow points to the fetal spine, which is the posterior aspect of the fetus. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.



• **Fig. 73.2** The parasternal long-axis of the heart can be obtained by slight rotation of the probe between a transverse and longitudinal plane. Ao, Aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

these mothers and fetuses to a center capable of advanced cardiac care.

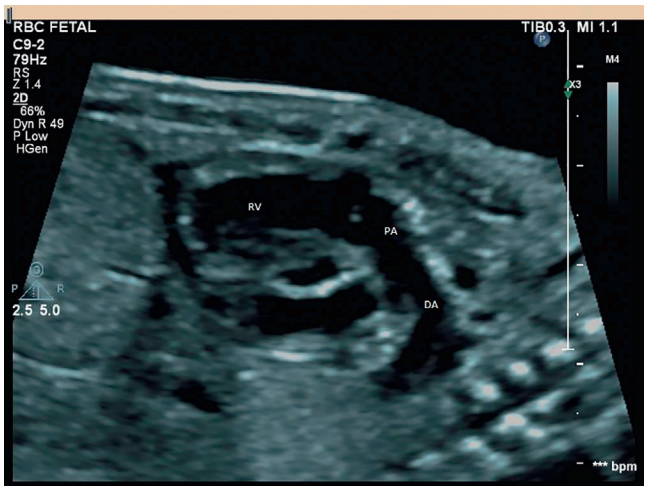
Performance of a Fetal Echocardiogram

Each fetal echocardiogram must be individualized, depending on the nature of the suspected cardiac lesion, as well as the status of the mother and fetus. At a minimum, it must include a thorough two-dimensional imaging, color Doppler, and spectral Doppler examination of the four-chamber view, both arterial outflow tracts, three vessels and trachea view, and an assessment of pulmonary venous return (Figs. 73.1 to 73.8). There is broad variation in anatomy in the spectrum of congenital heart disease, including situs inversus, ventricular inversion, transposition of the great arteries, heterotaxy syndromes, and a host of other complex configurations of the heart. Therefore, the examiner should confirm anatomical relationships and functional

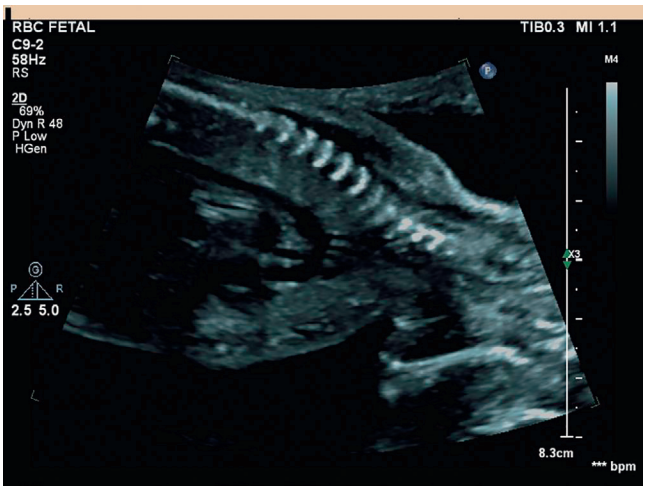


• **Fig. 73.3** A parasternal short-axis view of the fetal heart at the level of the mitral valve. LV, Left ventricle; RV, right ventricle.

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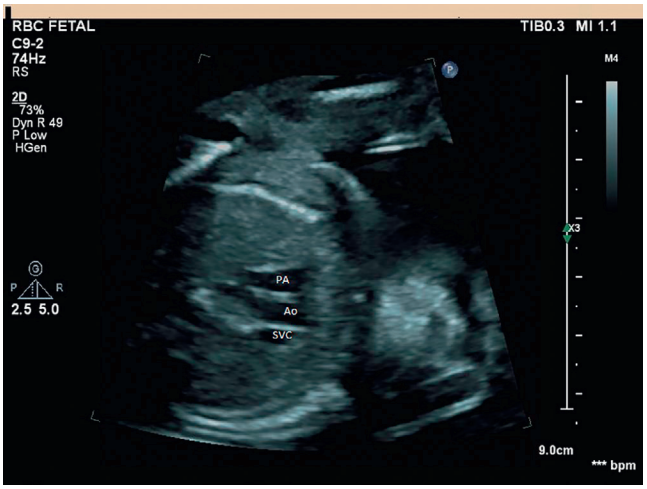
• **Fig. 73.4** A parasternal short-axis view of the fetal heart at the base of the heart. Ao, Aortic valve; IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle.



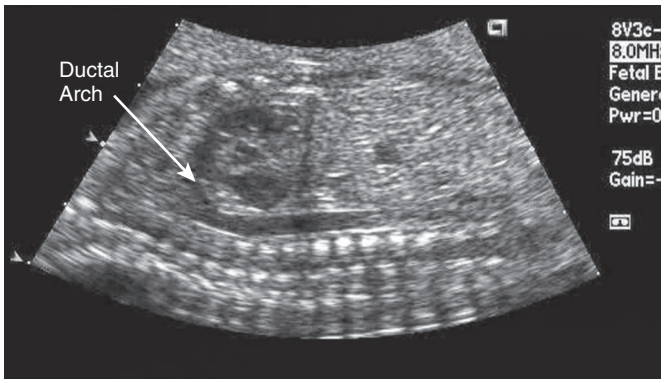
• **Fig. 73.7** The aortic arch view.



• **Fig. 73.5** The bicaval view, or "cava-cava" view, showing the superior and inferior vena cava entering the right atrium.



• **Fig. 73.8** The three-vessel view. Ao, Aorta; PA, pulmonary artery; SVC, superior vena cava.



• **Fig. 73.6** The ductal arch view. The arrow points to the ductal arch.

flow characteristics through a systematic analysis of the following areas:

- Ventricular morphology
- Cardiac axis and situs
- Pericardial effusions
- Venous-atrial, atrioventricular, and ventriculoarterial connections of the heart
- Interventricular septum, atrial septum, atrial chamber size, and foramen ovale
- Atrioventricular and semilunar valves
- Size and relationships of the left and right ventricular outflow tracts
- Ventricular morphology
- Ductal and aortic arches
- Pericardial effusions

The best approach to performing a fetal echocardiogram is to follow a segmental approach. The first step is to determine the fetal position in space and establish a right–left and cranial–caudal axis. The next step is to determine the fetal abdominal situs. This can be performed in the cross-sectional view of the abdomen. Next, using morphologic markers and a segmental approach, determine the following:

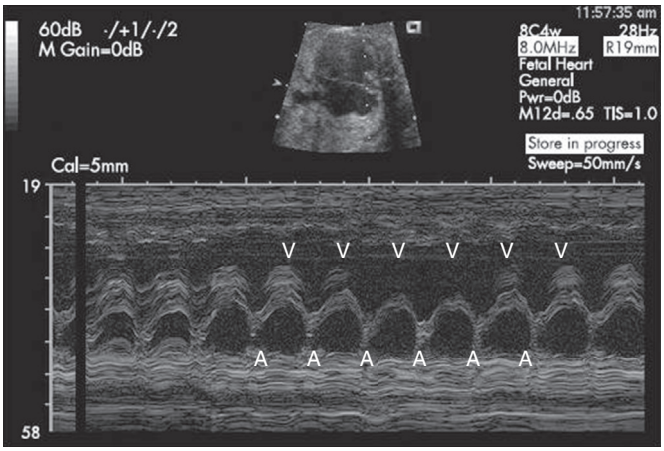
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- Atrial morphology
- Ventricular morphology and looping
- Great artery looping
- Venous connections
- Atrioventricular connections
- Ventriculoarterial connections
- Cardiac rhythm (Figs. 73.9 and 73.10)

Fetal Pathology

Fetal heart pathology can be divided into three broad categories: structural anomalies, functional anomalies, and rhythm disorders. Diagnosis of functional and structural anomalies of the fetus can provide guidance for postdelivery management.

Fetal rhythm disorders can be diagnosed on fetal echocardiogram and treated prenatally in most circumstances. In addition, fetal echocardiogram provides information regarding the cardiac functional state in fetal-specific disease states including twin-to-twin transfusion syndrome.

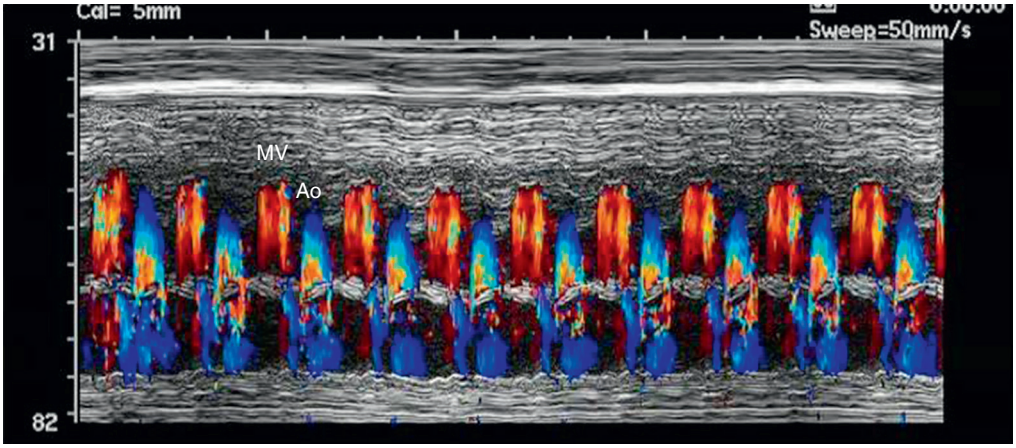


• **Fig. 73.9** M-mode fetal scan through the atrial and ventricular walls, demonstrating normal atrial to ventricular intervals. The atrial wall motion (*A*) is in a one-to-one relationship with the ventricular wall motion (*V*).

Most congenital heart defects can be diagnosed prenatally. Detailed discussion regarding specific structural cardiac anomalies is provided in subsequent chapters. However, there are specific findings on fetal echocardiogram that are useful in guiding management at the time of delivery and in the immediate postnatal period. Need for urgent postnatal procedures in cases of hypoplastic left heart syndrome and transposition of the great arteries and the need for prostaglandin (PGE) can be predicted based on fetal echocardiogram findings.

Prostaglandin-dependent CHD lesions can be divided into two categories—those with too little pulmonary blood flow and those with too little systemic blood flow. In its most extreme form, tetralogy of Fallot can be ductal dependent when the pulmonary stenosis is severe. There are markers on fetal echocardiogram that can help predict whether a fetus with tetralogy of Fallot will require PGE or an intervention in the neonatal period. Morphologic markers including the pulmonary valve (PV) annulus size, the pulmonary valve to aortic valve ratio, and the main pulmonary artery to pulmonary valve ratio have been shown to predict both ductal dependence and need for neonatal procedures.[9] Functional variables including PV peak velocity and reversal of blood flow in the ductus arteriosus also predict need for PGE and early intervention.[9] Reversed flow in the ductus arteriosus and reverse orientation of the ductus arteriosus have been shown to be excellent predictors for the need for PGE in the postnatal period in any CHD with right-sided outflow obstruction.[14]

Transposition of the great arteries (TGA) results in systemic venous return with relatively low oxygen content directed to the ascending aorta. This results in central nervous system and cardiac hypoxia. Atrial-level mixing in this lesion is required to provide adequate oxygen to the brain and myocardium as well as to sustain cardiac output. In fetal life, the size of the foramen ovale versus the septal length, a hypermobile primum atrial septum, and reversal of flow in the ductus arteriosus have been shown to be predictive of the need for urgent postnatal



• **Fig. 73.10** Color M-mode fetal scan through the atrium and ventricle, demonstrating that mitral valve inflow (*MV*) and aortic outflow (*Ao*) are in a one-to-one relationship. Notice there are approximately 2.5 heartbeats per second, resulting in a heart rate of 150 bpm.

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balloon atrial septostomy to insure adequate atrial level communication.[22,52]

Hypoplastic left heart syndrome with an intact or highly restrictive atrial septum has a mortality as high as 80 percent.[29,30] Urgent decompression of the left atrium after birth can improve survival. Fetal assessment of the pulmonary venous inflow and the vasoreactivity of the pulmonary vascular bed have been shown to be helpful in predicting the need for postnatal intervention. A normal pulmonary vein spectral Doppler typically shows a predominant antegrade wave form in systole and early diastole with flow reversal in late diastole. A flow reversal ratio of less than 5 [forward/reverse velocity time interval (VTI) <5] is highly predictive of need for emergent intervention in the immediate postnatal period.[31] Responsiveness of the fetal pulmonary vasculature to maternal hyperoxygenation (exposure of the mother to 60% inspired oxygen for 10 minutes) can also help identify fetuses that will require urgent postnatal intervention. Failure to augment fetal pulmonary arterial blood flow in response to maternal hyperoxygenation predicts need for emergent decompression of the left atrium[46] and may also identify candidates for fetal intervention with fetal atrial septoplasty and stent placement.

Fetal heart failure is associated with placental edema and resultant hypoxia. The mature heart's response to hypoxia is to increase the heart rate, but the fetus decreases its heart rate in response to hypoxia.[43] This results in hydrops fetalis. The differential diagnosis of the underlying cause of hydrops is broad (Box 73.1). Chemoreceptors in the fetal aorta respond to aortic pO_2 below 18-19 mm Hg, inducing bradycardia. The fetal cardiac output is maintained by redistributing blood flow. Blood flow to the myocardium, adrenal glands, and brain is increased (sampling of the middle cerebral artery may show increased diastolic velocities, the so-called brain sparing effect), while the flow to the renal system, skin, muscle, bones, and gastrointestinal system is decreased.[43]

One of the major causes of placental edema is increased right heart preload. This can be seen in any condition that volume-loads the right ventricle, including large AV malformations, sacrococcygeal teratomas, and twin–twin transfusion syndrome (TTTS).[43] There is a resultant increase in the combined cardiac output (CCO). The combined cardiac output increase reflects the amount of preload increase. Most infants do well without evidence of hydrops until the CCO reaches 700-800 mL/kg/min.[43]

A special situation of increased preload occurs in TTTS. The donor twin often exhibits volume depletion and nephrosclerosis. This results in elevated endothelin-1 and angiotensin II. Doppler of the umbilical artery shows decreased diastolic flow and increased resistance. The increased resistance rarely results in ventricular dysfunction. However, postnatal studies have shown abnormalities in vascular compliance and increased pulse wave velocities in the donor twin.[43] Donor hormones from the response to hypovolemia are transferred across the placenta to the recipient twin. The recipient is thus exposed to increased volume and vasoconstrictors. Angiotensin II is a potent stimulant for hypertrophy. Thus, the recipient twin often presents with cardiomyopathy; dilated, hypertrophic, or a combination of the two. Many fetuses demonstrate marked ventricular hypertrophy, which may result in right ventricular outflow tract obstruction, pulmonary stenosis, and tricuspid valve regurgitation.[43]

Studies have shown that fetal echocardiographic prognostic indicators can predict hydrops fetalis outcomes. These include the cardiac function; cardiac size; systemic venous Doppler profile of the ductus venosus or umbilical vein; presence of atrioventricular valve regurgitation; and presence of pericardial effusions, pleural effusions, ascites, or skin edema.[16] These indicators can be compiled to obtain a cardiovascular profile score (Table 73.2).[16] Treatment should be directed toward underlying pathology, including resolving abnormal peripheral impedance and treating high output failure, myocardial dysfunction, arrhythmia, anemia, or twin–twin transfusion.[16]

Doppler assessment of extracardiac structures can also provide information regarding fetal well-being and are thus included as part of a standard fetal echocardiogram. Assessment of the middle cerebral artery (MCA) helps assess effects of pathophysiologic states on the cerebrovascular flow.[33] Normally, resistance in the MCA is relatively high and diastolic velocity is low. In high output disease states such as anemia, the peak velocity of the MCA is frequently elevated.[33] In states of low cardiac output, the cerebral vascular resistance decreases in response to stress, resulting in increased diastolic velocity so as to preserve adequate blood supply to the brain (the brain sparing effect).[3]

Fetal rhythm abnormalities occur in up to 2% of all pregnancies and can be divided into three categories: ectopic beats, tachycardias, and bradycardias.[15] Accurate diagnosis of rhythm disturbances presents a unique challenge given the lack of access to conventional electrocardiogram. Diagnosis of fetal rhythm disturbances relies on ultrasound techniques including M-mode imaging, spectral Doppler, and tissue Doppler.[15,35,40] A more sophisticated modality to

• BOX 73.1 Differential Diagnosis of Causes of Hydrops Fetalis

- Immune
  - Rh incompatibility leading to anemia
  - Infection
  - Viral hepatitis leading to decreased protein production
  - Viral infection leading to anemia (parvovirus)
- Cardiac
  - CHD with severe tricuspid regurgitation (i.e., Ebstein anomaly)
  - Arrhythmia
  - Myocardial dysfunction
- Twin–twin transfusion
- Arteriovenous malformation
- Diaphragmatic hernia
- Cystic hygroma

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TABLE 73.2 Cardiovascular Profile Score

Category	2 Points	1 Point	0 Points
Hydrops	None	Ascites or pericardial or pleural effusion	Skin edema
Cardiothoracic area ratio	>0.2 and <0.35	0.35-0.5	<0.2 or >0.5
Cardiac function	Normal MV and TV filling, LV or RV shortening fraction >0.28	Holosystolic TR, LV, or RV shortening fraction <0.28	Holosystolic MR or TR dP/dt <400, monophasic diastolic filling
Arterial umbilical Doppler	Normal	Absent end diastolic flow	Reversed end diastolic flow
Venous Doppler	Normal	Ductus venosus atrial flow reversal	Umbilical vein pulsations

The cardiovascular profile score can be used for surveillance of congestive heart failure and aid in predicting outcomes in the fetus at risk for heart failure.
LV, Left ventricle; MR, mitral regurgitation; MV, mitral valve; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve.
Adapted from Wieczorek A, Hernandez-Robles J, Ewing L, et al. Prediction of outcome of fetal congenital heart disease using a cardiovascular profile score. *Ultrasound Obstet Gynecol.* 2008;31:284-288.

investigate fetal arrhythmia is magnetocardiography, which uses a magnetic field of the fetal heart to generate waveforms that are similar to an ECG. However, it requires magnetically shielded rooms and specialized equipment that are not universally available.[15]

Premature atrial beats are common, present in 1%-3% of pregnancies, and generally well tolerated unless a sustained tachycardia develops. The risk of fetal tachycardia once premature atrial contractions have been seen is approximately 0.5% to 1%, although couplets and blocked atrial bigeminy may increase this risk. Medical treatment is not recommended for either isolated premature atrial contractions or blocked atrial bigeminy; however, interval auscultation of the fetal heart rate by the obstetrician weekly is recommended for frequent premature atrial contractions or premature ventricular contractions until resolution of the arrhythmia is documented.[8]

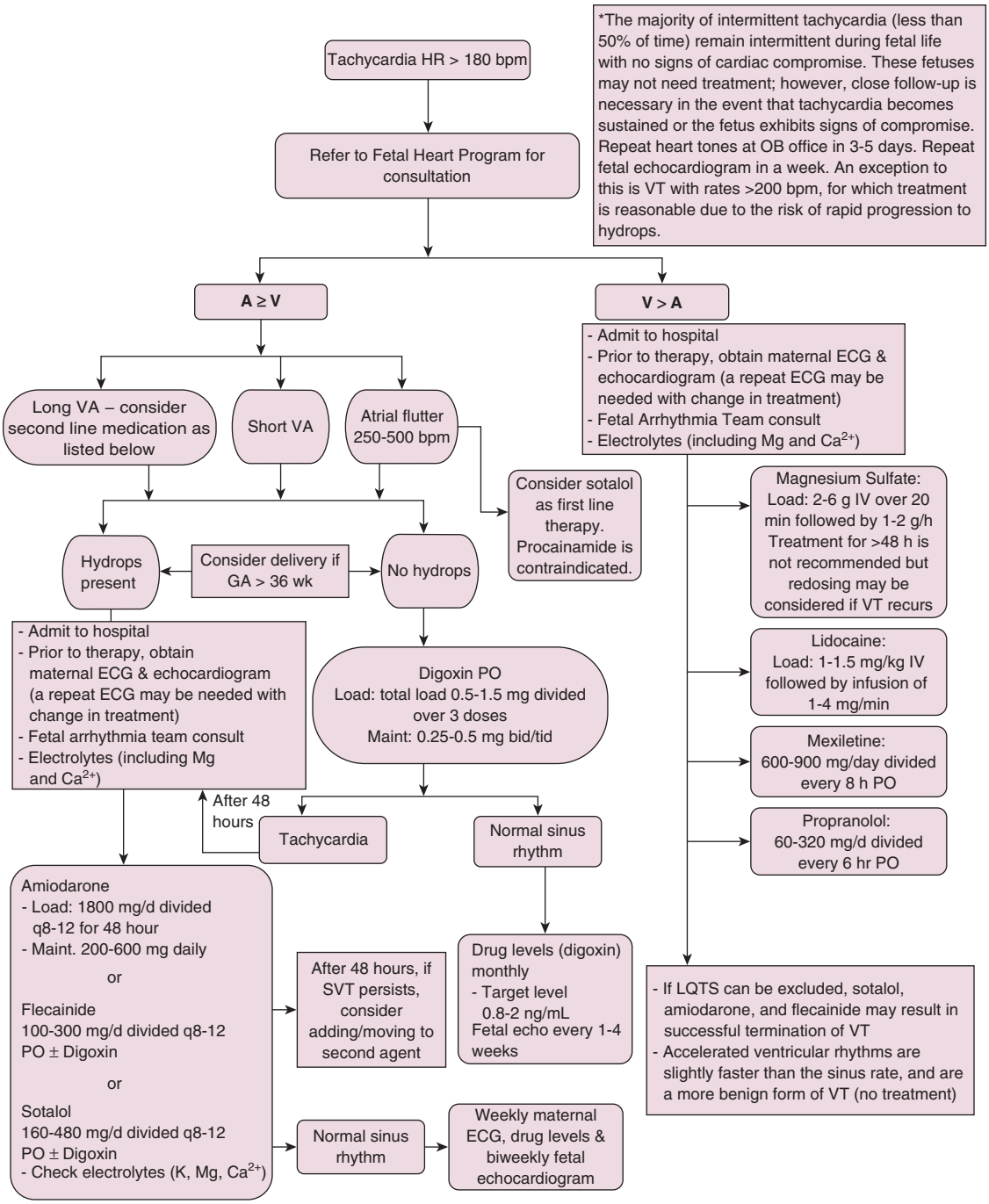
Fetal tachycardia is generally defined as fetal heart rates greater than 180 bpm. The majority of fetal tachycardias are supraventricular in origin, and ventricular tachycardias are very rare. Management of fetal supraventricular tachycardia is targeted to those at risk for heart failure. Intermittent tachycardia is generally well tolerated by the fetus, with the risk for hydrops increasing proportionally with increased time spent in the abnormal rhythm. Therapy is generally felt to be indicated for sustained tachycardias—those which occur greater than 50% of the time while monitored. Most of these tachyarrhythmias can be treated through maternal administration of antiarrhythmic medications with transplacental delivery to the fetus.[15] However, the influence of certain medications, such as amiodarone, on the developing fetus and fetal myocardium must be taken into account. Ventricular tachycardia is very rare in the fetus. It may be associated with myocardial disease or observed in the presence of cardiac tumors. Rarely, incessant ventricular tachycardia warrants maternal antiarrhythmic medication.[8,15] Fig. 73.11 outlines a decision tree for maternal–fetal pairs presenting with fetal tachycardia.

Fetal bradycardia is defined as a fetal heart rate less than 110 beats per minute.[8,15] The most common cause of bradycardia in the fetus is sinus bradycardia, which often occurs during compression during ultrasound examinations. Fetal atrioventricular (AV) block can present with varying degrees of bradycardia depending on whether it is first-, second-, or third-degree (complete) AV block. Fetal AV block is associated with maternal Sjögren antibodies (SSA/SSB) and complex structural heart disease.[8,15] Rarely, it is an isolated phenomenon. In the setting of immune-mediated heart block, fluorinated glucocorticoids and intravenous immunoglobulin have been used in therapy. Studies have supported the use of hydroxychloroquine in known SSA/SSB-positive mothers to prevent the development of heart block.[19] In the era of steroid use and postnatal cardiac intensive care with early pacemaker therapy, mortality for congenital AV block has decreased from 45% in the 1990s to less than 15% in the early 2000s.[15] Rarely, bradycardia may be a sign of long QT syndrome, and an ECG on the mother and family members is recommended. Fig. 73.12 outlines a decision tree for maternal–fetal pairs presenting with fetal bradycardia.

Parental Counseling after Fetal Diagnosis of Congenital Heart Disease

Effective counseling after the prenatal diagnosis of congenital heart disease can be summarized by four aims: to provide an accurate diagnosis of the malformation, to provide an honest prognosis, to review various treatment and management strategies, and finally, to support the family and help them reach a decision that is best for them.[2] Despite the benefits of accurate prenatal diagnosis of congenital heart disease, receiving a prenatal diagnosis can be a traumatic experience for parents. Posttraumatic stress, depression, and anxiety are common in mothers after a prenatal diagnosis of congenital heart disease. Psychological distress may

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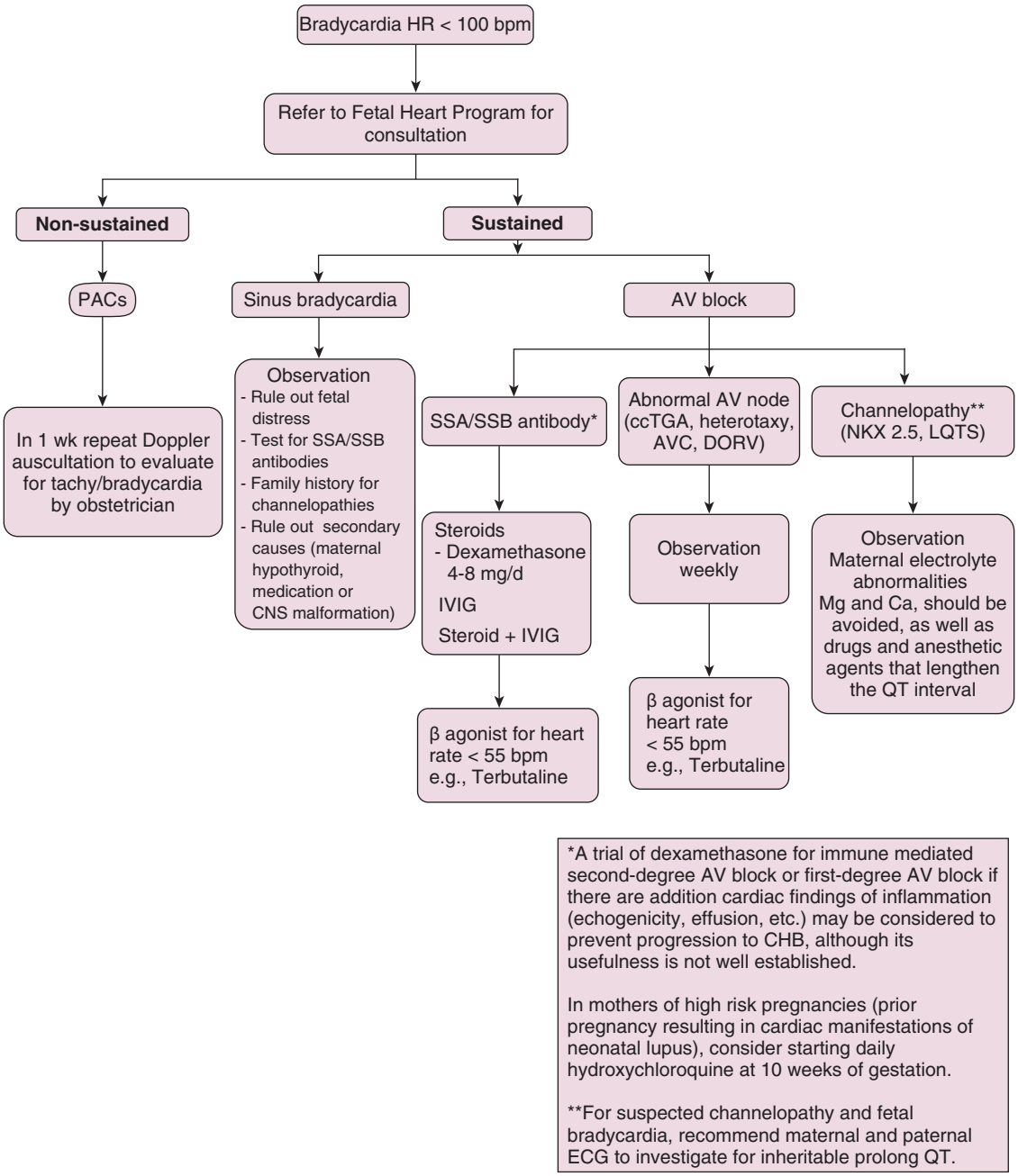


• **Fig. 73.11** Decision tree for maternal–fetal pairs presenting with fetal tachycardia. A, Atria; GA, gestational age; LQTS, long QT syndrome; SVT, supraventricular tachycardia; V, ventricle; VA, ventricular atrial; VT, ventricular tachycardia.

persist for months after birth. There is a need for research to determine the most effective techniques for counseling and family support, as well as investigating potential modifiable variables of maternal stress that may alter the impact.[42]

Prenatal diagnosis does allow for sustained education and guidance between diagnosis and delivery. Little research has been done looking into the most effective methods for prenatal counseling and family support. Some important elements to address during prenatal counseling include findings and limitations, results given in close proximity to the time of testing (preferably the same day), natural history in utero, prognosis for the remainder of pregnancy and beyond as able, possible associations with genetic anomalies, alleviating parental guilt, and potential range of management options.[8] The practitioner must utilize good communication skills and empathy. The level of parental understanding must be assessed continuously during

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• **Fig. 73.12** Decision tree for maternal–fetal pairs presenting with fetal bradycardia. AV, atrioventricular; AVC, atrioventricular canal; bpm, beats per minute; ccTGA, congenitally corrected transposition of the great arteries; CHB, congenital heart block; CNS, central nervous system; DORV, double outlet right ventricle; IVIG, intravenous immunoglobulin; LQTS, long QT syndrome; PACs, premature atrial contractions.

counseling, with the knowledge that understanding may be limited by grief and multiple counseling sessions may be required.[8]

Impact of Prenatal Diagnosis

The goal of early detection of a pathologic state is to alter long-term outcome in a favorable way. Early studies of the impact of fetal diagnosis on postnatal outcome were not satisfying. However, subsequent publications suggest an improvement in postnatal mortality and morbidity. One study looking at the impact of prenatal diagnosis in hypoplastic left heart syndrome (HLHS) showed that preoperative status and first-stage mortality were affected by prenatal diagnosis with a total survival of 75% in those who elected to undergo surgery. All of the patients who were diagnosed prenatally survived, whereas only 65% of the patients who were diagnosed postnatally survived. In addition, patients diagnosed prenatally had a lower incidence of preoperative acidosis, tricuspid regurgitation, and ventricular dysfunction

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and were also less likely to need preoperative inotropic medications or bicarbonate. Preoperative risk factors that correlated with early mortality included postnatal diagnosis, more severe acidosis, need for bicarbonate or inotropes, and ventricular dysfunction.[51] Another study on prenatal diagnosis of congenital heart disease evaluated the neurologic outcomes in fetuses with HLHS. Although the overall mortality did not differ in the prenatal versus postnatal groups, prenatal diagnosis was associated with fewer adverse neurologic events when compared with those with postnatal diagnosis.[28] Similarly, diagnosis, metabolic acidosis level, preoperative mortality, length of stay, and postoperative mortality were all significantly better in patients with a prenatal diagnosis of transposition of the great arteries compared with the group diagnosed postnatally.[5]

Although these data are encouraging, further studies are needed to evaluate the CHD outcomes in the setting of prenatal diagnosis. Certain populations continue to have poor outcome despite prenatal diagnosis, including those with HLHS with intact or restrictive atrial septum, right atrial and left atrial isomerisms (heterotaxy), and pulmonary atresia with intact septum with right-ventricular-dependent coronary circulation. Further studies into markers of outcome in these patients and improved survival may depend on fetal intervention.[27,47,48]

Specific findings on fetal echocardiogram allow for comprehensive delivery planning to prevent hemodynamic compromise in high-risk CHD. Disease-specific delivery room recommendations are currently well accepted in clinical practice.[8,21,37] Level-of-care recommendations should include follow-up, possible need for transport to a tertiary care center, likelihood of neonatal intervention (catheter-based or surgical), or in rare cases, the need for emergent intervention at the delivery. Table 73.3 summarizes risk-stratified level-of-care assignment and coordinating action plans based on reported algorithms.

Limitations of Fetal Echocardiogram

Advances in ultrasound technology have greatly improved the sensitivity of fetal echocardiogram over the past 15-20 years, and it is currently expected that fetal echocardiogram can diagnose even complex congenital heart disease in specific detail. However, it is important to realize that ultrasound and fetal echocardiography are more sensitive for some types of congenital heart disease than others. Even in the most optimal of situations, fetal echocardiography is less sensitive to detect abnormalities of smaller structures. Thus, diagnoses such as partial anomalous pulmonary venous return (PAPVR), small ventricular septal defects, and minor valve abnormalities including bicuspid aortic valve cannot be ruled out on fetal echocardiogram. In addition, fetal echocardiogram is limited by the necessary presence of fetal circulation, making it impossible to rule out atrial septal defects or patent ductus arteriosus prenatally. In addition, while certain findings can raise concern for coarctation of the aorta, including small isthmus diameter, great vessel discrepancy (smaller aorta than main pulmonary artery), abnormal aortic arch flow, left superior vena cava, and ventricular disproportion (smaller left ventricle than right ventricle), this diagnosis cannot be ruled out prenatally.[6] The rates of prenatal detection for specific types of CHD lesions offer some insight into which defects are more likely to be identified on obstetric ultrasound and subsequently on fetal echocardiogram (Table 73.4).[24]

Fetal Therapies

The first attempt at performing a fetal cardiac intervention was in 1987, when attempts were made to pace the fetal heart to prevent progression of hydrops fetalis. The first attempt at fetal aortic valve intervention was made more than 25 years ago by attempting to dilate the aortic valve in a fetus with severe aortic stenosis. This attempt was successful and the infant eventually underwent a biventricular repair.[10,26,29,30,36,47] To date, there is a growing body of evidence in support of fetal cardiac intervention. Several techniques have been attempted for fetal balloon interventions. Ideally, fetal cardiac interventional procedures are performed percutaneously to limit maternal risks. The least invasive technique involves maternal sedation with percutaneous access to the fetus. More invasive methods, which increase maternal risk, have the benefit of better fetal position.[10,26,29,30,36,47] The goal after fetal intervention is to allow the fetus to spend as much time in utero as possible to promote remodeling and allow the fetal lung to complete maturity. The underlying hypothesis in support of many fetal interventions is that the left ventricle undergoes severe myocardial injury or fibroblast damage, compromising the pressure-generating capability of the ventricle prenatally.[10,26,29,30,36,47] If the underlying cause of the injury, such as is the case in severe aortic stenosis, can be resolved, the left ventricle has the potential to remodel, allowing for improvement in contractile function, and hopefully, a biventricular repair.

As in all procedures, appropriate selection of patients is of utmost importance. The goal is to offer the appropriate procedure to the right patient. Criteria for selection for fetal aortic valve balloon dilation currently include: a large left ventricle with persistent patency of the aortic valve, a normal-appearing mitral valve, reversed flow in the aortic arch, and a left-to-right shunt at the atrial level.[10,26,29,30,36,47]

The most promising group to offer fetal intervention may be in the patients with HLHS with intact or restrictive atrial septum. Postnatal mortality is extremely high in this group of patients, with reported rates of 48%-80%. Intact atrial septum can be found in up to 6% of patients with HLHS, with the majority of their mortality reported during the first few weeks of life. This suggests that mortality risk may be associated with intrapulmonary arterial or venous changes.[29,30]

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TABLE 73.3 Risk-Stratified Level-of-Care Assignment and Coordinating Action Plans

Level of Care Code	Level of Care	Action	Examples
Code 0	No identified cardiac anomaly or resolution of cardiac anomaly	Delivery per obstetrician at patient's preferred hospital. Standard newborn care per neonatal team.	• Normal fetal echocardiogram • Premature atrial contractions that resolve
Code 0P	CHD in which only palliative care is planned	Arrange for family support/palliative care services. Delivery per obstetrician at patient's preferred hospital. Cardiology consult for supportive care and confirmation of diagnosis is available.	• CHD with severe/fatal chromosome anomaly or multisystem involvement
Code 1	Cardiac anomaly that is not expected to cause hemodynamic instability in the neonatal period	Delivery per obstetrician at patient's preferred hospital. Standard newborn care per neonatal team. Cardiology evaluation prior to hospital discharge or as an outpatient within 1-2 weeks if the patient is delivering at an outside hospital.	• Muscular ventricular septal defect • Atrial septal defect • Isolated ventricular septal defect
Code 2	Cardiovascular anomaly or disease expected to not cause hemodynamic instability at birth	Neonatology management in delivery room. Nonemergent cardiology consultation. For fetal echocardiogram findings of an unclear etiology, as long as the baby's clinical presentation allows, recommend a cardiology evaluation in conjunction with the neonatology team to confirm fetal findings prior to ultimate disposition (CTICU or NICU).	• Balanced atrioventricular canal • Tetralogy of Fallot (TOF) (pink) • Benign/controlled arrhythmia (nonsustained SVT without hydrops) • LV/RV size discrepancy without concern for coarctation • CDH without significant cardiac pathology
Code 3	Cardiovascular anomaly of moderate severity (including ductal dependent lesions) where hemodynamic instability is possible but not anticipated	Neonatology management in delivery room. May allow for maternal–infant bonding time. Transfer to NICU for transitional care and line placement. Transfer to the CTICU/NICU for further evaluation and management. Urgent cardiology consultation within 1 hour of delivery.	• HLHS with no risk factors • Single ventricle with critical RVOT or LVOT obstruction • Coarctation of the aorta • ToF with moderate to severe obstruction • Sustained tachyarrhythmia
Code 4	Cardiovascular anomaly with high likelihood of hemodynamic instability	Cardiology and neonatology notification of labor. Neonatology and cardiology to co-manage delivery. Disposition of the patient will be determined by clinical presentation. Emergent transfer to the operating or cardiac catheter lab may be necessary (see details medical record note). Lines may need to be placed in NICU, CTICU, catheter lab, or operating room pending disposition decision. Final disposition to CTICU- vs. NICU-based on established center guideline.	• Transposition of great arteries • ToF with absent pulmonary valve • HLHS with suspected atrial septal restriction • CHD with ventricular dysfunction • Complete heart block • Hydropic fetus with cardiac anomaly

CHD, Congenital heart disease; CTICU, Cardiothoracic Intensive Care Unit; HLHS, hypoplastic left heart syndrome; LVOT, left ventricular outflow tract; NICU, Neonatal Intensive Care Unit; RVOT, right ventricular outflow tract; SVT, supraventricular tachycardia.

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TABLE 73.4 Prenatal Diagnoses by Specific Congenital Heart Disease (CHD) Type

CHD Type	Percent Prenatal Diagnosis
Single ventricle (all)	85%
Hypoplastic left heart syndrome	83%
Complex single ventricle	87%
D-transposition of the great arteries (TGA) (all)	54%
D-TGA with intact ventricular septum	47%
D-TGA with ventricular septal defect	64%
Tetralogy of Fallot	75%
Isolated arch anomaly	58%
Arch anomaly with additional anomaly	75%
Total anomalous pulmonary venous return	2%
Pulmonary valve stenosis	44%
Double-outlet right ventricle	97%
Double-outlet right ventricle with malpositioned great vessels	83%
Balanced atrioventricular canal	79%
Interrupted aortic arch	61%

Novel Approaches to Prenatal Diagnosis of Congenital Heart Disease

Just as in fetal intervention, there continue to be advances in the diagnostic realm. Promising results have been seen with the performance of fetal echocardiograms during the first trimester. A study evaluating the feasibility and accuracy of first trimester echocardiography identified fetuses with ventricular septal defects, transposition of the great arteries, and HLHS. The sensitivity of these early echocardiograms compared with the standard study performed at 18-22 weeks' gestation was calculated as 60.0% and the specificity was 98.7%, with a positive predictive value of 75.0% and a negative predictive value that reached 97.4%.[32] Earlier detection of significant heart defects allows for more timely counseling and decision making.

Newer indices of ventricular performance including the Tei index (also known as the myocardial performance index) are currently being evaluated in the fetus. The Tei index has been used widely as a measure of global (combined systolic and diastolic) myocardial function in adults and children. It has also been shown to be useful in the assessment of fetal cardiac function.[1]

Three-dimensional fetal echocardiography also shows promise in both increasing efficiency of fetal echocardiography and accuracy of diagnosis. However, poor frame rates and false positive results continue to be an issue.

Summary

In summary, the field of fetal cardiology has experienced rapid growth in the last 40 years. Advances in image quality allow for the diagnosis of a wide array of cardiac pathology. This allows for well-coordinated, postdelivery care of complex congenital heart defects, preparation of the parents through prenatal counseling, and management of evolving fetal pathology, including arrhythmias and TTTS. Potentially, we may be able to alter the natural history of certain congenital heart defects through invasive fetal cardiac interventions. However, even with advances in echocardiography, one must be aware of limitations of fetal ultrasound when evaluating acutely ill neonates in the delivery room.

Key Points

- Congenital heart disease is common, and the vast majority of lesions can be detected prenatally on fetal echocardiogram.
- Indications for fetal echocardiogram are broad and include maternal factors, family history, and fetal factors.
- Details of fetal cardiac anatomy can be useful in delivery planning and prognosis of postnatal course, including need for prostaglandin therapy and/or neonatal intervention.
- Fetal arrhythmias are relatively common, rarely cause fetal compromise, and can be treated medically when necessary.
- Fetal cardiac intervention is a promising novel therapy that has the potential to alter the natural history of some severe types of congenital heart disease.

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74

Patent Ductus Arteriosus

WILLIAM E. BENITZ AND SHAZIA BHOMBAL

In utero, the ductus arteriosus provides a connection between the pulmonary artery and descending aorta through which deoxygenated blood returning to the right heart is diverted to the placenta for reoxygenation. Although essential to normal fetal physiology, it normally constricts, closes, and becomes a fibrous remnant after birth. Failure of those processes, resulting in persistent ductal patency into childhood or adulthood, has been recognized as a significant pathology for many years. Increasing survival of more immature infants, who are at greatest risk for persistent ductal patency, was quickly followed by recognition of a potential role of patent ductus arteriosus (PDA) in pathogenesis of disease in preterm infants. More than 50 years ago, Burnard reported that the murmur of a PDA was heard more frequently and for longer after birth in preterm infants and typically was associated with respiratory distress.[3] Subsequently, prolonged ductal patency in preterm infants was linked to more severe respiratory distress syndrome (RDS), prolonged assisted ventilation, pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), renal impairment, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, and death.[1] Recognition of these associations, appreciation of the hemodynamic effects of a large left-to-right shunt through the ductus, and the plausible hypothesis that these morbidities might be caused by excessive pulmonary blood flow or systemic ischemia led many practitioners to adopt strategies for closing the ductus, either in anticipation of or after confirmation of prolonged patency. Evidence of benefit from those interventions was slow to develop, however, and concerns arose about adverse effects of medical or surgical closure of the ductus. Although consensus regarding many aspects of management is lacking, the current approach consists of recognition of pathologic persistence of ductal patency, evaluation of hemodynamic consequences, and selection of strategies to minimize deleterious effects.

Pathogenesis

The ductus arteriosus is derived from the distal portion of the embryonic sixth brachial arch and is approximately the diameter of the descending aorta in utero. In the normal term infant, the ductus arteriosus constricts soon after birth, stimulated by the rapid postnatal increase in arterial oxygen tension. The muscularis of the ductus is uniquely responsive to oxygen, reacting to an increase in ambient oxygen with sustained contraction. The mechanisms of this response are not fully understood, but the cytochrome P450 system (CYP450), endothelin-1 (ET-1), and intracellular oxidation-reduction (redox) balance appear to be important.[8] Glucocorticoids may have an essential role in maturation of the ductal oxygen-sensing apparatus, as antenatal exposure to glucocorticoids is associated with both increased expression of genes for calcium and potassium channels implicated in the oxygen response and decreased risk of persistent ductal patency. This direct response is augmented by a rapid decline in circulating levels of PGE_2, a potent ductal smooth muscle relaxant that has a major role in keeping the ductus arteriosus open in the fetus. The placenta is the primary source of fetal PGE_2, leading to a precipitous fall in circulating levels upon umbilical cord clamping. Maximal effects of PGE_2 withdrawal seem to require antenatal priming of the ductal muscle by the rising levels of PGE_2 normally seen late in gestation. Dynamic functional closure initiates at the pulmonary end of the ductus and usually is complete within the first 4 days after birth, but anatomic obliteration is not achieved until after 1 week of age.

In otherwise normal infants born at or near term, it is unusual for the ductus arteriosus to fail to close within the first 4 days. With decreasing gestational age at birth, both the age at spontaneous closure and the proportion of infants with PDA at any postnatal age progressively increase.[29] Before interventions to close the PDA in preterm infants were widely adopted, ductal closure nearly always occurred spontaneously if given sufficient time, sometimes as late as 4-6 months of age. However, those observations date from an era before adoption of antenatal steroid treatment and availability of exogenous surfactant, when VLBW infants rarely and ELBW infants essentially never survived. Data from placebo arms of clinical trials since adoption of those measures indicate that many such infants never develop signs of a hemodynamically significant ductal shunt. In many trials, numerous control subjects were eventually

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Abstract

Approaches to management of patent ductus arteriosus in the preterm neonate continue to be a topic of discussion and controversy. Prolonged ductal patency in preterm neonates has been associated with morbidities such as bronchopulmonary dysplasia, necrotizing enterocolitis, and pulmonary hemorrhage, and with increased mortality. However, a multitude of studies have failed to demonstrate improvement in long-term outcomes with medical or surgical closure of the ductus. This chapter aims to present current evidence regarding diagnosis, evaluation, and management of the patent ductus arteriosus in the preterm neonate. In the normal term infant, the ductus arteriosus constricts soon after birth. With decreasing gestational age, the proportion of patients with a patent ductus and time to closure progressively increases. From the first report on prolonged ductal patency in the preterm infant over 50 years ago, approaches to the patent ductus arteriosus have ranged from prophylactic closure to conservative symptomatic management. Modalities for evaluation to identify patients at risk for adverse effects of ductal shunting, including echocardiography to assess hemodynamic significance, near infrared spectroscopy, and biomarkers, continue to evolve. Current approach to the patent ductus arteriosus in the preterm neonate consists of recognizing the pathologic persistence, evaluating consequences, and determining strategies to minimize deleterious effects. While a majority of premature patients will close their ductus without intervention and without increased long-term morbidities, further research is needed to identify those patients who may benefit from intervention to close the ductus arteriosus.

Keywords

patent ductus arteriosus
ductus arteriosus ligation
indomethacin
ibuprofen
preterm infant
ductal shunting
echocardiography

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treated to achieve ductal closure, typically late in or after the first week after birth, obscuring the natural course of spontaneous ductal closure as well as risk factors that might predict failure of that process. Nonetheless, ductal closure without intervention is very likely in babies who are born at greater than 28 weeks' gestation, weigh greater than 1000 g at birth, or do not have RDS. In recently reported cohorts of VLBW infants from centers that avoid interventions to close the ductus, including more than 800 subjects, more than 90% achieved ductal closure without treatment (87% before discharge).[5,22,29-31]

The mechanisms underlying delay or failure of ductal closure in preterm infants have not been fully elucidated.[8] Birth before term may simply come before the ductus is prepared, functionally or structurally, to respond to signals that normally induce closure. For example, lamb studies have demonstrated gestational age-dependent response of the ductus to oxygen. In addition, genes essential to ductal responses, including K^+ and Ca^{2+} channels involved in muscle contraction and phosphodiesterases that degrade cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) mediators of the vasodilator responses to nitric oxide (NO) and PGE_2, are developmentally upregulated in the ductus arteriosus of the fetus approaching term. Lack of preconditioning by PGE_2 in late gestation may make the ductus arteriosus less sensitive to withdrawal of that vasorelaxant. Inadequate glucocorticoid production, common in extremely preterm infants, may compromise oxygen-sensing pathways, particularly in infants not exposed to maternal antenatal steroids. Cytokines produced by a fetal inflammatory response, a frequent correlate of preterm birth, may directly impede ductal responses.[18] These potential mechanisms correspond to the clinical observations that PDA is strongly associated with extreme immaturity, lack of exposure to antenatal steroids, and signs of fetal inflammation or infection.

Pathophysiology

Before birth, the pulmonary vascular resistance is high and approximately 75% of the right ventricular output flows right-to-left through the ductus arteriosus. With the first breath, lung inflation and oxygenation produce a rapid decline in pulmonary vascular resistance, a decrease in pulmonary arterial pressures, and a large increase in pulmonary blood flow. Removal of the low-resistance placenta from the systemic circulation increases systemic arterial pressures, and ductal flow quickly reverses direction to left-to-right. Pulmonary blood flow substantially exceeds systemic cardiac output until the ductus arteriosus closes. If ductal closure occurs in the first few days, this imbalance in distribution of the total cardiac output is well tolerated. If the ductus arteriosus remains open, however, the continued decline in pulmonary vascular resistance over the first several days and weeks results in progressively increasing left-to-right shunting through the PDA, with excessive pulmonary blood flow, increased volume work for the left heart, and the potential for systemic ischemia.

Term infants can often tolerate large left-to-right shunts with high pulmonary-to-systemic blood flow ratios (Q_P:Q_S) without developing pulmonary edema. In preterm infants, surfactant deficiency, low serum oncotic pressures, and compromised capillary integrity (e.g., that which accompanies bacteremia) lower the threshold for development of pulmonary edema. Accumulation of alveolar and interstitial fluid increases the alveolar-arterial oxygen gradient and reduces lung compliance. A large left-to-right shunt increases volume work for the left heart, leading to atrial and ventricular enlargement and myocardial dysfunction. This may produce electrocardiographic and serum biomarker signs of myocardial ischemia, including ST segment depression and elevated serum troponin levels. In addition to documentation of left atrial and ventricular distention, echocardiography may demonstrate abnormal left heart function. The combination of left heart dysfunction and diversion of aortic flow into the lungs (a "ductal steal") compromises systemic cardiac output, with consequent risk of end-organ ischemia. Increasing ductal left-to-right shunting may be associated with Doppler ultrasound evidence of decreased, absent, or reversal of diastolic flow in the middle cerebral, superior mesenteric, and renal arteries, as well as the descending aorta. Impaired cerebral blood flow has been associated with PDA in several studies, implicating but not proving a causal role for PDA in development of IVH and, possibly, PVL. Similarly, bowel or kidney ischemia resulting from compromised mesenteric or renal arterial flow may be associated with NEC or impaired renal function. Reversal of aortic diastolic flow in term infants with surgical congenital heart disease has been associated with NEC, but empiric data have not demonstrated a direct correlation between estimates of severity of the ductal steal and the risk of ischemic complications in preterm infants with PDA.

Clinical Presentation

The clinical presentation of a preterm infant with a persistent PDA typically begins with recognition of the characteristic coarse systolic murmur, heard best along the left sternal border. The continuous "machinery murmur" typical of PDA in an older child is rarely present. Infants with a very large PDA and substantial pulmonary overcirculation may have no audible murmur. An increase in murmur intensity may reflect increasing flow velocity through a narrowing ductus arteriosus rather than increasing shunt volume. Hemodynamic effects of the large left-to-right shunt may be evident in an increased precordial impulse (owing to the increased left ventricular stroke volume) and in arterial pulses that are prominent, bounding, or palpable where they are not normally, such as in the palms (resulting from diastolic runoff into the low pressure pulmonary circulation). In preterm infants greater than 1000 g, systemic arterial diastolic blood pressures are reduced and pulse pressures may be increased. Among babies less than

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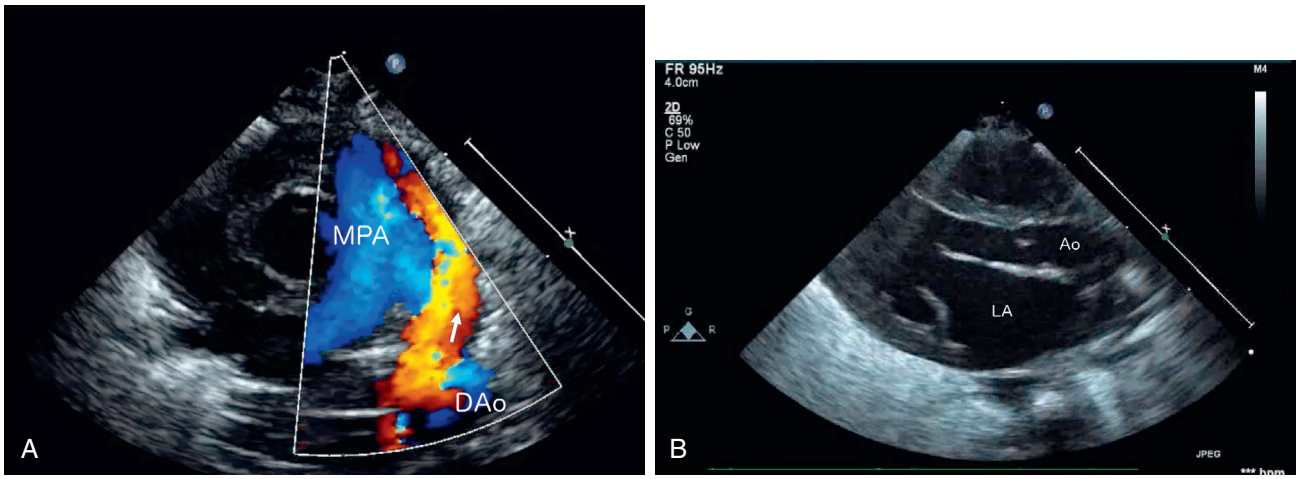
1000 g, reduction in both systolic and diastolic pressures without a widened pulse pressure is more typical. These findings are nonspecific, insensitive, and correlate poorly with echocardiographic findings. Similar physical findings may be present in infants with an aortopulmonary window, large arteriovenous malformation, hemitruncus, or certain other cardiac defects, or they may simply reflect a relatively hyperdynamic state of another cause. Often, a hemodynamically significant PDA is suspected only because of signs of excessive pulmonary perfusion, such as an increasing $Paco_2$ and/or alveolar-arterial oxygen gradient, decreasing lung compliance, or inability to wean the infant from supplemental oxygen, distending airway pressure, or positive pressure ventilation. Pulmonary hemorrhage is an infrequent complication that is usually attributed to pulmonary overcirculation from a PDA.

Diagnostic Evaluation

Patent ductus arteriosus is most readily confirmed by color Doppler echocardiography, which documents anatomic patency and the direction and velocity of ductal blood flow throughout the cardiac cycle (Fig. 74.1). Echocardiography also allows characterization of the hemodynamic consequences of the ductal shunt, including assessment of left heart volume load, cardiac function, and systemic hypoperfusion. Findings that correlate with a large shunt include large ductal diameter; increased left atrial to aortic root diameter (LA:Ao) ratio; left ventricular distention; and absent or reversed diastolic flow in cerebral, renal, or mesenteric arteries or descending aorta (Fig. 74.2). Measures of myocardial dysfunction, such as the velocity of a mitral regurgitant jet, ratio of early passive to late atrial contractile transmitral filling (E wave to A wave ratio), left ventricular isovolumic relaxation time (IVRT), and strain, have been proposed as potential indicators of hemodynamic significance (Table 74.1).[10] The utility of individual markers is low, but combination in composite scores appears to increase diagnostic utility, and preliminary results suggest that high composite scores may be predictive for development of chronic lung disease.[10,12,28] These results need to be confirmed and extended to other adverse outcomes potentially attributable to PDA but represent essential first steps toward establishing the role of such measures in identifying candidates for enrollment in management trials and ultimately for targeted interventions.

Near-infrared spectroscopy (NIRS) has also been proposed as a tool for assessing hemodynamic significance of the ductus arteriosus.[6] Echocardiographic findings consistent with hemodynamically significant PDA (using differing criteria) have been correlated with lower renal (r_rSO_2)[6] and mesenteric[19] (r_mSO_2) regional oxygen saturation levels. Lower regional cerebral oxygen saturations (r_cSO_2) correlated with larger ductal diameters but not with other echocardiographic measures of hemodynamic significance.[9] Other studies have failed to identify significant effects of ductal patency on r_rSO_2[32] or r_cSO_2,[24,32] however. In an observational study of the relationship of PDA and brain volumes measured by MRI at term-equivalent age, r_cSO_2 measurements were lower in infants treated with indomethacin for PDA and lowest in those who underwent surgical ligation.[21] Lower pretreatment r_cSO_2 values were associated with smaller cerebellar volumes in infants treated surgically but not in other infants. No studies have evaluated the utility of NIRS for identification of infants with PDA for selective treatment.

Serum biomarkers are potential tools for evaluation of hemodynamic significance of PDA, guiding treatment of PDA and predicting adverse outcomes.[35] Plasma levels of B-type natriuretic peptide (BNP) or NT-pro-BNP, an inactive byproduct of BNP production, are elevated in infants with significant PDA, correlate with echocardiographic



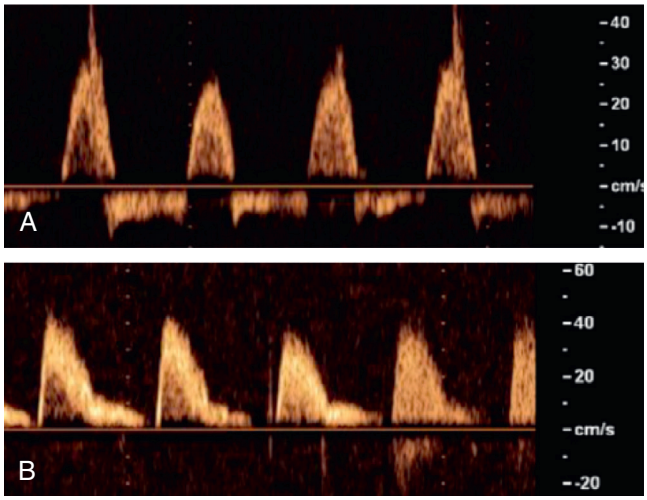
• **Fig. 74.1** Echocardiographic imaging determining severity of ductal shunting. **A,** Color flow Doppler study showing large patent ductus arteriosus with flow outlined by *arrow* from descending aorta (DAo) to main pulmonary artery (MPA) in parasternal short-axis view. **B,** Increased LA:Ao ratio with dilated left atrium (LA) compared to aorta (Ao) on parasternal long axis view.

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TABLE 74.1 Echocardiographic Correlates of Hemodynamic Significance of Patent Ductus Arteriosus*

Echo Assessment	Small PDA	Moderate PDA	Large PDA
Ductus arteriosus			
Narrowest diameter (mm)	<1.5	1.5-3	>3
Maximum flow velocity (m/s)	>2	1.5-2	<1.5
Ductal shunt magnitude			
Left ventricular output (mL/kg/min)	≤314	≤314	>314
Left atrial:aortic ratio	<1.4:1	1.4-1.6:1	>1.6:1
E wave to A wave ratio	<1	1-1.5	>1.5
Isovolumic relaxation time (ms)	>45	36-45	<35
Systemic hypoperfusion			
Descending aorta end diastolic flow	Normal	Decreased or absent	Reversed
Celiac artery end diastolic flow	Normal	Decreased or absent	Reversed
Middle cerebral artery end diastolic flow	Normal	Decreased or absent	Reversed

*Adapted from Sehgal A, McNamara PJ. Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus? *Eur J Pediatr*. 2009;168:907-914[27] and Sehgal A, Paul E, Menahem S. Functional echocardiography in staging for ductal disease severity: role in predicting outcomes. *Eur J Pediatr.* 2013;172:179-184.[28]



• **Fig. 74.2** Doppler findings with hemodynamically significant patent ductus arteriosus. **A,** Pulse wave Doppler demonstration of holodiastolic flow reversal in the descending aorta. **B,** Pulse wave Doppler demonstration of antegrade flow throughout diastole in the descending aorta following indomethacin treatment of the same infant.

markers of ductal shunting, and decrease after the ductus arteriosus closes. Among infants less than 32 weeks' gestation with PDA, NT-pro-BNP levels at 48 hours were higher in those who died or had grades III/IV IVH than in those who survived without IVH, and survivors with higher NT-pro-BNP levels had worse neurodevelopmental outcomes.[11] Elevated levels of troponin T at 48 hours of age are associated with presence of PDA, correlate with echocardiographic indicators of ductal shunting, predict death or grades III/IV IVH, and may help identify infants at greatest risk for poor neurodevelopmental outcome at age 2 years.[11] A recent review of the role of natriuretic peptides in PDA assessment noted substantial heterogeneity in laboratory methodologies and concluded that their utility should be limited to screening to identify candidates for echocardiography. There have been no studies evaluating these markers as criteria for intervention to close the ductus arteriosus.

Chest radiographs may demonstrate an enlarged cardiac silhouette, prominent pulmonary vascular markings, or evidence of pulmonary edema. Although these signs may suggest the diagnosis, they are nonspecific and insensitive.

Management

Because PDA in preterm infants is so strongly associated with several adverse outcomes, surgical and medical strategies for closing the ductus arteriosus were widely adopted soon after they became available. Surgical ligation in preterm infants with respiratory distress syndrome was first reported in an abstract in 1968, and the first case series appeared in 1972. Medical induction of ductal closure with indomethacin was described in 1976. The conviction that ductal closure was beneficial became so pervasive that the landmark National Collaborative Study of indomethacin in preterm infants with PDA had no nontreatment arm: all three regimens mandated ductal closure by either indomethacin or ligation. These reports were followed by numerous descriptions of successful surgical or medical closure of the ductus, which heavily influenced practice for many years, but the utility of routine intervention to achieve ductal closure late in the first or during the second week of life has come into question.

The seminal reports that nonsteroidal anti-inflammatory drugs (NSAIDs, now called cyclooxygenase inhibitors or COIs) induce constriction and closure of the ductus arteriosus have been followed by more than 50 randomized, placebo-controlled trials of COIs in preterm infants.[3] Indomethacin and ibuprofen are equally effective in reducing rates of persistent PDA, resulting in lower rates of ductal

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ligation. Indomethacin appears to be less likely to induce ductal closure in infants more than 10-14 days of age. Repeated courses of indomethacin or ibuprofen may be effective in infants who do not respond to the first or second course of treatment.[33] Neither individual trials nor meta-analyses have identified improvements in long-term outcome with these treatments.[1] Rates of any IVH and of grades III/IV IVH are reduced by indomethacin prophylaxis started within 12 hours of birth[1] but not by treatment later in the course. These effects do not correlate with improved long-term neurodevelopmental outcomes. Compared with placebo-treated controls, infants given low-dose indomethacin prophylaxis had better vocabulary skills and a lower probability of an IQ less than 70 at age 4.5 years, but their mothers were more likely to describe them as having significant problems on the daily living domain of the Vineland scale at age 8. No effects on many other neurodevelopmental outcome measures were evident. Indomethacin prophylaxis reduces severe pulmonary hemorrhage during the first week but not over the entire hospital course. Indomethacin reduces cerebral, mesenteric, and renal arterial blood flow. These effects are associated with diminished cerebral oxygen levels, reduced creatinine clearance, and oliguria. Meta-analyses of randomized trials indicate that these hemodynamic changes do not increase rates of mortality or potential complications, including BPD, NEC, bowel perforation, retinopathy of prematurity (ROP), or neurodevelopmental impairment.[1] Co-administration of indomethacin with a glucocorticosteroid increases the risk of bowel perforation, however. Ibuprofen has less impact on cerebral and renal blood flow and minimal if any effect on mesenteric perfusion. Consequently, ibuprofen is less likely than indomethacin to cause significant oliguria and may be less likely to be associated with NEC.[25] In vitro studies suggest that ibuprofen may displace bilirubin from its binding site on albumin. Ibuprofen does not have the short-term neuroprotective effects associated with indomethacin. Recent small case series have suggested that acetaminophen may be an alternative COI for PDA management,[14] but the role of this agent in management of preterm infants with PDA remains to be determined.

Although many case series of surgical ligation have appeared, only three randomized trials have assessed the impact of this intervention.[1] The two trials in which ligation was used to treat PDA after it was deemed pathologic demonstrated no improvement in mortality, BPD, death or BPD as a combined outcome, or NEC. The single trial of prophylactic ligation found no reduction in rates of mortality, IVH, grades III/IV IVH, or ROP; the rate of NEC was reduced and the proportion of infants who required supplemental oxygen at 36 weeks' postmenstrual age was significantly increased after ligation. Ligation is a reliable and fast method for closing the ductus arteriosus but is not without hazard. In up to one-third of infants, ligation precipitates severe left ventricular dysfunction and cardiorespiratory decompensation requiring major increases in intensive care support in the immediate postoperative period. The risk of this complication decreases with postnatal age, so later ligations (>4 weeks of age) are better tolerated than earlier surgeries. Infants who develop postoperative hypotension refractory to catecholamine infusion have lower postoperative serum cortisol levels than those who do not become hypotensive or respond to catecholamine treatment.[7] While some have reported that milrinone infusion reduces postoperative hemodynamic instability,[16] others have not found this treatment to be beneficial.[13] Other surgical complications include chylothorax, pneumothorax, phrenic or recurrent laryngeal nerve injury, and scoliosis.[2] Paralysis of the left vocal cord, which occurs in up to 67% of ELBW infants following ductal ligation,[4] is associated with prolongation of assisted ventilation and oxygen supplementation, a higher probability of BPD, feeding difficulties, tube feeding, longer neonatal hospitalization, and vocal and respiratory impairments in adulthood.[26] Infants who undergo early ductal ligation are at increased risk for BPD and have higher rates of neurodevelopmental impairment; these adverse outcomes may result from the indication for surgery rather than the surgery itself.

Closure of PDA in preterm infants by surgical ligation or medically with a COI may be justified on the basis of an expected reduction in severe IVH or severe early pulmonary hemorrhage with indomethacin prophylaxis or by reduction in NEC with prophylactic ligation. In most settings, these putative benefits are not sufficient to justify prophylactic intervention for all extremely low or very low birth weight neonates.[15] Current evidence indicates that routine, early treatment to achieve ductal closure does not improve long-term outcomes.[1] Because essentially all of the trials that provide that evidence addressed treatment early in the postnatal course, with frequent resort to treatment of infants in the "control" arm if PDA persisted beyond the second week or so,[3] the effects of prolonged exposure to a moderate or large left-to-right shunt in ELBW infants remain unknown. Consequently, the indications (if any) for, potential benefits from, and optimal timing of later ductal closure remain indeterminate. Similarly, these global observations do not imply that there cannot be some infants for whom ductal closure would be beneficial, particularly within groups that are not well represented in those older studies (e.g., those less than 26 weeks' gestation). Better strategies for assessment of the magnitude of ductal shunting, based on echocardiographic findings such as those listed in Table 74.1, or scores based on those measurements with or without additional clinical or biomarker variables,[10,12] promise to help identify infants who may be candidates for ductal closure,[10,28] but benefits of treatment for infants selected using such criteria remain to be demonstrated. Until such information is available, practice will be guided by consensus, belief, and individualized clinical judgment. The perceived balance between benefits (reduced IVH and early pulmonary hemorrhage) and disadvantages (more severe respiratory disease, intestinal perforation with concomitant glucocorticoid use) will guide the choice between use and avoidance of indomethacin prophylaxis. High rates

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of spontaneous closure in infants greater than 1000 g, and their demonstrated ability to tolerate longer periods of ductal shunting, support a permissive approach to PDA management in those infants. Infants less than or equal to 1000 g who develop hypotension or signs of overt congestive heart failure may be deemed to require ductal closure, but criteria for that decision remain uncertain. The decreasing efficacy of COIs and increasing safety of surgical ligation with postnatal age suggest that treatment, if indicated, might better consist of medical interventions in the third or fourth postnatal weeks and direct surgical management thereafter.

Experience with less aggressive strategies for management of PDA continues to accumulate.[1] While earlier studies mostly described effects of moderate reductions in the proportion of infants with PDA who received treatment, there are now several reports of cohorts in which treatment was rare (<10% of VLBW infants). In addition to informing the natural history of ductal closure (see above), these observations provide reassurance that strategies that permit prolonged ductal patency do not greatly increase adverse outcomes. Among 139 infants less than 30 weeks' gestation who required ventilation and surfactant replacement, elimination of COI treatment was associated with rates of chronic lung disease (8% vs. 18%-28%) and necrotizing enterocolitis (0% vs. 4%-6%) lower than contemporaneous network benchmarks, comparable rates of intraventricular hemorrhage (7% vs. 6%-7%) and mortality (13% vs. 12%), and use of ligation in fewer than 5%.[34] Adoption of a conservative treatment approach in 72 very low birth weight infants (<1500 g) was followed by significant reduction in the rate of oxygen use or ventilation at 36 weeks' postmenstrual age (from 49% in prior treatment eras to 18%) among those diagnosed with PDA, despite treatment of PDA with ibuprofen in only 7% and no use of ligation, without any increase in rates of necrotizing enterocolitis, intraventricular hemorrhage/periventricular leukomalacia, or death.[22] Among 132 infants 23-26 weeks' gestation who required ventilation and had a hemodynamically significant PDA at least 2 mm in diameter, transition from mandatory PDA closure to nonintervention eliminated indomethacin use and ligation (compared to baseline rates of 58% and 82%, respectively). Bronchopulmonary dysplasia declined from 58% to 38% ($P = 0.006$), without changes in other morbidities or mortality.[31] Semberova et al. reviewed experience in 321 infants <1500 g monitored by serial echocardiography at two centers. Fewer than 5% were treated for PDA, and rates of chronic lung disease; severe IVH, PVL, NEC; and severe ROP compared favorably to contemporaneous Vermont Oxford Network benchmarks.[29] These analyses do not prove that permissive management strategies for preterm infants with PDA result in improved outcomes, as outcome changes may result from contemporaneous changes in other practices, but they do suggest that permissive approaches to PDA management do not substantially worsen outcomes. Recent data indicate that in preterm infants age <28 weeks with moderate-to-large PDAs who were receiving respiratory support after the first week, early routine treatment did not reduce PDA ligations or the presence of a PDA at discharge and did not improve any of the prespecified secondary outcomes, but delayed full feeding and was associated with higher rates of late-onset sepsis and death in infants born at ≥26 weeks of gestation.[7a] The effect of prophylactic indomethacin on BPD remains unclear, with recent data from contemporary cohorts indicating either no reduced or increased risk or a decrease in BPD incidence.[17,23] Available data do not exclude possible effects of nontreatment that have not been studied, such as late development of pulmonary hypertension or pulmonary veno-occlusive disease, so vigilance for unexpected sequelae of practice changes is essential.

Growing awareness that aggressive intervention to achieve ductal closure may not be beneficial should not lead to an assumption that a persistently patent ductus arteriosus can simply be ignored. As with other large shunts, the hemodynamic and secondary pulmonary, cerebral, or visceral effects may require active management.[2] Factors that may delay ductal closure, such as late-onset bacterial infection and excessive fluid administration (>150 mL/kg per day), should be avoided. Furosemide apparently does not compromise ductal closure in response to indomethacin[20] but may prolong ductal patency in untreated infants. Circulatory imbalance while the ductus arteriosus remains patent may be managed by measures that increase pulmonary vascular resistance (permissive hypercapnia, increased distending airway pressure, or maintenance of a higher hematocrit) or that avoid or correct circumstances that may lower pulmonary vascular resistance (metabolic alkalosis, excessive supplemental oxygen, nitric oxide). Reduced systemic blood flow may be improved by agents that decrease systemic afterload (captopril, milrinone) or exacerbated by those that increase systemic vascular resistance (systemic vasopressor agents), which may increase diversion of cardiac output to the pulmonary circulation. Compromised systemic cardiac output may also be helped by measures that increase pulmonary vascular resistance, reducing ductal steal (Q_P/Q_S), and by increasing total cardiac output if Q_P/Q_S remains constant. Ensuring adequacy of preload may require invasive monitoring of central venous pressures or frequent assessment with functional echocardiography. Hydrocortisone and/or cardiotonic agents may be useful, particularly in hypotensive infants. Congestive heart failure can be managed with the usual strategies of preload reduction (fluid restriction, diuretics), inotropic support, and afterload reduction. It may be useful to prevent or correct ancillary factors that may predispose to pulmonary edema (hypoproteinemia, bacteremia) or augment the risk of injury to the brain (infection, anemia, hypoglycemia), kidneys (hypovolemia, nephrotoxic drugs), or bowel. These measures must be chosen and balanced carefully to ensure optimal effect; excessive fluid restriction to avoid pulmonary edema may exacerbate renal ischemia, for example. None of these strategies have been evaluated in clinical trials.

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Key Points

- Delayed closure of the ductus arteriosus is common in extremely premature neonates and is associated with a variety of untoward outcomes, but there is a lack of evidence for improvement in outcomes with treatment for closure.
- Observational studies of nonintervention strategies provide evidence that permissive approaches to PDA management do not appear to worsen outcomes; however, some data suggest an association between patency of a large ductus arteriosus and BPD.
- Presence of a ductus arteriosus in premature neonates may lead to hemodynamic and secondary pulmonary, cerebral, or visceral effects that may require active management, such as fluid restriction, ventilator adjustments, or circulatory support.
- Evaluation with clinical tools such as biomarkers or echocardiography may delineate a population of preterm infants who will benefit from medical or surgical closure of the ductus arteriosus.

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Congenital Defects of the Cardiovascular System

SANMIT K. BASU AND NANCY C. DOBROLET

Summary

Congenital heart defects are the most common type of birth defect in infants worldwide. The following chapter provides an overview of the anatomy, physiology, clinical presentation, diagnostic evaluation, and management strategies for a wide range of congenital heart disease encountered in neonates and infants. While the information herein is detailed, it is important to keep in mind that many different anatomic and physiologic variants are encountered in practice, often altering clinical management. The chapter is generally organized based on the predominant pathophysiology—cyanotic, obstructive, or shunting—for a given congenital heart defect. There can be considerable overlap between these physiologies, particularly in complex forms of congenital heart disease involving multiple defects. Defect physiology can also change considerably over time, particularly in the immediate postnatal transitional period around ductal closure. Prompt recognition and diagnosis of significant congenital heart defects contribute greatly to effective management and improved outcomes in affected infants.

Cyanotic Heart Defects: Mixing-Dependent

D-Transposition of the Great Arteries

Anatomy and Pathophysiology

In D-transposition of the great arteries (D-TGA), the aorta arises from the right ventricle, which receives systemic venous deoxygenated blood, and the pulmonary artery arises from the left ventricle, which receives pulmonary venous oxygenated blood. The blood flow in these patients is in parallel with the deoxygenated blood entering the aorta and recirculating to the body, while the richly oxygenated pulmonary venous return is recirculated to the lungs. In the absence of any shunting across connections between the systemic and pulmonary circulations to allow mixing of the deoxygenated and oxygenated blood, this results in systemic hypoxia and is often lethal. In D-TGA, three levels where mixing can occur are an atrial level defect (patent foramen ovale or atrial septal defect), patent ductus arteriosus (PDA), or ventricular septal defect (VSD). The best site of blood mixing has been shown to be at the atrial level through a patent foramen ovale (PFO) or atrial septal defect (ASD), with the other forms (PFO and VSD) being less reliable. It is, therefore, extremely important at birth to make sure not only that there is an atrial level communication, but also that it is adequate in size.

Associated Defects

Associated defects have a dramatic effect on the presentation and pathophysiology of newborn infants with D-TGA. At a minimum, an atrial level defect with balanced bidirectional shunting is essential for survival. The presence of a PDA also allows for additional shunting from the aorta (deoxygenated blood) to the pulmonary artery (oxygenated blood), resulting in increased pulmonary venous return and left-to-right shunt at the atrial level. A VSD occurs in about 25% of infants with D-TGA. Its presence contributes to mixing of the oxygen-rich and desaturated blood, but as previously stated, atrial level mixing is the most reliable. Coarctation of the aorta or aortic arch interruption can also occur in association with D-TGA with VSD.[72]

Clinical Presentation

D-TGA is the most common cyanotic heart defect identified in the first week of life, and the diagnosis should be considered in any cyanotic neonate. Fetal diagnosis is common but not uniform. Even with prenatal diagnosis, however, profound hypoxia caused by a highly restrictive atrial level defect can lead to rapid deterioration and death within the first hours of life.[48,82] Respiratory symptoms in this disorder are absent or limited to hyperpnea or tachypnea without dyspnea. The patient's second heart sound is loud and persistently single because of the anterior position of the aorta and the posterior position of the pulmonary artery. A holosystolic murmur, when present, suggests an associated VSD; a systolic ejection murmur is auscultated

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Abstract

Congenital heart defects are the most common type of birth defect in infants worldwide. This chapter provides an overview of the anatomy, physiology, clinical presentation, diagnostic evaluation, and management strategies for a wide range of congenital heart disease encountered in neonates and infants. While the information herein is detailed, it is important to keep in mind that many different anatomic and physiologic variants are encountered in practice, often altering clinical management. The chapter is generally organized based on the predominant pathophysiology—cyanotic, obstructive, or shunting—for a given congenital heart defect. There can be considerable overlap between these physiologies, particularly in complex forms of congenital heart disease involving multiple defects. Defect physiology can also change considerably over time, particularly in the immediate postnatal transitional period around ductal closure. Prompt recognition and diagnosis of significant congenital heart defects contribute greatly to effective management and improved outcomes in affected infants.

Keywords

congenital heart disease
congenital heart defects
cyanosis
echocardiography

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when the patient has pulmonary stenosis. In the absence of these associated defects, murmurs are generally not heard. The peripheral pulses are normal unless coarctation of the aorta is present. Persistent ductal patency or high pulmonary vascular resistance will affect the clinical findings of an associated ventricular septal defect or coarctation of the aorta.

Diagnostic Evaluation

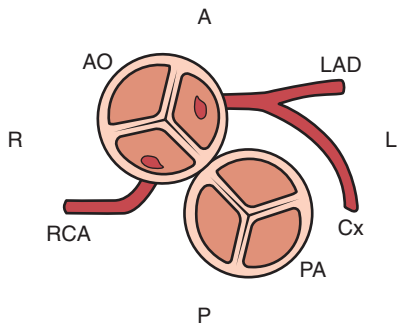
The electrocardiogram is normal or may demonstrate right ventricular hypertrophy after a few weeks of life. Similarly, the classic egg-shaped heart with increased pulmonary vascularity on the chest radiograph might not be seen in the newborn period. Echocardiography defines the associated defects and coronary artery anatomy, which is central to surgical planning.[57] Cardiac catheterization is usually reserved for neonates requiring balloon atrial septostomy, but it is occasionally useful for clarifying the coronary anatomy or other anatomic details (Fig. 75.1).

Management and Prognosis

Establishing patency of the ductus arteriosus with intravenous prostaglandin E_1 infusion in newborn infants with D-TGA often improves arterial oxygenation by increasing shunting from the oxygen-rich pulmonary artery to the deoxygenated aorta. Aortic to pulmonary artery shunting at the ductal level may increase pulmonary venous return, distending the left atrium and facilitating left-to-right atrial shunting of fully oxygenated blood across the atrial level defect. If the prostaglandin E_1 infusion does not result in adequate systemic oxygenation, a balloon atrial septostomy is performed either at the bedside or in the cardiac catheterization lab with echocardiographic guidance. This enlarges the atrial level defect, allowing improved atrial mixing of the systemic and pulmonary venous return.

History

Historically, the surgical interventions for D-TGA were the atrial switch operations of Senning (1959) and Mustard (1964). In these procedures, the deoxygenated blood from the vena cavae is baffled to the morphologic left ventricle and thence the pulmonary artery, while the oxygenated pulmonary venous blood is directed to the morphologic right ventricle and the aorta. This results in physiologic correction. However, the Senning and Mustard procedures are associated with a number of long-term consequences, including right ventricular dysfunction, systemic venous baffle obstruction and leaks, and atrial arrhythmias.[2,42]



• **Fig. 75.1** Most common coronary artery arrangement in D-transposition of the great arteries. The aortic root is anterior and rightward of the pulmonic root in D-TGA. The right coronary artery arises from the rightward posterior-facing sinus, whereas the left coronary artery arises from the leftward anterior-facing sinus. A, Anterior; Ao, aorta; Cx, left circumflex coronary artery; L, left; LAD, left anterior descending coronary artery; P, posterior; PA, pulmonary artery; R, right; RCA, right coronary artery.

Arterial Switch Operation

Drs. Jatene and Yacoub pioneered the anatomic repair of D-TGA via the arterial switch operation, which requires transection of the aorta and main pulmonary artery, reconnection to establish ventriculoarterial concordance (systemic left ventricle to the aorta and pulmonic right ventricle to the main pulmonary artery), and reimplantation of the coronary arteries to the neoaortic root. Other associated intracardiac defects are generally repaired at the time of surgery. The arterial switch operation is optimally performed in the first week of life for infants with D-TGA. If there is a prolonged delay, the risk increases for left ventricular deconditioning and resultant inability to function adequately as the systemic ventricle. The follow-up data on patients who have undergone the arterial switch operation are quite favorable.[59,82,89] Risk factors for early mortality include prematurity and right ventricular hypoplasia. Abnormal coronary anatomy (particularly intramural coronary arteries), a risk factor in earlier experiences, can now be managed effectively, although with potentially higher hospital morbidity.[57] Long-term follow-up studies demonstrate excellent ventricular function, normal rhythm, and low incidence of obstruction at the aortic and coronary suture lines.[19,75] Narrowing in the supravalvar pulmonary area and branch pulmonary arteries may require subsequent surgeries or catheter interventions.[30,82] Neoaortic root dilation and aortic regurgitation are found in some children, but these rarely require further intervention.[60,82] Follow-up data in children 16 years of age with D-TGA from the Boston Circulatory Arrest Study suggest that adolescents with D-TGA who have undergone the arterial switch operation are at increased neurodevelopmental risk and may benefit (along with other children born with congenital heart disease) from ongoing surveillance to identify emerging difficulties.[10]

Cyanotic Heart Defects: Restricted Pulmonary Blood Flow

Tetralogy of Fallot

Anatomy and Pathophysiology

In 1888, Fallot described the association of a large ventricular septal defect, infundibular (subvalvar) and valvar pulmonary stenosis, right ventricular hypertrophy, and a large aorta overriding the ventricular septum—the tetralogy which now bears his name. The spectrum of pulmonary

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lesions in tetralogy of Fallot (TOF) can range from mild pulmonary stenosis with excellent saturations to pulmonary atresia with very low saturations. Infants with severe pulmonary stenosis or atresia may have severely hypoplastic or absent pulmonary arteries with major aortopulmonary collateral arteries serving as the primary source of pulmonary blood flow. In TOF, cyanosis is proportional to the degree of right ventricular outflow tract (RVOT) obstruction, with severe obstruction limiting pulmonary blood flow and leading to very low saturations. Shunting across the VSD is determined by an intricate balance between the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Acute narrowing or stenosis from the release of endogenous catecholamines, for example, increases PVR more than SVR, resulting in right-to-left shunting and worsening systemic desaturations.

Associated Defects

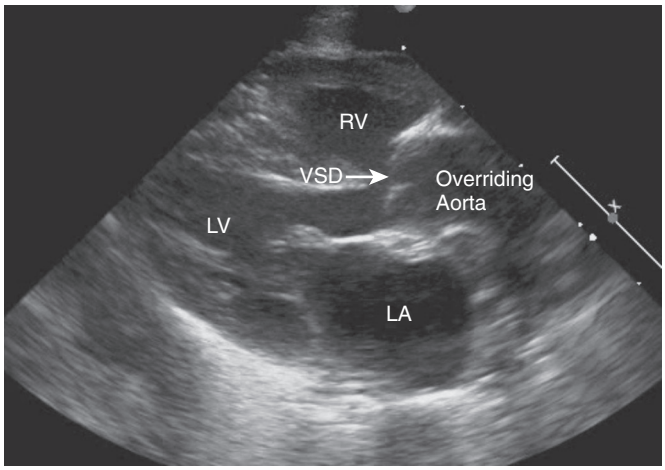
A right aortic arch is found in approximately 25% of patients with TOF. Coronary artery anomalies (e.g., left anterior descending coronary artery arising from the right coronary artery) are not uncommon and must be identified prior to surgical intervention. The branch pulmonary arteries may be stenotic or discontinuous with collateral supply from the aorta. Some patients also have multiple ventricular or atrial septal defects, anomalous systemic venous drainage, or atrioventricular valve abnormalities. A rare, complex form is tetralogy of Fallot with absent pulmonary valve, which results in pulmonary valve annulus hypoplasia and severe branch pulmonary artery dilation with significant bronchial compression and airway abnormalities, including bronchomalacia.

Clinical Presentation

The clinical presentation of TOF is directly related to the severity of RVOT obstruction. The intensely cyanotic newborn infant generally has severe pulmonary stenosis or atresia with markedly diminished pulmonary blood flow and right-to-left shunting across the VSD. The minimally cyanotic or acyanotic infant has a lesser degree of pulmonary stenosis with mainly left-to-right shunting across the VSD. On exam, in neonates with TOF, the primary murmur is a systolic ejection murmur along the left sternal border secondary to pulmonary stenosis/RVOT obstruction. There may also be a single second heart sound due to marked diminishment of its pulmonary component and a palpable right ventricular impulse. The VSD in TOF is generally large and unrestrictive and does not produce a significant murmur. A continuous murmur may suggest systemic-to-pulmonary collaterals as the source of pulmonary blood flow.

Diagnostic Evaluation

In the newborn with TOF, the classic finding on chest X-ray is a boot-shaped heart caused by right ventricular hypertrophy and consequent upturned cardiac apex. The pulmonary vascular markings should also be carefully examined and may indicate the severity of RVOT obstruction. Echocardiography is the primary diagnostic tool and illustrates the anterior malalignment VSD with RVOT obstruction, right ventricular hypertrophy, and overriding aorta (Fig. 75.2). The levels and degrees of pulmonary obstruction and the size of the main and branch pulmonary arteries should be elucidated, as well as other associated abnormalities, including coronary artery anomalies, additional VSDs, or collateral vessels. Presurgical diagnostic cardiac catheterization is only indicated if the pulmonary artery anatomy and pulmonary blood flow sources cannot be defined by noninvasive imaging modalities.



• **Fig. 75.2** Parasternal long-axis view on echocardiogram of a newborn infant with tetralogy of Fallot. The right ventricle (*RV*) is anterior, and left ventricle (*LV*) is posterior, with a large ventricular septal defect (*VSD*) and overriding aorta. LA, Left atrium.

Management and Prognosis

Neonates with severe cyanosis in the immediate postnatal period are stabilized via intravenous prostaglandin E_1 infusion to maintain patency of the ductus arteriosus and increase pulmonary blood flow. In general, these neonates require a palliative systemic-to-pulmonary shunt (e.g., Blalock-Thomas-Taussig or central shunt) or complete repair in the newborn period to provide a reliable source of pulmonary blood flow. Balloon dilation or stenting of the stenotic pulmonary valve or RVOT has been favored in a few centers as an alternative to shunts.[26] Rehabilitation of branch pulmonary artery stenosis by surgery or interventional catheterization is another important step at the time of primary repair or as part of a staged approach. This is of particular importance in patients with pulmonary atresia and major aortopulmonary collaterals.

Complete TOF repair consists of relief of pulmonary stenosis and RVOT obstruction (often with a transannular patch) and patch closure of the VSD. Associated intracardiac defects such as atrial level defects are also addressed. In the absence of marked pulmonary artery hypoplasia or unfavorable coronary artery anatomy, surgery can be undertaken at virtually any age, with most centers doing elective repairs when infants are between 4-6 months of age.

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Neonatal TOF repair is feasible for babies with normal or appropriate pulmonary artery size at birth.

Tricuspid Atresia

Anatomy and Pathophysiology

Tricuspid atresia (TA) is defined by platelike tissue in place of the tricuspid valve with no direct communication between the right atrium and right ventricle. Systemic venous return from the vena cavae enters the right atrium and crosses the atrial septum with resultant complete mixing of the systemic and pulmonary venous return in the left atrium. Pulmonary blood flow is supplied by left-to-right shunting through either a PDA or VSD. Associated right ventricular hypoplasia and pulmonary artery hypoplasia are proportional to the size of the VSD and the degree of subpulmonary and pulmonary stenosis. Systemic hypoxia is proportional to the relative systemic and pulmonary blood flows. Neonates with tricuspid atresia, a small VSD, and severe pulmonary stenosis have severely limited pulmonary blood flow and are ductal dependent. Those with a large VSD and no pulmonary stenosis have high pulmonary blood flow, and when PVR falls in the postnatal period, pulmonary flow dramatically increases with resultant pulmonary overcirculation and risk for respiratory issues and feeding/growth failure.

Associated Defects

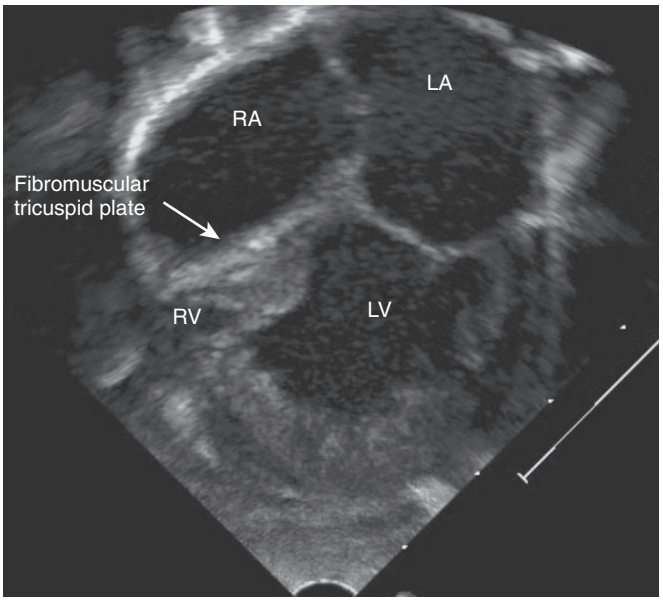
Tricuspid atresia is not a diagnosis that occurs in isolation. All neonates with TA must have an atrial level defect for postnatal survival. Other associated lesions include VSD, transposition of the great arteries (TGA), atrioventricular septal defect, and aortic coarctation. The size of the VSD is extremely important in neonates with TA with TGA since oxygenated blood flows through the VSD into the right ventricle and then the aorta. Any restriction through the VSD in this case severely compromises systemic circulation.

Clinical Presentation

The typical neonatal presentation of TA is cyanosis at or before ductal closure in an infant with a murmur. Precordial activity is normal, and the second heart sound is often single. There may be a systolic ejection murmur if there is RVOT obstruction. If the VSD is large, tachypnea, a left ventricular impulse, and a third heart sound may develop during the first few days of life as the PVR falls. Hepatic enlargement is an indicator of a restrictive atrial septal defect and elevated right atrial pressures.

Diagnostic Evaluation

The electrocardiogram is usually diagnostic in neonates with TA, demonstrating right atrial enlargement and left axis deviation. The chest radiograph tends to be nonspecific, although severely cyanotic neonates show decreased pulmonary vascularity. The echocardiogram (Fig. 75.3) clearly defines the anatomy in this disorder, particularly the RVOT, pulmonary arteries, atrial level defect, and PDA, in addition to the presence or absence of associated anomalies such as TGA or aortic coarctation. Catheterization is indicated only for balloon atrial septostomy in those with a restrictive atrial septum.



• **Fig. 75.3** Apical four-chamber view on echocardiogram of a neonate with tricuspid atresia. There is no tricuspid valve with a fibromuscular plate in its usual place. A large atrial septal defect permits flow from the right atrium (*RA*) to the left atrium (*LA*) and into the left ventricle (*LV*). The right ventricle (*RV*) is severely hypoplastic.

Management and Prognosis

Flow across the VSD to supply the pulmonary circulation may be adequate in the first months of life as long as the atrial level defect remains nonrestrictive. It is generally possible to predict by echocardiogram when infants require a PDA to maintain adequate arterial saturations. A balloon atrial septostomy is rarely necessary unless there is significant restriction at the atrial level. If an infant is ductal-dependent or if hypoxia increases in the first month of life, a systemic-to-pulmonary shunt is necessary to provide adequate pulmonary blood flow and oxygenation. Conversion to a bidirectional cavopulmonary (Glenn) anastomosis is usually considered when an infant is between 3 and 6 months of age.[50] Some infants with well-balanced systemic and pulmonary flows can proceed directly to an early bidirectional Glenn operation[74] or a total cavopulmonary (Fontan) operation at about 2-3 years of age. Among children who undergo the Fontan type of operation, those with TA have excellent long-term prognosis, with a low prevalence of ventricular dysfunction, mitral regurgitation, arrhythmias, and systemic venous congestion.[81]

Pulmonary Atresia With Intact Ventricular Septum

Anatomy and Pathophysiology

The pulmonary valve in pulmonary atresia with intact ventricular septum (PA/IVS) can range from a well-formed

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pulmonary annulus with a plate that obstructs outflow to complete absence of the valve. All forms may lead to severe right ventricular hypertrophy with right ventricular dysfunction and varying right ventricular hypoplasia. Since the ventricular septum is intact, pulmonary blood flow in PA/IVS is ductal-dependent and can only occur via shunting at the atrial level and flow through a PDA. The tricuspid valve is rarely normal in patients with PA/IVS, ranging from severely hypoplastic and stenotic to regurgitant.

Associated Defects

A very important prognostic feature in PA/IVS concerns the presence or absence of ventriculocoronary connections (sinusoids and fistulae) and coronary artery abnormalities. These must be well defined prior to surgical or transcatheter intervention. In the case of right ventricular (RV)–dependent coronary circulation, where coronary artery flow depends on high RV pressures for adequate myocardial perfusion, any decompression of the RV can lead to untoward consequences such as myocardial ischemia, infarction, and death.

Clinical Presentation

Fetal diagnosis of PA/IVS frequently identifies risk factors for subsequent transcatheter and surgical management, including tricuspid valve and RV hypoplasia and coronary sinusoids and fistuale.[32] Neonates with PA/IVS have severe hypoxia with PDA closure and can rapidly become unstable with tachypnea, tachycardia, hepatomegaly, and cardiorespiratory collapse. Cyanosis becomes apparent within hours of birth and is progressive. Tachypnea may be prominent. The first and second heart sounds are single, and there may be a holosystolic murmur heard best at the left lower sternal border consistent with tricuspid regurgitation. A PDA murmur may be audible, particularly following initiation of prostaglandin infusion. Unless there is severe tricuspid regurgitation or a restrictive atrial communication, the liver generally is not enlarged while ductal patency is maintained.

Diagnostic Evaluation

Chest radiography in PA/IVS often shows cardiomegaly, owing to right atrial enlargement. Echocardiography is diagnostic, demonstrating the pulmonary atresia, tricuspid valve abnormalities, RV hypoplasia severity, and coronary anomalies, including sinusoids and fistulae. Cardiac catheterization is indicated to assess coronary flow, the presence (including size and location) or absence of coronary sinusoids and fistulae, and pulmonary blood flow sources and for consideration of pulmonary valve intervention.

Management and Prognosis

Intravenous prostaglandin E_1 infusion is essential for maintaining ductal patency in PA/IVS. Careful assessment of the anatomy and physiology provides a framework for transcatheter and surgical management.[5] Balloon pulmonary valvuloplasty is feasible in infants with even a tiny orifice in the pulmonary valve, and other transcatheter techniques, including radiofrequency perforation of the valve, may be considered.[3] If interventional catheterization is unsuccessful, surgical valvotomy is indicated unless there is clear RV-dependent coronary flow. In that circumstance, RV decompression can result in coronary hypoperfusion, so a systemic-to-pulmonary shunt is recommended as initial palliation to provide pulmonary blood flow. In infants with successful surgical or transcatheter valvotomies, RV growth is possible and biventricular circulation can be restored.[41,44] Severe tricuspid and RV hypoplasia or RV-dependent coronary circulation is an indication for single ventricle palliation.[37] Infants with RV hypoplasia should also be considered candidates for superior cavopulmonary (Glenn) anastomosis combined with closure of the atrial level defect (the so-called 1.5 ventricle repair). This results in direction of inferior vena cava flow across the tricuspid valve into the RV, promoting potential RV growth.

Ebstein Anomaly

Anatomy and Pathophysiology

In Ebstein anomaly of the tricuspid valve, there is arrested delamination of the leaflets during valve development. In particular, the septal leaflet can become tethered to the interventricular septum to varying degrees with apical displacement of its annular attachment, potentially leading to significant tricuspid regurgitation. The anterior tricuspid leaflet can also become markedly enlarged and redundant ("sail-like"), causing RVOT obstruction with decreased blood flow and functional or anatomic pulmonary atresia. Secondary to apical tricuspid annular displacement into the right ventricle, a portion of the RV becomes atrialized, detrimentally affecting its contractile efficiency. Forward pulmonary blood flow is, therefore, dependent on the severity of tricuspid valve displacement and regurgitation and RV atrialization and dysfunction. If functional or anatomic pulmonary atresia occurs, an obligatory right-to-left shunt must exist at the atrial level. The degree of this atrial shunt is proportional to the severity of the tricuspid valve abnormality.

Associated Defects

Patients with Ebstein anomaly often have other associated intracardiac lesions, including the aforementioned pulmonary atresia and atrial level defects. Conduction system abnormalities such as accessory pathways (e.g., Wolff-Parkinson-White syndrome) are found in up to 20% of patients.

Clinical Presentation

Infants with severe manifestations of Ebstein anomaly may present with profound cyanosis, tachypnea, and cardiovascular collapse. Cyanosis is dependent on the extent of atrial right-to-left shunting. A low-frequency holosystolic murmur of tricuspid regurgitation is often heard on exam, and the first heart sound may be widely split.

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Diagnostic Evaluation

The electrocardiogram of infants with severe Ebstein anomaly shows an RSR′ pattern across the right side of the chest, suggesting RV dilation. Chest radiography can demonstrate severe cardiomegaly caused by right atrial dilation. Echocardiography helps delineate the extent of tricuspid valve displacement, atrial level shunting, and functional or anatomic pulmonary atresia. The ratio of the right atrial plus atrialized RV size to the functional RV plus left heart (left atrium and ventricle) size has been a useful measure of severity and outcome.[90]

Management and Prognosis

Mild forms of Ebstein anomaly require no specific treatment, and these infants in general do well. The severely affected neonate with severe tricuspid valve displacement and regurgitation is often ductal dependent with minimal or no anterograde flow across the pulmonary valve.[90] Maintaining ductal patency with prostaglandin E_1 infusion can be useful in the short term. However, ductal flow into the pulmonary artery can make anterograde flow more difficult. In severe Ebstein anomaly, measures to lower the pulmonary vascular resistance, including nitric oxide, and several attempts to wean prostaglandin E_1 might be necessary before anterograde flow across the pulmonary valve can be established. Brief support with extracorporeal membrane oxygenation to facilitate this fetal to neonatal transition has been successful in limited cases. Surgical repair or replacement of the valve is feasible in older children, but this is not useful in neonates. Either surgical exclusion of the right ventricle, with plans for a long-term, single-ventricle palliation, or transplantation might be the only alternatives for the neonate with severe Ebstein anomaly and persistent cyanosis.[54]

Cyanotic Heart Defects: Complete Mixing

Total Anomalous Pulmonary Venous Connection/Return

Anatomy and Pathophysiology

Total anomalous pulmonary venous connection or return (TAPVC/TAPVR) comprises a group of defects in which all the pulmonary veins carrying oxygenated blood drain into the systemic venous circulation rather than normally to the left atrium. A number of distinct variants have been identified:

1. Supracardiac type: A vertical vein emanates from the pulmonary venous confluence posterior to the left atrium and courses superiorly to the left innominate vein, which then drains to the superior vena cava and right atrium.
2. Infracardiac type: A descending vertical vein emanates from the pulmonary venous confluence posterior to the left atrium and courses inferiorly, crossing through the diaphragm and the liver with variable drainage to the ductus venosus, hepatic veins, portal vein, or inferior vena cava and eventual pulmonary venous return to the right atrium.
3. Cardiac type: Pulmonary veins drain to the right atrium via an intracardiac connection—generally the coronary sinus or directly to the right atrium.
4. Mixed type: Anomalous pulmonary venous connections occur at two or more levels. Typically, the left pulmonary veins may drain into the systemic veins through the ascending vertical vein (supracardiac), and the right pulmonary veins drain into the coronary sinus or directly into the right atrium (cardiac). Other complex variants exist as well (Fig. 75.4).

The supracardiac form is most commonly encountered, occurring in roughly half of cases, while the mixed form is least common. Infracardiac TAPVC in particular may present in extremis in the neonatal period, owing to obstruction of the descending vertical vein at either the diaphragm or the ductus venosus. The supracardiac form can also less commonly present with obstruction when the vertical vein passes between the left bronchus and the left pulmonary artery or at the junction of the superior vena cava and the innominate vein. In TAPVC, the oxygenated pulmonary venous return mixes completely with deoxygenated systemic venous return in the right atrium. Systemic blood flow is dependent on shunting from the right atrium to the left atrium through an atrial level defect. In the absence of any form of pulmonary venous obstruction, pulmonary blood flow is increased and hypoxia is mild. In contrast, if the anomalous pulmonary venous connection is obstructed at any point in its course, this results in pulmonary venous hypertension with pulmonary edema and decreased pulmonary blood flow. The combination of decreased pulmonary blood flow and impaired pulmonary function caused by edema produces profound systemic hypoxemia.

Associated Defects

An atrial level defect is essential for postnatal survival with TAPVC. Left-sided heart defects, transposition of the great arteries, and tetralogy of Fallot have also been reported in association with TAPVC. Neonates with heterotaxy syndrome commonly have associated TAPVC.

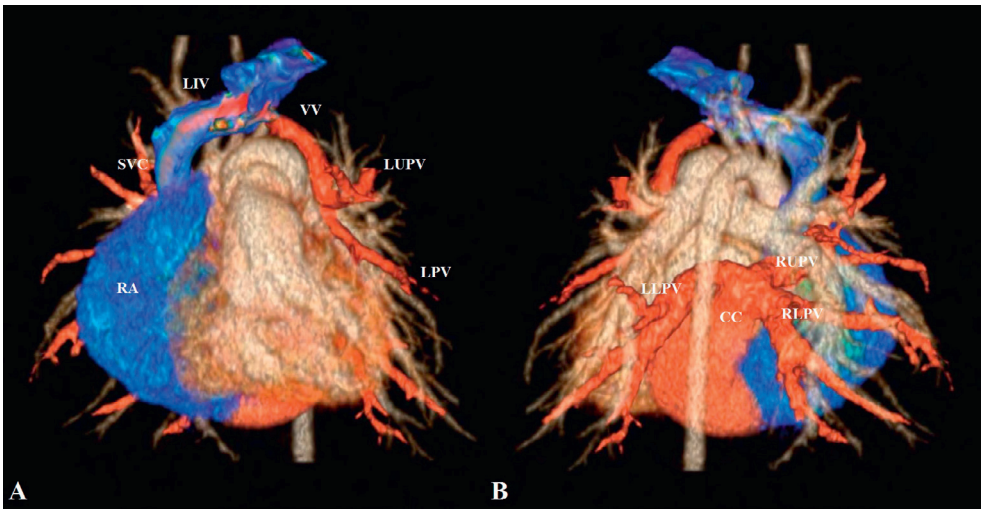
Clinical Presentation

The neonatal clinical presentation of unobstructed TAPVC is generally asymptomatic. These patients are either diagnosed at an older age secondary to recurrent pneumonias or are identified by echocardiogram in evaluation for a murmur. Cyanosis and respiratory distress are generally limited to infants with the severe form of obstructed pulmonary venous connections. In infants without obstruction, volume overload and increased pulmonary blood flow can gradually develop.

Diagnostic Evaluation

Chest radiography is very helpful in TAPVC since it may demonstrate pulmonary edema, which is highly suggestive of pulmonary venous obstruction. Dilated mediastinal

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• **Fig. 75.4** Three-dimensional reconstruction from computed tomography angiography demonstrating complex mixed (supracardiac + cardiac) total anomalous pulmonary venous connection (TAPVC) with the left upper and lingular pulmonary veins draining to the left innominate vein via a vertical vein (supracardiac) and the right upper, right lower, and left lower pulmonary veins draining to a common channel and then the coronary sinus (cardiac). **A,** Anterior view showing the left upper and lingular pulmonary veins draining to a vertical vein and then the left innominate vein, which drains into the SVC and right atrium. LIV, Left innominate vein; LPV, lingular pulmonary vein; LUPV, left upper pulmonary vein; RA, right atrium; SVC, superior vena cava; VV, vertical vein. **B,** Posterior view showing the right upper and lower and left lower pulmonary veins draining to a common channel and then the right atrium via the coronary sinus. CC, Common channel; LLPV, left lower pulmonary vein; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein.

veins give an appearance of fullness to the superior mediastinum (the snowman sign), although in neonates, this is usually masked by the thymus. An ECG is usually not helpful. Echocardiography is the gold standard, and careful examination of each pulmonary vein for its entry into the pulmonary venous confluence and drainage of the confluence is paramount. Sites of venous obstruction can also be illustrated via spectral and color flow Doppler imaging. The size of the individual pulmonary veins and the confluence should be measured since pulmonary vein diameters less than 2 mm have been associated with a poor prognosis. The atrial level defect must be imaged to document that it is not restrictive. If there is any question of a restrictive atrial level defect, balloon atrial septostomy is recommended. If echocardiography cannot provide all the necessary information, CT angiography (see Fig. 75.4), cardiac catheterization, or magnetic resonance imaging may be necessary.

Management and Prognosis

Unobstructed TAPVC generally requires minimal medical management until the infant is ready for surgical intervention. Neonates with restrictive atrial level defects should undergo balloon atrial septostomy. Neonates with pulmonary venous obstruction tend to be profoundly hypoxic and require significant respiratory and metabolic support. Extracorporeal membrane oxygenation has been used as a bridge to complete repair. Urgent neonatal surgery is essential for those with pulmonary venous obstruction. Elective repair via anastomosis of the common pulmonary venous confluence to the left atrium is done in neonates with unobstructed TAPVC in the first months of life. Postoperative pulmonary artery hypertension and pulmonary vascular reactivity is most troublesome in neonates with preoperative pulmonary venous obstruction. The long-term prognosis is excellent except in neonates with hypoplastic pulmonary veins or single ventricle anatomy.[40] Recurrent or persistent pulmonary venous obstruction at the anastomotic site or within the veins is difficult to treat by either surgery or interventional catheterization. Arrhythmias and poor chronotropic response to exercise have been reported in some patients after surgery.[85]

Truncus Arteriosus

Anatomy and Pathophysiology

In truncus arteriosus, there is common origin of aorta and pulmonary artery from a single arterial trunk. This single trunk overrides a large VSD that allows mixing of systemic and pulmonary venous return. In type I truncus, there is a short main pulmonary artery segment arising from the truncus, which then gives rise to branch pulmonary arteries. In type II truncus, both the branch pulmonary arteries have a direct origin from the truncus. In type III truncus, the pulmonary arteries arise from opposite sides of the truncus and are remote from each other. Both pulmonary and systemic blood flows are determined by the relative systemic and pulmonary vascular resistances. As the pulmonary vascular resistance falls, there tends to be increased

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pulmonary blood flow, resulting in pulmonary overcirculation and increased left atrial and ventricular size.

Associated Defects

A number of other cardiac defects are associated with truncus arteriosus. Most importantly, the single semilunar truncal valve demonstrates variable morphology with anywhere from one to six leaflets and differing degrees of valvar stenosis and regurgitation. The truncal valve leaflets also tend to be thickened and dysplastic. Unilateral or bilateral branch pulmonary artery stenosis occurs in about 10% of cases. If the origin of the pulmonary artery is atretic, there can also be aortopulmonary collaterals supplying the lungs. Coronary artery stenoses and malposition are rare but are surgically important variations.[1] A right aortic arch is found in 15%-25% of patients with truncus, and an aortic coarctation or interrupted aortic arch may also be present. In addition, 22q11 chromosomal microdeletion (DiGeorge) syndrome is a very common associated genetic abnormality, so all patients with truncus arteriosus should be screened.

Clinical Presentation

The neonatal presentation of uncomplicated truncus arteriosus can be subtle, with mild tachypnea or cyanosis being the only symptom. Systemic oxygen saturations are generally in the mid-80s, with higher saturations indicating falling pulmonary vascular resistance and increasing pulmonary blood flow. Lower saturations indicate increased pulmonary vascular resistance, branch pulmonary artery stenosis, or pulmonary dysfunction from edema. Acidosis can be present in infants with associated truncal stenosis and regurgitation or aortic arch interruption. As the pulmonary vascular resistance drops, pulmonary blood flow increases, resulting in signs and symptoms of pulmonary overcirculation. Truncal valve stenosis and regurgitation murmurs can be identified on exam. Infants may have bounding pulses and increased pulse pressures secondary to decreased diastolic pressure caused by runoff into the branch pulmonary arteries. Poor perfusion and decreased leg pulses may indicate aortic coarctation or arch interruption. Given the association with 22q11 chromosomal microdeletion syndrome, all patients with truncus arteriosus should also be screened for the presence of a thymus and serum calcium derangements.

Diagnostic Evaluation

Chest radiography in truncus arteriosus typically demonstrates cardiomegaly and pulmonary overcirculation. An electrocardiogram may show biventricular hypertrophy or be normal. Echocardiography is the gold standard for diagnosis—attention must be paid to define the truncal valve, branch pulmonary arteries, aortic arch anatomy, and coronary arteries. Cardiac catheterization, CT angiography, and MRI are reserved for neonates with pending questions after echocardiography. Chromosomal microarray testing should be done on all infants with truncus arteriosus.

Management and Prognosis

In infants with truncus arteriosus, increased pulmonary blood flow and resultant symptomatology generally respond well to agents such as diuretics and digoxin. Supplemental oxygen should be avoided since this decreases pulmonary vascular resistance, increasing pulmonary blood flow. Infants with moderate to severe truncal valve stenosis or regurgitation generally do not respond to medical management and require balloon dilation or early surgical repair. In 22q11 infants, careful management of calcium levels is required. Truncus arteriosus is typically repaired in the first months of life. This repair includes VSD closure and placement of a right ventricle to pulmonary artery (RV-PA) conduit. Associated defects, including truncal valve stenosis, aortic arch interruption, coronary abnormalities, and branch pulmonary artery atresia, increase procedural risk but do not preclude it.[86] If truncal valve stenosis or regurgitation is severe, then the truncal valve may be replaced to provide a competent neoaortic valve. The long-term prognosis for infants with uncomplicated truncus arteriosus status postrepair is excellent. RV-PA conduit replacement is generally required by age 5 years in about 20% of patients, and the conduit must always be replaced at some point in the child's life, sometimes multiple times. The truncal/neoaortic valve may develop worsening stenosis and can require valve repair or replacement in 25% of patients.[43] Ventricular dysfunction and arrhythmias are generally poor prognostic indicators.

Cyanotic Heart Defects: Variable Physiology

Single Ventricle Anatomy/Physiology

Congenital heart disease resulting in single ventricle anatomy or physiology encompasses a wide range of defects and structural variants. A methodical segmental approach to determine a patient's venous, atrial, ventricular, and arterial connections generally allows accurate diagnosis. Furthermore, basic physiologic principles help guide management in this population. For example, there must be adequate mixing of systemic and pulmonary venous return to support single ventricular output. This mixing occurs most effectively through an atrial level defect (PFO or ASD). Additional shunting and mixing can also occur via a VSD or PDA. The single ventricle predominantly pumps blood to either the systemic or pulmonary circulation, and the predominant circulation must then support the other via shunting through a PDA. Systemic oxygen saturations are determined by the relative resistances across the pulmonary and systemic vascular beds. It is important to recognize that many infants have low pulmonary vascular resistance, resulting in unrestricted pulmonary blood flow. Oxygen acts as a pulmonary vasodilator, further increasing pulmonary blood flow, often at the cost of systemic blood flow. This may produce acidosis and diminished end organ perfusion. Consequently, the use of supplemental oxygen

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or other pulmonary vasodilators must be very carefully weighed in the single ventricle population.

Once single ventricle anatomy/physiology has been diagnosed, the next step is to determine whether the pulmonary or systemic circulation requires support. This primarily guides the interventions needed for effective management, including long-term surgical planning. Increasing prenatal diagnosis via fetal echocardiography has allowed better expectant management and teamwork between obstetrics, pediatric cardiology, intensive care, and cardiothoracic surgery teams to optimize care for these patients, as well as better preparation for affected families for the complicated road ahead.

Hypoplastic Left Heart Syndrome

Before 1980, no effective palliation was available for infants with hypoplastic left heart syndrome. Staged surgical palliation, including the Norwood operation,[67] and neonatal cardiac transplantation have afforded new hope to the families of newborn infants with this otherwise uniformly lethal cardiac defect. Advances in both approaches have greatly improved duration and quality of life for these patients.

Anatomy and Pathophysiology

Hypoplastic left heart syndrome (HLHS) can result from a variety of congenital heart defects, but it is classically associated with abnormalities of the mitral and aortic valves, ranging from mitral stenosis and aortic stenosis to mitral atresia and aortic atresia in the most severe variants. There is resultant left ventricular (LV) hypoplasia and varying degrees of ascending aorta and transverse arch hypoplasia. Aortic coarctation may be present in rare cases. LV endocardial fibroelastosis or infarction can result from in utero subendocardial ischemia. Coronary artery abnormalities have also been identified but have uncertain impact on long-term myocardial function. In HLHS, the systemic circulation is ductal dependent—ductal flow courses retrograde to the transverse arch and ascending aorta to supply the head/neck vessels and coronary arteries, as well as anterograde to the descending aorta. In utero, when pulmonary vascular resistance is high, this circulation provides excellent organ perfusion, and fetal growth is usually normal. Postnatally, even as pulmonary vascular resistance falls and pulmonary blood flow increases, right ventricular output remains adequate to supply both the systemic and pulmonary circulations. However, ductal closure dramatically alters this balance, leading to profound systemic hypoperfusion with acidosis and multisystem organ failure.

Associated Defects

The most important associated intracardiac defect in HLHS is an unrestrictive atrial level shunt. An absent or restricted atrial defect in utero creates severe pulmonary venous hypertension, leading to detrimental pulmonary vasculature changes. Significant atrial restriction can result in greatly increased morbidity and mortality in the neonatal period and is a major negative prognostic factor in postnatal outcomes.[34] Other important associated defects for HLHS include pulmonary venous return anomalies. Occasional neonates with aortic atresia have a normal mitral valve and normal left ventricular size because of an associated ventricular septal defect. Central nervous system anomalies, including absent corpus callosum, are also quite common in infants with HLHS. Furthermore, there is increasing recognition of the in utero effects of congenital heart disease, including HLHS, on prenatal brain development and postnatal neurodevelopmental outcomes.[27,36,58]

Clinical Presentation

Increasing prenatal diagnosis of HLHS has greatly helped prepare affected families and contributed to improved coordination between the various medical teams involved in the delivery and initial management of these infants. Infants with HLHS often have tachypnea and mild cyanosis in the postnatal period. There can be a moderately increased right ventricular impulse on exam with a single second heart sound and variable murmurs. With ductal patency, pulses can be nearly normal. Pulse oximetry varies widely, ranging from 70% to greater than 90% depending on the amount of pulmonary blood flow and degree of pulmonary edema. A restrictive atrial level defect can produce significant pulmonary edema because of increased left atrial pressure and resultant increased pulmonary venous pressure. The combination of pulmonary edema and restricted pulmonary blood flow produces profound hypoxia.[34]

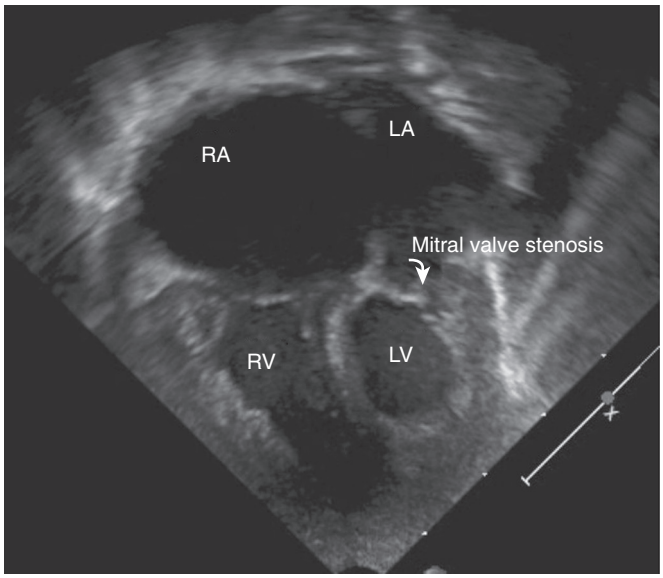
Diagnostic Evaluation

The electrocardiogram in HLHS generally demonstrates dominant RV forces, often with a QR pattern in the right chest leads. Chest radiography shows cardiomegaly and increased pulmonary blood flow with more prominent pulmonary vascular markings and pulmonary venous congestion. Echocardiography (Fig. 75.5) defines the underlying anatomy, including the atrial level defect and its degree of restriction, atrioventricular valve regurgitation, ventricular function, outflow tract obstruction, coronary anatomy, and aortic arch morphology, as well as associated abnormalities such as systemic or pulmonary venous return anomalies. All these are crucial to delineate prior to any type of intervention.

Management and Prognosis

In HLHS, there is ductal-dependent systemic circulation, so maintaining ductal patency in the immediate postnatal period with intravenous prostaglandin E1 infusion is critical for survival. Beyond this period, most centers use a staged surgical strategy to more definitely manage these infants. Neonatal cardiac transplantation[9] remains an option but is greatly limited by donor heart availability. No matter the chosen strategy, careful postnatal assessment and management to prevent complications from excessive pulmonary blood flow are essential for good long-term results. The overall goal of staged surgical palliation for HLHS is to

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• **Fig. 75.5** Apical four-chamber view on echocardiogram of a neonate with diminished pulses and poor perfusion. There is mitral valve stenosis with severely hypoplastic left ventricle (*LV*) and marked size discrepancy compared to the right ventricle (*RV*), consistent with hypoplastic left heart syndrome. LA, Left atrium; RA, right atrium.

separate the systemic and pulmonary circulations in stepwise fashion while ensuring adequate systemic blood flow at each stage and protecting the pulmonary vasculature from excessive flow and pulmonary hypertension. Surgical techniques and postsurgical management have evolved greatly over a number of decades to address the various issues and problems that have been recognized during the evolution of the current staged approach.

In most centers, initial (stage I) surgical palliation is done in the immediate postnatal period with a Norwood procedure, including aortic reconstruction, systemic-to-pulmonary arterial shunt placement (modified Blalock-Thomas-Taussig [mBTT] shunt or RV-PA conduit [Sano modification]),[14] and atrial septectomy. A Damus-Kaye-Stansel anastomosis may be utilized if the ascending aorta is of sufficient size.[66] Stage I palliation may also be accomplished via a hybrid procedure done by surgical and interventional catheterization teams working in tandem. Hybrid stage I palliation consists of surgical bilateral branch pulmonary artery banding and transcatheter PDA stent placement. The theoretical advantages of this approach are avoidance of cardiopulmonary bypass and circulatory arrest (and their potential associated adverse effects) in the neonatal period and delay of major aortic intervention/reconstruction to an older age when infants are larger.[31] The primary goals of both Norwood and hybrid stage I palliation are to provide adequate systemic blood flow and to effectively control pulmonary blood flow. Postoperative management requires very close monitoring of systemic perfusion and appropriate titration of medications and respiratory support as needed to avoid tissue/organ hypoxia. Typical systemic arterial saturations following stage I palliation are in the mid-60% to mid-70% range. Even with greatly improved surgical and intensive care techniques, a proportion of infants after stage I palliation require extracorporeal membrane oxygenation support to achieve stability with eventual poor results.[73]

Following either stage I technique, stage II palliation entails completing a superior cavopulmonary (Glenn) anastomosis or hemi-Fontan procedure to allow the superior vena cava to directly drain to the pulmonary arteries.[28] In the hybrid approach, the previously deferred aortic reconstruction must also be completed, and the total operation is denoted a comprehensive stage II procedure. Stage II palliation is typically completed between 2 and 6 months of age and results in systemic venous return from the upper body (via the SVC) being the sole source of pulmonary blood flow. Since SVC flow is no longer draining to the systemic single ventricle, ventricular volume load is reduced, lessening its overall work load and reducing the potential for ventricular dysfunction. Typical systemic arterial saturations following stage II palliation climb into the mid-70% to mid-80% range.

Staged surgical palliation for HLHS is completed at approximately 2-3 years of age via a total cavopulmonary connection (Fontan procedure) to direct inferior vena cava drainage to the pulmonary arteries. A number of different surgical techniques have been utilized through the years and are now grouped together as Fontan variants, including direct atriopulmonary anastomosis (the classic Fontan first done in 1973), intracardiac connection (lateral tunnel Fontan), and extracardiac conduit connection (extracardiac Fontan).[71] Following any Fontan variant, the pulmonary and systemic circulations have been separated, with the single systemic ventricle accepting oxygenated pulmonary venous return and supplying the systemic circulation in pulsatile fashion and systemic venous return passively draining to the lungs via the cavopulmonary anastomoses. This generally results in normal systemic arterial saturations greater than 90%.

The evolution of the current staged surgical palliation strategy for HLHS has been an iterative process with great advances achieved due to the coordinated and dedicated efforts of entire medical teams and heart centers, including nursing, social work, and multiple medical and surgical specialties. Mortality and morbidity were high during the development of the Norwood procedure, and early experiences with stage I palliation resulted in 1-year survival rates less than 50%. These results have greatly improved into the current era, and staged single ventricle palliation has resulted in significantly increased survival and quality of life.[4,17,25,47] A multicenter prospective clinical trial comparing the mBTT shunt and Sano modification in Norwood stage I palliation failed to show any major differences between the two procedures.[68] Most series comparing the different stage I strategies, including the hybrid approach, have failed to demonstrate a significant difference in outcomes, but there is some data demonstrating a survival benefit with the Norwood-Sano technique in certain HLHS

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variants.[29,33,45,88] Risk factors for poor stage I survival include low birth weight, a restrictive atrial level defect, ventricular dysfunction, and significant AV valve regurgitation.[25,78,87] Interstage mortality (between stage I and stage II palliation) remains a complicated, vexing issue. Long-term morbidity and mortality may occur secondary to recurrent coarctation or arch obstruction,[56] AV valve regurgitation, sinus node dysfunction, various arrhythmias, and ventricular dysfunction. Increasing data are demonstrating the association of HLHS and higher risk for neurodevelopmental issues.[6,27,35,36,58,62]

Double Outlet Right Ventricle

Anatomy and Pathophysiology

In double outlet right ventricle (DORV), the aorta and the pulmonary artery both arise from the right ventricle. There are four distinct subtypes based on the location of the VSD and its relationship to the great arteries: (1) subaortic, (2) subpulmonary, (3) doubly committed, or (4) remote from the great arteries. The Taussig-Bing malformation is a DORV variant with a subpulmonary VSD and transposition of the great arteries.[76] DORV physiology is determined by VSD location and associated defects, ranging from large VSD shunt physiology to transposition physiology.

Associated Defects

The most important associated defect in DORV is subpulmonary or pulmonary stenosis. The DORV variant with a subaortic VSD and pulmonary stenosis results in physiology similar to tetralogy of Fallot. The Taussig-Bing variant is particularly associated with aortic arch anomalies, including coarctation or interruption.

Clinical Presentation

Clinical presentation of DORV in the neonatal period can vary widely, including significant cyanosis in transposition variants or shock and cardiovascular with ductal closure in Taussig-Bing variants with coarctation or interrupted aortic arch. A murmur generally suggests the presence of pulmonary stenosis.

Diagnostic Evaluation

The electrocardiogram and chest radiograph in DORV are nonspecific. Echocardiography helps identify its important features, including VSD size and location, VSD relation to the great arteries, and great artery configuration. The relationship of the great arteries to each other and presence of pulmonary stenosis or aortic arch abnormalities should be easily identified.

Management and Prognosis

Surgical intervention for DORV is dependent on the predominant physiology, as well as VSD location and its relationship to the great arteries. Hence, definitive repair could simply entail VSD closure or become increasingly complex to involve components such as an arterial switch operation or coarctation/interrupted arch repair.[15,76] DORV repair is generally done in the first 6 months of life.

Obstructive Heart Defects

Valvar Aortic Stenosis

Anatomy and Pathophysiology

Isolated aortic valve disease ranges from asymptomatic bicuspid aortic valves to critical valvar aortic stenosis. Mild to moderate aortic valve stenosis is well tolerated in utero, generally resulting in left ventricular hypertrophy. Severe aortic stenosis in utero leads to significant left ventricular hypertrophy and compromised coronary circulation, sometimes resulting in endocardial fibroelastosis and eventual left ventricular (LV) dilation with poor systolic function. These patients often require ductal patency to maintain adequate systemic output to meet the body's metabolic demands.

Associated Defects

Mild aortic stenosis can be accompanied by a large patent ductus arteriosus, which may exaggerate the pressure gradient across the aortic valve because of pulmonary overcirculation and increased pulmonary venous return and left heart blood flow. Significant aortic insufficiency is rare in neonatal aortic stenosis. If present, it should raise suspicion for a tunnel from the LV to the aorta.[63] Aortic root dilation of varying severity is present in patients with aortic stenosis. Supravalvar aortic stenosis should prompt evaluation for Williams syndrome.[53] Diffuse aortic root or ascending aorta hypoplasia is generally a sign of associated aortic coarctation or left heart hypoplasia with severe aortic valve stenosis.

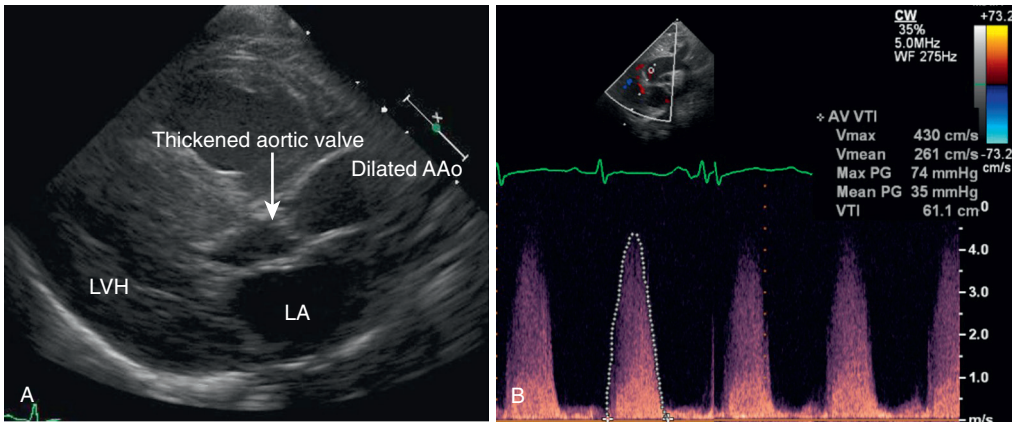
Clinical Presentation

The cardinal physical finding in neonatal aortic stenosis is a systolic ejection murmur radiating upward to the neck. Its intensity and length are dependent on the severity of stenosis and cardiac function/output. A systolic ejection click may also be appreciated at the apex of the heart. For critical aortic stenosis, ductal patency is required for adequate systemic perfusion, so ductal closure can lead to rapid cardiovascular collapse with shock, acidosis, and multiorgan failure.

Diagnostic Evaluation

Since the severity of neonatal aortic stenosis may be difficult to fully assess clinically, thorough diagnostic assessment is essential. The electrocardiogram is usually normal or may show left ventricular hypertrophy. Chest radiography is most useful in detecting pulmonary edema. Echocardiography (Fig. 75.6) is the standard for elucidating aortic valve anatomy, stenosis severity, including pressure gradient by spectral Doppler (see Fig. 75.6*B*), ventricular dysfunction, and other associated defects, including PDA and coarctation. A pulse oximetry differential between the upper and lower extremities suggests right-to-left shunting at the

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• **Fig. 75.6 A,** Parasternal long-axis view on echocardiogram of an infant with significant valvar aortic stenosis (AS). The valve leaflets are thickened with systolic doming (*arrow*). There is associated left ventricular hypertrophy (*LVH*) and ascending aorta (*AAo*) dilation. LA, Left atrium. **B,** Continuous-wave spectral Doppler interrogation of the left ventricular outflow tract from the suprasternal notch demonstrating peak velocities up of 4.3 m/sec (74 mm Hg peak gradient, 35 mm Hg mean gradient), consistent with severe AS.

ductal level. Arterial blood gas and serum biomarkers can be followed to assess tissue perfusion.

Management and Prognosis

Mild valvar aortic stenosis is well tolerated, with no immediate intervention required aside from outpatient follow-up. Moderate to severe aortic stenosis can progress in the first few months of life, necessitating closer follow-up. Any evidence of inadequate systemic perfusion or ventricular dysfunction in an infant with severe aortic stenosis is an indication for balloon or surgical valvotomy. Critical aortic stenosis is a neonatal emergency and continues to result in relatively high morbidity and mortality when not expediently diagnosed. Success rates with neonatal balloon aortic valvuloplasty have been good and considered acceptable when faced with the alternative of surgery, but the procedure can result in residual stenosis or iatrogenic insufficiency, eventually necessitating reintervention.[39,65] Surgical valvotomy remains an alternative as a primary intervention or secondary measure if balloon aortic valvuloplasty is unsuccessful. If the aortic valve or LV is unsuitable for these procedures, single ventricle palliation might be a more suitable long-term solution.[69] The selection of infants with borderline criteria for a two-ventricle approach remains controversial and challenging.[20,22]

Aortic Coarctation and Interrupted Aortic Arch

Anatomy and Pathophysiology

Aortic development is a complex embryologic process that can lead to a number of aortic arch variants and pathologic anomalies.[52] These anomalies can result in aortic obstruction distal to the valvar and supravalvar levels. The most common obstructive arch lesion is aortic coarctation. In its most simple form, coarctation consists of discrete narrowing in the juxtaductal region of the distal arch/aortic isthmus where the PDA joins the aorta. In more severe manifestations, it may be associated with more extensive transverse arch and isthmic hypoplasia. The most severe form of arch obstruction is an interrupted aortic arch (IAA) with complete aortic discontinuity. IAA is classified according to the location of the discontinuity in relation to the head and neck vessel origins. In type A IAA, the interruption occurs distal to the last head and neck vessel (typically the left subclavian artery) in the distal arch/isthmic region. In type B IAA, the interruption occurs more proximally between the second and third head and neck vessels (typically the left common carotid and left subclavian arteries). In type C IAA, the interruption occurs further proximally between the first and second head and neck vessels (typically the right brachiocephalic and left common carotid arteries). Type B is the most common IAA variant, occurring in just over half of cases. In both aortic coarctation and IAA, abnormalities of the head and neck vessel origins—e.g., an aberrant subclavian artery—may be present. Aortic coarctation and IAA produce increased LV afterload, resulting in systemic hypertension and LV hypertrophy. Severe aortic obstruction from a severe coarctation or IAA can lead to LV failure and inadequate perfusion distal to the obstruction, particularly with ductal closure. Thus, maintenance of ductal patency is critical to survival in these infants. Conversely, a significant coarctation may be unmasked during ductal closure. Aside from effects on the LV myocardium, neonatal coarctation may also affect the RV myocardium due to interventricular interactions, leading to RV hypertrophy and dysfunction.

Associated Defects

The most common defects associated with aortic coarctation are bicuspid aortic valve (50% to almost 85% of cases in some series) and VSD. Mitral valve anomalies may also be present. IAA is invariably associated with VSD. The VSD in coarctation or IAA is sometimes posteriorly

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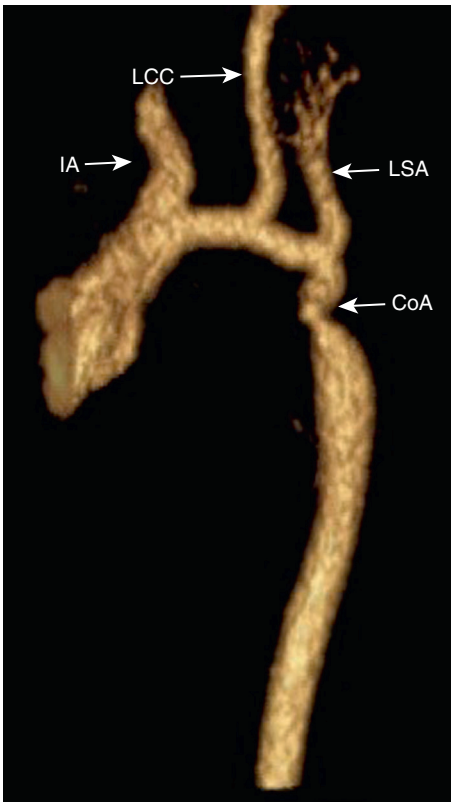
malaligned, causing subaortic obstruction. Other associated lesions include aortopulmonary window, truncus arteriosus, and transposition of the great arteries. Both aortic coarctation and IAA may complicate other forms of complex congenital heart disease. With regards to genetic disorders, aortic coarctation has a recognized association with Turner syndrome, and IAA can be seen with partial or complete 22q11 chromosomal microdeletion syndrome, particularly with right arch–sidedness and branching.

Clinical Presentation

Mild aortic coarctation with no valvar aortic stenosis or VSD is generally asymptomatic. These infants will often have diminished femoral pulses on exam but no other outward signs or symptoms. More severe manifestations can lead to tachypnea, tachycardia, poor feeding, and lethargy, particularly around the time of ductal closure. In cases of critical coarctation or IAA, rapid cardiovascular collapse with shock, hypoperfusion, and multiorgan dysfunction can occur with ductal closure. Early signs and symptoms of congestive heart failure in any infant with coarctation should raise concern about the presence of associated defects. The hallmarks of significant arch obstruction are diminished femoral pulses and blood pressure and oxygen saturation differentials between the upper and lower extremities, although all these may be less pronounced with cardiac dysfunction. Careful palpation of all pulses, including the carotid arteries, can provide valuable anatomic data. Blood pressure discrepancies should be evaluated with four-extremity measurements. Precordial hyperactivity, a single second heart sound, a gallop rhythm, and hepatomegaly are markers of significant obstruction or associated defects. The typical systolic murmur of aortic coarctation—most prominent over the left infraclavicular region and under the left scapula—is well appreciated in older children with coarctation but may not be heard in neonates.

Diagnostic Evaluation

The electrocardiogram of a neonate with aortic coarctation or IAA may demonstrate LV hypertrophy. Chest radiographs are usually normal. Significant cardiomegaly suggests associated lesions or ventricular dilation or dysfunction after ductal closure. Echocardiography generally defines the arch obstruction and morphology with considerable accuracy. However, ascertaining coarctation severity in the presence of a sizable PDA can be difficult. Fig. 75.7 shows a three-dimensional volume-rendered reconstruction of a CT angiogram in a neonate with coarctation. Clinically significant neonatal coarctation can also produce moderate to severe right heart dysfunction. Right-to-left shunting at the ductal level is an important sign of significant obstruction. Transverse arch hypoplasia, especially with an elongated segment between the left carotid and left subclavian arteries, also suggests significant aortic coarctation. Pre- and postductal pulse oximetry and arterial blood gas measurements in the upper and lower extremities are instrumental in assessing ductal shunting and perfusion.



• **Fig. 75.7** Three-dimensional reconstruction from computed tomography angiography demonstrating a severe aortic coarctation (*CoA*) just distal to the left subclavian artery take-off with associated transverse arch hypoplasia and post-stenotic descending aorta dilation. IA, Innominate artery; LCC, left common carotid artery; LSA, left subclavian artery.

Management and Prognosis

Neonates with aortic coarctation or IAA manifesting with signs or symptoms of congestive heart failure or poor perfusion must be started on intravenous prostaglandin E_1 infusion to maintain or restore ductal patency. All neonates with IAA undergo early surgical repair of the aortic arch abnormality and associated defects. Long-term results with IAA and aortopulmonary window or VSD are good, but recurrent arch obstruction and subaortic stenosis are frequent problems.[64] Mortality and morbidity in newborns with IAA and truncus arteriosus remain significant. Those with significant arch hypoplasia might require mobilization of the descending aorta to provide enough tissue to relieve the obstruction.[21] Neonates with aortic coarctation and a large VSD undergo early complete repair.[49] Simple (noncritical) aortic coarctation, on the other hand, is repaired electively in early childhood. Indications for early repair in infancy include significant hypertension, ventricular dysfunction, or cardiovascular collapse with ductal closure. Surgical repair remains the gold standard for primary intervention. In the absence of hemodynamically significant intracardiac defects, a lateral thoracotomy approach is utilized. A number of surgical repair techniques are used, including coarctation resection and end-to-end anastomosis. Balloon angioplasty of native aortic coarctation is usually reserved

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for older children but might be useful in the treatment of selected neonates, particularly as a palliative procedure.[77] This remains a topic of considerable debate. Postoperative systemic hypertension, a very common occurrence following coarctation repair in older children, occurs less frequently in neonates. However, long-term growth of the repaired aortic segment might be an issue in up to 30% of infants, resulting in significant aortic narrowing or recurrent coarctation, particularly in premature infants.[51] Balloon aortic angioplasty has become the preferred treatment for recurrent coarctation in infants and young children with demonstrated safety and efficacy.[79]

Serial Obstructive Left Heart Defects

When any form of left heart obstructive disease is suspected, the entire left heart must be thoroughly investigated with echocardiography. Mitral valve abnormalities are commonly encountered, including leaflet, chordae, or papillary muscles anomalies, including single mitral valve papillary muscle (parachute deformity).[80] Supravalvar mitral rings and subaortic membranes can also be identified and may become progressively obstructive, necessitating close longitudinal follow-up. Shone complex is a recognized association of multiple left heart lesions, including supravalvar mitral ring, parachute mitral valve, subaortic membrane/stenosis, and aortic coarctation, resulting in multilevel obstruction.[83]

Valvar Pulmonary Stenosis

Anatomy and Pathophysiology

Isolated neonatal valvar pulmonary stenosis (PS) most commonly results from dysplasia of the valve leaflets with resultant thickening and decreased mobility, leading to varying degrees of right ventricular outflow tract obstruction at the valvar level. Associated right ventricular hypertension and hypertrophy occur in proportion to obstruction severity. Post-stenotic main pulmonary artery dilation is also commonly found. Any atrial or ventricular level shunts are generally left-to-right unless there is severe obstruction with significantly elevated RV pressures.

Associated Defects

The most commonly associated abnormality with PS is subvalvar (infundibular) narrowing or stenosis. This can be fixed or dynamic. The combined subvalvar/valvar RVOT obstruction can be overestimated when atrial or ventricular shunts are present or underestimated in the context of increased pulmonary vascular resistance (especially in the immediate postnatal period) or decreased RV function. Valvar PS may also be associated with Noonan syndrome, so this should be investigated if there are additional findings such as characteristic facial features.

Clinical Presentation

Neonates with PS generally remain asymptomatic in the postnatal period and are initially identified via auscultation of a harsh systolic ejection murmur at the left upper sternal border radiating to the infraclavicular regions and over the back. Murmur intensity correlates with obstruction severity. In moderate to severe PS, an RV impulse may be noted.

Diagnostic Evaluation

Echocardiography delineates pulmonary valve morphology and extent of outflow obstruction in PS. The RVOT gradients by spectral Doppler are an accurate measure of severity. Neonates with mild valvar PS may not be initially diagnosed until they are noted to have a murmur beyond the immediate postnatal period as pulmonary vascular resistance falls and the pressure gradient across the RVOT and murmur intensity increase.

Management and Prognosis

The natural history of isolated valvar PS is excellent. Most studies demonstrate minimal progression of mild PS with spontaneous resolution in the majority of cases. However, up to a third of patients in some series may progress to moderate or severe obstruction, typically in the first 6 months of life. Moderate to severe PS may also worsen during the first year of life, although there are cases of severe PS that spontaneously resolve as well. In rare cases of critical PS with ductal-dependent pulmonary blood flow, neonatal intervention via transcatheter balloon valvuloplasty or surgical valvotomy may be necessary. Generally, neonatal valvar PS should be longitudinally monitored over the first 6-12 months of life for any worsening. Transcatheter balloon pulmonary valvuloplasty is indicated for persistent severe PS, with intervention timing determined by the severity of RVOT obstruction and RV hypertrophy on echocardiogram or evidence of RV dysfunction. Even with significant RVOT obstruction, however, infants with isolated valvar PS are rarely symptomatic. In the current era, surgical pulmonary valvotomy is reserved for patients with significantly dysplastic valves not responsive to balloon valvuloplasty or valvar PS with concomitant intracardiac defects requiring repair.[70]

Shunting Lesions

Ventricular Septal Defect

Anatomy and Pathophysiology

Ventricular septation is a complex embryologic process involving the development and fusion of the muscular ventricular septum, membranous ventricular septum, conal (outlet) septum, and atrioventricular endocardial cushions to form the interventricular septum. Abnormalities in this process result in abnormal interventricular communications, or ventricular septal defects (VSDs). VSDs are the most common congenital heart defect, making up 20% of identified lesions in some population studies. They are classified according to their location: perimembranous, muscular, inlet, or conal (supracristal or subpulmonary). Perimembranous VSDs are the most common, representing approximately 80% of VSD lesions. The amount of

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shunting through these defects is dependent on their size, as well as the relative pulmonary and systemic vascular resistances. Isolated VSDs have left-to-right shunting given higher LV (systemic) pressures compared to RV (pulmonic) pressures under normal circumstances. In the immediate neonatal period, when PVR and RV pressures remain high, left-to-right flow may be more limited. However, with normal postnatal physiologic transition, PVR falls significantly over the first hours to days of life, with more gradual decrease to adult levels within the first couple of months. This results in lower RV pressures and increasing left-to-right shunting. With sizable defects, pulmonary overcirculation can become considerable with resulting clinical sequelae, as well as intracardiac effects, namely left atrial and ventricular dilation.

Associated Defects

VSDs often exist as a component of more complex congenital heart disease, including many defects discussed elsewhere in this chapter. Their presence can result in different pathologic variants and dramatically alter the natural history and outcomes of lesions such as D-TGA, DORV, and aortic coarctation.

Clinical Presentation

VSDs can be identified by their characteristic holosystolic murmur and location on exam, generally best heard along the left sternal border with localization to the left lower sternal border. This murmur is produced by disturbed shunt flow through the defect. For muscular VSDs, the murmur may be more of a crescendo–decrescendo systolic ejection murmur caused by changes in the defect size as the muscular septum contracts during systole. Larger VSDs can be more difficult to identify in the immediate postnatal period given elevated PVR and less disturbed shunt flow. Similarly, clinical evidence of significant left-to-right shunting and resultant pulmonary overcirculation may not become apparent until PVR drops after the immediate neonatal period. Most infants with isolated VSDs are discharged home with no symptoms, and many VSDs are not diagnosed until initial follow-up visits with primary care providers.

Diagnostic Evaluation

Smaller VSDs are routinely diagnosed with careful clinical examination, given their characteristic murmur location and quality. Echocardiography identifies and defines all types of VSDs in detail, including location and size, as well as other associated defects.

Management and Prognosis

Most VSDs require no intervention and undergo spontaneous closure within the first few months to years of life, particularly small to medium perimembranous and muscular VSDs. These lesions are hemodynamically insignificant and generally remain asymptomatic. Larger VSDs of any type can result in considerable left-to-right shunting with pulmonary overcirculation and associated symptomatology, including tachypnea, increased work of breathing, poor feeding, and suboptimal weight gain. These are all indications for initiation of medical therapy, which usually starts with oral diuretics to help reduce pulmonary symptoms and improve feeding and growth. Exposure to significant left-to-right shunting and pulmonary overcirculation over the long-term can precipitate maladaptive pulmonary vascular changes with increased risk for pulmonary vaso-occlusive disease. Indications for surgical VSD closure include persistent respiratory symptoms or suboptimal feeding and growth despite maximal medical therapy, evidence of right ventricular hypertension, deleterious intracardiac changes such as left heart dilation or aortic valve leaflet prolapse/insufficiency, or defect types with minimal likelihood of spontaneous closure (e.g., supracristal or subpulmonary VSD).

Atrial Septal Defect

Similar to ventricular septation, embryologic atrial septation is a complex process, and derangements in this process can result in abnormal interatrial communications in various parts of the atrial septum. Atrial septal defects (ASDs) are classified according to their location and embryologic origin. There are four major types: ostium secundum ASD, ostium primum ASD, sinus venosus (superior and inferior) ASD, and coronary sinus ASD. Secundum ASDs are the most common type, representing over two-thirds of cases. Primum ASDs are a cardinal component of atrioventricular septal defects. Sinus venosus ASDs are associated with partial anomalous pulmonary venous return given their location. Isolated secundum ASDs diagnosed in a neonate are generally an incidental finding and may represent persistence, stretching, or incomplete closure of the foramen ovale rather than a true septal defect. True secundum ASDs rarely cause clinical sequelae in the immediate postnatal or neonatal period in the absence of other associated defects or conditions. Isolated small to moderate secundum ASDs often close spontaneously over time. However, persistent or more sizable secundum ASDs with left-to-right shunting must be longitudinally monitored for intracardiac effects such as right heart dilation or evidence of increasing right ventricular pressures, indicative of developing pulmonary vascular disease. The most severe manifestation of pulmonary vascular disease due to persistent shunting is Eisenmenger syndrome, with shunt reversal (right-to-left), cyanosis, and irreversible pulmonary hypertension. Therefore, continued shunting with intracardiac sequelae is an indication for secundum ASD closure. Transcatheter ASD device closure has become the preferred method with excellent overall results in children.[24]

Atrioventricular Septal Defect

Anatomy and Pathophysiology

Atrioventricular septal defects (AVSDs) lie on a spectrum of malformations resulting from failure of the endocardial

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cushions to fuse during embryologic cardiac development. The most severe form is a complete AVSD, consisting of an ostium primum ASD, inlet VSD, and common atrioventricular (AV) valve. Other commonly seen variants include partial AVSD (ostium primum ASD with a cleft mitral valve) and transitional AVSD (ostium primum ASD, cleft mitral valve, and small inlet VSD). The pathophysiology of any AVSD variant is dependent on the extant lesions and resultant shunting. For example, the physiology of a partial or transitional AVSD mirrors that of a simple ASD since the majority of shunting occurs at the atrial level. The physiology of a complete AVSD, on the other hand, combines ASD and VSD physiology since considerable shunting occurs at both the atrial and ventricular levels. These lesions are rarely symptomatic in the postnatal or neonatal period in the absence of other defects or conditions.

Associated Defects

The common AV valve in AVSD is often structurally abnormal and can demonstrate varying degrees of regurgitation. Common AV valve abnormalities may also cause unbalanced ventricular development, leading to right- or left-ventricular dominance or outflow tract obstruction. In more extreme cases, this produces single ventricle anatomy and physiology. A common atrium with near complete absence of the atrial septum can be found in some AVSD variants. Systemic and pulmonary venous anomalies may also be present. AVSD may exist in conjunction with other complex congenital heart disease, including tetralogy of Fallot and double outlet right ventricle. There is a very well-recognized, strong association between complete AVSD and trisomy 21, with almost 20%-30% of trisomy 21 patients also having a complete AVSD.[23]

Clinical Presentation

Significant common AV valve regurgitation, if present, can be appreciated as a holosystolic murmur at the apex on exam. If regurgitation is significant, pulmonary venous congestion may result with increasing pulmonary edema and associated symptomatology, including tachypnea and increased work of breathing. The ostium ASD and inlet VSD components do not tend to produce significant or characteristic murmurs, particularly in the immediate postnatal phase with elevated PVR and more limited shunting across the defects. Systemic oxygen saturations tend to be normal in complete AVSD. Cyanosis is generally encountered with more complex AVSD variants, such as severely unbalanced AVSD with single ventricle physiology or tetralogy of Fallot with AVSD.

Diagnostic Evaluation

The electrocardiogram in neonates with AVSD can be characteristic with significant left axis deviation and right atrial enlargement. The axis deviation results from displacement of the conduction pathways away from their usual locations because of the intracardiac defects. Echocardiography is the primary diagnostic tool and should delineate the different AVSD components, including the septal defects and shunts, AV valve morphology and function, ventricular morphology and balance and function, outflow tracts, and other associated anomalies.

Management and Prognosis

A balanced, complete AVSD with no significant common AV valve abnormalities, ventricular dysfunction, or outflow tract anomalies is repaired on an elective basis in the first 4-6 months of life with a high degree of success.[84] Infants with trisomy 21 sometimes undergo earlier repair because of the potential for early development of significant pulmonary hypertension. Following complete repair, long-term issues primarily involve AV valve function (stenosis or regurgitation). Infants with a partial AVSD can often wait until almost 1 year of age for complete repair in the absence of any respiratory or feeding or growth issues.

Patent Ductus Arteriosus

Please see Chapter 74 for additional coverage.

Anatomy and Pathophysiology

The ductus arteriosus connects the pulmonary artery to the aorta in utero and is an essential structure during fetal life. Since fetal pulmonary vascular resistance is very high, only 10%-15% of blood ejected by the right ventricle goes to the lungs, with the rest flowing through the ductus into the descending aorta. The ductus arteriosus generally undergoes spontaneous closure in the immediate postnatal period, and the entire RV output is then ejected to the pulmonary circulation. If the ductus arteriosus remains patent postnatally, the shunt becomes primarily left-to-right (aorta to pulmonary artery) as PVR falls in normal fashion, resulting in left heart (left atrial and ventricular) volume loading. An important exception to this pattern of left heart volume loading occurs in neonates with persistent transitional circulation. In these infants, PVR is comparable to or higher than the systemic vascular resistance, resulting in bidirectional shunting through the PDA. If PVR is significantly higher than SVR, the shunting can become exclusively right-to-left (pulmonary artery to aorta), causing systemic desaturations.

The mechanisms responsible for postnatal ductal closure are not fully understood. The ductus arteriosus is highly sensitive to changes in oxygen tension, so the normal postnatal increase in arterial oxygen tension may serve as the stimulus for ductal closure. The mediation of this response is less certain and is likely attributable to a complex interaction between autonomic chemical mediators, nerves, prostaglandins, and the ductal musculature. The ductus arteriosus functionally closes in most full-term infants during the first day of life, but anatomic obliteration of the ductus arteriosus generally does not occur until after the first week of life. A persistent PDA is uncommon in otherwise normal children. In contrast, 30% of infants with birth weights less than 1.5 kg have a PDA, possibly as a result of hypoxia and

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immaturity of the ductal closure mechanisms, and spontaneous PDA closure by the fourth postnatal day only occurs in approximately one-third of infants less than 1000 g birth weight.[55] Therefore, a majority of significantly premature infants are potential candidates for pharmacologic or surgical intervention, though the merits of active therapy for PDA closure remain controversial.

Associated Defects

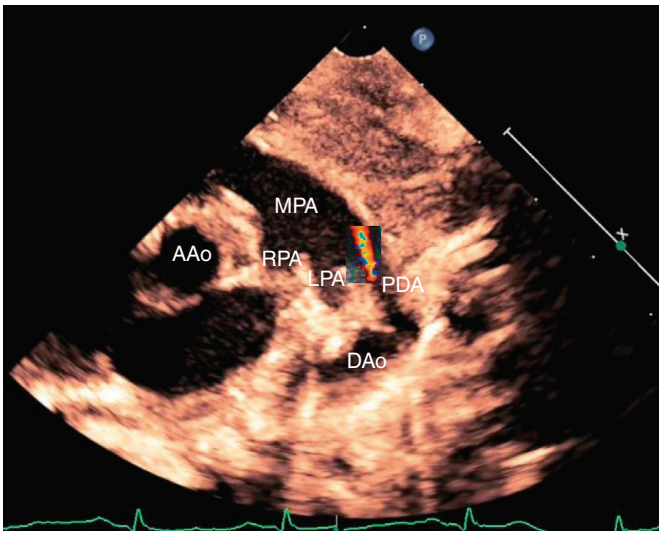
A PDA is present at birth in infants with all but a few congenital heart defects. Although the presenting features of the associated defects are usually clear, occasionally the PDA is the most easily recognized component clinically and by echocardiogram. Aortic coarctation in particular is more difficult to definitively diagnose in the presence of a large PDA. Absence of the ductus arteriosus is notable in some neonates with tetralogy of Fallot and pulmonary atresia. In these infants, the central pulmonary arteries are markedly hypoplastic where the ductus arteriosus would insert, and multiple aortopulmonary collateral vessels may be present. The ductus arteriosus is also often absent in neonates with the absent pulmonary valve TOF variant in which the failure of ductal formation or closure at a critical time in cardiogenesis may play a role in the pathogenesis of the pulmonary valve and arterial abnormalities.

Clinical Presentation

The murmur heard in a neonate with a PDA may be unlike that heard in an older infant or child with a persistent PDA, where the classic continuous (machinery) murmur is present. In newborn infants, especially premature ones, diastolic flow through the PDA may be limited because of persistently elevated PVR and consequently is difficult to hear. A systolic murmur of uneven intensity throughout systole may be appreciated at the left upper sternal border. Even in the absence of a murmur, however, the hemodynamic consequences of a sizable PDA can become clinically evident. Significant left-to-right shunting with resultant increased blood flow and pulmonary overcirculation may result in a supplemental oxygen requirement to maintain appropriate saturations or cause weaning difficulties in infants with existing ventilatory support. A sizable PDA can also result in wide pulse pressures with bounding pulses caused by run-off into the pulmonary arteries during diastole. Clinical evidence of a hemodynamically significant PDA may lag behind echocardiographic signs.

Diagnostic Evaluation

In symptomatic infants, clinical suspicion of a PDA should be confirmed by echocardiography. Echocardiography (Fig. 75.8) permits accurate diagnosis—with assessment of both the hemodynamic impact of the shunt, reflected by the extent of left heart enlargement, and estimated pulmonary artery pressures—and excludes other defects presenting with similar symptomatology, including an aortopulmonary window or significant aortopulmonary collateral vessels. Chest radiography may demonstrate pulmonary vascular congestion but is generally not diagnostic. Serum B-type natriuretic peptide (BNP), produced in response to myocardial stretch with chamber dilation, may be a useful bedside screening tool for response to therapy in premature infants with PDA.[38,46]



• **Fig. 75.8** Parasternal short axis view on echocardiogram with color flow Doppler imaging demonstrating a patent ductus arteriosus (*PDA*) with flow from the descending aorta (*DAo*) to the main pulmonary artery (*MPA*). AAo, Ascending aorta; LPA, left pulmonary artery; RPA, right pulmonary artery.

Management and Prognosis

Full-term infants with a small PDA are followed clinically, and spontaneous ductal closure generally occurs in the first months of life. Isolated moderate or large PDAs may also close spontaneously but require longitudinal follow-up, often with repeat imaging to assess the shunt and potential intracardiac effects. Closure is indicated for any PDA with symptoms associated with significant left-to-right shunting or pulmonary overcirculation, left heart dilation, or evidence of increasing right-sided pressures on echocardiogram. Conventional surgical closure or video-assisted thoracoscopic surgery[16] is appropriate for infants with a moderate to large PDA, while transcatheter closure with coils is often pursued for smaller defects. Newer devices such as specifically designed ductal occluders have allowed increasing transcatheter closure of larger ducts with excellent results and minimal complications.[13]

In premature infants, spontaneous ductal closure is common, but persistent or recurrent symptoms and respiratory distress caused by shunting and pulmonary overcirculation may require therapy for ductal closure. The optimal approach to the PDA in preterm infants is still unknown. A proportion of infants will have spontaneous closure over the first week of life. Thus, some have advocated for delaying assessment of patency until the end of the first week of life. However, there is concern that prolonged exposure to a large hemodynamically significant PDA may compromise

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the pulmonary vascular bed and may be associated with an increased risk of bronchopulmonary dysplasia.[12,18] Progressive increases in ventilator or supplemental oxygen support requirements in these infants may also be manifestations of an increasingly hemodynamically significant PDA. Medical management with fluid restriction and diuretics is occasionally effective at improving symptomatology. Indomethacin, a prostaglandin synthetase inhibitor, and ibuprofen, a nonselective cyclooxygenase inhibitor, have both been shown to close persistent PDAs in a large fraction of premature infants up to 14 days of age and occasionally as late as 1 month of age. Ibuprofen has been further shown to be equally effective for ductal closure with fewer renal side effects. Surgical PDA ligation is also an option but has been associated with increased morbidity and adverse neurodevelopmental outcomes,[61] as well as a relatively high incidence of postoperative left vocal cord paralysis in extremely low birth weight infants.[11] Surgical intervention remains a consideration if a PDA remains hemodynamically significant by clinical or echocardiographic criteria following indomethacin or ibuprofen therapy or if pharmacotherapy is contraindicated. There is also increasing evidence for effective transcatheter PDA device closure in infants at weights less than 6 kg, including extremely (<2 kg) and very low (2 to <4 kg) birth weight infants, but the risks of associated adverse events must be carefully weighed.[7]

Aortopulmonary Window

Anatomy and Pathophysiology

An aortopulmonary (AP) window, as its name implies, is an abnormal connection between the ascending aorta and the main pulmonary artery. It forms from failure of the conotruncal ridges to fuse during cardiac development. The defects tend to be large, allowing high-pressure shunting from the systemic to the pulmonary circulation and resulting in considerable pulmonary overcirculation. AP window pathophysiology mimics that of a large VSD or PDA with significant left-to-right shunting that increases as the pulmonary vascular resistance falls.

Associated Defects

AP windows exist in conjunction with other cardiac anomalies in approximately half of cases, including other conotruncal defects such as tetralogy of Fallot, transposition of the great arteries, and interrupted aortic arch (type A). Additional associated abnormalities include right pulmonary artery origin from the aorta and anomalous coronary artery origin from the pulmonary artery.

Clinical Presentation

Patients with an AP window are at increased risk of early pulmonary overcirculation and associated symptomatology, often in the first weeks of life. On examination, the precordium is active, and there is single second heart sound with bounding pulses.

Diagnostic Evaluation

Chest radiography often demonstrates cardiomegaly and increased pulmonary vascular markings consistent with significant pulmonary overcirculation. Echocardiography can visualize the defect nicely, but special care must also be taken to identify an associated patent ductus arteriosus or interrupted arch, as well as coronary artery or branch pulmonary artery abnormalities.

Management and Prognosis

Surgical closure of an AP window is usually done shortly after diagnosis with excellent short- and long-term results.[8] Delaying repair risks development of significant pulmonary vascular hypertension and potential irreversible vascular disease with Eisenmenger syndrome.

See Table 75.1 for findings to aid in the diagnosis of common congenital heart diseases.

Acknowledgments

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TABLE 75.1 Important Findings That Aid in the Diagnosis of Common Congenital Heart Diseases

Cardiac Diagnosis	Physical Examination	Chest X-Ray	ECG
Atrial septal defect	Wide and fixed splitting of S2 Pulmonary flow murmur	Pulmonary overcirculation proportional to the left to right shunt	Right atrial dilation RVH
Common atrioventricular canal defect	Occasional loud P2	Pulmonary overcirculation when pulmonary vascular resistance falls	Left axis deviation/abnormal superior vector Biventricular hypertrophy
Coarctation of aorta	Radiofemoral pulse delay Weak femoral pulses Upper and lower extremity BP discrepancy (UE > LE by at least 15-20 mm Hg)	Rib notching in long-standing cases only with severe coarctation and collateral formation	Biventricular hypertrophy based on severity

Continued

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TABLE 75.1 Important Findings That Aid in the Diagnosis of Common Congenital Heart Diseases—cont'd

Cardiac Diagnosis	Physical Examination	Chest X-Ray	ECG
Ebstein anomaly	Cyanosis Multiple systolic clicks	Massive cardiomegaly or wall-to-wall heart	Right atrial dilation Bundle branch block
Hypoplastic left heart syndrome	Cyanosis Single S2 Shock	Nondiagnostic	RVH
Partial anomalous pulmonary venous return	Pulmonary flow murmur	Scimitar sign if RLPV to the IVC Increased pulmonary vascularity	RVH
Patent ductus arteriosus	Wide pulse pressure Bounding pulses	Increased pulmonary vascularity	Left atrial dilation LVH
Pericardial effusion/ tamponade	Pulsus paradoxus Hypotension	Water bottle appearance	Decreased voltages
Pulmonary hypertension	Loud P2 With PDA and right-to-left shunt, the LE oxygen saturations can be lower than UE saturations	Peripheral pruning in severe cases	RVH
Pulmonary atresia with intact ventricular septum	Severe cyanosis Single S2	Pulmonary oligemia	
Pulmonary stenosis	Soft P2 Systolic ejection click	Pulmonary oligemia	RVH
Total anomalous pulmonary venous return	Cyanosis	Snowman sign in supracardiac type Increased pulmonary vascularity	RVH
Tetralogy of Fallot	Cyanosis ± pulmonary ejection murmur Soft P2	Boot-shaped heart Absent thymus (in the presence of 22q11 deletion) Look for right aortic arch	RVH
Transposition of great arteries	UE saturations are lower than the LE (at least by 5%) Cyanosis No murmur	Increased pulmonary vascularity Egg on string appearance	
Tricuspid atresia	Cyanosis Single S1	Left axis deviation	LVH
Truncus arteriosus	Cyanosis Single S2	Increased pulmonary vascularity	

BP, Blood pressure; IVC, inferior vena cava; LE, lower extremity; LVH, left ventricular hypertrophy; P2, pulmonary component of second heart sound; PDA, patent ductus arteriosus; RLPV, right lower pulmonary vein; RVH, right ventricular hypertrophy; S1, first heart sound; S2, second heart sound; UE, upper extremity.

Key Points

- Congenital heart defects are the most common type of birth defect worldwide and are often encountered in neonates and infants.
- Specific heart defects generally have a predominant pathophysiology—cyanotic, obstructive, or shunting—that can be considerably altered in the presence of associated defects.
- Complex forms of congenital heart disease often involve multiple defects, complicating pathophysiology and management.
- Defective physiology can change considerably over time, particularly in the immediate postnatal transitional period around ductal closure.
- Clinical presentation of significant congenital heart disease can vary widely, so recognition of typical patterns (e.g., tachypnea and increased work of breathing with significant pulmonary overcirculation) is invaluable for early diagnosis.
- Echocardiography is the major diagnostic tool for congenital heart disease, but very useful information can

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be gleaned from careful physical examination and other work-up prior to echocardiography, including ECG, chest radiography, pre- and postductal saturations, and four-extremity blood pressures.

- Early recognition of ductal-dependent congenital heart defects is critical for effective management and improved outcomes in affected infants.
- Infants with congenital heart defects often have other associated conditions, including genetic abnormalities and disorders, which must be investigated and identified.

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76

Cardiovascular Problems of the Neonate

CHRISTINA M. PHELPS AND JILL SHIVAPOUR

Cardiac Malposition and Abnormalities of Abdominal Situs

Bodily Arrangement and Situs

The development of morphologically right-sided structures on one side of the body, and morphologically left-sided structures on the other side, is termed *lateralization* or *situs*. The normal arrangement, in which right-sided structures are on the right side of the body and vice versa, is known as *situs solitus*. The term *visceroatrial situs* is often used to refer to the situs of the viscera, or noncardiac organs, and *atria* when their situs is in agreement. In normal atrial arrangement or *atrial situs solitus*, the left atrium is on the left side and right atrium is on the right side. In *atrial situs inversus*, the left atrium is on the right side and right atrium is on the left side. The morphology of the lungs and the relation between the tracheobronchial tree visible on chest radiograph[37,45] and the pulmonary arteries are useful in determining situs. A morphologically right lung typically has three lobes, and a morphologically left lung typically has two lobes. Furthermore, the right lung tends to have an eparterial bronchus, or one that branches superior to the first lobar division of the pulmonary artery, in contrast to the left-sided lung, which has a hyparterial bronchus, or one that branches inferior to the first lobar division of the respective pulmonary artery (Fig. 76.1).

Visceral situs solitus occurs when the abdominal organs are lateralized normally with the spleen and stomach on the left side and liver on the right side. The assessment of abdominal situs can be made by physical examination and other routine tests, such as radiography and ultrasound. The liver is palpable on the left in situs inversus with the stomach bubble on the right side. Ultrasound of the abdomen will confirm these findings along with demonstration of other structures such as the kidneys and spleen. If the spleen is not visible on routine abdominal ultrasound, an abdominal CT or MRI may be indicated to demonstrate the presence or absence of a spleen. A nuclear scan is rarely indicated. Another finding that is generally present if the spleen is absent or nonfunctional is Howell-Jolly bodies on the peripheral smear, because these are usually removed by a normal spleen.

Dextrocardia is present when the base to apex axis of the heart is directed to the right side of the chest (Fig. 76.2). Another possible location for the heart is mesocardia, where the apex is in the midline. Situs solitus is the normal location of the atria and abdominal organs as described previously. Situs inversus is present when the right atrium is on the left, the left atrium is on the right, and the liver and stomach are similarly reversed. Situs ambiguous, with the liver and stomach in the midline, is seen in neonates with either bilateral right-sidedness or left-sidedness, also commonly referred to as *heterotaxy syndrome*. Babies with bilateral right-sidedness tend to have asplenia, and their atrial and pulmonary morphologic features are characteristic of bilateral right atria and lungs. Babies with bilateral left-sidedness tend to have polysplenia and bilateral morphologic left atria and lungs. These conditions are invariably associated with a multitude of other intracardiac abnormalities.

Associated Lesions

Dextrocardia with situs inversus is referred to as the mirror image; dextrocardia may be a part of Kartagener syndrome or immotile cilia syndrome but is generally associated with normal cardiac anatomy. It is frequently detected by clinical exam with the heart sounds auscultated in the right chest and incidental chest radiograph demonstrating dextrocardia (see Fig. 76.2). In contrast, babies born with dextrocardia and situs solitus frequently have associated congenital heart defects, ranging from simple septal defects to complex lesions such as L-transposition of the great arteries.[13] The same is true for those neonates with situs inversus of their abdominal organs with levocardia (normal cardiac position with base to apex axis to the left) who almost always have associated cardiac defects.

Asplenia syndrome or bilateral right-sidedness should be suspected whenever complex cardiac defects are identified

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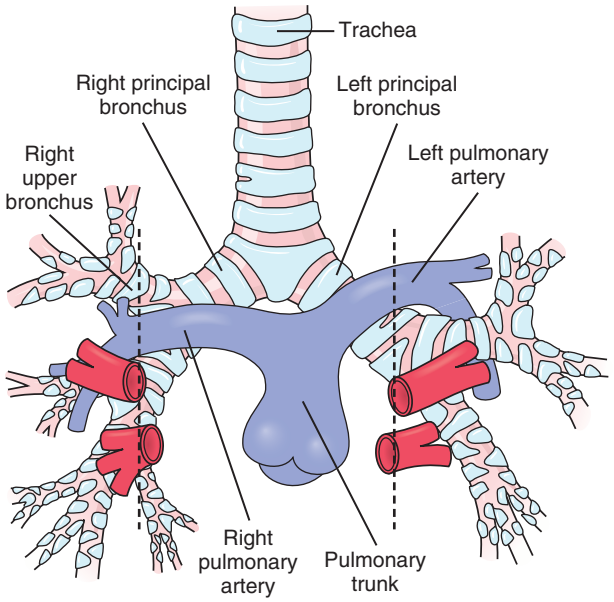
Abstract

Cardiovascular issues in the neonate may present within the first few days of life and are easily delineated and classified with noninvasive testing. Outcomes for each of these disorders are worse in those with significant early symptomatology requiring intervention whether with heterotaxy and right atrial isomerism, neonatal cardiomyopathy, symptomatic PDA in a preterm infant, neonatal Marfan syndrome, or Vein of Galen malformation presenting with heart failure before 5 months of age. The high morbidity and mortality associated with these lesions necessitates accurate diagnosis and expert medical, interventional, and surgical management. Early involvement of palliative care after diagnosis may mitigate parental distress and enable consistent messaging regarding the infant's expected course.

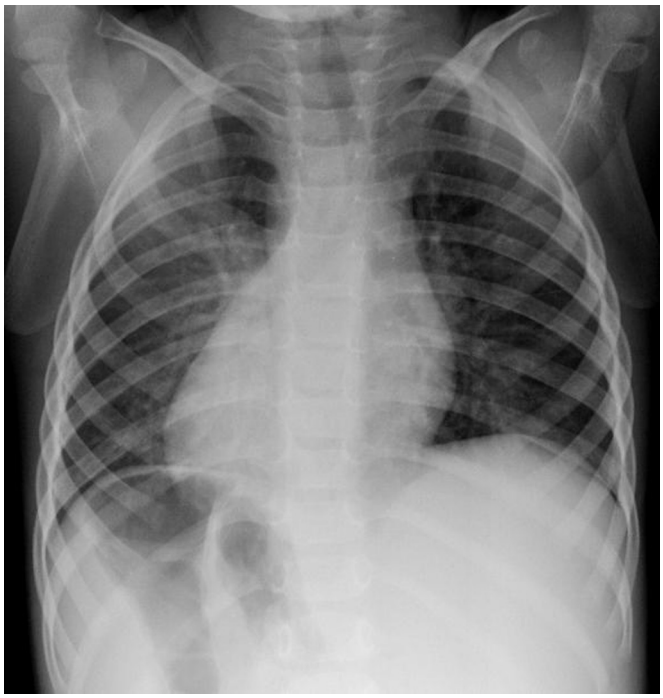
Keywords

cardiomyopathy
vascular ring
patent ductus arteriosus
cerebral AVM

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• **Fig. 76.1** Figure showing the normal relationship of pulmonary arteries and bronchi. Note that the first branch of the right main stem bronchus is superior to the right pulmonary artery (eparterial bronchus), whereas the first branch of the left main stem bronchus is inferior to the left pulmonary artery (hyparterial bronchus).



• **Fig. 76.2** Chest radiograph showing dextrocardia with apex pointing to the right. Also note the right bronchus being more horizontal than the left mainstem bronchus, suggesting situs inversus. The stomach bubble is on the right side of the abdomen, and the liver shadow is on the left side.

in association with total anomalous pulmonary venous connection.[61] Because there is no morphologic left atrium, pulmonary venous drainage is rarely directly to the patient's left-sided atrium. Similarly, in this condition, the coronary sinus, which lies posterior to the normal left atrium, is usually absent. Systemic venous return is also abnormal, with the presence of bilateral superior vena cava. The left superior vena cava may enter directly into the roof of the left-sided morphologic right atrium or the coronary sinus, whereas the right superior vena cava generally enters the right atrium in a normal fashion. The right inferior vena cava is present, and there might be an additional left inferior vena cava. Another relatively common variety encountered in cardiac position is dextrocardia with an associated common atrium and a single atrioventricular valve, resulting in either a common ventricle or a large ventricular septal defect. Severe pulmonary stenosis or atresia is common in this particular defect.[17] Surgical palliation beginning as a neonate and terminating in a palliated univentricular circulation is the norm for over 80% of asplenia patients. Survival at 5 years in a live-born cohort of asplenia infants is 53% and is worse in those with stenotic pulmonary veins.[24] In addition to their complex congenital heart disease, these babies are often immunologically compromised because of the lack of a spleen.[62] Severe, life-threatening septic events are a considerable concern and daily, lifelong administration of a prophylactic antibiotic to reduce the risk for bacterial sepsis is critically important.

Absence of the hepatic segment of the inferior vena cava, so-called interrupted inferior vena cava, is an excellent clue to the presence of polysplenia or bilateral left-sidedness in a neonate with ambiguous abdominal situs.[70] Because the baby has no true right atrium, the course of the inferior vena cava is abnormal. Drainage of the inferior vena cava is through the azygos or hemiazygos veins and into the superior vena cava. With bilateral left atria, the pulmonary veins usually return to the heart in a bilateral fashion to their closest atrium (right-sided pulmonary veins return to the right-sided atrium). The presence of polysplenia is often associated with levocardia, normally related great arteries, a common atrium, and two ventricles with a ventricular septal defect. The pulmonary valve in these cases is usually normal. A quarter of fetuses with polysplenia may have bradyarrhythmias in utero, including sinus bradycardia and complete heart block.[24] Survival to birth in fetal bradyarrhythmia associated with polysplenia is nearly 80% in fetuses where termination is not chosen upon diagnosis.[24,25] Survival at 5 years in a live-born cohort is 86% in polysplenia.[24] Although the patient has multiple small spleens, splenic function can be either normal or abnormal regardless of the presence of Howell-Jolly bodies on blood smear, which as previously stated may indicate hyposplenism.[56] Assessment of splenic function and identification of the subset requiring daily prophylactic antibiotics are important prior to discharge home from the hospital following birth.

Arteriovenous Malformations

Arteriovenous malformations (AVMs) are an abnormal, direct connection between arteries and veins via a network of vessels called the nidus that lack an intervening capillary bed. Depending upon the type of cerebral AVMs,

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manifestation in the neonatal period with signs of congestive heart failure, including a hyperdynamic precordium and hepatomegaly, may result. Most of these are vein of Galen malformations, although neonates with large pial malformations and congestive heart failure have been described. Vein of Galen malformations can be classified as choroid and mural type, of which the choroidal type usually presents in the neonatal period.[36]

Diagnosis

Even large vein of Galen malformations may not result in fetal heart failure, because the low resistance of the malformation is offset by the utero-placental circulation. Thus, fetal cardiac failure is an ominous sign.[55] As systemic vascular resistance increases at birth, progressive blood flow is diverted into the malformation from the systemic circulation. Congestive heart failure, right heart dilation, lactic acidosis, persistent pulmonary hypertension of the newborn, and diastolic runoff in the ascending aorta or arch on echocardiogram are clues to the diagnosis. Presence of cranial bruit, a louder pulmonary component to the second heart sound, and a systolic ejection murmur of increased aortic and pulmonary artery flow are also typically present. The chest radiograph shows cardiomegaly. Early heart failure presentation of vein of Galen malformations is associated with worse outcomes.[55] An ECG may demonstrate right ventricular hypertrophy and ST-T wave abnormalities due to coronary artery steal. In addition to flow reversal in the aorta, an echocardiogram will frequently demonstrate a dilated, noncompliant right ventricle with systemic or suprasystemic pulmonary artery pressures and a hyperdynamic left ventricle. Ductal flow may be right to left resulting in significant cyanosis. Diagnosis is confirmed with CT or MRI.

Treatment

Arteriovenous malformations in the neonatal period usually present as congestive heart failure, and initial medical management goals consist of stabilizing systemic cardiac output. Recently, milrinone and inhaled nitric oxide have been utilized along with loop diuretics.[27,55,59] Half of patients are unable to be medically managed and are referred for a procedural palliation.[12]

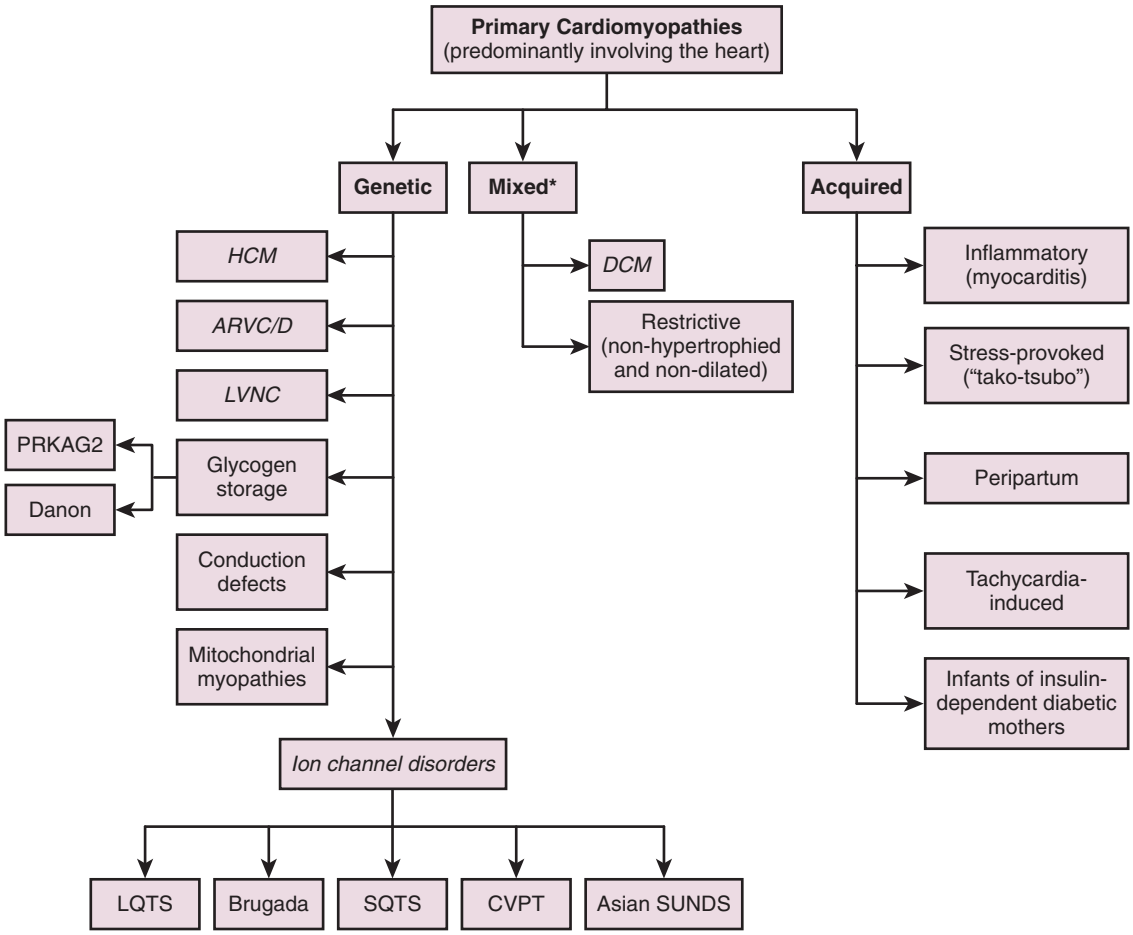
Endovascular embolization has replaced surgery as the mainstay of treatment of vein of Galen malformation.[51] The goal is reduction in the size of the shunt and resultant heart failure symptoms. Complete occlusion is not required during the initial procedure. Outcomes have improved and a neurologically normal to mild developmental delay is expected.[31,33,40,60,81] Neonates showed the worst mortality rate of 52%, following endovascular treatment with only 36% of survivors being neurologically normal.[40,55] If symptoms can be managed medically, survival after treatment from 5 months to 2 years increases to more than 90%, with 78% of survivors classified as neurologically normal.[55]

Myocardial Diseases: Cardiomyopathy and Myocarditis

Cardiomyopathy refers to a diverse group of myocardial diseases with multiple causes. These are rare disorders that account for only approximately 1% of childhood cardiac disease. In 1995, the World Health Organization classified cardiomyopathies into hypertrophic, dilated, restrictive, and mixed type.[63] This classification is based on the pathophysiology of the disease. However, with rapid evolution of molecular genetics in cardiology, the American Heart Association in 2006 has classified cardiomyopathies into two major groups based on predominant organ involvement and etiology.[48] Primary cardiomyopathies are those solely or predominantly confined to heart muscle and are relatively few in number (Fig. 76.3). Secondary cardiomyopathies show pathologic myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders (Box 76.1).[48] Myocarditis, an inflammatory, usually infectious process affecting the myocardium, may also result in either a dilated (common) or restrictive (rare) cardiomyopathy.

Dilated cardiomyopathy is characterized by left ventricular enlargement, with systolic dysfunction of either the left ventricle or both ventricles causing variable degrees of congestive heart failure. The patient's cardiac output (heart rate × stroke volume) is often decreased, and ventricular filling pressures are increased. Total ventricular mass is increased, but chamber volume is disproportionately enlarged. These neonates present with symptoms of poor cardiac output, including pallor, irritability, poor feeding, respiratory distress, and diaphoresis. Physical signs include tachypnea, tachycardia, narrow pulse pressure, and hepatomegaly. Decompensated infants will present with shock and cardiovascular collapse. Cardiac auscultation often reveals muffled heart sounds with a gallop rhythm (S3, S4). Occasionally, a murmur of mitral regurgitation can be auscultated. Arrhythmias, although rare, are an ominous, often undetected presentation.[64] The electrocardiogram in a patient with dilated cardiomyopathy shows flattening of the T waves with possible depression of the ST segments. The chest x-ray often shows cardiomegaly with pulmonary edema. Echocardiogram is diagnostic, illustrating dilation of the ventricle(s) and poor cardiac contractility. Cardiac MRI is increasingly part of the diagnostic work-up, often demonstrating myocardial fibrosis and scarring. MRI has become useful in differentiating dilated cardiomyopathy from acute myocarditis, both of which can appear clinically and echocardiographically nearly identical. An extensive family history is essential when evaluating neonates, specifically asking for the first-degree relatives with dilated cardiomyopathy, metabolic disorders, degenerative neurologic diseases, or diseases of mitochondria. The management of these patients involves targeting the body's neurohormonal activation during heart failure, including spironolactone and loop diuretics, angiotensin-converting enzyme inhibitors or receptor blockers, and inotropes for acute decompensation.

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• **Fig. 76.3** Primary cardiomyopathy classifications. ARVC/D, Arrhythmogenic right ventricular cardiomyopathy/dysplasia; CVPT, catecholaminergic ventricular polymorphic tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; SQTS, short QT syndrome; SUNDS, sudden unexplained nocturnal death syndrome. (Adapted from Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006;113:1807-1816.)

There is conflicting data in neonates and infants for use of beta-blockers in management of dilated cardiomyopathy, with many experienced institutions continuing to add carvedilol to augment medical management.[58] The primary goal of therapy is to relieve symptoms and prolong survival. Often, these patients may require the use of extracorporeal membrane oxygenation (ECMO) and/or ventricular assist device (VAD) as a bridge to recovery or transplant. As mechanical support technology has improved, ventricular assist devices have demonstrated improvement in survival over ECMO.[26] All forms of mechanical support have a high incidence of adverse event rates, particularly hemorrhage and thrombosis events in children under 10 kg.[46]

Hypertrophic cardiomyopathy is characterized by increased cardiac mass and wall thickness that generally affects the left ventricle. The left ventricular mass/volume ratio is increased, resulting in a left ventricular cavity that is decreased in size because of thickening of the muscle, particularly in the interventricular septum, resulting in dynamic outflow obstruction. The systolic function of the heart is preserved or increased in this disorder when assessed by echocardiogram. The patient's clinical picture is generally dominated by diastolic dysfunction, with elevated ventricular filling pressures. Infants who have hypertrophic cardiomyopathy present with symptoms of congestive heart failure, including tachypnea, poor feeding, and growth failure. The diagnosis is frequently made during screening because of a known immediate family member with hypertrophic cardiomyopathy or an unexplained early death in the family.[18] Occasionally, a near-miss sudden death episode with arrhythmia is the sentinel event. In babies with a primary disorder of the myocardium, either hypertrophy and/or myofibrillar disarray is often the result of mutations of the proteins of the cardiac sarcomere.[47,53] The ECG often shows left ventricular hypertrophy with

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• BOX 76.1 Causes of Secondary Cardiomyopathies

- Infiltrative
  - Amyloidosis (primary, familial autosomal dominant*, senile, secondary forms)
  - Gaucher disease*
  - Hurler disease*
  - Hunter disease*
- Storage
  - Hemochromatosis
  - Fabry disease*
  - Glycogen storage disease* (type II, Pompe)
  - Niemann-Pick disease*
- Toxicity
  - Drugs, heavy metals, chemical agents
- Endomyocardial
  - Endomyocardial fibrosis
  - Hypereosinophilic syndrome (Löeffler endocarditis)
- Inflammatory (Granulomatous)
  - Sarcoidosis
- Endocrine
  - Diabetes mellitus*
  - Hyperthyroidism
  - Hypothyroidism
  - Hyperparathyroidism
  - Pheochromocytoma
  - Acromegaly
- Cardiofacial
  - Noonan syndrome*
  - Lentiginosis*
- Neuromuscular/Neurologic
  - Friedreich ataxia*
  - Duchenne-Becker muscular dystrophy*
  - Emery-Dreifuss muscular dystrophy*
  - Myotonic dystrophy*
  - Neurofibromatosis*
  - Tuberous sclerosis*
- Nutritional Deficiencies
  - Beriberi (thiamine), pellagra, scurvy, selenium, carnitine, kwashiorkor
- Autoimmune/Collagen
  - Systemic lupus erythematosus
  - Dermatomyositis
  - Rheumatoid arthritis
  - Scleroderma
  - Polyarteritis nodosa
- Electrolyte Imbalance
- Consequence of Cancer Therapy
  - Anthracyclines: doxorubicin (adriamycin), daunorubicin
  - Cyclophosphamide
  - Radiation

*Genetic (familial) origin.

Adapted from Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation.* 2006;113:1807-1816.

ST and T changes that may be consistent with s rain. The echocardiogram is generally diagnostic for this disorder and is helpful in assessing overall myocardial thickness, chamber dimensions, and systolic and diastolic performance of the ventricle. Cardiac MRI can demonstrate myocardial fibrosis and scarring even early in the time course.[35] The primary goal of management of these patients is similar to that of dilated cardiomyopathy—symptomatic relief and prolonging survival. Medical management includes the use of beta-blockers to augment diastolic filling time, thereby increasing the left ventricular cavity and thus relieving dynamic outflow obstruction. Diuretics are counterproductive, because they decrease the patient's overall volume, thereby decreasing the ventricular cavity and increasing the outflow tract obstruction. Systemic vasodilators, such as ACE inhibitors, and inodilators, such as milrinone, again increase the ventricular outflow gradient and, therefore, should be avoided. Negative inotropes such as calcium channel blockers may be used judiciously, as the neonatal myocardium is particularly reliant on calcium. The prognosis of hypertrophic cardiomyopathy in this age group is rather poor compared with older children.[42] Neonates with underlying inborn errors of metabolism and malformation syndromes have a poorer prognosis when compared to neonates with idiopathic infantile hypertrophic cardiomyopathy.[42]

Another form of hypertrophic cardiomyopathy seen in the neonatal period is the myopathy of infants of diabetic mothers, which carries an excellent prognosis with complete resolution within the first 6 months of life, and steroid-induced hypertrophic cardiomyopathy, which typically resolves after discontinuation of the steroids.[69,76] Dexamethasone and methylprednisone both have an increased risk of developing hypertrophic cardiomyopathy in the early newborn period in premature infants.[21] Therefore, the American Academy of Pediatrics cautioned against the treatment with dexamethasone of infants with birth weights less than 1500 g (very low birth weight) and recommended to limit its use to exceptional clinical circumstances.[77] Left ventricular noncompaction is an imaging-based diagnosis referring to prominent left ventricular trabeculae, a thin compacted layer, and deep recesses continuous with the LV cavity.[3] Noncompaction may be associated with muscular dystrophies, Barth syndrome, or with hypertrophic or dilated cardiomyopathy. Genetic testing for common mutations is available. Several genes overlap with known mutations affecting the conduction system and contributing to prolongation of the QT interval and polymorphic ventricular tachycardia.[3] Individual treatment plans should be tailored toward associated arrhythmia or cardiomyopathy risks. Restrictive cardiomyopathy is an extremely rare condition in which ventricular cavities are small, and there is impaired diastolic function of both the ventricles, with preserved systolic function, at least initially. Neonates with this disorder present with signs and symptoms of congestive heart failure and pulmonary hypertension. The ECG often shows conduction abnormalities and evidence of ischemia

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at faster heart rates. The echocardiogram shows normal or small ventricles with dilation of both atria and signs of right ventricular pressure load. Although uncommon in neonates, it should be differentiated from constrictive pericarditis, as the conditions could have similar presentation. Median transplant-free survival for newly diagnosed restrictive cardiomyopathy is very poor. In the Pediatric Cardiomyopathy Registry analysis, freedom from death or transplant was 48% at 1 year in patients with pure restrictive cardiomyopathy.[78] Recommendations for early evaluation and listing for transplantation at the time of diagnosis persist.[78]

Diagnosis and Treatment

The approach to neonates with suspected cardiomyopathy or myocarditis must include a methodical approach to the diagnosis (Box 76.2) and a level of support appropriate for their clinical symptoms. The evaluation and management are multidisciplinary, involving neonatology, metabolism, genetics, cardiology, and psychological and family support. Specialized early referral to heart failure and cardiac transplant teams is critical in long-term management of these infants. Endomyocardial biopsy can guide therapy and help in defining the prognosis by identifying pathologic features, but is not routinely recommended due to its not insignificant risks including tamponade and lethal arrhythmia. The improvement in MRI technology has permitted noninvasive diagnosis.[19,29,66] Evidence of active inflammation or immune suppression can be treated with intravenously administered immune globulin, although its role in the treatment of myocarditis, especially in neonates and infants, remains to be fully validated.[23,29,34,49] The prognosis is often good if the baby can be managed through an episode of myocarditis. In contrast, if a biopsy shows endocardial fibroelastosis or the echocardiogram shows endocardial thickening, the likelihood of recovery of myocardial function is very poor.

•BOX 76.2 Laboratory Studies to Be Considered in Infantile Cardiomyopathy

- Blood
  - Carnitine
  - Amino acids
  - Blood gases
  - Lactate, pyruvate
  - Leukocyte preparations for enzyme assays
  - Genetic testing for mutations of the cardiac sarcomere
- Urine
  - Amino acids
  - Organic acids
- Electromyography
- Skin Biopsy
  - Morphologic studies for storage disorders
  - Fibroblast cultures for specific enzymatic studies
- Muscle Biopsy
  - Morphologic studies for skeletal myopathy
  - Biochemical studies for carnitine deficiency and mitochondrial disorders
- Myocardial Biopsy
  - Light and electron microscopy
  - Viral ribonucleic acid
  - Mitochondrial function

Pericardial Diseases

A pericardial effusion is present when there is increased fluid within the existing pericardial space. This fluid can be serous, serosanguinous, pus, lymph, or blood. Pericardial effusion is usually seen in neonates who have fetal hydrops resulting from a variety of etiologies. Small effusions may also be found in neonates with neonatal pneumonia. Pericardial effusions can also be the result of open heart surgery, specifically repair of atrial septal defects and/or complications of hyperalimentation through central venous catheters, resulting from local irritation of the atrial or superior vena caval wall by fluids with high osmolality. Pneumopericardium is a complication of mechanical ventilation and can have hemodynamic effects similar to those of fluid. If the pericardial fluid accumulates gradually, the intrapericardial pressure remains low and symptoms are generally absent until the effusion becomes large. Rapid accumulation of a pericardial effusion, regardless of etiology, can result in pericardial tamponade, even with small volumes.

The diagnosis of pericardial tamponade is clinical and should be suspected in any baby with early signs of poor cardiac output, including tachycardia and poor perfusion. Pulsus paradoxus, an exaggerated fall in blood pressure with inspiration, is easiest to observe in neonates with arterial lines for continuous blood pressure monitoring. A dramatic increase in heart size on a chest radiograph supports the clinical diagnosis. Intrapericardial air is usually obvious on the radiograph and can be differentiated from mediastinal air because it encircles the heart. Echocardiography is the best way to confirm the diagnosis of pericardial effusion and to assess the physiologic impact of the effusion. Diastolic collapse of the right atrium and right ventricle is highly specific for diagnosing tamponade physiology. Respiratory variation of tricuspid and mitral inflow can exceed 30% and confirm the clinical picture.[2] Pericardiocentesis by the subxiphoid approach can be used to drain fluid or air to help alleviate symptoms. If fluid or air returns, a small catheter can be placed percutaneously or surgically and left to continuously drain the fluid.

Pericarditis is an uncommon diagnosis in the neonatal period and usually is associated with myocarditis and/or systemic inflammation. Treatment is symptomatic and consists of nonsteroidal anti-inflammatory agents. Prognosis is generally good, but this condition can lead to constrictive pericarditis.

Cardiac Tumors

Primary cardiac and mediastinal tumors are rare at all ages and even less common in infants and children. Most of

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the cardiac tumors reported are benign. Rhabdomyoma is the most common tumor type in this age group, whereas malignant cardiac or mediastinal tumors are extremely rare.[9,15,41,73,75] Clinical manifestation of these tumors varies from incidental findings on fetal or neonatal echocardiogram to life-threatening cardiac events.[1,30]

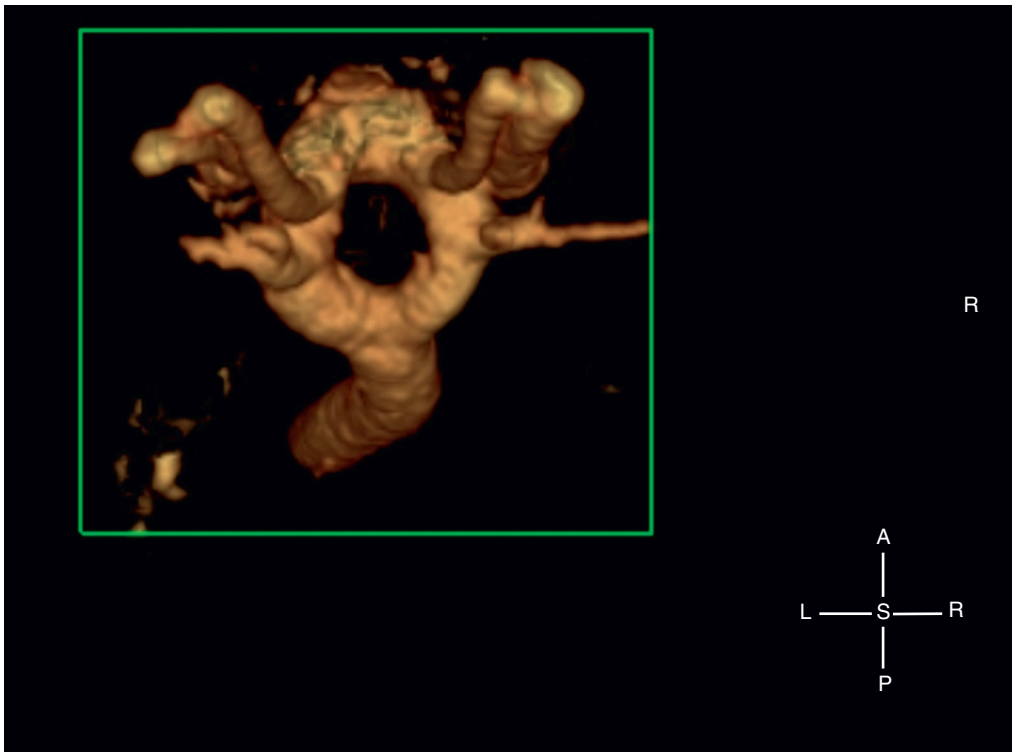
In 30%-91% of cases, cardiac rhabdomyomas are associated with tuberous sclerosis.[30] Depending upon the size and placement, rhabdomyomas can interfere with ventricular filling or emptying. When they are located near the atrioventricular valves, the tissue can serve as a bypass tract and mimic the features of Wolff-Parkinson-White syndrome.[52] Confirmation by myocardial biopsy in a symptom-free neonate is not necessary, especially if the skin and central nervous system features of tuberous sclerosis are present. Rhabdomyomas typically regress,[50] and surgical excision is not necessary unless the tumor is obstructing flow and is discrete or pedunculated enough to allow excision.

Other rare tumors that can occur in the neonate include myocardial hemangioma,[14] hamartomas,[41] fibromas, and pericardial teratomas. Myocardial hemangiomas are tumors with dense capillary beds that can have connections to the coronary arteries. They are on the epicardial surface with intrusion into the myocardium. Hemangiomas can cause subpulmonary stenosis if they are located in the right ventricular outflow tract. Small hamartomas cause histiocytoid or oncocytic cardiomyopathy, which is associated with severe and persistent ventricular arrhythmias. Myocardial fibroma can be located in the myocardium or on the atrial wall or can involve the mitral valve and cause obstruction. Fibromas can also disrupt the conduction system and contribute to ventricular arrhythmias. Intrapericardial teratoma is a benign tumor attached to the base of the aorta. It is associated with mediastinal compression and pericardial effusion in the fetus, neonate, or young infant. Successful excision of intrapericardial teratoma has been reported, although large tumors can cause fetal death. Atrial myxomas have not been reported in the neonatal period. Surgical excision is required if there is obstruction to the inflow or outflow of the heart. Associated arrhythmias should be treated with antiarrhythmics as described in the other sections of this book. There is an increasing role of cardiac MRI in distinguishing cardiac tumors and avoiding cardiac surgery for biopsy.[28]

Vascular Rings and Slings

Vascular rings are anomalies that result from abnormal development of the aortic arch complex and cause compression on the trachea, esophagus, or both.[65] Vascular rings can be complete (double aortic arch or right aortic arch with left ligament) or incomplete (innominate artery compression and pulmonary slings).[65]

If both the right and left fourth branchial arches persist, this results in a double aortic arch with each of the arches passing above the main stem bronchus on the right and left side and joining together behind the trachea to form the descending aorta (Fig. 76.4). These result in compression of



• **Fig. 76.4** Computed tomographic (CT) angiogram of the arch, showing double aortic arch with each arch giving rise to a carotid and subclavian artery. A, Anterior; L, left; P, posterior; R, right; S, superior.

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the trachea, causing symptoms such as respiratory distress and stridor. In most cases of double aortic arch, the right arch is the dominant one, with the left arch being smaller.

If the left fourth arch involutes, it results in a right aortic arch. Not all patients with a right aortic arch have vascular rings. Only if the ligamentum arises from the descending aorta and attaches to the pulmonary artery does it form a complete vascular ring with compression of the trachea between the arch on right side and ligamentum between the descending aorta and pulmonary artery on the left side. Patients with a right aortic arch and a left ligamentum may also have a Kommerell diverticulum at the origin of the left subclavian artery from the descending aorta.[38]

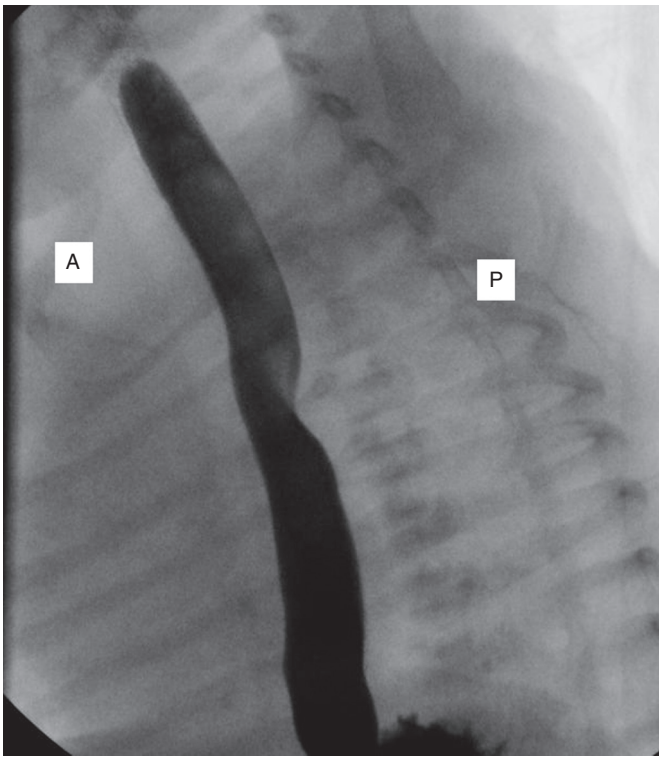
A pulmonary artery sling is caused when the origin of all or part of the left pulmonary artery comes from the right pulmonary artery.[10] The embryonic origin of a pulmonary artery sling occurs when the developing left lung captures its arterial supply from derivatives of the right sixth arch through capillaries caudal, rather than cephalad, to the developing tracheobronchial tree.[67] The left pulmonary artery passes around the right main stem bronchus and courses between the trachea and esophagus, forming a "sling." This might be associated with circumferential cartilage rings in the trachea with absence of the membranous portion posteriorly, the so-called ring-sling complex.[11]

Innominate artery compression syndrome is caused by the anterior compression of the trachea anteriorly by the innominate artery. The exact etiology of this syndrome is not well understood. The innominate artery in some children originates more posteriorly in the left aortic arch, and as it courses posteriorly and superiorly, anterior to the trachea, it causes compression.[4,68]

An aberrant subclavian artery (left aortic arch with retro-esophageal right subclavian artery) results from disappearance of the right fourth aortic arch. The right subclavian artery arises from the descending aorta, coursing superiorly behind the esophagus. This is the most common arch anomaly seen in 0.5% of the general population.[79] Most infants are asymptomatic, and the diagnosis is suspected on an incidental echocardiogram. Barium swallow is usually diagnostic, showing posterior indentation on the esophagus (Fig. 76.5). Right aortic arch with retro-esophageal left subclavian artery is usually associated with other conotruncal abnormalities.

Clinical Presentation and Diagnosis

Many children with vascular rings presenting within their first year of life require surgery.[5] These infants commonly present with respiratory difficulties (e.g., stridor or wheezing), recurrent pulmonary infections, and/or difficulty feeding.[22,32] Infants may hold their heads hyperextended, thereby decreasing the obstruction. In older infants and children, the presenting features might be dysphagia with solid foods. Children with innominate artery compression may present with apnea. The diagnostic evaluation includes chest radiography, echocardiogram, barium swallow studies, CT angiogram, and cardiac MRI. A CT-angiogram often provides the final diagnosis and is considered the gold standard diagnostic test.[6]



• **Fig. 76.5** Barium swallow study showing posterior indentation by the aberrant left subclavian artery passing posterior to the esophagus. A, Anterior; P, posterior.

Treatment

Surgery is indicated in all symptomatic vascular rings. Delayed treatment may result in sudden death or further tracheobronchial damage. All patients referred for surgery should have a bronchoscopy performed to evaluate for the site of tracheal stenosis and evaluation of cartilage rings.[65] The nondominant arch is divided in the case of a double aortic arch. Coarctation and other associated anomalies should be ruled out before referral for surgery. The ligamentum is divided and ligated in the case of a right arch and left ligamentum. If a Kommerell diverticulum is 1.5-2 times the size of the left subclavian artery, it should be resected.[65] Management of compression of the trachea by the innominate artery may be treated by reimplanting the innominate artery. A pulmonary artery sling is corrected by reimplantation of the left pulmonary artery into the main pulmonary artery anterior to the trachea. An aberrant subclavian artery needs treatment only if associated with aneurysm at the origin of the subclavian artery.[39]

Neonatal Marfan Syndrome

Marfan syndrome is an infrequent diagnosis in infancy. The cardiovascular complications associated with this disorder

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are the major cause of morbidity and mortality in Marfan syndrome. Prognosis and morphologic characteristics in infantile Marfan syndrome may be quite different from those reported in older patients. The diagnosis of neonatal Marfan syndrome, because of its clinical and phenotypic variability, is made following criteria of skeletal, ocular, cardiovascular, cutaneous, neurologic, and pulmonary manifestations, as well as family history.[44]

Morbidity and mortality tend to be high when Marfan syndrome is diagnosed during infancy, and prompt recognition of this phenotype can facilitate management and counseling. Most such severe cases appear to be caused by a sporadic mutation in a single germ cell of one parent. Many familial cases may have milder manifestations, be more difficult to detect during infancy, and have a better prognosis.[54] Skeletal features are recognizable, and clinical signs of congestive heart failure caused by mitral or tricuspid regurgitation could be evident in the first days of life. Aortic root dimensions are often increased, and aortic regurgitation can be seen by color flow mapping. Genetic testing to exclude Loeys-Dietz syndrome may also be indicated in the neonate presenting with physical findings of connective tissue abnormalities.[43] This exclusion may be recognized clinically, as infants with Loeys-Dietz syndrome will have a bifid uvula and, more critically, severe dilation of the aorta and cerebral arteries leading to earlier pathology and rupture. Surgery is often required early in these infants because of persistent heart failure and the risk of death from aortic rupture. In a rare case, quadruple valve replacement has been reported.[71]

The Premature Baby With Congenital Heart Disease

The prevalence of congenital heart disease in low birth weight infants born between 25 and 32 weeks is as high as 116 per 1000 in contrast to 10 per 1000 term births with a five-fold increase in severe congenital heart disease.[16] Although outcomes of neonates with congenital heart disease have improved significantly over the past few decades, low birth weight and prematurity remain challenging problems. Infants with birth weights less than 2.5 kg have 1.5 to 3 times higher mortality.[20] When compared with term infants, low birth weight/premature infants were more likely to have pulmonary atresia with ventricular septal defect, complete atrioventricular septal defect, coarctation of the aorta, tetralogy of Fallot, and pulmonary valve stenosis. Fewer low birth weight/preterm infants had pulmonary atresia and intact ventricular septum, transposition of the great arteries, and single ventricle.[72] Perioperative management of these high-risk infants must take into account the patient's small size; the clinical implications of prematurity; IUGR and associated extracardiac anomalies; the cardiac pathophysiology; and issues related to anesthesia, surgery, and cardiopulmonary bypass.[80]

Systemic to pulmonary artery collaterals are seen in 66% of very low birth weight infants between 1-90 days of life. Often, these are infants who require surfactant therapy or need closure of a patent ductus arteriosus either by surgery, catheter, or medical treatment. Comorbidities with surgical and medical management of persistent ductus arteriosus in the preterm infant have sparked interest in catheter-based closure.[7,57,74] The combination of low birth weight, prematurity, and congenital heart disease makes the management of these patients challenging. It is unclear whether a strategy of medical management and deferment of surgical intervention is beneficial over more expeditious intervention.

Palliative Care

Many congenital cardiac centers are engaging palliative care services at the time of diagnosis for complex congenital disease. The cardiovascular disorders noted in this chapter have high morbidity and mortality rates when symptomatic in the neonatal period. Early input and consistent messaging from the medical teams can be augmented by the addition of palliative care from the onset.[8]

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Key Points

- Earlier symptomatic presentation of Marfan syndrome and vein of Galen malformation are associated with worse outcomes.
- Cardiomyopathies diagnosed in the neonate should prompt expert heart failure team involvement to determine genetic or underlying causes and to assist in management.
- Right and left atrial isomerism associated with heterotaxy syndrome have distinct cardiac presentations and different mortality risks.
- Preterm infants with cardiac disease are at increased risk for complications and mortality compared with term peers.
- Early involvement of palliative care after cardiac diagnosis may mitigate parental distress and enable consistent messaging.

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77

Disorders of Cardiac Rhythm and Conduction in Newborns

BRYAN CANNON AND CHRISTOPHER S. SNYDER

Neonates experience a variety of cardiac arrhythmias, varying from benign and asymptomatic to life threatening. In this chapter we will discusses the normal and abnormal variations in cardiac rate and rhythms that are frequently encountered in the newborn period.

Normal Sinus Rhythm and Sinus Node Dysfunction

Normal Sinus Rhythm and Its Variations

The initiation of cardiac electrical activity typically begins in the sinus node, a small, epicardial structure that is located at the posterior junction of the superior vena cava and right atrium.

The sinus node receives input from both the sympathetic and parasympathetic nervous systems. The balance of the two inputs determines the underlying heart rate at any given moment. At rest and during sleep, vagal nerve stimulation (parasympathetic) is increased, resulting in slowing of the heart rate and potentially sinus bradycardia. During periods of stress, stimulation, or activity, the sympathetic nervous activity tone predominates, leading to an increase in heart rate and potentially sinus tachycardia.

It is important to remember that in children with normal cardiac anatomy, sinus bradycardia or sinus tachycardia are usually physiologic findings. It can be determined that the electrical impulse is generated from the sinus node, characterized on the electrocardiogram (ECG) by a positive P wave deflection in leads I and aVF; it is quite rare to have an underlying cardiac conduction issue.

Sinus Bradycardia

Sinus bradycardia is defined as heart rate less than 60 beats per minute (bpm) in older children and adults. However, in newborns, the resting heart rate is typically faster with a normal resting heart rate between 90 and 160 bpm, with intermittent decreases to as low as 70 bpm during rest or sleep.

Sinus bradycardia generally is physiologic in infants with a structurally normal heart and is secondary to transient increases in vagal tone. This increase in vagal tone is almost always related to an underlying process, such as increased intracranial pressure, an acute abdominal process (e.g., necrotizing enterocolitis), suctioning of an endotracheal tube, gastric reflux, apnea of prematurity, or medications (e.g., sedatives, beta blockers).

Most episodes of sinus bradycardia in neonates are episodic and related to an abrupt increase in vagal tone that may result in sinus pauses or dropped heart beats, resulting in heart rate decreasing to 40-50 beats per minute. Episodic abrupt decreases in the heart rate with an otherwise normal heart are caused by a secondary process and almost never have a primary cardiac etiology, but the pauses can be relatively long lasting, up to several seconds.

The initial evaluation of bradycardia involves obtaining an electrocardiogram (ECG) to ensure that there is no evidence of atrioventricular (AV) block or other primary cause such as a cardiac channelopathy as the cause of the bradycardia. The primary method used to assess the overall function of the sinus node in a neonate is a 24-hour cardioscan monitor (Holter) that records every electrical cardiac impulse during the monitoring period. This monitor is used to evaluate the infant's heart rate variability as well as maximum and minimum heart rates. Even though rarely there are ways to demonstrate that sinus bradycardia is caused by increased vagal tone and is not secondary to sinus node disease, administration of a vagal nerve antagonist such atropine (muscarinic-cholinergic blocking agent) increases heart rate almost immediately if the bradycardia is secondary to vagotonia, although this is only rarely clinically indicated. There is minimal or no heart rate increase to atropine in those infants and children with primary sinus node dysfunction. Patients with sinus node dysfunction also typically have bradycardia that persists throughout the day and may only reach a maximum heart rate of 100-130 beats per minute.

Treatment of sinus bradycardia is rarely required. Evaluation for an underlying cause (e.g., seizures, reflux, or apnea) should be undertaken, particularly in cases of episodic bradycardia. If a neonate has a slow underlying rate but has no evidence of hemodynamic compromise, in general, no

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Abstract

In this chapter, we describe the findings of the normal cardiac conduction as well as the abnormal conduction. We give examples of both and discuss the diagnosis as well as the treatment for each of the conduction abnormalities found in neonates. With regard to treatment, we discuss options from observation to medications to cardioversion and pacing.

Keywords

sinus tachycardia
sinus bradycardia
premature beats
supraventricular tachycardia
complete atrio-ventricular block

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intervention is required. A pacemaker may be placed if there is persistent hemodynamically significant sinus node dysfunction, but this is exceptionally rare in the neonatal population.

Sinus Tachycardia

Sinus tachycardia is defined as increase in the sinus rate above 160-180 bpm in infants. It is usually a normal physiologic response to anemia, hyperthyroidism, fever, agitation, infection, or medications to name just a few causes. It is rarely caused by a primary cardiac etiology, unless there is underlying cardiac dysfunction such as seen with myocarditis.

It is important to ensure that an elevated heart rate is truly sinus tachycardia and is not caused by an abnormal cardiac rhythm such as supraventricular tachycardia (SVT). The typical maximum heart rate in a "normal" infant is 220 bpm minus the age of the patient. Critically ill neonates may sometimes exceed this rate; sinus tachycardia at rates greater than 220 bpm should warrant evaluation for the presence of pathology.

Some other findings that suggest a pathologic mechanism of tachycardia are:

1. The lack of heart rate variability
2. Abnormal P-wave morphology or axis (normally upright in leads I and aVF) on ECG
3. Prolongation of PR interval
4. Very rapid increases or decreases in heart rate
5. Abnormal cardiac function on echocardiogram

The best method for initial evaluation of sinus tachycardia typically involves obtaining an ECG to ensure that there is no evidence of a pathologic arrhythmia. Similar to sinus bradycardia, a 24-hour Holter can be helpful in ruling out SVT in questionable cases when one evaluates it for heart rate variability, episodes of pauses, and/or changes in the P-wave axis.

Treatment of sinus tachycardia is directed at treating the underlying cause. Neonates with high resting heart rates generally do not require any treatment but should be closely evaluated to make sure they do not have a secondary cause such as infection or anemia.

Sinus Arrhythmia

In children with sinus arrhythmia, sometimes called respiratory sinus arrhythmia, phasic variations in heart rate are seen with an increase in heart rate during inspiration and a decrease in heart rate with expiration (Fig. 77.1).

Sinus arrhythmia is caused by the so-called Bainbridge reflex (baroreceptor reflex). During inspiration, the intrathoracic pressure decreases and triggers increased venous blood return to the right atrium. The increased volume in the right atrium is registered by stretch receptors, which causes increase in heart rate. The opposite situation occurs during expiration, and heart rate decreases.

This variation is sometimes thought to be a pathologic arrhythmia, because the heart rate variability is often quite pronounced during auscultation in young children and infants. However, in most situations, the diagnosis can be made by noting heart rate variation that correlates with the respiratory cycle. Appropriate ECG interpretation is helpful if the diagnosis is in question. On an ECG, there is variation in the rate but no change in the appearance of the P-wave morphology or axis, thus confirming the diagnosis.

This condition is physiologic and does not require any treatment or follow-up.

Tachyarrhythmias

Atrial Tachycardia

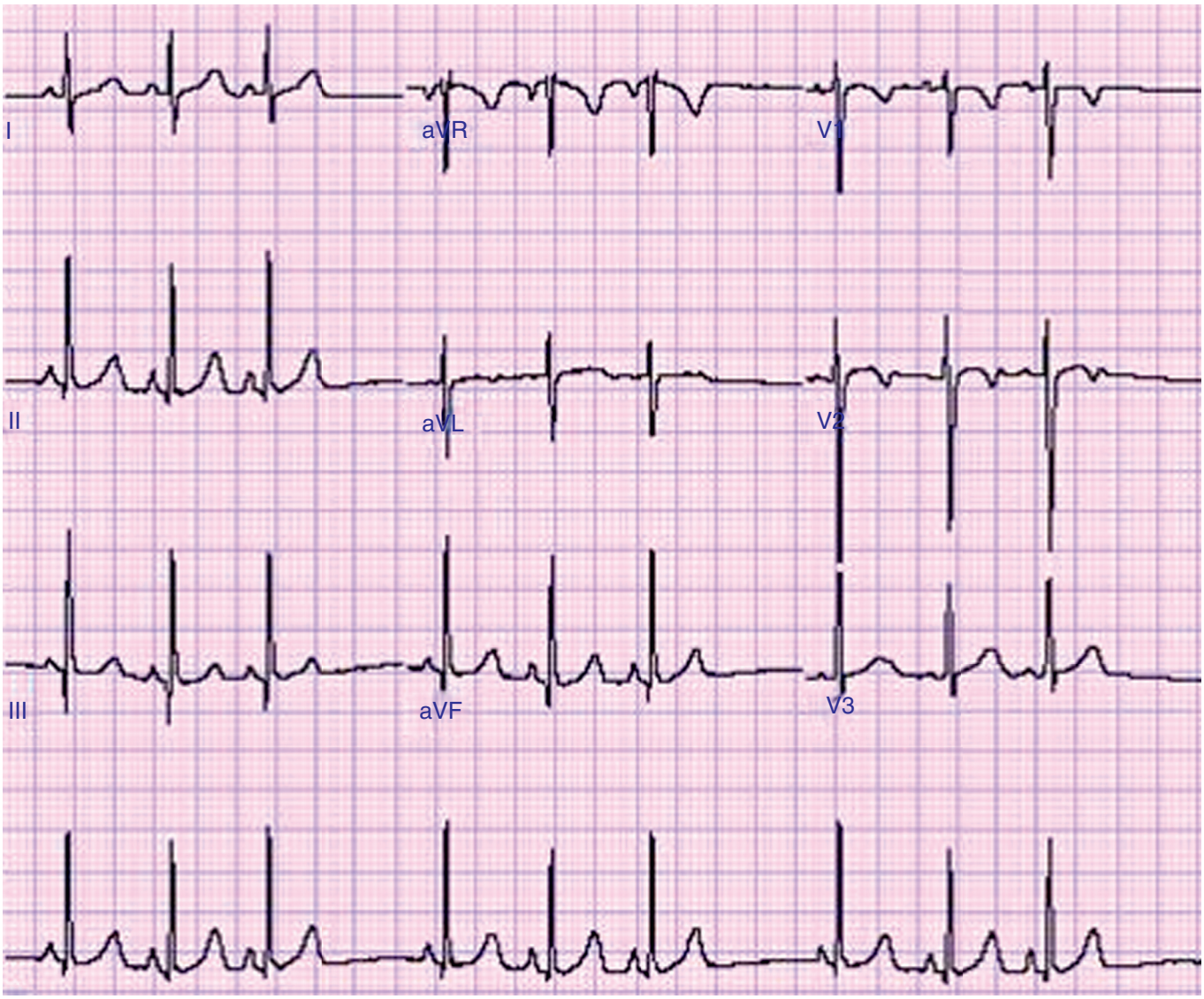
Premature Atrial Contractions

Premature atrial contractions (PACs) are early depolarizations of atrial tissue distinct from the sinus node. As the impulse originates from the area different than the sinus node, the P wave will often have a different morphology than the "normal" P wave from the sinus node.

Premature atrial contractions usually conduct through the AV node, bundle of His, and right and left bundle branches to the ventricles. If atrial activation occurs early enough that the AV node or bundle of His is refractory, the PACs will not be conducted to the ventricle; this is commonly referred to as a "blocked" PAC. In this case, the premature P wave is seen without a following QRS complex. When this occurs clinically, these block PACs are often read as bradycardia, which is not an accurate description of what is occurring electrically in the heart. If a PAC activation wavefront passes through the AV node, but either the right or left bundle branch is still refractory, then it will be followed by a wide QRS (aberrant ventricular conduction). This can be mistaken for a premature ventricular contraction, but close observation will show atrial activation before the QRS, thus making the diagnosis of a premature atrial contraction. All three of these examples, conducted, nonconducted, and aberrantly conducted PACs, may be present in the same patient.

Premature atrial contractions are commonly seen in healthy newborns and may occur frequently (>200 per hour) in an individual patient. In patients with isolated PACs, they may occur in a pattern of two PACs in a row, which is referred to as an atrial couplet. If every other beat is a PAC, then this pattern is referred to as *atrial bigeminy*. Atrial couplets and bigeminy are benign and make no impact on the individual's prognosis when compared with those with isolated PACs as long as no evidence of atrial tachycardia is present. Rarely, PACs in a bigeminal pattern will block (i.e., every other beat is a nonconducted PAC), thus resulting in bradycardia. It is important to evaluate the ECG in fetuses and neonates with bradycardia to ensure that this pattern is not the cause of their "bradycardia." This pattern is especially common in fetuses that are referred for episodes of extreme bradycardia with intermittent episodes of normal conduction. These fetuses are usually not in distress, and it is worthwhile to explain these circumstances

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• **Fig. 77.1** Sinus arrhythmia in a healthy child. Note that all P waves look exactly the same, although there is marked variation in their rate.

to other care providers before any rush decisions are made concerning early or emergent delivery.

Isolated PACs usually are benign and do not require any therapy. In most newborns, PACs will resolve in the first few months of life and cause no hemodynamic compromise or clinical symptoms. A follow-up visit with a pediatric cardiologist may be recommended at 4-6 months postdelivery to ensure resolution.

Atrial Ectopic Tachycardia

When three or more consecutive PACs occur in an infant or neonate at a rate faster than 120 beats per minute, the term *atrial ectopic tachycardia* (AET) is used. Atrial ectopic tachycardia is typically the result of an increased automaticity of atrial myocardium. With this mechanism, there is abnormal firing of atrial tissue originating outside the sinus node. With an automatic focus, there are typically "warming up" and "cooling down" periods for the tachycardia. This frequently involves rapid increases or decreases in heart rate over several beats rather than initiation or termination in a single beat. Most AETs are paroxysmal in nature, resulting in little if any harm to the patient, but they may be incessant. The majority of neonates with AET also have frequent isolated PACs. The abnormal focus can be located almost anywhere in the atrium, with common foci being along the crista terminalis in the right atrium or the pulmonary veins. In AET, the activation of atria is different from that of normal sinus rhythm, resulting in a different P-wave morphology on the ECG. Occasionally, the focus may occur near the sinus node (i.e., right upper pulmonary vein or right atrial appendage), producing P-wave morphology similar to the one in sinus rhythm, so careful inspection of the P-wave morphology using a 12- or 15-lead ECG is warranted to look for subtle changes in P-wave morphology.

Although an abnormal focus of atrial tissue is the usual cause of atrial tachycardia, mechanical stimulation of the

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• **Fig. 77.2** Atrial flutter with 4:1 AV conduction in a 1-day-old newborn.

atria can also cause an atrial tachycardia. This is frequently seen in neonates who have an intravenous catheter with the tip located in the atrium. This catheter then creates an atrial tachycardia by directly stimulating the atria. One differential clue to the mechanism of this unique form of SVT is a very fast and irregular atrial tachycardia. A chest radiograph to visualize line position should be performed to ensure that the cause of the tachycardia is not line related before initiation of treatment.

Evaluation of an atrial tachycardia involves an ECG and Holter monitoring. Rapid, incessant AET can negatively affect ventricular function because of the heart's inability to "rest" or slow down. Therefore, an echocardiogram is usually part of the initial evaluation in the newborn period to evaluate function and rule out congenital heart disease with a dilated atrium as the cause of the atrial tachycardia. Electrolyte disturbances are a very rare cause of AET in neonates but should be corrected if present.

Treatment of atrial ectopic tachycardia may be attempted with medications such as beta blockers (propranolol), sodium channel blockers (flecainide), or class III antiarrhythmic medications (sotalol, amiodarone). The majority of neonatal AETs resolve spontaneously in the first 6 months of life, and long-term therapy is rarely necessary. Cardiac catheterization and radiofrequency ablation (RFA) are very high-risk procedures in neonates and are typically not performed except in extreme cases of medically refractory atrial tachycardia with depressed function. In very rare cases, mechanical support using extracorporeal membrane oxygenation (ECMO) is required to support the circulation until the tachycardia can be controlled.

Atrial Flutter

Atrial flutter is a classic example of atrial reentry tachycardia. In this type of tachycardia, the circuit or substrate for reentry is the atrial myocardium located around the tricuspid valve. The area of relatively slow conduction in this type of arrhythmia is generally located between the inferior vena cava (IVC) and the tricuspid valve annulus in an area referred to as the *isthmus*. The velocity of the impulse propagation is slow through the isthmus, allowing recovery of the atrial myocardium ahead of it and, therefore, allowing the atrial wave front to propagate.

The typical atrial rate of neonatal atrial flutter is between 300 and 600 beats per minute and is much faster than the flutter seen in older children and adults. However, the ventricular rate is much less because of the decremental properties of the AV node not allowing for such rapid conduction. The conduction to the ventricles is generally 2:1, 3:1, or 4:1 (Fig. 77.2) and may vary among these conduction rates, resulting in an irregular rhythm. Occasionally, the AV conduction can be rapid, resulting in ventricular rates greater than 200 bpm, which can be poorly tolerated by the fetus and neonate alike.

In most cases, the diagnosis can be made with a simple surface ECG, noting the continuous sawtooth pattern of atrial activity. However, it may be necessary to administer adenosine to the patient while recording an ECG, which blocks atrial conduction down the AV node and allows for rapid, easy identification of the sawtooth pattern classically described for this arrhythmia in patients when the P waves are masked by QRS complexes or T waves.

The initial treatment for atrial flutter is synchronized electrical cardioversion with 0.5-2 Joules per kilogram, but higher doses may be required because of the relatively small surface area of the cardioversion paddles/patches in neonates.[3,9] The best position for the paddles or patches is front to back, slightly to the left side of the chest, and it is often necessary to turn the infant on its side to get the paddles into position. Rapid atrial pacing (overdrive pacing) may also terminate the tachycardia but is difficult to achieve with the rapid atrial rate seen in neonatal flutter and has a lower overall success rate.[11,20] In addition to these two methods, some physicians use antiarrhythmic medications and observe for up to 48 hours to see if the tachycardia terminates spontaneously, but this method has lower success rates when compared to synchronized cardioversion.

Atrial flutter in an otherwise healthy newborn generally does not return once the patient is successfully treated unless there is another arrhythmia such as atrial tachycardia. Therefore no routine antiarrhythmic treatment is necessary for either short- or long-term treatment of standard atrial flutter once the patient is cardioverted.[3,9,11,20] If there is underlying atrial dilation, recurrent atrial flutter, or structural heart disease, treatment with antiarrhythmic medications such as propranolol or digoxin may be warranted.

Atrial Fibrillation

Neonatal atrial fibrillation (AFib) is an exceptionally rare dysrhythmia in this patient population and is typically seen only in patients with severe structural congenital heart disease (such as Ebstein anomaly of the tricuspid valve) or in conjunction with an accessory pathway (Wolff-Parkinson-White) or those with cardiac channelopathies.[25]

It is important to distinguish atrial fibrillation from a rare form of AET called chaotic atrial tachycardia (or multifocal atrial tachycardia) because both result in an irregular tachycardia with disorganized atrial activity on the ECG.

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Chaotic atrial tachycardia (also referred to as multifocal atrial tachycardia) is a form of atrial tachycardia in which there are rapid bursts of tachycardia from multiple areas of the atria. Atrial fibrillation is an incessant arrhythmia that typically will respond to cardioversion. However, chaotic atrial tachycardia tends to occur in short bursts with sinus beats interspersed with runs of tachycardia and a varying P-wave axis. This type of tachycardia either does not respond to cardioversion or quickly returns after cardioversion.

Treatment of AFib in neonates involves synchronized cardioversion. Pediatric cardiology consultation should be obtained because AFib is extremely rare in neonates and generally occurs in only the sickest neonates with other cardiac disorders. Chaotic atrial tachycardia requires medical treatment with antiarrhythmic medications such as beta blockers, flecainide, sotalol, or amiodarone, alone or in combinations, with a goal simply to control the ventricular rate, not to cure the atrial tachycardia.

Reentrant Supraventricular Tachycardia

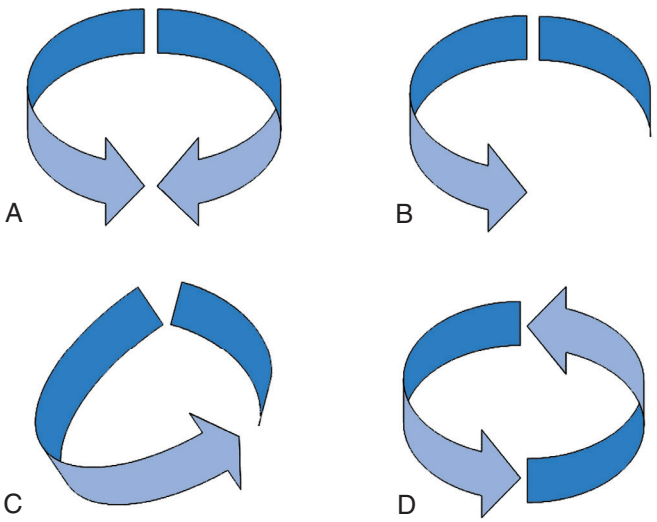
Supraventricular tachycardia (SVT) caused by a reentrant mechanism is the most common form of SVT in this population. In a reentrant tachycardia, there are two distinct conducting pathways linked around an area of nonconducting tissue. Failure to conduct in one of these pathways (block) causes the impulse to turn around in the other pathway, creating an electrical loop that causes tachycardia (Fig. 77.3).

There are two common reentrant mechanisms of supraventricular tachycardia seen in the neonatal population. The first, and by far the most common in newborns and infants, is caused by an accessory pathway.[1] The second form is due to reentry around the atrioventricular node, also known as atrioventricular nodal reentry tachycardia or AVNRT.

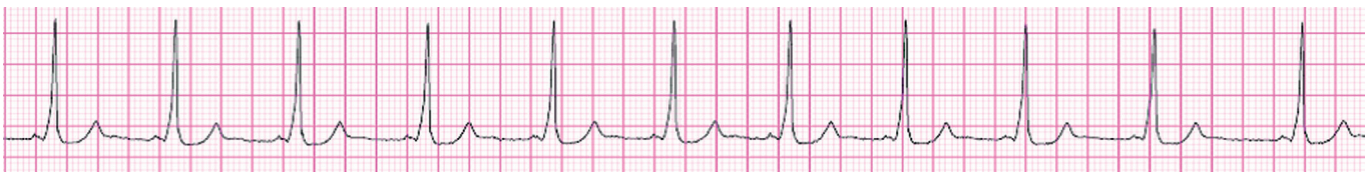
Supraventricular Tachycardia Caused by a Manifest Accessory Pathway

In the normal cardiac conduction system, only a single connection exists linking atrial impulses to the ventricles, which is the bundle of His. The bundle of His penetrates the fibrous atrioventricular ring and normally is the only structure capable of conducting electrical impulses from the atria to the ventricles. During normal sinus rhythm, the activation wavefront travels from the sinus node across the atrial myocardium, then to the atrioventricular node, bundle of His to the right and left bundle branches, and ultimately exiting to the ventricular myocardium to cause a depolarization.

If an accessory pathway is present, it serves as an additional conduction pathway for electrical impulses to travel between the atria to the ventricles. Accessory pathways can conduct an impulse in both directions (antegrade, from atria to ventricles, and retrograde, from ventricles to atria) or only in one direction (either exclusively from the atria to the ventricles or from the ventricles to the atria). If an accessory pathway is capable of conducting the impulse only from the ventricles to the atria (retrograde), it is referred to as a *concealed accessory pathway*, and the baseline ECG will appear normal. If an accessory pathway is capable of conducting an impulse from the atria to the ventricles, it is referred to as a *manifest accessory pathway*,[12] resulting in what is known as preexcitation on the baseline ECG. Patients with preexcitation (also known as Wolff-Parkinson-White [WPW]) have an area of early ventricular activation on their ECG. This early ventricular activation on the ECG is called a delta wave and results in a short PR interval and widened QRS complex (Fig. 77.4). Preexcitation is present because the electrical impulse travels from the atria to the ventricles over two pathways—through the AV node/bundle of His, which has decremental properties, and down the accessory pathway. When activation travels down the conduction system (AV node), a normal physiologic delay of conduction occurs. This delay is necessary



• **Fig. 77.3** Re-entrant supraventricular tachycardia (SVT): **A,** Normal conduction down both sides of a re-entrant circuit. The electrical impulses collide and there is no reentry. **B,** Block in one pathway and conduction in the other. **C,** The impulse from the conducting pathway reaches the other pathway. **D,** This pathway now conducts setting up an electrical circuit of reentrant tachycardia.



• **Fig. 77.4** Electrocardiogram of a patient with Wolff-Parkinson-White syndrome shows a short PR interval, widened QRS, and slurring of the upstroke of the QRS.

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to make sure that atrial systole will occur before ventricular systole. Although there is a delay in conduction through the AV node, no such delay exists when electrical activity conducts down the manifest accessory pathway. Therefore, the atrial impulse travels quickly from the atria to the ventricles across the accessory pathway and activates the ventricular myocardium before it would normally be activated through the normal conduction system, resulting in a delta wave on the ECG.

About 20% of patients with Wolff-Parkinson-White have underlying structural heart disease (most commonly Ebstein anomaly); therefore, an echocardiogram should be performed when the diagnosis is made. Wolff-Parkinson-White syndrome can be hereditary but most times is sporadic, occurring in about 1-3 per 1000 individuals.[22]

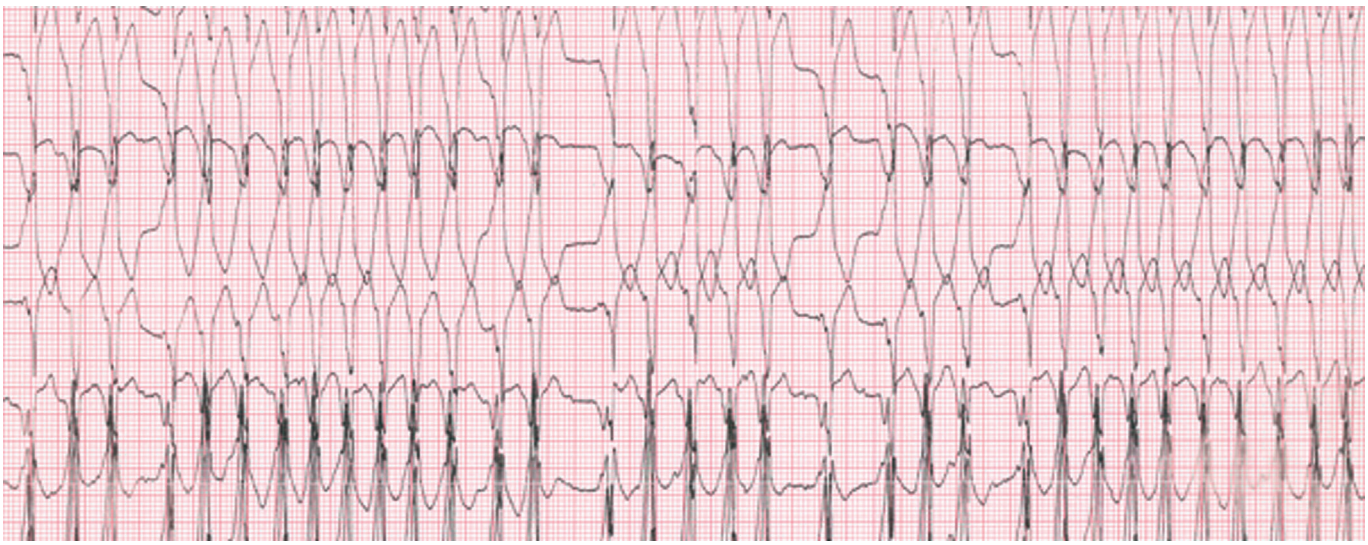
Patients with WPW, a manifest accessory pathway, have an increased risk of atrial fibrillation for reasons that are not well understood. If atrial fibrillation occurs in a patient with WPW, an irregularly irregular wide complex tachycardia ensues (Fig. 77.5). In infants and neonates, there are almost no other causes of an irregularly wide complex tachycardia other than atrial fibrillation in the presence of an accessory pathway, although this occurrence is extremely rare in infants and neonates. Patients with WPW and atrial fibrillation also have the risk of sudden cardiac death.[16] In atrial fibrillation, these accessory pathways may conduct atrial impulses rapidly to the ventricles, resulting in rapid ventricular activation that may result in ventricular fibrillation and cardiac arrest. For this reason, adenosine, which blocks AV nodal conduction, should be used in a very controlled environment by an individual with knowledge of how to resuscitate an infant in cardiac arrest. In addition, other medications such as digoxin that block AV nodal conduction are relatively contraindicated with WPW.

Supraventricular Tachycardia Caused by a Concealed Accessory Pathway

Patients with a concealed accessory pathway are at risk of developing supraventricular tachycardia secondary to a reentrant mechanism.[8,37] Supraventricular tachycardia is usually initiated by a premature atrial or ventricular contraction. The premature beat will block in one of these two conduction pathways—the accessory pathway or the AV node. If the premature beat blocks in the accessory pathway, the activation wavefront travels down the normal conduction system (AV node and bundle of His) to the ventricles. The conduction wavefront then passes through the ventricular myocardium. The wavefront then reaches the accessory pathway, which has had time to recover and is able to conduct electrical impulses. The electrical impulse travels retrograde, from the ventricle to the atria then back down the AV node to perpetuate the tachycardia. This type of tachycardia, known as *orthodromic* tachycardia, is generally a narrow complex in nature as it travels down the normal conduction system to get to the ventricles. Each of the components of this circuit is integral to allow for propagation of the tachycardia, and disruption of the circuit in any of the limbs will terminate the tachycardia (Fig. 77.6).

Supraventricular Tachycardia Caused by Atrioventricular Nodal Reentry Tachycardia

A third form of reentrant tachycardia seen in neonates is atrioventricular nodal reentry tachycardia (AVNRT). In this form of SVT, the entire circuit is contained within the proximal portion of the AV node and no true accessory pathway is present. Its reentry circuit is located between the slow and fast pathway limbs of the atrioventricular node.[2,10] In most individuals, the AV node has both of these inputs, which coalesce to form the compact AV node,



• **Fig. 77.5** Preexcited atrial fibrillation in a patient with Wolff-Parkinson-White syndrome. Note the irregularly irregular wide complex rhythm.

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• **Fig. 77.6** Baseline electrocardiogram (first 10 beats) shows preexcitation. The QRS complex #11 *(arrow)* represents premature atrial contraction followed by a reentrant narrow complex tachycardia (orthodromic supraventricular tachycardia).

which then continues to the bundle of His. Because slow and fast pathways have different conduction properties, a reentry tachycardia between these inputs can and often does occur. The resulting tachycardia is referred to as *atrioventricular nodal reentry*. Because AVNRT has a reentry mechanism, it is usually started by a premature atrial or ventricular beat. On ECG, it usually presents as a narrow complex tachycardia that is indistinguishable from an accessory pathway-mediated tachycardia. Atrioventricular nodal reentry tachycardia has a developmental component and is rare in neonates and infants but is relatively common as a mechanism of tachycardia in older teenagers and adults.[1]

Supraventricular Tachycardia

The clinical presentation of SVT in neonates or infants with AVRT and/or AVNRT are the same, with a rapid increase in heart rate and narrow complex tachycardia on ECG. Ventricular rates are typically greater than 200 beats per minute, but rates as fast as 300 beats per minute can be seen. It is rare to have a sinus rate greater than 220 beats per minute, and any rate exceeding this number should raise the possibility for the presence of an abnormal mechanism of tachycardia, including reentrant SVT.

In the neonatal period, it is not uncommon for SVT to present as a wide complex tachycardia, generally with a left bundle branch block. In this situation, there is aberrant conduction to the ventricles because of a long recovery or refractory period of one of the bundles, generally the left. The differential diagnosis for a wide complex tachycardia in a newborn is ventricular tachycardia or SVT with aberrancy, with the latter being much more common in this age group.

In patients with a concealed accessory pathway or AV node reentry tachycardia, the major clinical manifestation is a rapid heart rate discovered either by auscultation or monitoring. Occasionally, infants can present with depressed myocardial function if the tachycardia is persistent. Infants generally tolerate these rapid heart rates for hours to days, manifesting generalized symptoms such as poor feeding and irritability. Patients with WPW (manifest accessory pathway) may be diagnosed when tachycardia occurs or if preexcitation is noted on a monitor or routine ECG.

Asymptomatic patients with WPW syndrome and no evidence of tachycardia do not require medical treatment.[4] They should be followed by a pediatric cardiologist or electrophysiologist to ensure that SVT does not develop, but up to 80% have spontaneous resolution of their preexcitation within the first year of life.[23]

If a patient presents with an acute episode of SVT, the goal is to terminate the tachycardia in the most humane, stable way in an environment in which intubation, cardioversion, and resuscitation can be carried out capably. If the patient is hemodynamically unstable, the doctor must decide which method of cardioversion is immediately available, whether adenosine or direct current cardioversion. The doctor must also be prepared to intubate the patient and have intravenous pressors and even ECMO available to support the infant afterward. The typical dose required to cardiovert a neonate is between 0.5 and 1 joule per kilogram, but larger doses may be required, particularly in smaller neonates. If there is a QRS complex that is generating a pulse, the cardioversion should be synchronized to the QRS complex.

If the patient is hemodynamically stable, other methods should be attempted before heading directly to electrical cardioversion. Automated blood pressure machines may not register an accurate blood pressure in the face of a rapid tachycardia, and other methods of assessing cardiac output such as skin perfusion, level of consciousness, and peripheral pulses may be needed to determine if adequate perfusion is occurring. The first line of therapy in the hospital used for cardioversion in a neonate is either adenosine administration or vagal stimulation. Vagal stimulation slows conduction through the AV node and interrupts a reentrant supraventricular tachycardia. An effective maneuver frequently utilized to convert infants is placing a small bag or glove filled with ice over the entire face for 10-15 seconds. To elicit the appropriate dive reflex, the majority of the face/mouth and nose must be covered. Care must be exercised not to cause frostbite to the delicate neonatal skin from prolonged or repeated ice exposure. Holding a child upside down (with proper support) can also induce a vagal response. Gagging, ocular pressure, and anal stimulation in general should be avoided in the neonatal population.

If the child is in the hospital, IV adenosine (0.1-0.4 mg/kg per dose) would generally be the recommended step to convert the infant/neonate back into normal rhythm. Adenosine must be administered in a rapid IV push followed by a 5-10 cc bolus of normal saline or Ringer's lactate. This form of cardioversion is extremely effective, resulting in normalization of the neonate's rhythm in the vast majority of cases.

The use of IV digoxin has fallen by the wayside since the advent of adenosine. The use of IV (or oral) calcium channel

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blockers is relatively contraindicated in patients less than 1 year of age, because there have been reports of sudden death, likely caused by the extreme sensitivity of the infantile conduction system to calcium. The use of IV amiodarone is included in Pediatric Advanced Life Support (PALS) and Neonatal Advanced Life Support (NALS) algorithms, but the use of this medication should be reserved for the conversion of refractory cases of SVT and is best administered in conjunction with consultation by a pediatric cardiologist who can assist with the long-term management of the patient, especially considering that the half-life of amiodarone can be up to 90 days in a neonate.

The long-term goal is to prevent SVT recurrence. Around 60%-80% of supraventricular tachycardias that present in the neonatal period resolve spontaneously within the first year of life.[7,39] In older patients, generally around 15 kilograms, there is the possibility of performing a cardiac catheterization and electrophysiology study with the potential for an ablation to eliminate the mechanism of tachycardia. The risks of this procedure are significantly higher when performed in children less than 4 years of age.[34] For this reason, ablations in neonates and infants are reserved for those patients with drug-refractory tachycardias and decreased function in whom no other options exist. In general, medical treatment is recommended after a single episode of tachycardia for the vast majority of cases.

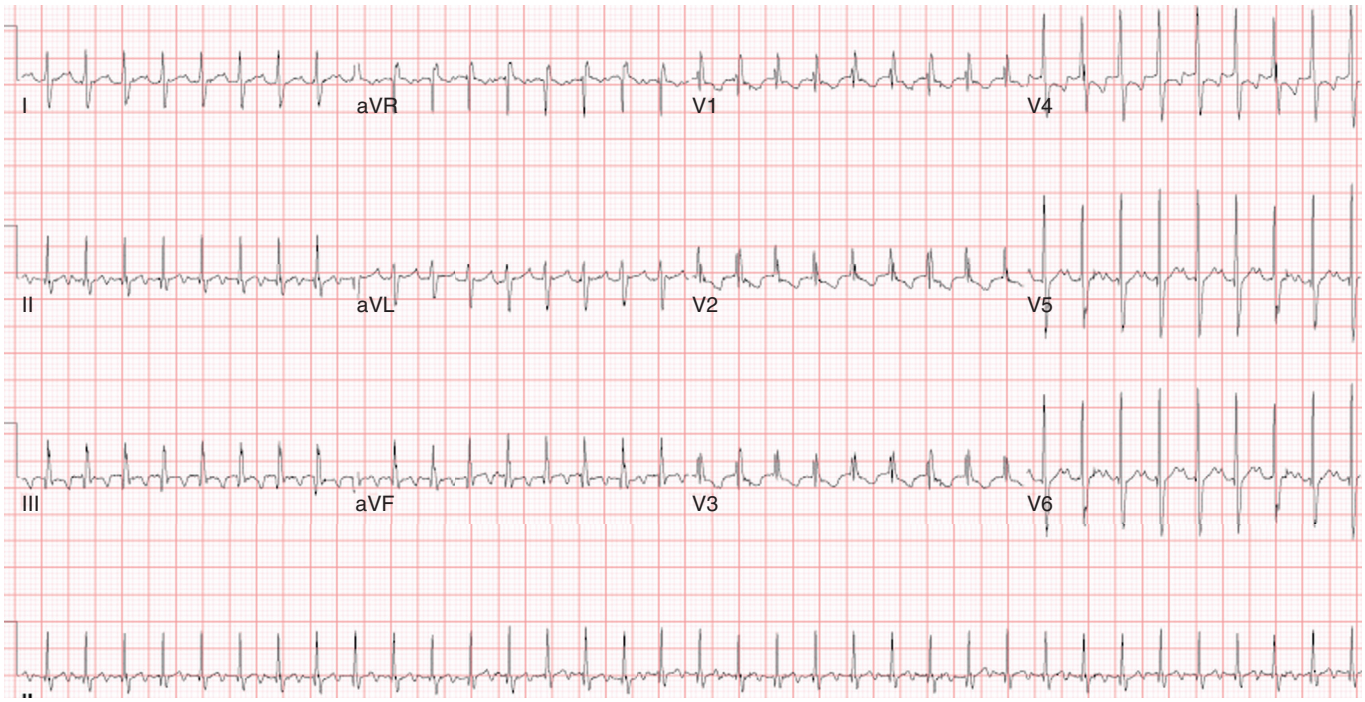
Beta blockers such as propranolol are a generally safe and quite effective first-line medical therapy for the treatment of SVT. Propranolol is dosed at 4 mg/kg per day or 1 mg/kg per dose, dispensed every 6 hours or every other feed in a neonate. Once the infant begins sleeping through the night, the dosing can be spaced out to every 8 hours. Some centers also use digoxin, another relatively effective first-line agent in the treatment of SVT. Digoxin is frequently used to successfully treat fetal tachycardias. Digoxin is generally dosed at 4-5 μg/kg per dose given twice a day.

Second-line agents for the treatment of neonatal tachycardias, when propranolol and/or digoxin have failed to completely control the arrhythmia, include sotalol, flecainide, or amiodarone.[13,18] Each of these potent medications works extremely well for the treatment of neonatal tachycardias, but all have potential side effects. Before the use of any of these medications alone or in combination, consultation with a pediatric cardiologist is recommended.

Permanent Form of Junctional Reciprocating Tachycardia

A unique type of accessory pathway–mediated tachycardia is the permanent form of junctional reciprocating tachycardia (PJRT). Initially, this tachycardia was thought to arise from the AV junction, but it is actually caused by a concealed, slowly conducting retrograde-only accessory pathway. Because these accessory pathways conduct very slowly, the tachycardia presents with P waves clearly visible on the surface ECG.[15] The ECG in tachycardia has a characteristic morphology with deeply negative P waves in the inferior leads II, III, and aVF (Fig. 77.7).

This type of tachycardia frequently is present immediately after birth, but because of its slow rate (potentially as slow as 150 beats per minute), it may not be noted during examinations in newborns and infants. In addition, the tachycardia has P waves before each QRS complex, which



• **Fig. 77.7** Electrocardiogram in a patient with permanent form of junctional reciprocating tachycardia shows a narrow complex tachycardia with negative P waves in the inferior leads II, III, and aVF.

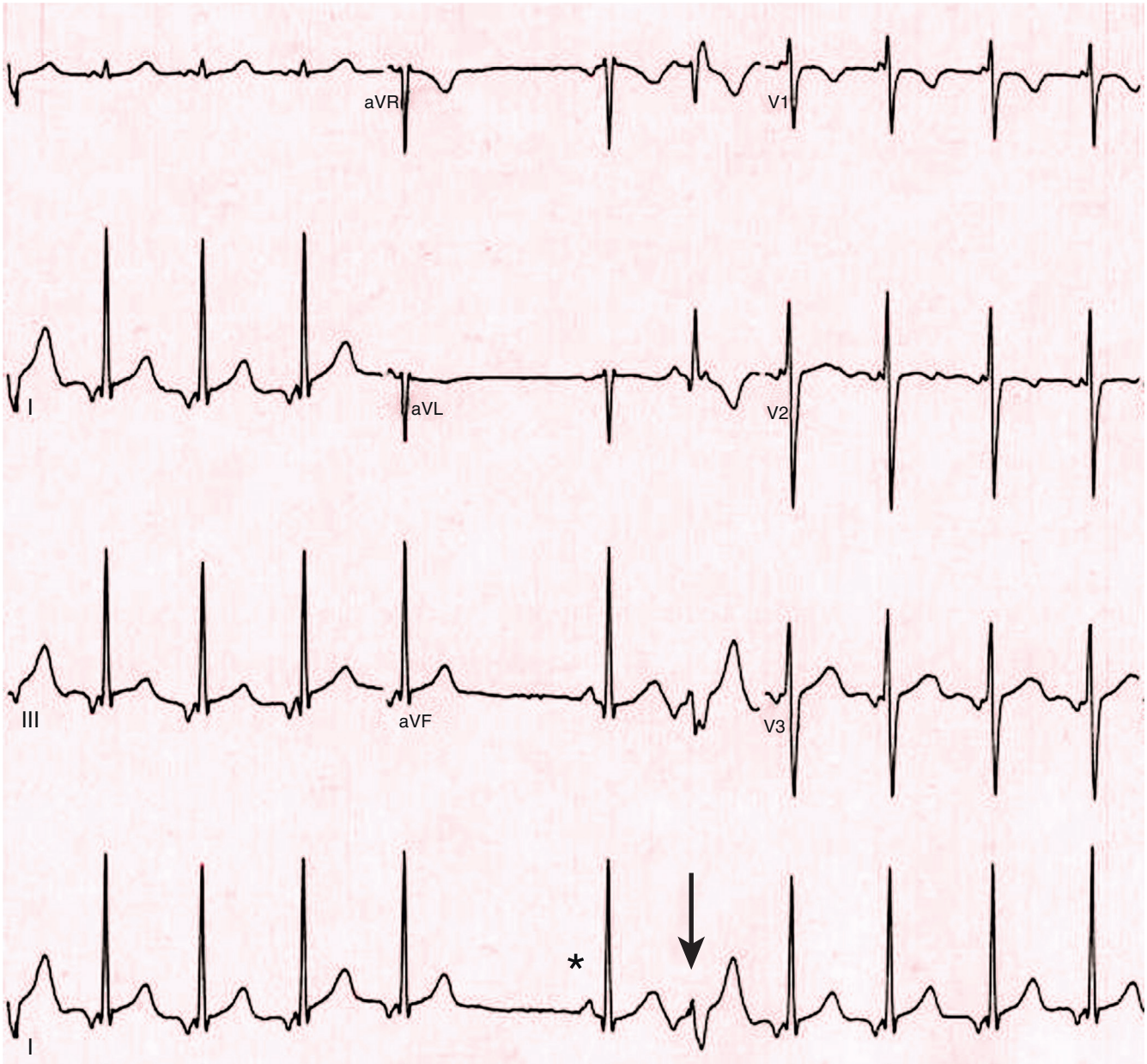
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may be mistaken for sinus rhythm if it is not recognized that the atrial impulse is not coming from the sinus node (sinus P waves should be positive in leads I, II, and aVF). Permanent form of junctional reciprocating tachycardia also tends to be an incessant tachycardia with minimal variation in the heart rate and may lead to a tachycardia-induced cardiomyopathy if left untreated. There may be spontaneous termination of the tachycardia followed by several sinus beats with spontaneous reinitiation of the tachycardia (Fig. 77.8).

Treatment of PJRT in the neonatal and infantile period is typically done with antiarrhythmics. Beta blockers may be initiated but are frequently ineffective. Flecainide is currently the treatment of choice for this incessant tachycardia, and it is often effective, even after a single dose. Ultimately, the vast majority of these patients will require an ablation when they are older because this form of tachycardia does not resolve spontaneously.

Junctional Ectopic Tachycardia

In patients with junctional ectopic tachycardia (JET), the focus of tachycardia is located within the bundle of His (most commonly) or proximal bundle branches (very rarely). The mechanism of JET is caused by increased automaticity in this region.[10] Junctional ectopic tachycardia can be either congenital, of which many are of genetic



• **Fig. 77.8** Permanent form of junctional reciprocating tachycardia with deeply negative P waves in leads II, III and aVF. Note the spontaneous termination followed by a sinus beat (denoted by *) and reinitiation of the tachycardia, with the first beat of tachycardia being aberrantly conducted (*arrow*), seen on the rhythm strip at the bottom of the electrocardiogram.

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• **Fig. 77.9** Narrow-complex tachycardia with VA dissociation (no relationship between the P waves and QRS complexes) diagnostic of junctional ectopic tachycardia.

etiology, or acquired, which occurs after congenital cardiac surgery. Congenital JET is rare but very frequently leads to arrhythmia or tachycardia-induced cardiomyopathy, resulting from its incessant and rapid rates upwards of 260 beats per minute. Congenital JET generally presents in fetuses, neonates, and infants less than 6 months of age and is likely to be incessant, have faster rates, and have an associated mortality rate of greater than 50% (Fig. 77.9).[14,36]

Postoperative JET is seen in patients who have undergone surgical repair of congenital heart defects. The cause of JET in these patients is multifactorial and is thought to be caused by swelling/edema, electrolyte imbalances, catecholamine surges, and use of certain pressor medications such as epinephrine and dopamine, as well as longer aortic cross clamp and bypass times. As the localized edema or the electrolyte or catecholamine imbalance resolves, the JET will frequently subside. If not, short-term medical management with amiodarone or procainamide is warranted.

Because the focus of tachycardia is located within the His complex, the QRS complexes are expected to be narrow and identical to the sinus QRS.[5] Because the focus of the tachycardia is located within the bundle of His, the relationship between the atria and ventricles is variable. The typical presentation of this tachycardia is no association between the P waves and the QRS complexes on the ECG (VA dissociation), with the narrow ventricular rate being faster than the atrial rate. However, in the majority of pediatric cases, there is retrograde conduction through the AV node, resulting in 1:1 VA conduction, or VA Wenckebach is present with the P wave occurring simultaneously with the QRS complex. The tachycardia typically has minimal response to adenosine other than it can be used to disassociate the atrium from the ventricle, with continuity of the tachycardia at the same rate.

Congenital JET is a rare, life-threatening tachycardia that may not respond to any form of intervention. The current medical management for JET is to remove additional catecholamines and initiate amiodarone, which is currently considered the most effective antiarrhythmic agent available.

Postoperative JET generally resolves within 3-5 days after surgical repair. The decision to treat or not to treat these fragile neonates depends on the overall patient status. The heart rate during JET generally is in the range of 150-170 beats per minute, but the main question is whether the patient is hemodynamically stable. If so, then no specific treatment is required. In postoperative neonates when JET does affect hemodynamic status, the following steps should be taken:

1. Treat fever and/or cool the patient.
2. Decrease/wean all catecholamines.
3. Initiate atrial pacing at rates faster than the JET rate to restore AV synchrony.
4. Administer amiodarone or procainamide intravenously for at least 48 hours.

Ventricular Arrhythmias

Premature Ventricular Contractions

A premature ventricular contraction (PVC) is a spontaneous depolarization of the ventricle myocardium resulting in an early or premature ventricular contraction (Fig. 77.10). PVCs in infants or neonates may not have as wide of a QRS duration as seen in older patients, but they frequently have a morphology that is different and wider than that of the normal sinus QRS. Intermittent preexcitation or an aberrantly conducted premature atrial contraction are in their differential diagnosis, but these can be ruled out with a simple ECG. Premature ventricular contractions in neonates with a structurally normal heart typically have a benign prognosis and do not require any form of treatment. Exceptionally rarely, PVCs may cause symptoms or a decrease in systolic function if they occur with an extremely high frequency.

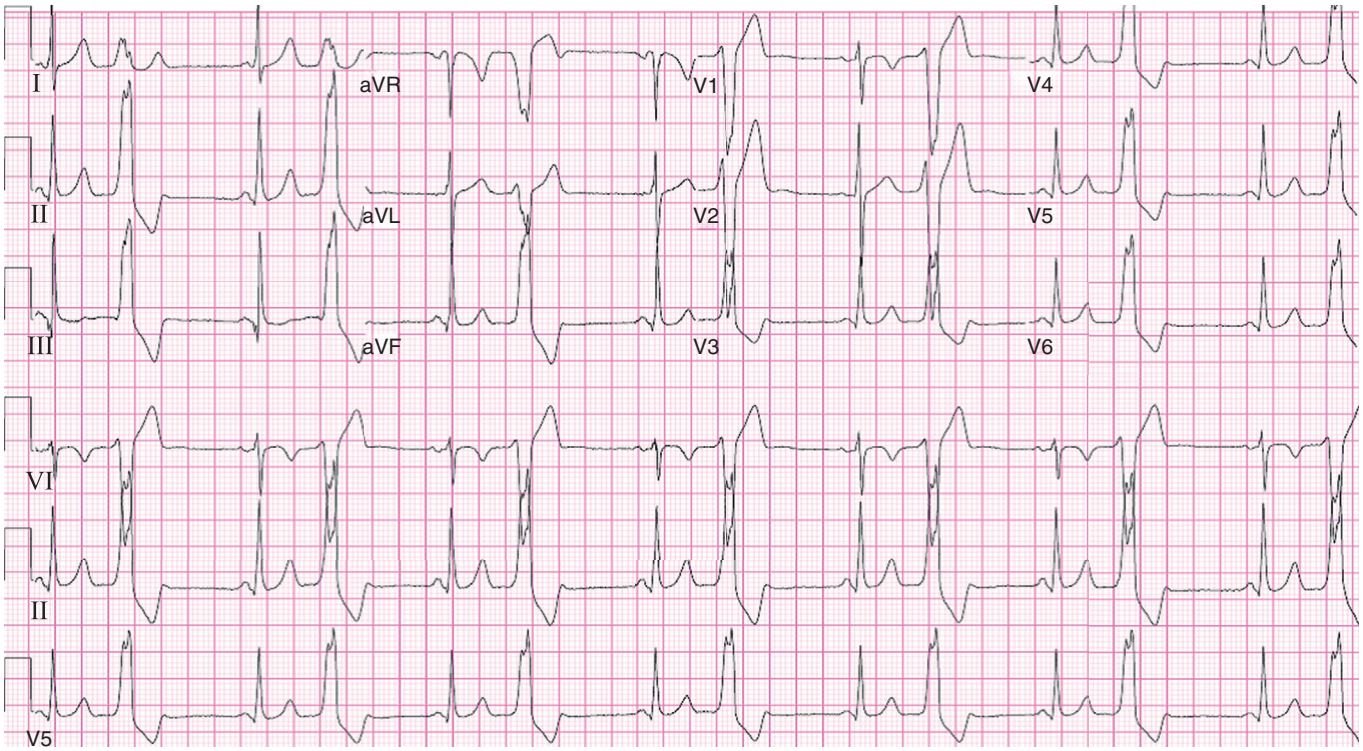
Characteristics of Benign Premature Ventricular Contractions

1. Lack of symptoms
2. Structurally normal heart and normal cardiac function by echocardiogram
3. Disappearance of PVCs at faster heart rates
4. Negative family history for sudden death or inherited arrhythmia disorder

Evaluation

Premature ventricular contractions in this population are generally heard on physical exam as either an extra or skipped beat, or they may be found during routine monitoring on babies in the newborn nursery or intensive care unit for other reasons. The standard for evaluation of PVCs is first an ECG to make the appropriate diagnosis, then a 24-hour Holter monitor to quantify the burden of

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• **Fig. 77.10** A patient with a structurally normal heart and frequent monomorphic premature ventricular contractions in bigeminy pattern.

ventricular ectopy and to evaluate for ventricular tachycardia (three or more PVCs in a row.) It is reasonable to perform an echocardiogram on selected patients with PVCs to evaluate for the presence of congenital heart disease and to assess ventricular function. It is very rare for electrolyte abnormalities or hyperthyroidism to result in PVCs, but these, plus the placement of all intravenous lines, should be evaluated if clinically indicated.

Treatment

The vast majority of infants and neonates with isolated PVCs and a negative family history for sudden cardiac death or channelopathies require no treatment. The only recommendation is that these patients follow up with a pediatric cardiologist within their first 3-6 months of life to assess if the PVCs are still present. If they persist, the pediatric cardiologist may wish to place another 24-hour Holter monitor and potentially re-evaluate their cardiac function if PVCs remain frequent.

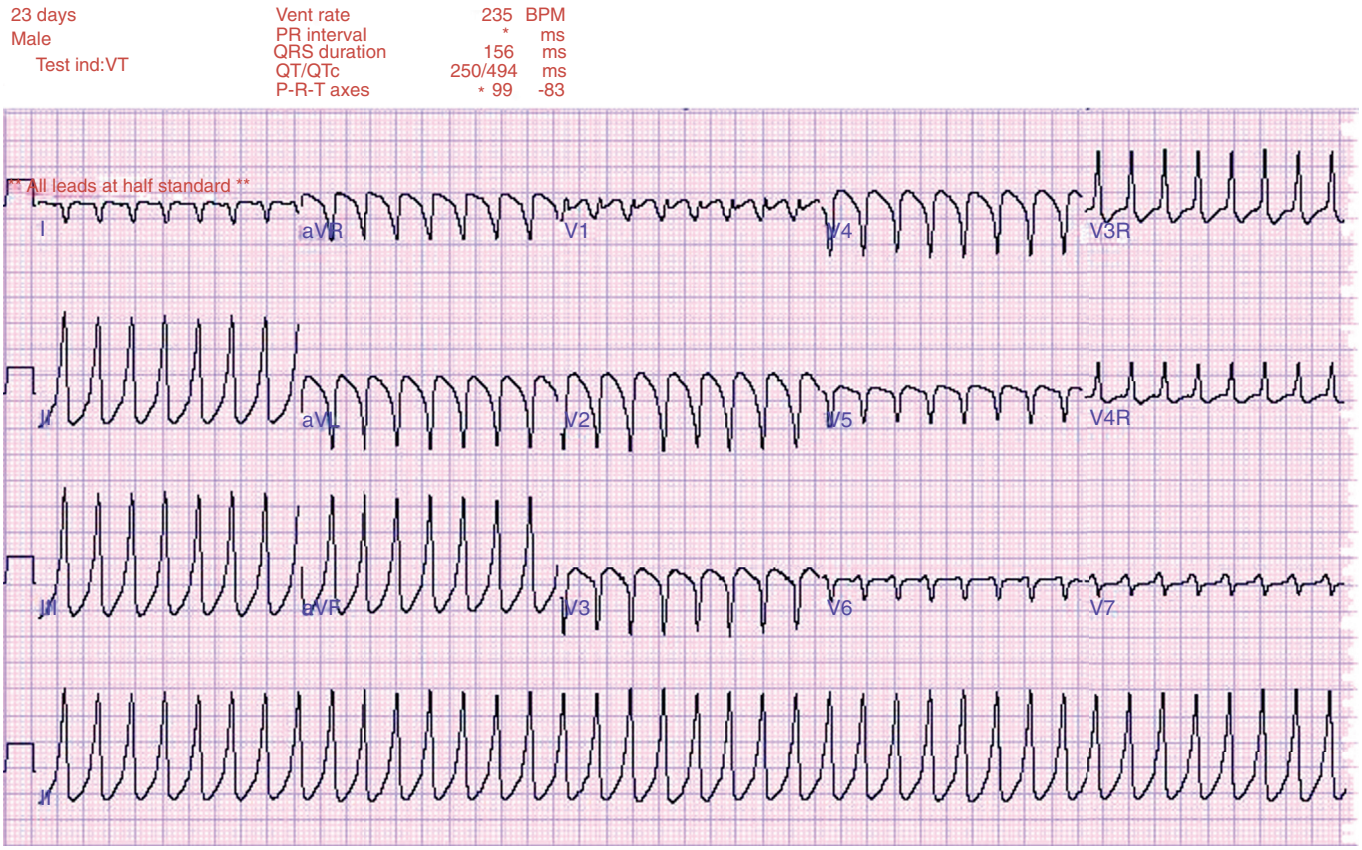
Ventricular Tachycardia

Ventricular tachycardia (VT) is a rhythm disturbance that originates below the bifurcation of bundle of His. This typically presents with a wide complex rhythm, which in neonates constitutes a QRS duration of greater than 80 ms (Fig. 77.11). Any time one is faced with a patient with "ventricular tachycardia," one must differentiate it from the benign rhythm called accelerated ventricular rhythm or *idioventricular rhythm*. Idioventricular rhythm is characterized by its rate, which by definition is no more than 20% faster than the underlying sinus rate and the patient is asymptomatic and hemodynamically stable. This rhythm is almost always considered benign and requires no intervention.[24] In infants with structurally normal hearts, true VT is quite rare and generally has a benign prognosis. However, there are ventricular tachycardias that are either so fast or so frequent that they may affect the patient's hemodynamics and cardiac function and require aggressive treatment.

In neonates with structurally normal hearts, VT generally is caused by an automatic focus. The focus of the tachycardia is frequently from the outflow tract (most commonly the right ventricular outflow tract) or one of the fascicles in the left ventricle (most commonly the left posterior fascicle). Additional, yet rare, causes of neonatal ventricular tachycardia are myocardial hamartomas or tumors. These extremely rare causes of neonatal ventricular tachycardia tend to be incessant and extremely difficult to control with medications. However, if the tachycardia can be controlled, hamartomas frequently regress in the first several years of life, but some cardiac tumors require surgical resection.

Infants with poor ventricular function (e.g., patients with neonatal myocarditis) or structural cardiac disease can also present with ventricular tachycardia; therefore, it is very important to assess these patients with a complete echocardiogram prior to the initiation of any form of treatment to help assess the overall patient's status and potentially get clues as to the longevity of treatment and the patient's prognosis.

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• **Fig. 77.11** A 15-lead electrocardiogram in a 23-day-old patient with a structurally normal heart with ventricular tachycardia. Note the relatively narrow QRS complex.

Treatment

1. In children with a structurally normal heart, the type of therapy usually depends on the stability of the patient and the rate and frequency of the tachycardia. In asymptomatic individuals with idioventricular rhythm, no therapy is required, but close follow-up is recommended. Frequently, this type of ventricular dysrhythmia resolves in the first several months of life.
2. In patients with rapid (above 200-220 bpm) or frequent ventricular tachycardia and normal ventricular function, therapy with beta blockers, generally propranolol at 1 mg/kg per dose every 6 hours, is the initial choice. If propranolol is ineffective, or beta blockers are contraindicated, then treatment with flecainide, sotalol, or amiodarone may be used with close follow-up for potential side effects.
3. In children with very fast or incessant tachycardia, or in those with decreased ventricular function, rapid control of tachycardia is important. This is best achieved with the use of intravenous medications such as amiodarone or sotalol.

Long-term therapy of neonatal ventricular tachycardia depends on its underlying cause. Many neonatal ventricular tachycardias resolve spontaneously within the first several months to years of life. Radiofrequency ablation is an option to treat those patients with refractory tachycardia but is generally not performed in these patients except under the direst of circumstances because of the risk in patients this age. If a hamartoma or tumor is identified, surgical excision should be considered, because these tumors' borders or edges are frequently visible to the naked eye on the ventricular myocardium and removing them often eliminates the tachycardia. In neonates with poor ventricular function and ventricular tachycardia, these patients may require ventricular assistance until cardiac function recovers. In severe cases, ECMO may be required to sustain perfusion until the arrhythmias can be controlled.

Implantable cardioverter-defibrillator (ICD) therapy is quite difficult in this size of patient, at least in part because of the size and bulk of the device. Their placement is typically not possible in neonates and small infants because of the large size of the ICD, ICD lead, and coil necessary for the system to function properly, but has been done.[31] The implant of these life-saving devices can be considered in children less than 1 year who are at high risk for recurrent, life-threatening ventricular arrhythmias such as long QT syndrome with multiple ventricular tachycardia/fibrillation episodes, but this is quite difficult and requires a very knowledgeable team consisting of a pediatric electrophysiologist and cardiovascular surgeon. Placing an ICD in young children is typically done by an epicardial approach requiring a median sternotomy to position. The shocking coil can either be placed over the heart or outside the pericardium, or arrays can be placed in the subcutaneous

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tissue that will allow for the appropriate delivery of energy to the patient.

Toxicities and Depletions

Hyperkalemia, medication overdosing, and other metabolic disturbances such as acidosis or hypoxemia can affect the ventricular depolarization and myocardial function and result in arrhythmias. Neonates, particularly the most premature ones, may be more susceptible to these conditions, and recognizing this and the ECG characteristics of each of these conditions is important. The hallmark feature of severe electrolyte or acid-base disturbances is a loss of delineation between the QRS complex and the T wave. This ultimately results in a "sine wave" pattern on the ECG.[19] Additional abnormalities caused by electrolyte excess include a peaked appearance of T waves, ST segment elevation, and prolongation of the QT interval (Fig. 77.12). Recognition of these patterns, especially in premature neonates, allows for rapid treatment to correct the underlying disturbance, because antiarrhythmic medications are generally not helpful in these situations. For hyperkalemia, treatment depends on the severity of the hyperkalemia and ranges from removal of supplemental potassium to calcium gluconate, administering glucose, and insulin to dialysis.

Tachycardia-Induced Cardiomyopathy

In some cases, incessant tachycardia can result in a decrease in the patient's ventricular function. When dysfunction occurs, it is often described as severe. It is important to perform an echocardiogram on all neonates with tachycardia episodes if the duration of the episode is unknown to evaluate their ventricular function or contractility and to evaluate for underlying structural abnormalities. Any form of tachycardia, be it SVT or VT, can result in depressed cardiac function if the rate is fast enough and the duration is long enough. Knowing the patient's function, by a quick function check prior to cardioversion, is a critical part of the planning for this procedure and can assist with the patient's outcome post-cardioversion. Rarely, these patients' function is so bad prior to cardioversion that they may require intubation and even circulatory assistance with either pressors or ECMO.[6]

Atrioventricular Conduction Disturbances

During normal sinus rhythm, the electrical activation wavefront initiates from the sinus node to activate the right and left atria. The activation wavefront reaches the AV node, bundle of His (the only structure penetrating fibrous AV annulus connecting atria and ventricles), and finally travels to the right and left bundle branches to activate the right and left ventricle correspondingly. There is typically a delay as the impulse goes through the AV node and bundle of His, and this delay creates the PR interval noted on the ECG in neonates.

First-Degree Atrioventricular Block

First-degree AV block (FAV) is manifested by prolongation of the PR interval on the ECG while each sinus or atrial

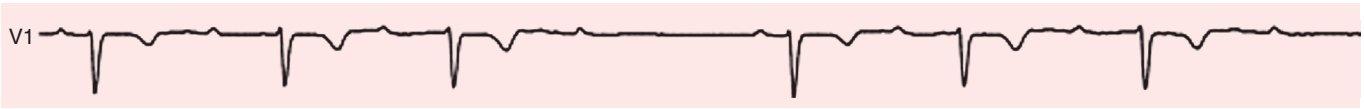


• **Fig. 77.12** Electrocardiogram in a patient with hyperkalemia (potassium level of 11 mEq/L). Note the sine wave pattern (particularly in lead V1) with no distinction between the QRS and T waves.

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• **Fig. 77.13** Example of first-degree atrioventricular block.



• **Fig. 77.14** Patient with type 1, second-degree heart block during sleep. Progressive PR prolongation seen until QRS complex drop.

beat reaches the ventricles (Fig. 77.13). To make the diagnosis of FAV in the newborn or neonate, the PR interval needs to measure longer than 160 msec. The PR interval reflects the time from initiation of atrial activation, travel time through the atrial tissue and the AV node. Any delay of impulse propagation at any level during this activation will result in prolongation of the PR interval and the diagnosis of FAV. Although this is referred to as *first-degree heart block*, it is not true block within the conduction system, and a better terminology is "prolonged AV conduction."

The AV node, similar to the sinus node, receives innervation from both parasympathetic and sympathetic nervous systems. Increased parasympathetic or vagal tone often leads to delay in impulse conduction through the AV node. This increase in vagal tone is the most common cause of first-degree heart block. A first-degree block frequently resolves when a catecholamine or sympathetic surge is present. The abnormal or nonphysiologic reasons for PR prolongation in a neonate are cardiomyopathies, congenital heart disease (Ebstein anomaly, primum atrial septal defect, and AV canal), and medications like digoxin.

No treatment is indicated for first-degree AV block. In cases in which a significant PR prolongation is seen, periodic follow-up may be indicated to ensure that a more advanced block does not develop. An increase in vagal tone that can be seen with reflux or apnea can result in transient prolongation of the PR interval with rapid normalization after the episode. Secondary causes such as this should be evaluated for in patients that experience episodic PR prolongation. In the neonatal period, persistent PR prolongation is uncommon and should warrant evaluation, including an echocardiogram to evaluate for structural abnormalities or myocarditis.

Second-Degree Atrioventricular Block

In patients with second-degree AV block, some, but not all, sinus beats do not conduct to the ventricles. On ECG, this results in some of the P waves not being followed by a QRS complex.

Second-degree AV block is usually divided into two forms, type 1 and type 2 block. Type 1 second-degree AV block is also referred to as Wenckebach. The ECG in patients with Wenckebach shows progressive lengthening of the PR interval until one QRS is not conducted or is "dropped." The next conducted beat typically will have a normal PR interval (Fig. 77.14). Wenckebach frequently is a physiologic phenomenon and is caused by increase in vagal tone, which can be seen in normal sleeping infants. As common as this disorder is, it is relatively rare in neonates and requires further evaluation with a Holter monitor and a cardiology consult to determine if there are any other causes. The same potential causes for sinus bradycardia also apply to Wenckebach, and careful observation for reflux, apnea, or seizures is indicated.

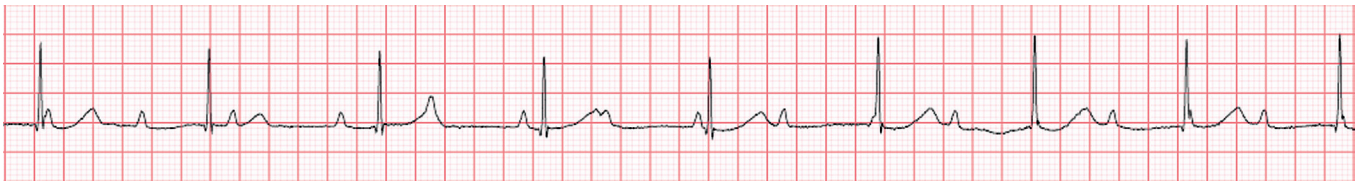
Second-degree type 2 AV block is another conduction abnormality that is almost never seen in the neonatal population. This type of block involves a failure of propagation of a P wave without prolongation of the PR interval before the block. Careful measurement of the PR interval is essential to determine the difference between type 1 and type 2 AV block in neonates, because the prolongation of the PR interval may be only a few milliseconds in type 1 AV block. Type 2 second-degree AV block is abnormal and requires pacemaker implantation.[12]

Third-Degree Atrioventricular Block

In the patients with third-degree or complete AV block (Fig. 77.15), there is no conduction of sinus beats from the atria to the ventricles due to abnormality of the AV node or bundle of His or both bundle branches. In this situation, ventricular activation will depend on the underlying junctional or ventricular escape rhythm from below the level of the block. The underlying junctional rhythm is typically a narrow complex, because it comes from a junctional focus. If the escape rhythm originates below the His bifurcation, the QRS will be wide.

To make the diagnosis of complete AV block, there should be no relationship between the atria and ventricles (atrioventricular dissociation) at any time. The atrial rate should be faster than the ventricular rate, and there should be P waves present that should conduct but do not. It is frequently necessary to obtain a long ECG strip or Holter

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• **Fig. 77.15** Complete AV block with AV dissociation and a narrow complex junctional escape rhythm.

monitor to confirm the diagnosis, because the atrial rate and ventricular rate may be similar, giving the appearance of AV conduction when actually none is present.

Complete AV block can be either acquired or congenital. The acquired form of complete AV block in neonates is usually a complication of cardiac surgery but rarely can be caused by myocarditis or endocarditis.

The congenital form of complete AV block may be seen as an isolated anomaly or in association with a congenital heart defect. As an isolated anomaly, complete AV block is seen in children born to mothers with systemic lupus erythematosus or mixed connective tissue disease, particularly Sjögren syndrome. Antibodies that are present in the mother (most commonly anti-Ro and anti-La antibodies) cross the placenta and directly affect the function of the AV node.[29] The majority of mothers are asymptomatic during their pregnancy but have detectable antibodies when tested. Occasionally, there will be progression of the AV block from second degree to complete AV block during the pregnancy.

Congenital complete AV block occasionally goes unnoticed for many years in the patient if the underlying junctional rate is relatively fast, especially considering that most young patients tolerate complete AV block without symptoms.

Fetuses with complete heart block diagnosed in utero should *not* be delivered early solely on the basis of their heart rate. If poor ventricular function or hydrops fetalis is present, a decision should be made about delivery timing with the obstetrician, neonatologist, and pediatric cardiologist. In the immediate newborn period, assessment of hemodynamic stability should be performed immediately. Neonates frequently tolerate heart rates as slow as 50 to 60 bpm with little or no hemodynamic compromise.[26]

If temporary pacing is required to assist with hemodynamic compromise, this requires insertion of a temporary transvenous pacing lead since long-term transcutaneous pacing is technically challenging because of the size of the pads and the patient's need for sedation and muscle relaxation.

Long-term treatment of third-degree AV block requires the placement of a pacemaker. In many children with congenital heart block, the pacemaker implantation can be delayed until they are older, unless there are specific indications for permanent pacemaker placement, including[21,35]:

1. Presence of symptoms
2. Wide-complex escape rhythm
3. Significant pauses (more than 3 seconds or more than 2-3x the underlying basic cycle length) on Holter monitor or ECG monitoring
4. The mean heart rate below 50 bpm in patients with a structurally normal heart or 70 bpm in patients with coexisting significant congenital heart disease
5. Left ventricular dysfunction
6. Complex ventricular ectopy

If indicated, pacemakers can be placed using a transvenous (insertion through the subclavian vein, across the tricuspid valve into the right ventricle) or epicardial approach in which leads are directly sewn onto the epicardial surface of the heart after a sternotomy. In general, an epicardial approach is almost always used in neonates because of the small size of the veins and heart and the patient's future growth.

Genetic Arrhythmia Syndromes

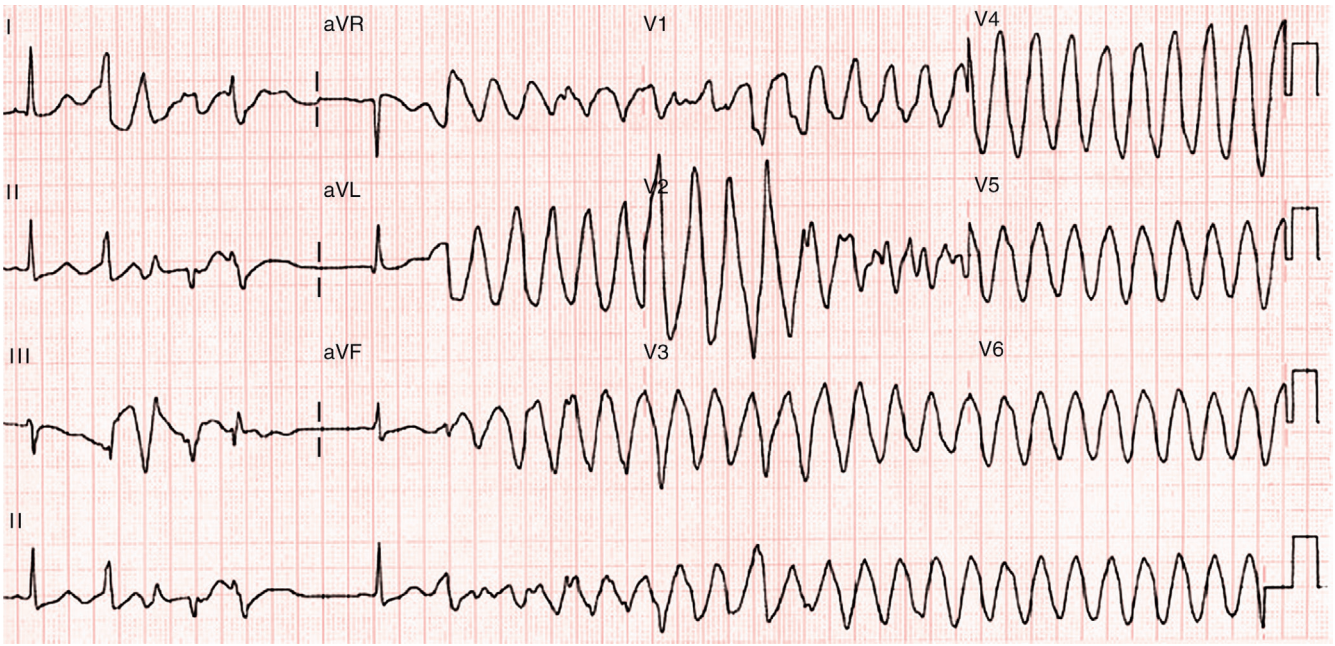
Genetic arrhythmia syndromes are inherited disorders that lead to cardiac dysrhythmias and even death. Most of these genetic disorders are categorized as channelopathies that affect myocardial ion channels (e.g., sodium, potassium, calcium) that are responsible for the electrical impulses within the myocardium. Disruptions in these channels result in altered electrical depolarization and repolarization that can lead to atrial and/or ventricular arrhythmias. Examples of channelopathies include long QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome, and short QT syndrome. Although CPVT may be a potential cause of sudden infant death syndrome (SIDS), generally long QT syndrome is likely a major culprit of neonatal arrhythmia and sudden death.

Long QT Syndrome

Congenital long QT syndrome (LQTS) is a multifaceted genetic disorder that manifests by prolongation of the corrected QT interval (QTc) on the ECG. The clinical importance of this syndrome is that it is associated with potentially lethal cardiac arrhythmias such as torsades de pointes (TdP) (Fig. 77.16). Torsades de pointes is a form of polymorphic ventricular tachyarrhythmia that frequently degenerates into ventricular fibrillation and may lead to sudden death. Because TdP frequently is not sustained, the patient with LQTS may present with recurrent syncopal episodes or seizure episodes. The syncope is the result of significantly reduced cardiac output during the arrhythmia and brain hypoperfusion that can result in true seizures.

Based on the type of channels or currents that are malfunctioning, LQTS is subdivided into multiple different subtypes. The majority of known LQT cases are caused by

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• **Fig. 77.16** Episode of torsades de pointes initiation in a patient with long QT syndrome.

LQT1, LQT2, and LQT3 syndromes, and the type of mutation frequently can be determined by genetic testing.

Although patients may have a prolonged QT interval on their ECG, they may not have long QT syndrome. There are other causes of a prolonged QT interval on the ECG, including medications (methadone, erythromycin, albuterol, etc.) and electrolyte disturbances (hypocalcemia, hypokalemia). These must be evaluated as a cause or exacerbating factor for the prolongation of the QT interval on the neonate's ECG. Drug-induced QT prolongation (particularly when the QTc is >500 msec) can result in life-threatening ventricular arrhythmias similar to congenital long QT syndrome.

Clinical Presentation

In older patients, there are typical triggers for each of the long QT syndromes. The typical event triggers in patients with LQT type 1 are exercise or emotional stress. In patients with LQT type 2, symptoms are usually triggered by sudden noise (e.g., alarm clock, doorbell), but can be caused by exercise as well. Patients with type 3 LQT syndrome typically become symptomatic at rest or during sleep.

In neonates, LQTS can present in a multitude of ways. It may be picked up incidentally on an ECG done for another reason or done for a family history of LQTS. It may present as a pseudo or pure AV block, either complete or 2:1. In any patient with AV block, the QT interval must be carefully evaluated to ensure that an underlying diagnosis of long QT syndrome is not present. Long QT syndrome may also present with ventricular arrhythmias. In fact, some SIDS cases may result from arrhythmias due to LQTS.[27,38] Any patient presenting with torsades de pointes should have a high index of suspicion for having long QT. Other ventricular arrhythmias should warrant evaluation of the QT interval on a routine ECG.

Electrocardiogram Findings and Diagnosis

The hallmark of LQTS is prolongation of the corrected QT interval. Measuring the QT interval in newborns can be difficult, because they frequently have flattened T waves, making determination of the exact end point of the T wave difficult. There may be transient prolongation of the QT interval seen immediately after birth that may resolve in the first week of life. QTc intervals greater than 500 msec should always be considered to be abnormal and require further evaluation. Intervals greater than 500 msec are likely caused by LQTS in the absence of a medication prolonging the QTc, electrolyte disturbances, or other medical conditions known to prolong the QTc interval (e.g., brain injury). In the immediate newborn period, QTc intervals are typically less than 450 msec, but those identified between 450 and 500 msec require further evaluation, because many patients with corrected QT intervals in this range will not have an underlying channelopathy. However, the longer the QTc interval, the more likely it is that the patient has an abnormality causing the QT prolongation, and a QTc of >500 is never normal.

By general consensus, the QTc interval is best measured in leads II and V5 on the ECG. To prevent common errors in measuring and overestimating the QT interval, the complex with a sharp T-wave ending should be selected if possible. U waves that are not greater than 50% of the height of the T wave should not be included when measuring the QT interval. Because the QT interval varies with heart rate, it must be corrected using one of several formulas. The most commonly used is Bazett's formula, in which

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the measured QT interval is divided by the square root of the previous R to R interval (interval from one QRS complex to the next QRS complex) with all values measured in seconds (not milliseconds):

$$\text{Corrected QT } (QT_C) = \text{QT Interval (sec)} \Big/ \sqrt{(\text{RR interval})}$$

Because a long QT syndrome is a genetic disorder, screening with an ECG of all first-degree relatives of affected individuals is recommended. If a positive genetic test is noted in the index case for a long QT mutation, genetic testing is recommended on all first-degree relatives. Genetic testing is available and positive in at least 75%-80% of patients with long QT syndrome. If no genetic testing is available, ECG screening of all first-degree relatives should be performed. Genetic testing should be considered in all patients with LQTS, because it may predict the course of disease and suggest medication therapy.

Treatment

All patients with LQTS should avoid medications known to have QTc prolonging effect (www.crediblemeds.org, accessed February 18, 2018). Patients with LQTS should be started on a nonselective beta blocker (typically nadolol or propranolol) as soon as a diagnosis is made or suspected and consultation with a pediatric cardiologist with expertise in long QT syndrome is indicated.[28,33] Neonates with AV block caused by LQTS are at a particularly high risk of life-threatening ventricular arrhythmias and sudden death. Pacing may be an effective treatment in preventing episodes of pause-dependent torsades de pointes in this population, and placement of a permanent pacemaker is generally indicated in these patients prior to discharge. Some have attempted sympathectomy.[30]

Treatment of Torsades de Pointes

In patients who present with recurrent TdP, in addition to standard therapy, the following therapy should be considered:

1. Discontinue any potential offending drug. Avoid amiodarone if possible because this may further prolong the QT interval.
2. Magnesium bolus and continuous infusion even if the serum magnesium level is normal. Magnesium decreases calcium influx, thus lowering the amplitude of early after-depolarizations (EAD), which frequently cause TdP.[17,32]
3. Isoproterenol can be used if magnesium is unsuccessful. Isoproterenol may increase the baseline heart rate and may prevent bradycardia or pause-dependent episodes.

Key Points

- Neonates can experience all forms of arrhythmias from the benign to life threatening.
- Atrial flutter is seen in newborn babies, and the initial treatment is synchronized cardioversion.
- Intravenous adenosine is the treatment of choice for the hospitalized neonate in supraventricular tachycardia to convert the baby back into normal rhythm.
- Sixty to eighty percent of newborn supraventricular tachycardias resolve by 1 year of age.
- Not all patients born with congenital complete atrioventricular block require the immediate implantation of a pacemaker.

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78

Neonatal Management of Congenital Heart Disease

MARTIN L. BOCKS, BRIAN A. BOE, AND MARK E. GALANTOWICZ

Introduction

Neonates with congenital heart disease require a well-integrated and multidisciplinary team approach to achieve optimal outcomes. The complexity of managing a critically ill newborn is compounded greatly when the cardiovascular physiology and/or anatomy are significantly altered. Many of the important management principles routinely followed by neonatologists can be applied to critically ill newborn cardiac patients, including thermal regulation, prematurity issues, nutritional strategies, and ventilator support. However, cardiac-specific management strategies, procedures, and surgeries are often required during the neonatal period for patients with congenital heart disease (CHD). These unique strategies must be understood and carefully integrated into the management plan. The objective of this chapter is to describe these management strategies and procedures typically performed based on the prevailing anatomic or physiologic deficit faced by the infant during the neonatal period, as opposed to each specific anatomic variant of CHD. Since many of these conditions have similar underlying physiologies as well as early goals for palliation or treatment, the strategies employed can be applied to many different disease conditions.

As described in earlier chapters, the vast majority of congenital heart conditions (e.g., small ventricular septal defects [VSD] or bicuspid aortic valves) either do not require any interventions whatsoever or require interventional or surgical procedures later in infancy or early childhood. Although patients in the latter category may be managed in the neonatal ICU or co-managed with the pediatric cardiology service, their clinical courses are often straightforward and team discussions are typically focused on the anticipated follow-up and postdischarge planning. Examples of such conditions include the "pink" tetralogy of Fallot patient that will undergo surgical repair at 4-6 months of age or the mild valvar pulmonary stenosis patient that develops worsening obstruction in the coming months requiring balloon pulmonary valvuloplasty. This chapter focuses on congenital heart disease typically requiring medical management, catheter-based interventions, or surgeries in the neonatal period. It describes current approaches to moderate and severe forms of congenital heart disease in which neonatal palliation or treatment is required to avoid early mortality or long-term disability. The chapter also discusses those situations in which early intervention would not alter clinical course and for which the best course of management may be cardiac transplantation or palliative comfort measures.

Moderate and severe forms of congenital heart disease can be largely grouped as cyanotic and acyanotic conditions (Table 78.1). Within these major silos, conditions can also be classified based on the degree of pulmonary blood flow and whether or not they are dependent on the patent ductus arteriosus (PDA) for either pulmonary or systemic blood flow. By classifying these conditions in this manner, neonatologists will be able to more readily identify the major physiologic deficit and anticipate necessary treatment options. For patients requiring surgery in the neonatal period, the focus within this chapter is on the indications and types of surgery that can be offered. The postoperative management of these patients is not discussed, as a detailed description of the theories and summary of available evidenced-based practice is outside the scope of this chapter.

Cyanotic Congenital Heart Conditions

Cyanotic congenital heart disease (CCHDs) includes a broad class of anatomic and physiologic derangements that result in patients with decreased systemic oxygenation following birth, including 1) obstruction to pulmonary blood flow with an intracardiac shunt such as an atrial septal defect (ASD) or VSD or 2) admixture lesions in which there is a common site for mixing of systemic and pulmonary venous blood (atria or ventricles) which is pumped to both circulations, 3) transposition physiology in which systemic venous blood is pumped to the systemic circulation, 4) pure right to

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Abstract

Neonates with congenital heart disease require a well-integrated and multidisciplinary team approach to achieve optimal outcomes. The complexity of managing a critically ill newborn is compounded greatly when the cardiovascular physiology and/or anatomy are significantly altered. Many of the important management principles routinely followed by neonatologists can be applied to critically ill congenital heart patients; however, cardiac-specific management strategies, procedures, and surgeries are often required during this period to allow for long-term survival and to avoid significant morbidity. These unique strategies must be understood and carefully integrated into the management plan. The objective of this chapter is to describe these management strategies and procedures that are used to achieve early repair or temporary palliation for these many different disease conditions.

Keywords

congenital heart disease
medical management
interventions
prostaglandin
heart surgery
systemic-pulmonary shunt
stents
balloon septostomy

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TABLE 78.1 Physiologic Classification of Congenital Heart Disease

Cyanotic			Acyanotic	
Right-side Obstruction	Admixture Lesions	Transposition Physiology	Left-side Obstruction	Left-to-right Shunts
Pulmonary atresia with intact ventricular septum	Common atrium	Transition of the great arteries	Aortic stenosis	Atrial septal defect
Pulmonary atresia, VSD, and MAPCAs	Double inlet left ventricle		Coarctation of the aorta	Atrioventricular septal defect
Pulmonary stenosis	Double outlet right ventricle		Interrupted aortic arch	Patent ductus arteriosus
Tetralogy of Fallot	Hypoplastic right/left heart syndrome			Ventricular septal defect
	Total anomalous pulmonary venous connection			
	Tricuspid atresia			
	Truncus arteriosus			

MAPCA, Major aortopulmonary collateral arteries; VSD, ventricular septal defect.

left shunting (e.g., pulmonary arteriovenous (AV) malformations). The first three broad categories are more frequently encountered in the neonatal period and will be discussed more in the coming sections. The therapies required for palliation or repair of CCHDs differ tremendously within these three classes depending on other anatomic variations that are present. For example, in the admixture lesion tricuspid atresia, pulmonary blood flow is determined by the size of the VSD and relationship of the great arteries. If the VSD is large and the great arteries are normally related (i.e., the pulmonary artery arises off the rudimentary right ventricle), there is normal to increased pulmonary blood flow. This infant's oxygen level will be fairly normal in the neonatal period. However, if the VSD is restrictive and/or the great arteries are transposed (i.e., the pulmonary artery is remote from the VSD and right ventricle), pulmonary blood flow can be considerably limited, resulting in significantly low oxygen levels in the absence of a PDA. Therefore, as we discuss cyanotic congenital heart disease palliation and treatment, the following sections focus more on the immediate goals required to stabilize, palliate, or definitively treat patients in the neonatal period, including approaches for maintaining patency of the ductus arteriosus and less on the specific type of CCHD. Historically, most of these conditions requiring neonatal treatment were managed in the operating room, including a number of surgeries still currently performed (Table 78.2). However, advancements in device technology and increasingly available devices small enough for neonatal use, has led to an increasing number of CCHD that are treated via transcatheter interventions (Table 78.3).

Procedures to Increase Pulmonary Blood Flow

There are many CCHDs in which obstruction of pulmonary blood flow (PBF) is the underlying etiology for systemic desaturation. The specific anatomic or physiologic issue causing the limited PBF varies considerably and, therefore, the approach to augment pulmonary blood flow is situation dependent. The different methods and approaches used to increase pulmonary blood flow are described in this section.

Balloon Pulmonary Valvuloplasty

Balloon pulmonary valvuloplasty (BPV) was first described by Kan in 1982[27] and is an effective strategy to increase pulmonary blood flow in patients with either isolated pulmonary valve stenosis or when found in combination in more complex congenital heart disease (Fig. 78.1*A, B*). Current indications for balloon pulmonary valvuloplasty include patients with either critical pulmonary stenosis (ductal-dependent pulmonary blood flow and/or severe right ventricular dysfunction) or in a patient with a peak instantaneous gradient of ≥40 mm Hg on echocardiography.[16] The procedure typically results in a significant reduction in the pressure gradient across the valve and carries very good mid- and late-term results.[11,59,63] A small number of patients will develop significant subvalvar gradient immediately following balloon pulmonary valvuloplasty secondary to significant right ventricular hypertrophy and infundibular narrowing. This temporary obstruction can be managed medically with increased right ventricular volume and beta blockers.[60] Balloon pulmonary valvuloplasty can also be performed in patients with tetralogy of Fallot when the predominant level of obstruction is at the valvar level. This is typically a palliative intervention to allow patients to mature and grow until a complete repair can be done at 4-6 months of age.

Pulmonary Valve Perforation With Balloon Pulmonary Valvuloplasty

Pulmonary atresia with intact ventricular septum is a right-sided obstructive lesion in which there is no antegrade

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TABLE 78.2 Common Named Cardiac Operations Performed in Infants

Named Surgery	Surgical Description	Purpose
Norwood	Anastomosis of PA to hypoplastic ascending aorta, arch augmentation	Create new "aorta" from pulmonary trunk and patch
Damus-Kaye-Stansel	Anastomosis of PA to ascending aorta	Combine great arteries for systemic flow to bypass subaortic obstruction
Blalock-Taussig shunt	Gore-Tex tube from subclavian artery to PA	Supply pulmonary blood flow
Sano shunt	Gore-Tex tube from the RV to PA	Supply pulmonary blood flow
Bidirectional Glenn	Anastomosis between SVC and PAs	Supply low-pressure pulmonary blood flow
Fontan	Anastomosis between IVC and PAs	Supply low-pressure pulmonary blood flow
Jatene	Arterial switch for d-transposition of the great arteries	Anatomical correction
Rastelli	VSD closure and RV-PA conduit placement	Create new "main pulmonary artery"

IVC, Inferior vena cava; PA, pulmonary artery; RV, right ventricle; SVC, superior vena cava; VSD, ventricular septal defect.

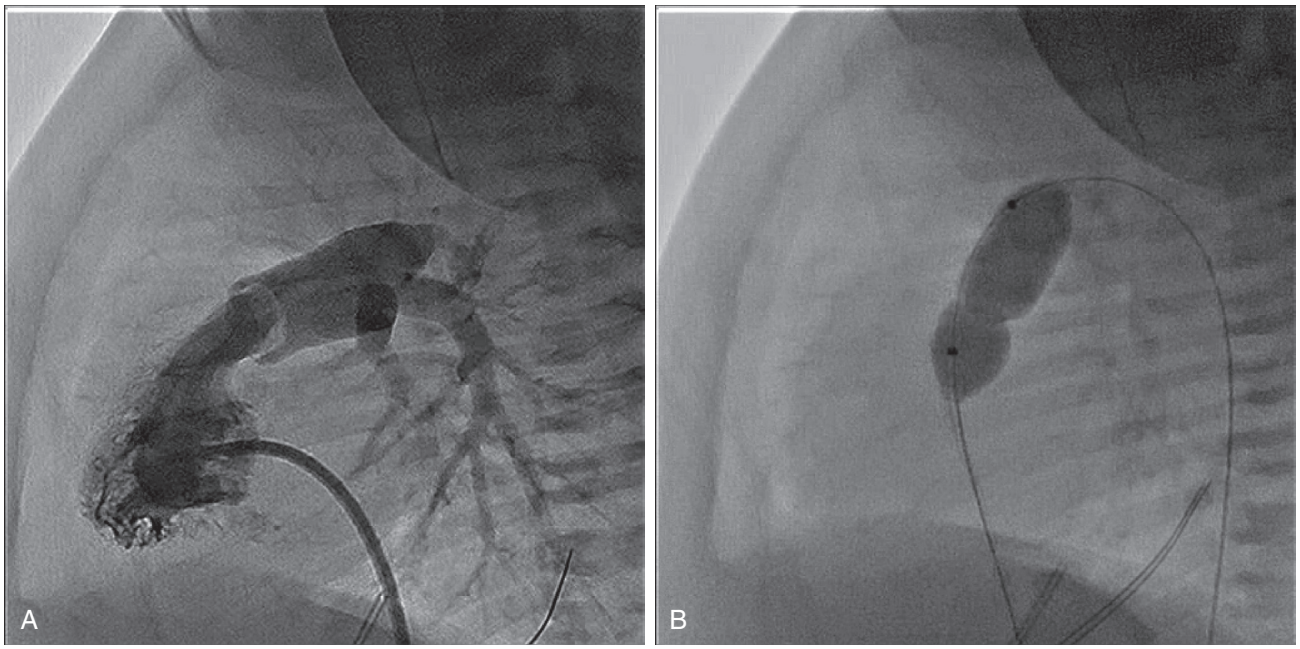
TABLE 78.3 Neonatal Cardiac Lesions and Typical Catheter-Based Therapy

Primary Problem	Hemodynamic Etiology	Defects	Intervention(s)	Result
Cyanosis	Atrial septal restriction	d-TGA with restrictive atrial septum	Balloon atrial septostomy	Improvement in atrial mixing and oxygen saturation
	Decreased pulmonary blood flow	Critical pulmonary stenosis Pulmonary atresia	Balloon pulmonary valvuloplasty Valve perforation and valvuloplasty	Improvement in pulmonary blood flow and oxygen saturation
		TOF	RVOT stenting PDA stenting	
		BT shunt occlusion (HLHS, TOF, TA, PA)	BT shunt balloon dilation and/or stenting	
Left-sided obstruction	Left ventricular outflow tract obstruction	Critical aortic stenosis	Balloon aortic valvuloplasty	Decrease left-sided obstruction
		Critical coarctation	Angioplasty/stenting of coarctation	
Decreased cardiac output	Pulmonary overcirculation causing congestive heart failure	Patent ductus arteriosus Atrial septal defect* Ventricular septal defect	Device closure*	Eliminate or decrease left-to-right shunt
Vascular obstruction	SVC syndrome	Typically iatrogenic	Angioplasty and/or stent*	Unobstructed flow

BT, Blalock-Taussig; HLHS, hypoplastic left heart syndrome; PA, pulmonary artery; PV, pulmonary vein; RVOT, right ventricular outflow tract; SV, single ventricle; SVC, superior vena cava; TA, tricuspid atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot.
*Only rarely performed in the neonatal period.

flow from the right ventricle, and pulmonary blood flow is entirely dependent on the PDA. Complete mixing occurs at the atrial level, and all blood is pumped from the left ventricle to the aorta. In this condition, neonates must be started on prostaglandins to maintain ductal patency immediately after birth. If the tricuspid valve and right ventricle are of adequate size, a biventricular repair may be considered. In these situations, patients will be referred to the catheterization laboratory to ensure the coronary arteries fill normally from the aorta and not the hypertensive right ventricle (i.e., not right ventricular–dependent coronary circulation). Pulmonary valve perforation with

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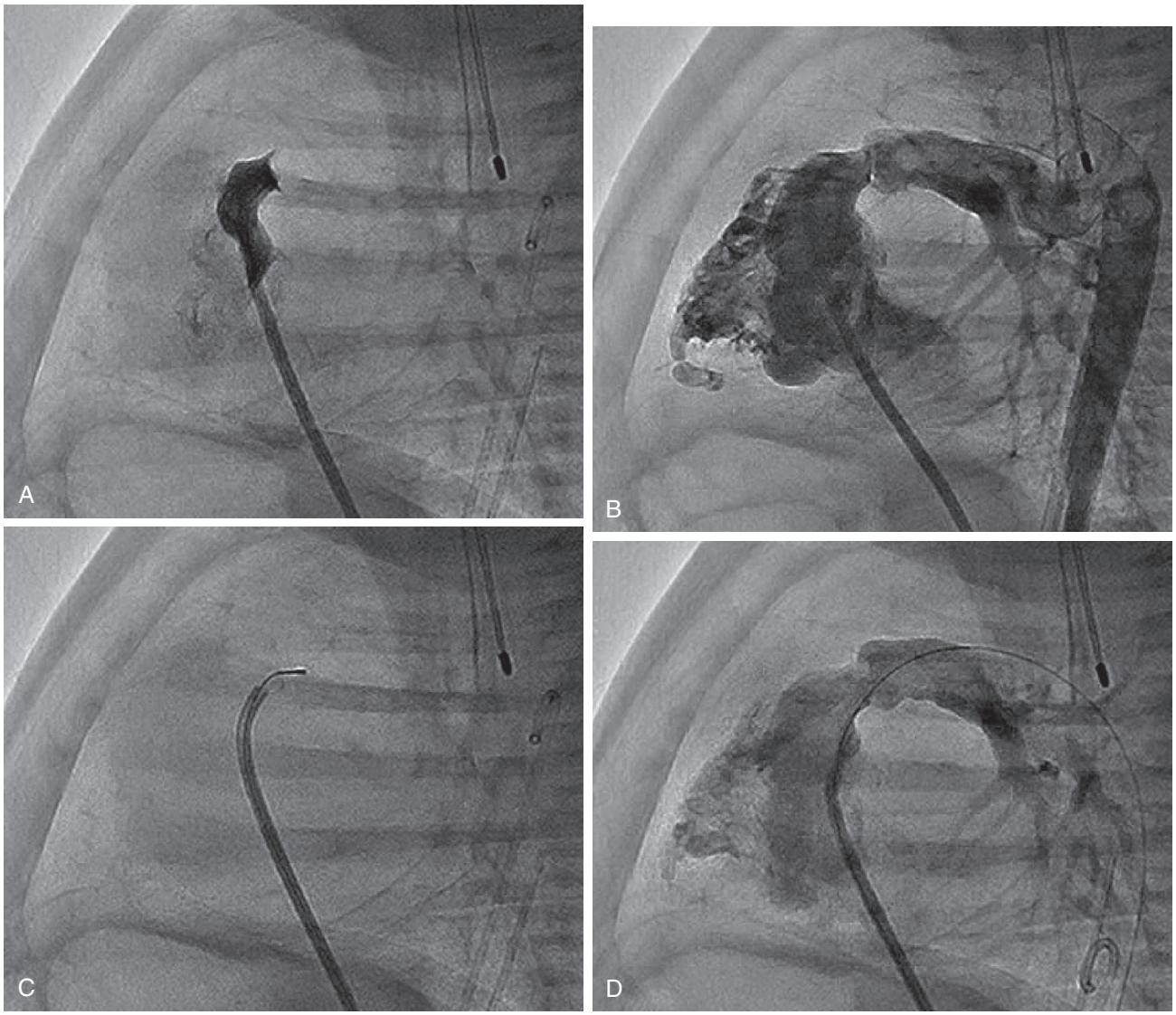
• **Fig. 78.1** Balloon pulmonary valvuloplasty in a neonate with critical pulmonary valve stenosis. A baseline lateral angiogram shows the stenotic and doming pulmonary valve **(A)**, which then undergoes balloon pulmonary valvuloplasty using a standard balloon **(B)**. During balloon inflation, a waist is seen at the level of the valve annulus.

balloon pulmonary valvuloplasty is indicated in patients with favorable anatomy (membranous atresia) without right ventricular–dependent coronary circulation. This intervention was first reported by Latson in 1991.[31] The technique involves advancing a guidance catheter antegrade from the femoral vein, across the tricuspid valve, and into position directly beneath the atretic pulmonary valve. The optimal target site for perforation is then defined by both right ventricle angiography and aortic angiography, which fills the main pulmonary artery via the PDA. Currently, the most commonly performed method to perforate the membrane is to advance a small radiofrequency (RF) wire within the guide catheter into contact with the membrane. The RF wire delivers a focused energy pulse at the tip to precisely "burn" a small hole in the pulmonary valve membrane. The RF wire is passed through the pulmonary valve membrane into the main pulmonary artery. Perforation can also be accomplished by using a small coronary wire, but the RF wire approach is considered safer and more controlled. Once the valve is perforated and crossed, balloon pulmonary valvuloplasty is performed (Fig. 78.2*A-D*). This procedure can result in improved antegrade flow from the right ventricle to the pulmonary artery, often allowing for the eventual discontinuation of prostaglandins. This process can sometimes take many weeks before prostaglandins can be discontinued and months before growth of the annulus and entire right ventricular outflow tract is observed. It is not uncommon for patients to require repeat balloon pulmonary valvuloplasty in the first 6 months. If repeat balloon pulmonary valvuloplasty does not result in adequate antegrade pulmonary blood flow, surgical intervention is typically required.[35]

Right Ventricular Outflow Tract Stenting

Severe obstruction of the right ventricular outflow tract (RVOT) can be seen in patients with tetralogy of Fallot and double outlet right ventricle leading to severe cyanosis. Some patients will undergo a complete surgical repair in the neonatal period depending on the patient's weight, size of branch pulmonary arteries, and extracardiac medical issues. Certain centers will perform aortopulmonary shunts (see below) for cyanotic patients with small branch pulmonary arteries and bring them back for complete surgical repair at 4-6 months of age. Balloon pulmonary valvuloplasty is typically not effective in this anatomy given the severe subvalvular obstruction across the right ventricular outflow tract. Over the past 10 years, centers have started palliating these patients by implanting stents across the right ventricular outflow tract.[12,20] During the procedure, the RVOT and main pulmonary artery are imaged using angiography. The RVOT is then crossed with a catheter, and wire position is established to guide the procedure. A stent is selected based on the size of the right ventricular outflow tract. The stent is advanced over the wire and typically through a long introducer sheath until it is positioned across the RVOT. The stent is deployed within the RVOT and follow-up angiography is then performed to assess the adequacy of antegrade flow through the implanted stent. Multiple stents may need to be placed depending on the anatomy of the right ventricular outflow tract. Most patients maintained on prostaglandins can be weaned off the medication following stent implantation within the right ventricular outflow tract. In premature or small neonates or those with vascular access issues, hybrid per-ventricular stenting of the RVOT, whereby

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• **Fig. 78.2** Pulmonary valve perforation in a neonate with pulmonary atresia and intact ventricular septum. The lateral view of the right ventricular outflow tract angiogram confirms the diagnosis **(A)**. Simultaneous right ventricular and aortic angiogram show both sides of the pulmonary valve plate **(B)**. The valve is perforated with a radiofrequency wire **(C)**, and subsequent balloon valvuloplasty results in good antegrade flow through the right ventricular outflow tract **(D)**.

the pediatric heart surgeon places the sheath directly into the right ventricle via a small sub-xiphoid incision, allows effective palliation in this challenging population.[10] In either approach, these stents are removed at the time of surgical repair, which is ultimately delayed to allow for growth in both the patient and branch pulmonary arteries.[55]

Surgical Opening of the Right Ventricular Outflow Tract

In neonates that are not candidates for a complete surgical repair or palliation with balloon angioplasty/stenting of the RVOT, either percutaneously or using hybrid techniques, an open surgical procedure can be used. The operation is performed via a median sternotomy on cardiopulmonary bypass. The goal of the procedure is complete relief of right ventricular outflow tract obstruction whereby the actual technique used depends on the level of obstruction—valvar, supravalvar, or subvalvar—and can range from a simple pulmonary valvotomy or valvectomy to a complete transannular patch opening of the subvalvar, pulmonary valve, and supravalvar regions. The resultant pulmonary insufficiency is usually very well tolerated.

Implantation of a Stent in the Ductus Arteriosus

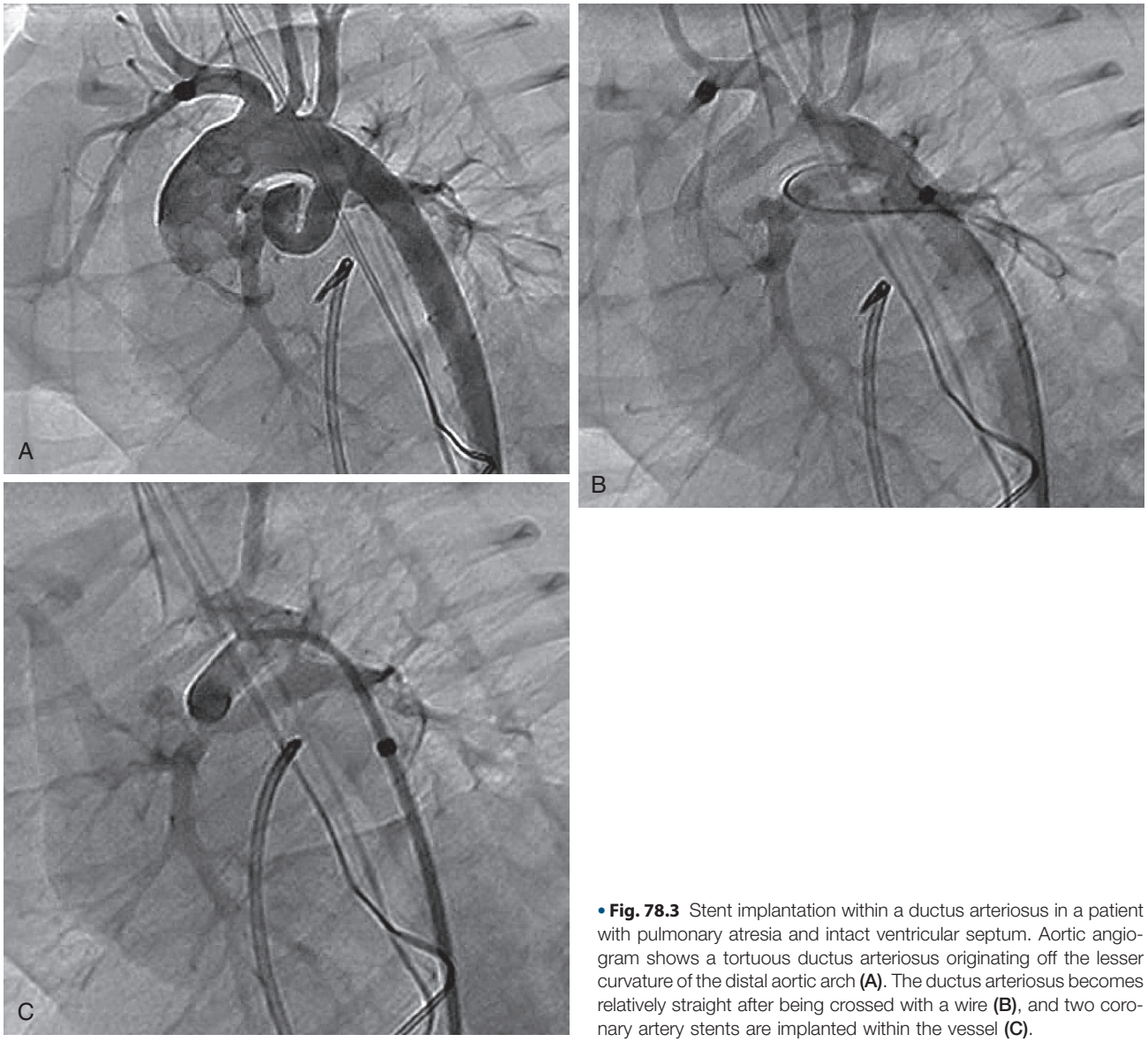
There are many congenital heart defects in which pulmonary blood flow is dependent on flow via the ductus arteriosus. The most common of these lesions are the more severe cases of tetralogy of Fallot. Additional congenital heart lesions where pulmonary blood flow is dependent on ductal arterial flow includes pulmonary atresia with and without a

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VSD, double outlet right ventricle with pulmonary atresia, and some forms of tricuspid atresia. The vast majority of these patients are typically treated with surgical palliation, including an aortopulmonary shunt (e.g., modified Blalock-Taussig shunt). Similar to RVOT stenting, advancements in catheter-based technology and techniques have allowed for some of these patients to be palliated by implantation of a stent in the ductus arteriosus. The procedure is typically performed retrograde from the femoral artery or via a vessel off the aortic arch (carotid or axillary artery). The procedure may also be accomplished antegrade from the femoral vein, particularly when there is antegrade flow through the right ventricular outflow tract.[58] The prostaglandin infusion is usually stopped a few hours before the anticipated start of the procedure to allow for some constriction of the ductus arteriosus to occur. Prostaglandins are kept in line in case of severe ductal spasm causing profound cyanosis. Angiography is performed to delineate the length and size of the ductus arteriosus. A guide wire is used to carefully cross the often tortuous ductus arteriosus and used for procedural guidance. An appropriately sized stent is then advanced over the wire and deployed across the ductus arteriosus (Fig. 78.3*A-C*). This interventional palliation procedure can last many months until the patient can undergo complete surgical repair.[53]

Systemic to Pulmonary Artery Shunts

The ability to augment pulmonary blood flow by a surgically created shunt between the aorta, or one of its branches, and the central pulmonary arteries has a long history dating back to 1945 with the introduction of the Blalock-Taussig (BT) shunt. The classic BT shunt was performed using the divided subclavian artery as an end-to-side anastomosis to the pulmonary artery. Soon other shunt techniques were introduced, such as the Potts shunt, a direct anastomosis between the descending aorta and the left pulmonary artery,



• **Fig. 78.3** Stent implantation within a ductus arteriosus in a patient with pulmonary atresia and intact ventricular septum. Aortic angiogram shows a tortuous ductus arteriosus originating off the lesser curvature of the distal aortic arch **(A)**. The ductus arteriosus becomes relatively straight after being crossed with a wire **(B)**, and two coronary artery stents are implanted within the vessel **(C)**.

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and the Waterston shunt, a direct anastomosis between the ascending aorta and the right pulmonary artery. These techniques had in common a shunt that not only augmented pulmonary blood flow but could palliate over a long period of time because of the growth potential of the native tissue construction of the shunt. These shunt techniques are essentially obsolete today for two reasons: 1) with growth of the shunt there is a lack of control over the amount of pulmonary blood flow creating the risk of pulmonary overcirculation, pulmonary vascular disease, and pulmonary hypertension; and 2) the advent of rapid second-stage procedures for successful infant complete repair for two ventricle anatomies or the use of subsequent cavopulmonary shunts for single ventricle anatomies. Therefore, today the most common palliative, neonatal surgical shunt is the modified BT shunt whereby a prosthetic graft is anastomosed proximally end-to-side to the innominate artery or ascending aorta and distally end-to-side to the central pulmonary artery, with flow being controlled by the diameter of the graft chosen, typically 3-4 mm in a neonate.

Procedures to Decrease Pulmonary Blood Flow

In the previous section, the focus was on cyanotic CHD in which pulmonary blood flow is restricted. The conditions described in that section usually tend to make intuitive sense since less pulmonary blood flow is easily reconciled with cyanosis and hypoxia. However, there are forms of cyanotic heart disease, particularly admixture lesions, in which there is often excessive pulmonary blood flow and arterial saturations are often only mildly decreased.

Admixture lesions are forms of congenital heart disease in which blood from the systemic and pulmonary veins mix within the heart via a single or multiple defects (predominantly at the atrial level). When blood is completely mixed within the heart, then arterial saturation is dependent on the size of the left-to-right shunt or amount of pulmonary blood flow and whether or not there is preferential streaming of saturated or desaturated blood to the aorta. Variations in the size and location of the outflow tracts determine where the "mixed" blood is ejected. Patients with admixture lesions and unrestricted pulmonary blood flow develop pulmonary overcirculation which can result in respiratory distress/failure, difficulty feeding, failure to thrive, and potentially necrotizing enterocolitis. If left unabated, excessive pulmonary blood flow (PBF) can lead to changes in the pulmonary arterioles causing irreversible elevation of the pulmonary vascular resistance. This is of particular importance for single ventricle patients as elevated pulmonary vascular resistance can make the patient ineligible for eventual Fontan surgical palliation. To prevent these problems from developing, patients with admixture lesions and excessive PBF require interventions to limit or control the amount of flow to the lungs, often as part of a series of staged palliation surgeries for functional single ventricle anatomy and physiology.

Pulmonary Artery Banding

The current mantra in congenital heart surgery is early complete repair due to improved operative techniques as well as improved peri-operative management, resulting in excellent outcomes even with complex neonatal CHD. Therefore, the tendency is away from palliating babies to allow for growth or an older age before two ventricle repair is considered. Nevertheless, there are certain forms of CHD in which a palliative step, such as pulmonary artery banding to restrict pulmonary blood flow is necessary before complete repair is attempted. Examples include anatomic defects that continue to carry a higher risk of suboptimal early repair, such as multiple apical ventricular septal defects or patients with otherwise repairable anomalies, but have significant associated co-morbidities, such as prematurity or intracerebral hemorrhage. In these situations, a pulmonary artery band can be an effective palliative technique to control pulmonary blood flow. Also, pulmonary banding is frequently used as a first-stage procedure in the management of certain single ventricle physiologies, such as tricuspid atresia or double inlet left ventricle. The procedure can be performed via a thoracotomy or sternotomy depending on the anatomy, planned concomitant procedures, and surgeon preference. Technical aspects include creating a space between the aorta and main pulmonary artery through which a nondistensible band of prosthetic material is passed as a ring around the main pulmonary artery. The band is located between the valve and the origin of the branch pulmonary arteries. The band is then tightened to the desired effect again based on the underlying anatomy, physiology, and planned next stage. In general, the goals of a pulmonary artery band are to improve the balance of systemic to pulmonary artery circulation and to protect the distal pulmonary vasculature from unrestricted pressure and flow. Achievement of balanced flow guided by the changes in systemic oxygen saturation with tightening, and the pressure restriction is demonstrated by reduction in the pulmonary artery pressure distal to the band. In patients without a main pulmonary artery, such as truncus arteriosus, and those in which complete neonatal repair is not possible, separate banding of the left and right branch pulmonary arteries is possible. Recovery from pulmonary artery banding is usually fairly quick and patients are often easier to manage once the degree of PBF is appropriately restricted.

Procedures to Increase Mixing of Systemic and Pulmonary Venous Blood

Certain forms of cyanotic congenital heart disease are dependent on adequate intracardiac mixing of blood to maintain adequate oxygen saturations in the neonatal period. This includes conditions with transposition physiology and most admixture lesions. When inadequate mixing occurs in patients with admixture lesions, disproportionate streaming of the deoxygenated blood to the systemic circulation results

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TABLE 78.4 Congenital Heart Lesions That May Require Neonatal Atrial Septostomy

Diagnosis	Reason for Intervention	Flow after Intervention	Special Considerations
d-Transposition of great arteries	Cyanosis	Bidirectional	
Tricuspid atresia	Decreased cardiac output	Right-to-left	If late—may need blade septostomy or stent placement
Ebstein anomaly	Decreased cardiac output	Right-to-left	
Total anomalous pulmonary venous return	Decreased cardiac output	Right-to-left	
Hypoplastic left heart syndrome	Pulmonary edema	Left-to-right	If septum is thick—may need septostomy or stent placement

in severe cyanosis. To demonstrate this, consider hypoplastic left heart syndrome (HLHS), in which the left-sided structures are not adequate to support a full cardiac output. To provide the systemic circulation with adequate quantities of oxygenated blood, there must be unrestricted flow from the left atrium to the aorta (left atrium→right atrium→right ventricle→pulmonary artery→ductus arteriosus→aorta). Thus, unrestricted atrial communication is necessary for both adequate oxygenation and maintenance of cardiac output. Furthermore, without unrestrictive atrial communication, left atrial hypertension develops because of the inability of pulmonary venous return to unload. This leads to pulmonary venous hypertension and subsequent pulmonary edema with pulmonary artery hypertension. This can be devastating for patients with single ventricle admixture lesions.

In the cyanotic condition d-transposition of the great arteries (D-TGA), the pulmonary and systemic circulations are maintained in parallel as opposed to in series. Oxygenated blood is pumped from the right ventricle to the lungs and deoxygenated blood is pumped from the left ventricle to the aorta. Unlike admixture lesions, cardiac output to the systemic circulation is normal and is not dependent on atrial level shunting. Similarly, though, if there is inadequate mixing of blood predominantly at the atrial level, the resulting physiology is not compatible with survival because of the development of severe hypoxemia. In the early newborn period, for a D-TGA patient with restrictive or intact atrial septum, the patent ductus arteriosus provides the minimal mixing necessary to maintain arterial saturations still compatible with life. However, as the ductus arteriosus constricts, the two circulations have almost no communication and severe prohibitive cyanosis results. For these patients, it is crucial to begin a prostaglandin infusion immediately after birth when the diagnosis is known or suspected. In these situations, despite maintenance of a PDA, severe cyanosis results as the ductus arteriosus alone is not an adequate source of mixing, and atrial opening is required.

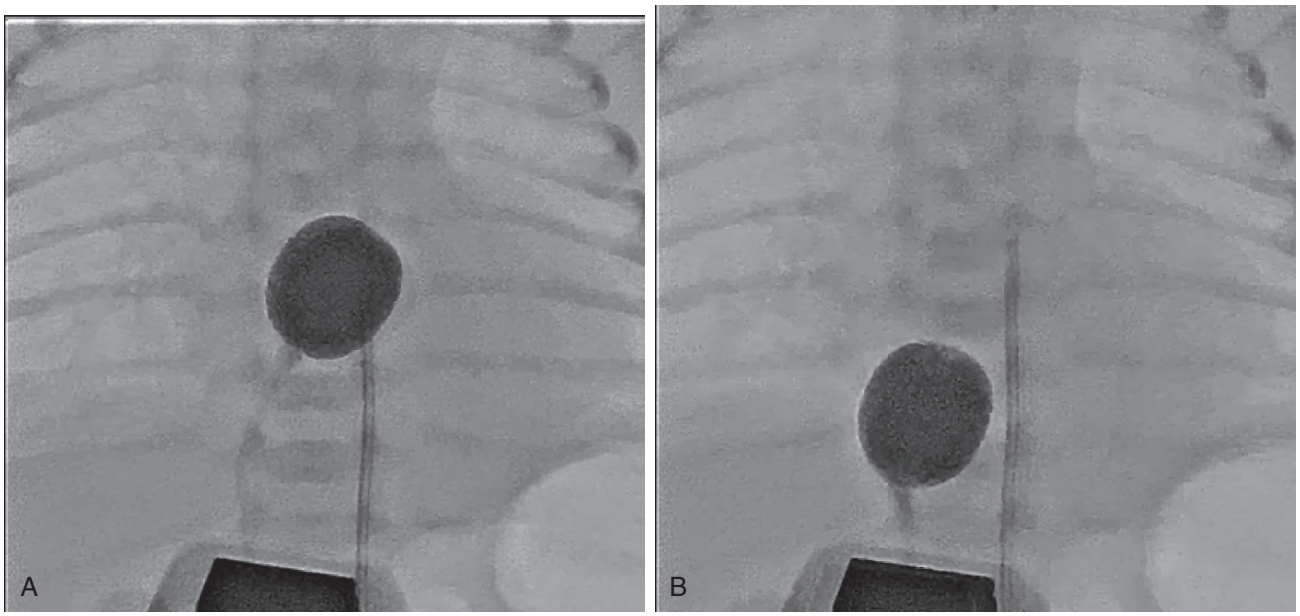
In summary, all admixture lesions and conditions with transposition physiology require adequate mixing at the atrial level for survival in the neonatal period. In some cases, this involves the creation of an atrial level communication, and in other cases, enlargement of a restrictive existing communication (patent foramen ovale [PFO] or ASD) is required. In this section, we describe current approaches available to provide unrestrictive atrial level communication for both admixture lesions and conditions with transposition physiology (Table 78.4).

Balloon Atrial Septostomy

Balloon atrial septostomy (BAS) is the standard method for enlarging an existing atrial communication when there is inadequate mixing. The most common indication is d-transposition of the great arteries with restrictive atrial septum, which occurs in one-third of neonates with this condition.[5] Following TGA, the second-most common indication for balloon atrial septostomy occurs in the single ventricle admixture lesion HLHS. The balloon atrial septostomy procedure has been performed for more than 50 years and remains the optimal approach in most cases because of the relative safety and efficacy when performed by experienced operators.

The standard BAS procedure can be done either in the catheterization laboratory or bedside in the neonatal intensive care unit. Procedural guidance is typically provided by fluoroscopy, echocardiography, or combination of both. Performing the procedure in the catheterization laboratory allows for additional procedures to be performed (i.e., coronary angiography) and allows easy access to additional catheterization equipment should the procedure be technically difficult. Bedside BAS under echocardiographic guidance has been shown to be a safe and more cost-effective approach in patients with d-transposition of the great arteries.[67] The procedure can be performed via femoral venous access or by taking over the umbilical vein catheter. The BAS catheter is advanced under fluoroscopic or echocardiographic guidance until it is seen to be in the left atrium across an existing PFO/ASD (Fig. 78.4*A, B*). The balloon is inflated in the left atrium and a quick, forceful, yet controlled, "jerk" is performed to pull the inflated balloon through the existing communication. The septum tears during this process,

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• **Fig. 78.4** Still fluoroscopic images of a balloon atrial septostomy with transthoracic echocardiographic guidance in a child with d-transposition of the great arteries and restrictive atrial septum. The septostomy balloon is inflated within the left atrium **(A)** and pulled across the atrial septum into the right atrium/inferior vena cava **(B)**.

resulting in a larger atrial communication and hopefully unrestricted atrial shunting.

In the event of a thick septum that does not tear, repeat BAS is not advised and a different approach must be sought for the patient. If the patient is profoundly hypoxemic before and during the procedure, it is not uncommon to develop pulmonary hypertension or maintain high pulmonary vascular resistance (PVR). In this setting, pulmonary blood flow is restricted and does not allow for enough of the mixed blood to be pumped to the lung to receive oxygen. Profound cyanosis may persist despite echocardiographic evidence of an unrestrictive atrial communication. In these situations, patients should be started on inhaled nitric oxide and allowed time for their pulmonary vascular resistance to drop, which results in improved arterial saturations.

Other Atrial Septostomy Techniques

Balloon atrial septostomy may not be effective if the atrial septum is thick or completely intact. If there is an existing communication between the atria, this can be crossed and made larger with other transcatheter interventions. If no atrial communication exists, the atrial septum may be crossed using the radiofrequency wire (described in the RVOT perforation section), a radioperforation transseptal needle, or with a standard transseptal needle.[9,23,32] Once the thick or intact septum is perforated, a guidewire can then be passed through the perforation and positioned into a left-sided pulmonary vein. At this point, there are multiple options that the operator can choose for opening the atrial septum, including static balloon septoplasty, blade atrial septostomy, and atrial septal stenting.

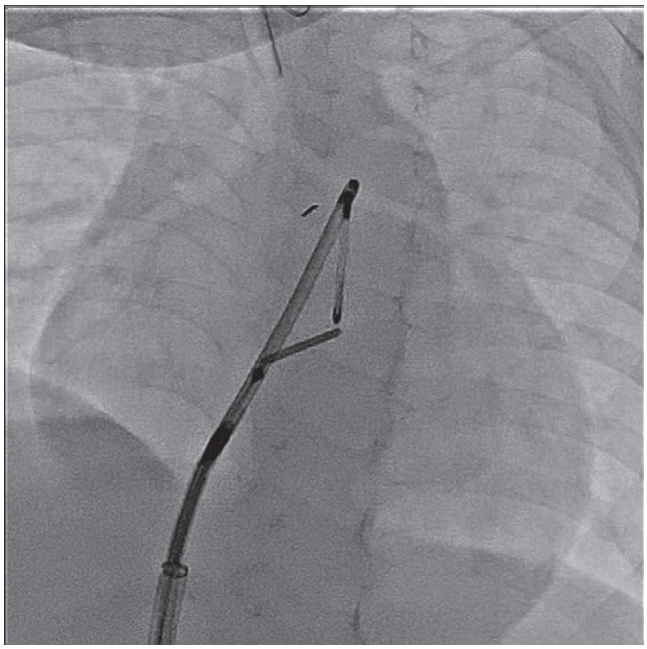
Static Balloon Septoplasty

Static balloon atrial septoplasty involves inflating a balloon that is stretched across the newly created perforation. As opposed to a standard BAS, a static BAS is repeated several times with progressively larger balloons. Static BAS is rarely effective for a sustained period of time if only standard angioplasty balloons are utilized. Cutting balloon septoplasty is much more effective at widening a newly created perforation and producing a more sustained outcome. Cutting balloons have four small atherotomes (microsurgical blades) attached to the longitudinal surfaces positioned 90 degrees to each other. These are designed to score the tissue against which it is in contact during inflation. The balloon is deflated and rotated/repositioned, and additional inflations are performed to create more score lines. The opening can then be further dilated with larger diameter static balloons, which tears the tissue along the multiple scored cut lines.

Blade Atrial Septostomy

The Park blade septostomy catheter is a catheter with a retractable blade at its distal end (Fig. 78.5). Once the atrial septum has been crossed, typically a long sheath is advanced over the wire into the left atrium. The blade septostomy catheter is advanced out the tip of the sheath, which is withdrawn into the right atrium. The blade is then pulled back through the septum, slicing the atrial septal tissue along the way. The blade produces a deeper slice in the atrial tissue compared to the cutting balloons, so it is important that the septum is crossed at a fairly central point. After blade septostomy, the cut hole can then be dilated with progressively larger static balloons.

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• **Fig. 78.5** A blade septostomy performed in a patient with tricuspid atresia who underwent banding of the main pulmonary artery. The procedure involves opening a retractable blade on the end of a catheter and making a small slice in the atrial septum. This is followed by a balloon septostomy or septoplasty.

Atrial Septal Stenting

In very small patients with thick and/or intact atrial septa, cutting and static BAS are often ineffective and the blade septostomy unsafe, as the blade is too large for the small left atrium. In these situations, an atrial communication is best created by implanting a premounted stent across the atrial septum. After perforating, crossing the atrial septum, and gaining stable wire position, a long sheath is passed into the left atrium. A premounted stent (typically 6-8 mm in diameter) is advanced through the delivery sheath and over the guidewire until half of it is seen in the left atrium using fluoroscopy and transesophageal echocardiography guidance. The delivery sheath is slowly retracted and efforts are made to ensure positioning is balanced on both sides. Once this is confirmed, the balloon is inflated and the stent is deployed (Fig. 78.6*A-C*). The stent is resected with the atrial septectomy procedure during a subsequent planned surgical operation.

Atrial Septectomy

A hybrid approach to opening the atrial septum is sometimes an option whereby the surgeon places a sheath directly into the atrium, without the use of cardiopulmonary bypass, through which the interventional cardiologist can perform the atrial septal balloon or stenting techniques previously described. In newborns that are not candidates for hybrid or percutaneous transcatheter strategies to open the atrial septum, a surgical atrial septectomy can be performed. The operation is performed through a median sternotomy on cardiopulmonary bypass. The goal of the operation is complete excision of the atrial septum creating a reliable and durable opening. Surgical atrial septectomy in the neonate is almost exclusively performed on patients with single ventricle anatomy and physiology.[23]

Acyanotic Congenital Heart Conditions

Acyanotic forms of congenital heart disease represent a much more straightforward class compared to the cyanotic conditions discussed in the prior sections. Acyanotic conditions that require interventions or medical management in the neonatal period are typically those that involve outflow obstruction. As such, the management approaches tend to be more standardized and consistent, but patient comorbidity and clinical status can necessitate the use of novel methods of treatment.

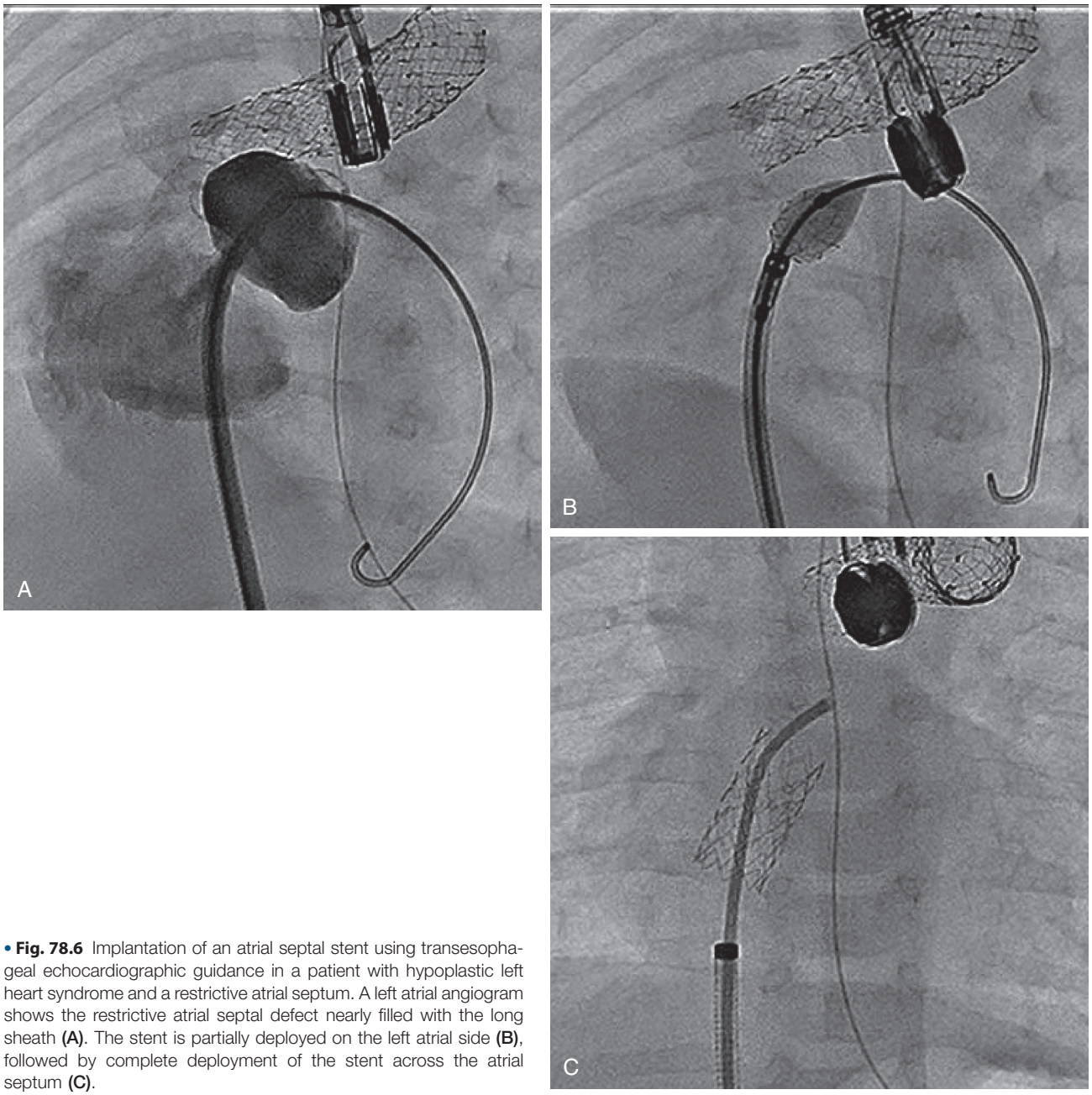
Left-Sided Obstruction

Patients born with obstruction on the left side of the heart (e.g., valvar aortic stenosis, interrupted aortic arch, coarctation of the aorta) are often asymptomatic in the immediate newborn period. The oxygen saturation might be normal during the screening pulse oximetry if only checked in the upper extremity. These patients may appear well clinically and have been discharged to home. However, as the ductus arteriosus closes, systemic cardiac output is dramatically reduced and the neonate will present in shock and with end organ dysfunction. Although the incidence of undiagnosed postnatal presentation has dramatically dropped with contemporary prenatal and postnatal congenital heart disease screening, studies have shown that the prenatal detection rate for isolated aortic arch obstruction still hovers around 20%-30%.[51] Therefore, there continues to be a significant number of patients who will present postnatally every year, and the neonatologist will need continued vigilance for these patients. The approaches to dealing with these left-sided obstruction lesions are discussed in the following sections.

Balloon Aortic Valvuloplasty

Balloon aortic valvuloplasty is performed in the newborn period in patients who present with critical or severe valvar aortic stenosis. The first reported balloon aortic valvuloplasty was reported in 1983 by Lababidi, and the procedure has been markedly improved upon over the last few decades, predominantly related to the availability of a compliant balloon with very small crossing profiles (down to 3 French).[64] Recommendations for limiting the balloon diameter:annulus ratio to 80%-100% has greatly improved the procedural results, in which relief of obstruction is obtained without causing severe degrees of valvar regurgitation.[7,38] However, the procedure itself can be technically difficult and has a much higher risk profile in the neonatal population, and balloon aortic valvuloplasty should only be performed by experienced operators and with surgical backup nearby. The condition is most commonly approached retrograde

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• **Fig. 78.6** Implantation of an atrial septal stent using transesophageal echocardiographic guidance in a patient with hypoplastic left heart syndrome and a restrictive atrial septum. A left atrial angiogram shows the restrictive atrial septal defect nearly filled with the long sheath **(A)**. The stent is partially deployed on the left atrial side **(B)**, followed by complete deployment of the stent across the atrial septum **(C)**.

from the femoral artery but can also be performed via the femoral vein if an atrial communication is present. In smaller patients, the procedure can be performed via a surgical cut-down or direct percutaneous access of the common carotid artery.[46] A smaller balloon:annulus ratio can be performed first, with progressively larger balloons if a significant residual pressure gradient remains. Multiple studies have defined a successful neonatal balloon aortic valvuloplasty as a reduced aortic valve gradient ≤35 mm Hg with no worsening aortic valve insufficiency.[7,50,61]

Surgical Aortic Valve Repair or Replacement

In newborns with aortic valve stenosis not amenable to transcatheter techniques, surgical repair or replacement is indicated. These operations are performed via a median sternotomy on cardiopulmonary bypass with aortic cross-clamping, allowing direct visualization of the aortic valve. In the newborn with isolated aortic valve stenosis, the most common anatomic construct is a bicuspid or unicuspid valve with fused commissures. In this setting, a controlled commissurotomy can effectively increase the valve orifice without significant insufficiency. Other surgical repair techniques can be utilized depending on the anatomy encountered.

For neonates with aortic valves that cannot be repaired, replacement options are limited and suboptimal, because there are no bioprosthetic valves manufactured small enough to fit a neonate, and even if there were, they cannot grow to match

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the rapid somatic growth of an infant. In these situations, or in infants with combined aortic valvar and left ventricular outflow tract (LVOT) obstruction, the only option is aortic root replacement with either a cryopreserved human cadaveric homograft or the patient's own pulmonary valve as an autograft (Ross procedure). The disadvantage of a homograft includes the known risk of early calcification especially in the neonate, leading to valve dysfunction, the lack of growth potential, and the increased risk of repeat coronary artery reimplantation. Therefore, the Ross procedure has become the replacement option of choice in neonates.[14,39] The principles of the operation include reconstructing the LVOT and replacing the aortic valve with the child's own living tissue—a pulmonary root autograft (rim of right ventricular muscle, valve, and the main pulmonary artery), reimplantation of the coronary arteries, and replacement of the pulmonary valve with a pulmonary valve homograft. In theory, this operation exchanges aortic valve disease for pulmonary valve disease with the reasoning that repeat interventions on the aortic valve carry increasing risk, while repeat interventions on the pulmonary valve are not only less frequent but less risky.

Coarctation of the Aorta

Coarctation of the aorta is often discovered on prenatal ultrasound and with early postnatal screening. However, as stated above, many cases are still missed even when standard prenatal care is provided. The cases of coarctation detected prenatally are typically the more severe forms, and it is usually recommended that these mothers deliver these infants at centers where neonatal and surgical treatment can be provided. For cases in which prenatal detection has not occurred, postnatal symptoms develop with the advent of ductus arteriosus closure. These symptoms include poor feeding, respiratory distress, and eventually shock-like appearance because of low cardiac output. The postnatal diagnosis is typically confirmed using surface echocardiogram, which typically shows isthmus hypoplasia (periductal area), a posterior shelf causing flow acceleration on Doppler interrogation, and often varying degrees of transverse arch hypoplasia. The severity and even presence of coarctation of the aorta can often not be fully appreciated in the setting of a moderate- or large-sized patent ductus arteriosus, so it is helpful to get echocardiographic confirmation as soon as possible when a prostaglandin infusion is started. However, in cases of severe low cardiac output, the initiation of prostaglandins should not be withheld to allow time to obtain the echocardiogram. Coarctation of the aorta that presents in the neonatal period is often long segment and less likely to be discrete. Surgical repair of native coarctation presenting in the neonatal period remains the standard treatment of choice. Interventional therapies can be considered in certain situations, in which surgery is thought to be too high risk and an interim palliative procedure is required.

Surgical Repair of Coarctation

The most common form of neonatal coarctation is often referred to as "juxtaductal" coarctation, which manifests as a discrete area of aortic narrowing at the junction of the ductus arteriosus to the aortic isthmus. It occurs within the first few days or weeks of life as the constrictive process that normally closes the ductus arteriosus extends into the adjacent aortic tissue leading to the clinical manifestations previously described. In this setting, the typical operation is a coarctation segment resection with a primary end-to-end anastomosis of native aortic tissue. This operation is performed via a thoracotomy without cardiopulmonary bypass. The principles of the operation include division of the ductus arteriosus, complete resection of the coarctation segment of the aorta and any adjacent ductal tissue, and mobilization of the proximal and distal segments of aorta, establishing a tension free end-to-end anastomosis. Sometimes the proximal opening needs to be extended into the undersurface of the distal aortic arch to enlarge that segment, hence the term extended end-to-end anastomosis. The benefits of this operation include complete relief of obstruction, and growable and durable repair, at very low risk. The potential downsides of the operation include inability to address any transverse aortic arch hypoplasia as well as a circumferential aortic suture line that may develop resistant scar tissue leading to recurrent stenosis at this site.

The other form of neonatal coarctation is hypoplasia of the entire aortic arch. This is repaired via a median sternotomy on cardiopulmonary bypass, allowing access to the entire aortic arch. The typical reconstruction includes division of the ductus arteriosus, resection of ductal tissue, and long segment patch augmentation of the entire aortic arch from distal ascending aorta to mid-descending thoracic aorta. The patch augmentation leaves a posterior wall of native aortic tissue that allows growth of the reconstructed aorta.

Transcatheter Treatment of Coarctation

Transcatheter therapies for neonatal coarctation are typically performed when definitive surgical repair is deferred because of patient comorbidities. The most common reason for intervention is a patient presenting in shock because of ductal closure in whom the ductus arteriosus cannot be opened or cannot be opened enough to allow for effective resuscitation and resolution of end organ dysfunction.[52] In these situations, the coarctation is treated with balloon angioplasty, during which a balloon is inflated across the lesion to provide temporary relief of the obstruction and resuscitation of end organs until eventual surgical correction can be performed. The most common acute complication associated with balloon angioplasty is femoral arterial injury. Long-term complications of balloon coarctation angioplasty that does not end up needing surgical repair include pseudoaneurysm formation and recurrent coarctation. Recurrent coarctation of the aorta following surgery is often treated in the catheterization laboratory with balloon angioplasty and/or implantation of a stent.[6,17] Implantation of a stent across a neonatal coarctation lesion is rarely performed, and usually only when palliative angioplasty alone does not open the obstructed area adequately. The use of primary stenting in the neonatal period is limited by the size of introducer sheath required to implant the stent

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via the femoral artery. This limitation can be overcome by using a hybrid surgical approach via a cut-down on the carotid artery or percutaneously via direct carotid access. Work is currently underway to develop bioresorbable stents that could be implanted in the neonatal period, dissolve over a period of 6-18 months, and then be stented again with larger stents, potentially obviating the need for surgical repair.[22]

Pulmonary Artery Stenosis

Isolated branch pulmonary artery stenosis outside of the commonly encountered peripheral pulmonic stenosis (PPS) is rarely encountered in the neonatal period. The most common cause is due to constriction of the proximal left pulmonary artery following ductus arteriosus closure. In severe cases, the left pulmonary artery can become completely obstructed or isolated if not treated early. Moderate lesions can typically be treated via balloon angioplasty, but severe lesions often require stent implantation for a sustained result. Although there are stents that can be placed in the neonate, many of them cannot be dilated to the size of an adult pulmonary artery. As a result, these stents are placed as a palliative step when future surgical intervention is anticipated. At the time of surgical intervention, these small stents can either be surgically removed or transected, allowing for enlargement of the vessel. Studies have demonstrated that some of these stents may be fractured with high pressure balloons or "unzipped," but this is highly dependent on the type of stent used.[40,57] Similar to neonatal stenting of aortic coarctation, bioresorbable stents may prove to be a useful therapeutic option in this patient population.[37]

Treatment of Patent Ductus Arteriosus

A patent ductus arteriosus is commonly encountered in the premature neonate. Large PDAs can result in significant left-to-right shunting with medical consequences, including respiratory failure, renal insufficiency, and feeding intolerance. The management of hemodynamically significant PDAs in the neonatal period, particularly the premature and extreme premature population, is controversial and very institutional and provider dependent. Longstanding methods for PDA closure include medical therapy with prostaglandin inhibitors and surgical ligation. Medical closure of PDA is covered extensively in other chapters (Chapter 74), so will not be addressed in this section. Surgical closure has been the gold standard for over 60 years and remains the standard approach when medical therapy fails. This is performed via posterolateral thoracotomy, and typically a clip is placed on the PDA vs. suture ligation and division. Surgical PDA ligation is essentially 100% effective and is typically performed safely when done by experienced operators. However, the procedure is not without risk, and complications include vocal cord paralysis, pneumothorax, diaphragm paralysis, and postligation cardiac syndrome. Much of the morbidity and mortality of PDA surgical ligation is related to the preoperative clinical status of the neonate and, therefore, the timing of when patients are referred for surgical ligation is crucial.

Over the past 5 years, many institutions have started pursuing transcatheter approaches for neonatal PDA closure using off-label devices approved for other vascular occlusion indications. Transcatheter PDA closure in older infants and children with stainless steel coils and nitinol-based devices has been performed since the 1970s with great success. As a result, PDA surgical ligation outside of the neonatal population is almost never performed. The unique neonatal ductal anatomy and small patient size have limited the occlusion of neonatal PDAs with traditional FDA-approved devices. However, the development of smaller interventional devices and delivery catheters has now allowed for safe transcatheter occlusion of the ductus arteriosus in premature neonates.[33,56,66] Although a learning curve for this procedure exists and widespread experience is limited, by instituting a thoughtful and intentional approach, PDA device closure can be performed safely and effectively in premature infants.[3,33,56,66] To this point, the FDA recently approved the first device designed for occlusion of a PDA in a neonate (Piccolo, Abbott). The most common complication is arterial vascular injury when arterial access is used as part of the procedure.[3] When only venous access route is used, obstruction of the left branch pulmonary artery or descending thoracic aorta is the next most commonly observed issue. This is usually discovered before the device is released by angiography or transthoracic echocardiogram, at which time the device can be safely removed and another size or device can be tried, or the patient is referred for surgical ligation. Further research and cumulative experience with both approved (on-label) and off-label devices will hopefully demonstrate transcatheter PDA closure to be safe and effective for many premature infants.

Miscellaneous Procedures

Some heart conditions or combination of conditions cannot be easily placed into one of the major physiologic groups detailed above or deserve special attention on their own. The following section contains surgical, transcatheter, or hybrid interventions that do not fall fully into one of the rubrics above.

Pulmonary Vein Stenosis

Isolated pulmonary vein stenosis is a rare anomaly in the neonate, is associated with poor outcomes, and is commonly seen in conjunction with other defects. Stenosis of multiple pulmonary veins is associated with pulmonary venous hypoplasia, poorer prognosis and is more common in infants born extremely premature, especially those with coexisting intracardiac shunt lesion.[13] This condition can be congenital or acquired after a pulmonary vein repair operation. Interventional experience with this condition is growing, with multiple case series describing balloon angioplasty (both conventional and cutting balloons) and stent implantation for this lesion.[4,47] The process of progressive pulmonary vein

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stenosis is poorly understood but appears inflammatory or sclerosing in nature. There have been some reports of successful outcomes using drug-eluting stents and balloons to attempt to reduce or halt the inflammatory process.[42]

There are few neonatal cardiac surgeries that need to be performed emergently, as medical or catheter-based therapies can usually allow more time for adequate diagnostic imaging and screening. An exception to this is obstructed total anomalous pulmonary venous return, wherein pulmonary venous blood does not have an adequate egress. This leads to pulmonary edema and severe pulmonary hypertension. Respiratory failure quickly develops, followed by a drop in cardiac output caused by profound cyanosis and sequestered pulmonary venous blood from the heart. Stenosis of a vein that drains pulmonary venous flow in total anomalous pulmonary venous return (i.e., vertical vein) can be stented to stabilize or palliate the patient until a surgical repair can be performed.[29] Surgical treatment of obstructed total anomalous pulmonary venous return is described in the next section.

Surgical Repair of Total Anomalous Pulmonary Venous Return

Total anomalous pulmonary venous return (TAPVR) is an embryologic failure of fusion of the confluence of the pulmonary veins to the adjacent left atrium. The pulmonary venous return finds its way back to the heart via a communicating vein in one of four ways: 1) supracardiac—is the most common, whereby the confluence of the pulmonary veins drain into an ascending vertical vein that connects to the innominate vein then the superior vena cava; 2) infracardiac—has a descending vertical vein draining into the portal vein or inferior vena cava; 3) cardiac—has a direct communication from the confluence to the coronary sinus; and 4) mixed— is the least common and has some combination of the previous three. If there is any obstruction or stenosis of this communicating pathway, profound cyanosis and hemodynamic compromise rapidly ensues, creating a surgical emergency. Often these newborns are in crisis before a diagnosis is made, winding up on ECMO support without a clear etiology. Once on ECMO, the diagnosis may be more difficult to make by echocardiography; therefore, the treating clinicians need to maintain a high index of suspicion for TAPVR, sometimes requiring advanced imaging or catheterization to confirm the diagnosis. The surgical repair of TAPVR is done via a median sternotomy on cardiopulmonary bypass. The principles of the operation include direct anastomosis of the anterior wall of the confluence of the pulmonary veins to the posterior wall of the adjacent left atrium as well as ligation of the communicating vein. Typically, a PFO or small atrial septal defect is left to help the management of potential postoperative pulmonary hypertensive events.

Central Line Placement

Neonates with congenital heart disease often require indwelling central venous catheters and arterial monitoring lines for prolonged periods of time. This is the reason there is a high prevalence of venous and arterial occlusion in the congenital heart disease population, especially in those with functional single ventricle heart conditions. The importance of obtaining umbilical venous and arterial access immediately after birth cannot be emphasized enough. Studies have shown that single ventricle patients who have umbilical venous lines placed instead of femoral lines have had significantly lower complication rates of vascular thrombosis and occlusion.[1] Furthermore, these patients require multiple catheterization procedures in their lifetime, and occluded femoral veins or arteries complicate these procedures considerably and can make some future interventions impossible to perform. If nonumbilical access is required, practice is to use the smallest catheter necessary for medical management. Use of single lumen instead of double lumen results in less vascular occlusion. Tunneling central lines is associated with less thrombosis and a decreased rate of central line–associated blood stream infections. Placement of catheters in the upper extremities or neck vessels is not recommended in single ventricle patients prior to the Fontan operation. If catheters are necessary in these positions, anticoagulation should be administered immediately after placement, and the line should be removed as soon as it is safely possible to reduce the risk of vascular stenosis or occlusion. Finally, when other alternative sites of access have been exhausted, transhepatic lines can be placed in the catheterization laboratory and have been shown to be a feasible and safe alternative in infants with otherwise limited access.[41]

Pericardiocentesis

Pericardiocentesis or pericardial drain placement can be safely performed in the neonate. The procedure is typically guided by transthoracic echocardiogram but can be performed by landmark alone in emergency cases when the patient is suffering from cardiac tamponade. There are multiple causes for tamponade, but in the neonate one of the most common causes is associated with indwelling central venous catheters. It is not known whether the mechanism of tamponade is perforation or simple diffusion across a very thin atrial wall, but analysis of the effusion often shows similar fluid composition to the infusate.[62]

Fetal Cardiac Intervention

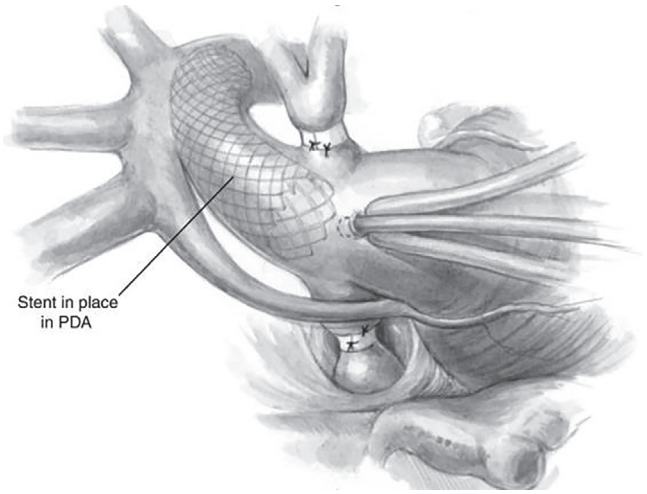
Fetal cardiac intervention (see Chapter 13) has been the subject of much interest over the past 10 years. Its use is attractive in some of the congenital cardiac defects with poor outcomes secondary to valvar obstructions, which can lead to ventricular hypoplasia. There are currently three catheter-based interventions that have been performed in fetuses with congenital heart disease: balloon valvuloplasty in aortic valve stenosis (with impending hypoplastic left heart syndrome), balloon valvuloplasty in pulmonary atresia with intact ventricular septum (with impending hypoplastic

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right ventricle), and atrial septal defect creation or enlargement in hypoplastic left heart syndrome with restrictive or intact atrial septum. Fetal cardiac interventions are not performed as standard of care at all heart centers and are typically only performed at centers with experienced teams made up of high-risk OB (maternal-fetal medicine), fetal cardiology, and interventional cardiology. As such, it is common for centers who do not offer the procedure to refer patients to one of the experienced centers. There is a non-insignificant risk to the fetus and potentially the mother, so candidates for fetal cardiac intervention must be carefully screened and vetted before the decision to proceed is made. Accurate diagnosis and referral for intervention must be made early enough in gestation to allow for potential reversal of disease progression following. Lastly, information regarding the natural history of these defects is not completely understood, making it difficult to predict which fetus will develop ventricular hypoplasia and should undergo these high-risk fetal interventions.[34] The mortality associated with these procedures is improving as experience is gained. Nevertheless, it is still not clear-cut that early fetal intervention will consistently alter disease progression beyond the watchful waiting and treating the high risk neonate with established strategies.[36]

Hybrid Stage I Palliation

The hybrid approach has emerged as an alternative treatment strategy for the management of hypoplastic left heart syndrome (HLHS) and other complex neonatal heart anomalies beginning in the early 1990s.[19,54] The term *hybrid* refers to procedures performed, during which a combination of surgical and interventional methods are utilized. Because published medium-term results of the hybrid procedure demonstrated outcomes comparable to surgical palliation, this alternative approach was adopted by many more institutions.[18] The initial palliation with a Hybrid Stage 1 procedure is performed without the use of cardiopulmonary bypass and typically includes three steps: 1) bilateral branch pulmonary artery bands that protect the lungs from persistent high pressure and flow, while balancing the pulmonary versus systemic circulations 2) a stent in the patent ductus arteriosus (PDA) to assure unobstructed systemic blood flow; and 3) atrial balloon septostomy, or rarely stenting, to assure unrestricted flow from the left atrium to the right atrium (Fig. 78.7). This Hybrid Stage 1 palliation has been used successfully in patients with standard risk factors, those with a high-risk profile, as a tool for salvage, as a bridge to heart transplantation, and as a bridge to a two-ventricle repair. All forms of HLHS have been successfully palliated with a Hybrid Stage 1 procedure including aortic atresia/mitral atresia with a diminutive ascending aorta. Moreover, neither patient size nor prematurity have proven to be a contraindication to using this strategy nor has significant associated co-morbidities. That is why the Hybrid Stage 1 is used in many centers for their high-risk patients with known poor outcomes with more traditional surgical approaches. The Hybrid Stage 1 procedure is performed via a median sternotomy, without cardiopulmonary bypass, whereby bilateral branch pulmonary artery bands are placed and a PDA stent is inserted. A balloon atrial septostomy (BAS) can be performed at the same time using a hybrid transatrial approach or standard percutaneous femoral approach, or the BAS can be performed several days later in the cardiac catheterization lab. Serial echocardiography is used to assess for obstruction at the atrial septum, through the PDA stent, or restriction to antegrade or retrograde flow in the transverse aortic arch. Any sign of obstruction and/or worsening right ventricular function or worsening tricuspid valve regurgitation warrants a cardiac catheterization. Any obstruction can almost always be successfully treated in the cardiac catheterization lab with return to baseline function.

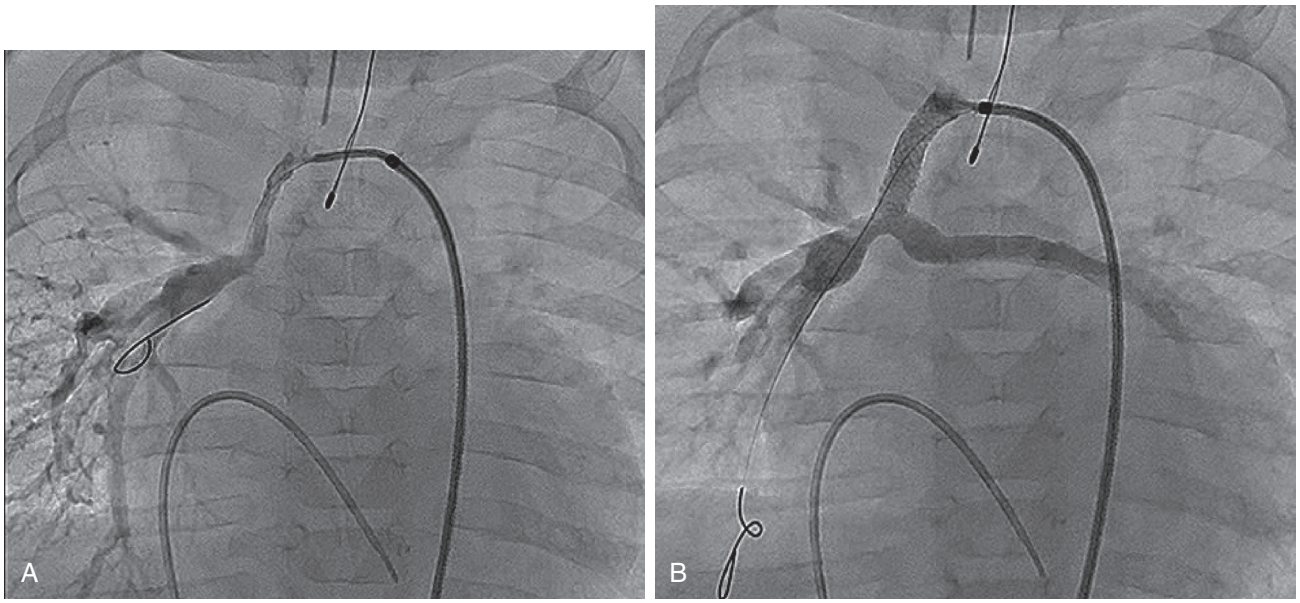


• **Fig. 78.7** Artistic depiction of a Hybrid Stage I palliation from the surgical view. Surgical bands have been placed on the bilateral branch pulmonary arteries. The main pulmonary artery is directly accessed above the pulmonary valve and a stent has been implanted along the entire length of the ductus arteriosus (from branch pulmonary arteries to the descending aorta).

Shunt Obstruction

One of the most feared complications of systemic to pulmonary artery shunts is complete or near complete shunt occlusion in patients dependent solely on the shunt for pulmonary blood flow. When severe cyanosis develops secondary to shunt obstruction, the two treatment strategies include surgical revision or transcatheter intervention. If possible, this is best dealt with in the cardiac catheterization lab to avoid another midline sternotomy. In the event of complete occlusion, patients sometimes need to be stabilized on extracorporeal membrane oxygenation (ECMO) to provide adequate oxygenation and then can be transported to the cardiac catheterization lab. Transcatheter interventions include simple balloon dilation, thrombus evacuation, or stent implantation within the shunt (Fig. 78.8*A, B*).[28] Interventions for modified Blalock-Taussig shunt obstructions are usually approached from the femoral artery. RV-PA (Sano) shunts are typically approached from the femoral

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• **Fig. 78.8** Stent implantation within a modified Blalock-Taussig shunt. A selective angiogram shows a stenotic shunt with poor filling of the left pulmonary artery (**A**). Following stent implantation, there is improved diameter of the shunt and improved filling of the left pulmonary artery (**B**).

vein.[48] For partial or near occlusion, these procedures carry a high risk, as crossing the already obstructed shunt further decreases the diminutive pulmonary blood flow and can lead to severe cyanosis and cardiac arrest. Nevertheless, when performed by experienced operators the success rate is encouraging and surgical revision is rarely required.

Neonatal Heart Transplantation

Heart transplantation in the neonate continues to be reserved for those babies with congenital cardiac anomalies or cardiomyopathies that are not amenable to repair. Even high-risk single ventricle conditions such as hypoplastic left heart syndrome are rarely treated primarily with heart transplantation. The reasons for this are many, as highlighted in the 2017 report of the International Society for Heart and Lung Transplantation.[8] The number of infant (<1 year old) heart transplantations performed in North America and Europe combined has been stable for years at only about 120 per year. Not only is this a reflection of the limited indications for transplantation, but more importantly it reflects the severely limited donor pool of this rare resource. Patient survival is about 75% at 8 years and 50% at 22 years, which is somewhat better than reported results for older children.[26] Reasons for the improved survival rate include the immaturity of the immune system leading to decreased antibody-mediated rejection. In addition, neonatal transplant patients have been shown to have less graft vasculopathy[68] and require less immune suppression.[25] However, there are lifelong challenges with immunosuppression and the balance of rejection and infection that lead to a continuous risk hazard of significant morbidities. The continuous risk of developing a malignancy is 10% at 10 years, primarily lymphomas as well as the continuous risk of life-threatening infections. The cumulative risk of graft failure secondary to cardiac allograft vasculopathy is 50% at 15 years. Unfortunately, despite the ability to perform re-transplantations for graft failure, both patient and graft survival are less compared to primary transplantation. Therefore, considering a lifelong management strategy for newborn congenital heart disease transplantation needs to be reserved for those without other options. Nonetheless, in neonates that require transplantation there are ongoing efforts to expand the donor supply, for example, by considering donation from anencephalic donors. Also, the ability to successfully perform ABO-incompatible heart transplantation is unique in the neonate by taking advantage of their somewhat naïve immunologic response to antigens.[65]

Medical Management

Prostaglandin E_1

In infants with a known prenatal diagnosis of ductal-dependent CHD, prostaglandin E1 (PGE1) infusion should be initiated shortly after birth and after intravenous access is obtained. For infants in whom ductal-dependent CHD is suspected based on cyanosis or shocklike clinical picture, PGE1 infusion should also be initiated immediately and continued until further testing, usually an echocardiogram, can be performed to either confirm or negate the diagnosis. In these undiagnosed clinical situations, prompt initiation of PGE1 is critical and can be lifesaving. PGE1 can be infused through virtually any vascular access that can be obtained, including the intraosseous route. The standard dose for maintenance of ductal patency is 0.03 mcg/kg/min. For infants with suspected ductal-dependent CHD who present with severe cyanosis or shock, an initial dose

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of 0.1 mcg/kg/min is often a recommended starting dose to open the ductus arteriosus. This dose can be increased in certain situations to 0.2 mcg/kg/min if the ductus arteriosus remains closed at the 0.1 mcg/kg/min dose. Conversely, the dose can often be decreased back to a maintenance dose of 0.03 mcg/kg/min once the ductus arteriosus is reopened and the infant has begun to stabilize clinically. The short-term side effects of PGE1 include apnea/hypopnea, skin flushing, and fever, and these tend to be dose-dependent effects.[24] If side effects are occurring and causing management issues, the dose can be titrated down to as low as 0.01 mcg/kg/min as long as the ductus arteriosus remains patent and an adequate size at that level. There is no limit for how long PGE1 can be infused, and sometimes it is necessary to maintain an infant on PGE1 for prolonged periods of time, especially for those infants with significant medical co-morbidities or extreme prematurity. As stated in the previous sections, the alternative for prolonged PGE1 infusion is implanting a ductal stent to maintain patency and, therefore, avoid the long-term effects of PGE1, including periosteal hyperostosis[15] or gastric outlet obstruction.[30,49]

Oxygen and Ventilation

Most patients with mild and moderate forms of congenital heart disease do not require special consideration regarding oxygen therapy and ventilation strategies. They can typically be managed following standard neonatal strategies appropriate for age and size. Patients with single ventricle physiology and some with two ventricles who will require a PDA for ductal-dependent CHD require more specific management strategies to maintain pH levels within tighter ranges and judicious use of delivered oxygen. Neonates with single ventricle heart conditions in which the systemic and pulmonary circulations are connected by the PDA have oxygenation, cardiac output, and tissue perfusion that is extremely dependent on relative changes in the vascular resistances. As the pulmonary vascular resistance drops over the first week, keeping an appropriate balance of circulations becomes more difficult and close attention to arterial blood gas parameters becomes increasingly important. The most exemplary situation when ventilation and supplemental oxygen therapy can affect the balance between the systemic and the pulmonary vascular beds is in the care of infants with hypoplastic left heart syndrome.[2] Preoperatively, systemic output is dependent on right-to-left flow across the PDA, which is typically maintained by PGE1. When pulmonary vascular resistance (PVR) is high, blood flow through the PDA is right-to-left in systole as well as during a portion of diastole. As such, oxygen saturations will be relatively low because of relatively reduced amounts of pulmonary blood flow, and systemic perfusion will be adequately maintained. As the PVR falls during the first day to week of life, blood flow remains right-to-left in systole across the PDA but becomes left-to-right in all of diastole, resulting in rising oxygen saturations with increasing pulmonary blood flow. If the PVR falls significantly and measures are not taken to counterbalance this change in physiology, systemic perfusion can become inadequate and end organ injury (acute renal insufficiency, necrotizing enterocolitis) can result. This condition termed "pulmonary overcirculation/systemic hypoperfusion" can happen after even a very short period of time in the preoperative period. As such, regular checks of arterial blood gases (preferably) or capillary gases can provide significant insight into the balance of circulations. Elevation in arterial lactate levels can precede clinical instability and end organ injury, so it is recommended to follow and trend these levels serially. In general, pH should be maintained at 7.34-7.40 and alkalosis should be avoided. The P_{CO_2} and serum bicarbonate levels are less reliable to follow, especially when the neonate is receiving diuretics, because of the contraction alkalosis these medications can cause. If pH is maintained in this range, most patients will not overcirculate to a significant degree. In nonintubated neonates, relative overcirculation can lead to hyperventilation, and respiratory rates in the 80s to 90s are not uncommon. In these situations, the neonate may develop hypocapnia, leading to alkalosis and worsening pulmonary overcirculation. When these situations arise, it is sometimes necessary to intubate and assume control of the ventilation by dropping rate and minute ventilation until the pH is back into the desired range.

Oxygen, particularly alveolar or delivered oxygen, is a potent pulmonary vasodilator. The administration of supplemental oxygen can lead to dramatic drops in PVR and increasing pulmonary blood flow. In general, supplemental oxygen should be avoided in single ventricle patients, especially HLHS, unless there is significant lung disease leading to suspected pulmonary venous desaturation in which saturations are consistently less than 70%. On the contrary, in patients with high saturations from pulmonary overcirculation, it is sometimes necessary to provide subambient levels of oxygen, which raises the PVR and "discourages" pulmonary blood flow. Subambient oxygen can be administered by bleeding in nitrogen gas into a ventilation tent or through the endotracheal tube in an intubated infant. An FiO_2 of 18%-20% can be effective at raising PVR, but close monitoring of oxygen saturations and PaO_2 is necessary if this therapy is pursued.

Blood Products

Infants with cyanotic congenital heart disease often have deficient oxygen delivery to vital tissue and organs because of the high levels of fetal hemoglobin and its high oxygen affinity. Therefore it is important to maximize the oxygen-carrying capacity in these patients, and studies have shown that increasing the hemoglobin to >13 gm/dL or hematocrit to >40% is ideal. This can be accomplished in the short term by transfusing packed red blood cells (15-20 cc/kg) or over a longer period of time by administering weekly erythropoietin injections.[45] The exposure to many different blood donors can lead to antigen sensitization and make future

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matches for cardiac transplantation difficult. Furthermore, excessive use of packed red blood cell transfusions has been linked to transfusion-related acute lung injury (TRALI), prolonged length of ICU stay, increased risk of infection, and higher mortality. Therefore, neonatal transfusions should be used only when absolutely necessary for optimizing clinical status. Platelet transfusions are uncommon in the preoperative state in neonatal patients with CHD. The presence of thrombocytopenia in neonatal CHD is likely related to other perinatal pathophysiology and unlikely related to the cardiac diagnosis. Usual replacement practices should be followed by the neonatology team in these cases. Similarly, the need for fresh frozen plasma, cryoprecipitate, or other factor replacement is rare in the preoperative state for neonates with CHD. Postoperatively, however, the need for platelets and plasma is common and usually directed by the cardiothoracic intensive care unit (CTICU) team or cardiac intensivists to address postoperative bleeding and to optimize oxygen delivery.

Preload

Preload or the overall volume status of neonates is often very difficult to assess because of the tendency for capillary leak and the third-spacing of fluid. For neonates with congenital heart disease, especially those with fetal hydrops or those who develop edema shortly after birth, trying to assess and optimize preload can be extremely difficult. However, preventing fluid overload when hypotension is present and withholding fluid when the neonate appears edematous from third-spacing in the presence of end organ hypoperfusion are management decisions that have potential for tremendous impact on the overall course for neonates requiring complex operations. Profound fluid overload has been correlated with increased duration of mechanical ventilation, prolonged ICU times, and delayed recovery of kidney function. These situations can develop even in the absence of concomitant conditions such as atrioventricular or semilunar valve dysfunction, hypoalbuminemia, anemia, and sepsis, which can all make assessments and treatment decisions that much more complex and difficult. Therefore, it is crucial that the management teams pay close attention to daily weights, input/output totals, clinical exam findings such as liver span and fullness of fontanelle, and electrolytes and renal function (BUN and creatinine) on a daily if not shift basis. Teams must take the entirety of information into account to decide if fluid restriction or resuscitation is required.

There are specific times when fluid management techniques may differ from simply attempting to achieve euvolemia. In the postoperative period, edema is extremely common because of fluid received in the operating room, capillary leak syndrome associated with cardiopulmonary bypass, and the need for perioperative blood products. In an attempt to combat this fluid overload, crystalloid or colloid administration should be used judiciously while maximizing the cardiac output with the use of inotropic and vasoactive agents. Often, medication drips or hyperalimentation can be concentrated or even discontinued if not immediately critical. Urine output can be maximized by maintaining good cardiac output and the aggressive use of diuretics. First-line diuretic therapy is generally a loop diuretic such as furosemide or bumetanide, often used in combination with a thiazide diuretic such as chlorothiazide for potentiation of effect. Hypokalemia is common with higher doses of loop diuretics, and patients may require either potassium supplementation or a potassium-sparing diuretic such as spironolactone (which also has beneficial ventricular remodeling properties) to avoid the hypokalemic hypochloremic metabolic alkalosis associated with long-term diuretic therapy.

Besides the postoperative period, it is common for patients with lesions resulting in pulmonary overcirculation (left-to-right shunts) to become fluid overloaded and need diuretic therapy. Although the pulmonary vascular resistance is still somewhat elevated and may temporarily protect the patient from overcirculation, certain lesions, such as a large patent ductus arteriosus, unrestrictive ventricular septal defects, certain forms of truncus arteriosus, and large aortopulmonary collaterals will result in excessive pulmonary blood flow, and diuretics will almost certainly be required prior to neonatal surgical repair.

In other situations, it may be beneficial to keep the patient relatively fluid loaded but not overloaded. For example, in patients with RVOT obstruction, such as tetralogy of Fallot, subpulmonary obstruction is somewhat dynamic, and a preloaded right ventricle can help to keep these patients from having hypercyanotic spells. A volume-loaded right ventricle will physically stretch or distend the subpulmonary area thereby decreasing the amount of dynamic collapse that leads to limited pulmonary blood flow and cyanosis. Similarly, patients with certain forms of cardiomyopathy will have stiff, noncompliant ventricles with significant diastolic dysfunction. These patients also need to have adequate preload to maintain ventricular filling and stroke volume.

Afterload

Afterload refers to the cumulative pressure against which the systemic ventricle must work to eject blood during systole. Although systemic blood pressure makes up the most significant portion of the afterload, the condition of the ventricle (wall stress and preload) must also be considered. For example, in a healthy heart with normal systolic and diastolic ventricular function, increasing afterload can be overcome by the ventricle by increasing ventricular wall stress and contractility. If the high afterload is chronic, myocardial hypertrophy will develop to assist the ventricle in overcoming this stress. However, in a dysfunctional ventricle the capacity to overcome acute and chronically elevated afterload is not as robust. In this situation, high afterload leads to higher systolic pressures and wall stress, which then leads to rising filling pressures and atrial hypertension. Although

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fluid resuscitation may allow for maintained cardiac output over a short period of time, fluid overload may ensue and other measures are required to assist the diseased ventricle. Oral afterload-reducing agents are typically antihypertensive medications that lower systemic vascular resistance and systemic blood pressure. Although medications like angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) do provide long-term ventricular remodeling effects, in the short term they only affect afterload by the blood-pressure-lowering effects. For critically ill neonates, these medications are rarely used. The medication most commonly utilized for this situation is milrinone, which has afterload-reducing, inotropic, and lusitropic (ventricular relaxing) properties. The net effect of milrinone is to have improved ventricular filling, improved stroke volume, and lower afterload for overall increase in cardiac output. Dobutamine has similar effects but usually results in significantly elevated heart rate. For neonates that have much higher resting heart rate, the tachycardia of dobutamine makes it less desirable compared to milrinone. Nitroprusside infusion is rarely used in neonates as it is a potent vasodilator and afterload-reducing agent but lacks the inotropic and lusitropic properties of milrinone. The relatively low blood pressure of most neonates does not lend itself to treatment by this drug on a regular basis.

To reduce afterload in the subpulmonary ventricle, any agent that selectively decreases pulmonary vascular resistance can be considered in neonates. Oxygen and inhaled nitric oxide are potent pulmonary vasodilators and reduce pulmonary afterload very well. Other agents (sildenafil or bosentan) used to treat pulmonary hypertension can be considered for use under the guidance of pediatric pulmonary hypertension experts.[43]

Contractility

Agents that increase inotropy and cardiac contractility can improve cardiac output. A commonly used oral agent to increase contractility is digoxin, which has been shown to be safe in the neonate with left ventricular volume overload and systolic dysfunction.[21] However, this oral medication is rarely used in the neonatal period solely for the purpose of treating ventricular systolic dysfunction or heart failure unless added to a regimen that includes afterload-reducing agents and diuretics, as it is typically a secondary or tertiary agent.

Intravenous inotropic support is more commonly encountered in the neonatal period to treat perinatal, preoperative, and postoperative systolic dysfunction.[44] Dopamine and dobutamine have similar inotropic effects, although dopamine is usually preferred because of its greater effect in premature infants and because it causes less tachycardia and systemic vasodilation than dobutamine. Epinephrine is used in low doses for its inotropic effect, although counterintuitive effects of increasing myocardial oxygen demand through increased heart rate and systemic vascular resistance can limit its use. As discussed in the afterload section, milrinone is commonly used in the postoperative period because of its improved inotropy, lusitropy, and afterload-reducing effects.

Treatment of Hypercyanotic Spells

Hypercyanotic spells or "tet spells" are acute episodes that can develop in patients with tetralogy of Fallot when there is dynamic subpulmonary obstruction of the right ventricular outflow tract. When acute worsening of RVOT obstruction develops, there is a significant decrease in pulmonary blood flow and subsequent shunting of blood right to left at the ventricular level leading to severe hypoxia and cyanosis. The infundibulum of the right ventricle is thought to be reactive to circulating catecholamines, which increase with increasing patient agitation, resulting in increased gradient across the RV outflow tract forcing deoxygenated blood across the ventricular septal defect into the aorta, resulting in cyanosis. Other factors such as decreased right ventricular filling owing to relative hypovolemia and lack of preload or tachycardia may further predispose these patients to hypercyanotic episodes. The treatment for hypercyanotic episodes is to find ways to decrease the subpulmonary obstruction, encourage more pulmonary blood flow, and increase the relative degree of left to right shunting at the ventricular level. If these maneuvers are followed, hypercyanotic spells can often be treated quickly before the infant is hypoxic for an unsafe amount of time. Some of these maneuvers and the physiologic rationale for their use are illustrated in Table 78.5.

What the Future Holds

The field of congenital heart disease is constantly changing and innovation is typically the rule and not the exception. The past 20 years have seen a tremendous improvement in the medical, surgical, and interventional therapies for neonates and children with congenital heart disease. Fortunately, through the fervent work of many individuals and organizations (www.pediatricdeviceconsortium.org; www.pediaworks.org), the FDA became more aware of these limitations in the treatment of children and in 2007 passed the Pediatric Medical Device Safety and Improvement Act. The PMDSIA was the first major legislation ever exclusively directed toward pediatric devices and has already stimulated innovation, provided new incentives for pediatric device development, and allowed for better safety monitoring of devices. In 2012, the PMDSIA was renewed by congress and additional funding for the Pediatric Device Consortium Grant Program was secured.

Pediatric Interventional Cardiology has benefitted recently from the approval of two transcatheter pulmonary valves: Medtronic's Melody Transcatheter Pulmonary Valve in 2010 and the Edwards Sapien XT Transcatheter Heart Valve for Pulmonic Indications in 2016. The first FDA-approved stent for coarctation of the aorta was approved in 2016 after an extensive investigation of the NuMED

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TABLE 78.5 Treatment Strategies and Physiologic Rationale for Hypercyanotic Episodes Associated With Tetralogy of Fallot

Treatment of Cyanotic Episodes	Rationale/Physiologic Effect(s)
100% oxygen	Decreases PVR and improves oxygen delivery
Knees to chest	Increases SVR and preload
Manual compression of abdominal aorta	Increases SVR
Nonprovocation	Decreases catecholamines and infundibular spasm
Fluid bolus (0.9% saline, 5% albumin, blood), 10-20 mL/kg	Increases RV preload
Morphine, 0.1-0.2 mg/kg IV/IM/SC	Decreases catecholamines and infundibular spasm
Ketamine, 0.4-1 mg/kg IV/IM	Decreases catecholamines and infundibular spasm
Fentanyl, 1-4 mcg/kg IV/IM/SC	Decreases catecholamines and infundibular spasm
Phenylephrine, 5-20 mcg/kg IV bolus or IV infusion 0.1-0.5 mcg/kg/min, 0.1 mcg/kg SC/IM	Increases SVR
Propranolol, 0.05-0.15 mg/kg slow IV	Increases RV filling and decreases catecholamines

IM, Intramuscular; IV, intravenous; PVR, pulmonary vascular resistance; RV, right ventricular; SC, subcutaneous; SVR, systemic vascular resistance.

Cheatham Platinum (CP) Stent System. Although these valves and stents are not currently for use via typical transcatheter route in neonates and infants, the miniaturization of this technology is underway so that more infants will be candidates for hybrid implants in the near future. Furthermore, devices used for transcatheter occlusion of PDAs are currently being studied for their use in the premature infant population, and the first occluder, Piccolo (Abbott Medical) has just been approved by the FDA.

Biodegradable materials and devices remain one of the most important focuses of research and are at the forefront of innovation in pediatrics because of the ideal potential to allow placement or implantation of a device that would eventually resorb or degrade and not inhibit growth of the vessel or heart structure in which it has been placed or inhibit access to a particular area of the heart. Catheters are also being made smaller and more versatile to avoid some vascular complications that occurred using adult-sized equipment in children.

We are also becoming more organized in the way we share information. Patient populations are too heterogeneous to be able to provide good, large-scale evidence for the therapies provided. Multi-institutional and even multinational registries (IMPACT, CCISC, C3PO, NPC/QIC, etc.) are now allowing compilation of more useful data than ever before and will certainly be sources of solid evidence-based studies in the future. This will allow the field to advance, given that only 2% of the 2011 AHA recommendations on cardiac catheterization in children are level of evidence A.[16]

Key Points

- Neonates with congenital heart disease require a well-integrated and multidisciplinary team approach to achieve optimal outcomes.
- The vast majority of congenital heart disease does not require specific neonatal management.
- Moderate to severely complex congenital heart conditions can be classified into cyanotic and acyanotic forms.
- Cyanotic congenital heart disease includes conditions with too little pulmonary blood flow and excessive pulmonary blood flow.
- Surgical methods to increase pulmonary blood flow in cyanotic CHD include surgical systemic-pulmonary artery shunts and surgically opening the right ventricular outflow tract.
- Interventional methods to increase pulmonary blood flow include PDA stenting and RVOT stenting.
- The most reliable approach to limit pulmonary blood flow is placement of a main pulmonary artery band.
- Numerous methods exist to improve mixing at the atrial level in conditions such as transposition of the great arteries.
- In premature infants, PDA closure can be done medically, surgically, and now via interventional approach with small vascular plugs.
- Prompt initiation of PGE1 infusion in patients with suspected ductal-dependent CHD who present with cyanosis or shocklike picture can be a life-saving treatment.

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79

Hematologic and Oncologic Problems in the Fetus and Neonate

JOHN LETTERIO, IRINA PATEVA, AGNE PETROSIUTE, AND SANJAY AHUJA

Human Hematopoietic Development

Hematopoietic Stem Cells

Blood cells arise from the differentiating embryonic mesoderm. Human erythroid and macrophage progenitor cells have been observed in the yolk sac by days 16-19 and at day 19 in the aortic-gonad-mesonephros (AGM). After the development of the circulatory system on day 21, pluripotent hematopoietic cells localize in the AGM, placenta, and liver by days 24-28. Myeloid, lymphoid, and megakaryocytic precursors have been noted in fetal liver at this stage. Definitive erythropoiesis occurs in the fetal liver, thymus, spleen, and bone marrow. A knowledge gap exists regarding the details of in situ hematopoiesis between weeks 3 and 12, but fetal liver is recognized as the major site of hematopoiesis between weeks 6 and 16. The bone marrow assumes this role by week 24 (Fig. 79.1).[58]

Proper blood cell formation is necessary for survival. Much has been learned about the origin and regulation of blood cells through studies of congenital and acquired defects in hematopoiesis. Studies of mouse hematogenesis identified pluripotent cells in the murine inner cell mass. These embryonic stem (ES) cells are capable of self-renewal as well as differentiation into hematopoietic cells. Human ES cells were isolated in 1998, fueling research efforts to generate pluripotent stem cells from early embryos and to perform genetic manipulation of differentiated somatic cells. Somatic cells can be reprogrammed into an ES-like state, and these induced pluripotent stem (iPS) cells are another tool researchers are using both to understand and manipulate progenitor cells.[58]

The earliest blood cells produced by colony-forming cells (CFCs) in the yolk sac are very large, primitive erythroid cells expressing embryonic globins. Subsequently, CFCs produce definitive erythrocytes expressing fetal globins and macrophages. Later still, multipotent CFCs and lymphoid progenitor cells arise. The adult-type globins are not expressed until just before birth and rapidly assume primacy afterward (Table 79.1; Fig. 79.2). With each transition from primitive to definitive to adult erythroid cells, the mean corpuscular volume (MCV) decreases.

Regulation of Hematopoiesis

Few hematopoietic stem cells enter the cell cycle at any given time. Most are in a resting state. Proliferation and differentiation occur within a suitable microenvironment of stroma and humoral factors. The WNT/β-catenin and Notch-δ signaling pathways drive stem cell development. Transcription factors involved in stem cell development include GATA2, RUNX1, TEL/ETV6, SCL/TAL1, and LM02. Other transcription factors such as PU.1, GFIX, C/EBPα, and GATA1 are considered to be more lineage-specific, but most also participate in lineage priming, where stem cells differentiate along a pathway depending upon cellular and environmental stimuli. Multiprotein complexes assemble and bind DNA regulatory elements to modulate transcription. Epigenetic regulatory mechanisms of transcription include DNA methylation on CpG residues and histone modification.[58]

Factors promoting hematopoiesis include BMP4, VEGF, WNT, and FGF. Hematopoietic cytokines such as stem cell factor, fms-like tyrosine kinase receptor-3 ligand, interleukin-6, thrombopoietin, erythropoietin, and granulocyte colony-stimulating factor (G-CSF) play critical roles in the maintenance and differentiation of human hematopoietic cells. Some hematopoietic growth factors are produced in the vicinity of hematopoietic progenitors, and others are synthesized remotely (Table 79.2). Few of the glycoprotein growth factors are available for clinical use, but that number is expected to increase.

Some of the earliest hematopoietic growth factors discovered were referred to as *colony-stimulating factors* (CSFs), because in culture they stimulate progenitor cells to form colonies of recognizable maturing blood cells. The prefixes refer to the maturing cell produced. GM-CSF is granulocyte-macrophage CSF. The interleukins (ILs) were named for the fact that they are derived from, or act upon, leukocytes. Other factors are named for the cell surface receptor to

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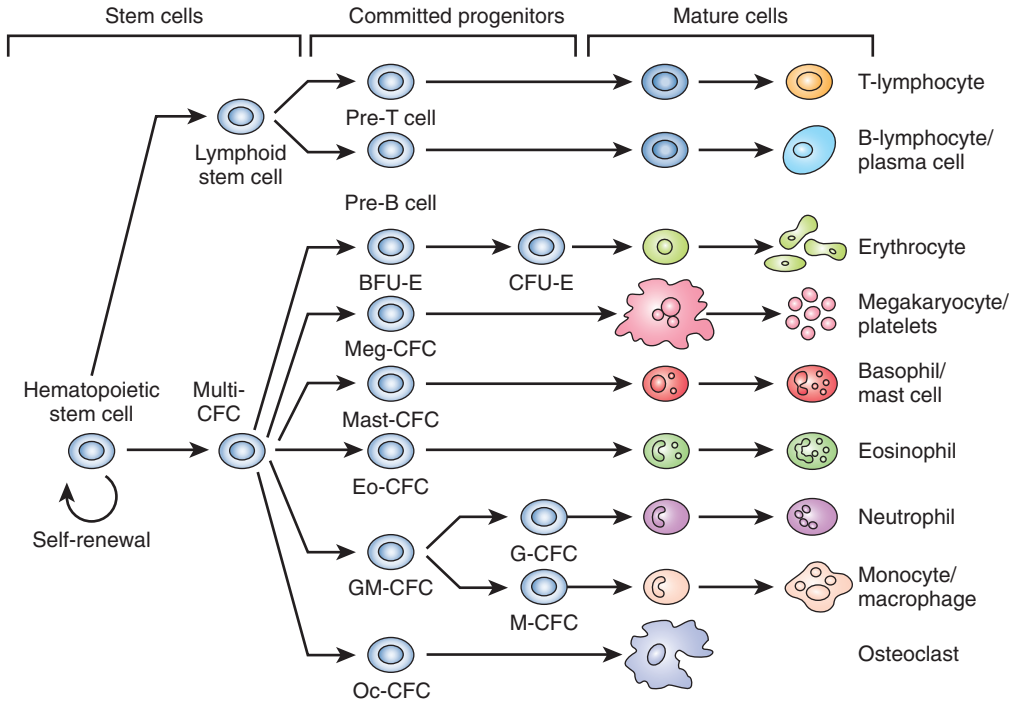
Abstract

The newborn faces a unique and diverse spectrum of hematologic problems that are a consequence of events such as maternal–fetal blood group incompatibilities, maternal drug usage and medications, prematurity, birth asphyxia, and other systemic disorders. The growth of knowledge regarding the etiology and treatment of these conditions has led to the emergence of neonatal hematology as a complex subspecialty of pediatric hematology. The co-management of these conditions by hematologists and neonatologists is necessary to insure careful assessment of the unique aspects of the maternal–fetal relationship, the delicate balance of coagulation factors, and the distinctive physiologic conditions of the newborn period that influence the production of blood elements necessary for tissue oxygenation, clotting, and immunity. This chapter reviews specific hematologic disorders that commonly present in the newborn period, as well as oncologic conditions that may present in the neonatal period. A review of disease pathophysiology is accompanied by a discussion of signs and symptoms associated with various hematologic conditions that present in the newborn period and current treatment strategies.

Keywords

hematopoiesis
coagulation
anemia
thrombocytopenia
neutropenia
hemoglobinopathy

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• **Fig. 79.1** Hematopoietic stem cell differentiation. BFU-E, Burst-forming units, erythroid; CFC, colony-forming cells; CFU-E, colony-forming unit, erythroid; Eo-CFC, eosinophil colony-forming cells; G-CFC, granulocyte colony-forming cells; GM-CFC, granulocyte-macrophage colony-forming cells; M-CFC, macrophage colony-forming cells; Meg-CFC, megakaryocyte colony-forming cells; Oc-CFC, osteoclast colony-forming cells.

TABLE 79.1 Human Hemoglobins Expressed during Development

Hemoglobin	Predominates	Globin Composition
Hb Gower 1	Embryonic (yolk sac)	$\zeta_2\varepsilon_2$
Hb Gower 2	Embryonic (yolk sac)	$\alpha_2\varepsilon_2$
Hb Portland	Embryonic (yolk sac)	$\zeta_2\gamma_2$
Hb F	Fetal (liver)	$\alpha_2\gamma_2$
Hb A	Adult (bone marrow)	$\alpha_2\beta_2$
Hb A2	Minor adult (bone marrow)	$\alpha_2\delta_2$
Hb Barts	Fetal-alpha thalassemia	γ_4
Hb H	Adult-alpha thalassemia	β_4

which they bind, such as thrombopoietin receptor agonists that stimulate megakaryocyte differentiation and platelet production. Growth factors such as IL-3 and GM-CSF stimulate proliferation, differentiation, and survival of a broad range of precursors, including stem cells. Others such as erythropoietin and granulocyte CSF (G-CSF) are lineage restricted.

Red Blood Cells

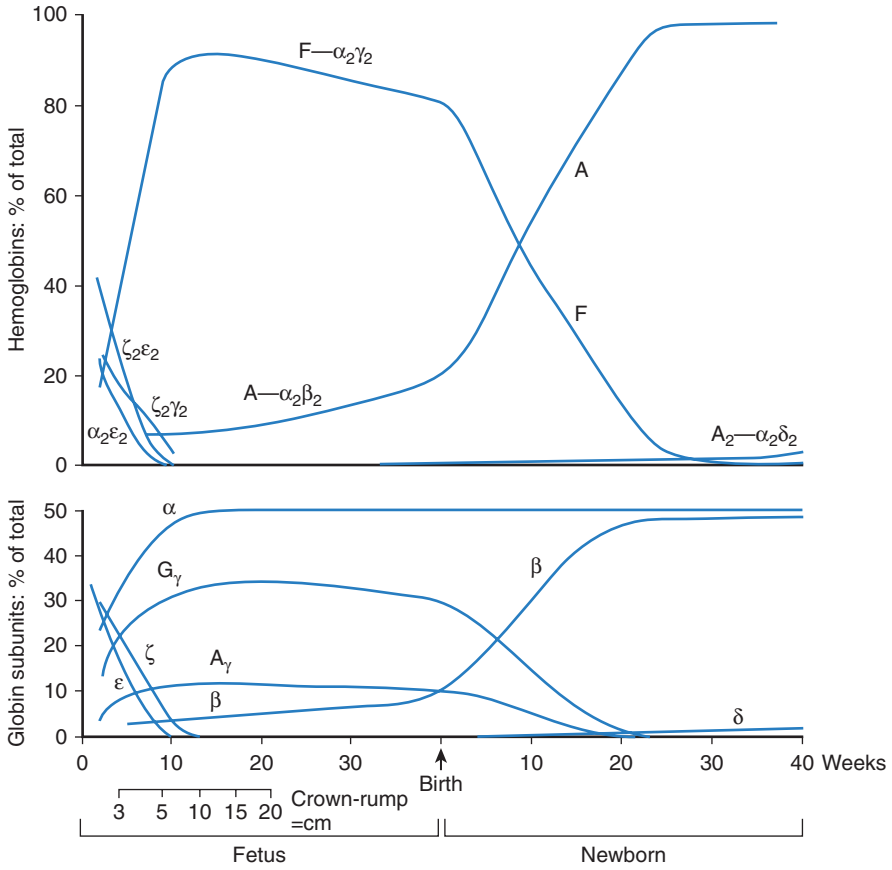
Hemoglobin and Oxygen-Carrying Capacity

The function of red blood cells (RBCs) is to transport oxygen (O_2) to tissues to meet metabolic demands. Hemoglobin (Hb), the most abundant protein in erythrocytes, facilitates oxygen delivery by reversibly binding O_2 molecules. The binding of oxygen to hemoglobin tetramers is cooperative, resulting in the familiar sigmoidal oxygen dissociation curve (Fig. 79.3). The affinity of Hb molecules for oxygen is influenced by a variety of factors, including temperature, pH, carbon dioxide pressure (P_{CO_2}), and the concentration of red blood cell organic phosphates (2,3-biphosphoglycerate or 2,3-BPG, also known as 2,3-diphosphoglycerate or 2,3-DPG). In the case of adult hemoglobin (Hb A), oxygen affinity for the molecule varies directly with pH and inversely with temperature and the concentration of 2,3-BPG. Fetal hemoglobin (Hb F) has a high oxygen affinity. Some mutations of hemoglobin affect oxygen affinity, as explained later.

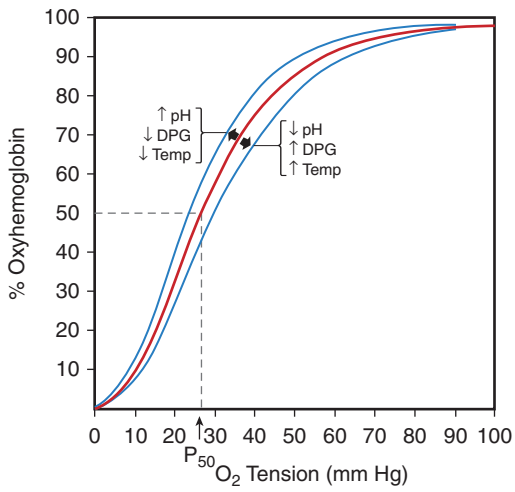
Hemoglobin Switching

The hemoglobin tetramer is composed of two heterodimers consisting of an α- and β-type globin. Different globin genes are sequentially expressed in RBC precursors, a process known as *hemoglobin switching* (see Fig. 79.2 and Table

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• **Fig. 79.2** Changes in expression of hemoglobin tetramers (*upper panel*) and individual globin chains (*lower panel*) during development. (Adapted from Bunn HF, et al. *Hemoglobin: molecular, genetic, and clinical aspects*. Philadelphia: Saunders; 1969.)



• **Fig. 79.3** Oxyhemoglobin dissociation curve. Factors that influence the position of the curve are indicated. DPG, Diphosphoglycerate. (Adapted from Bunn HF, et al. *Hemoglobin: molecular, genetic, and clinical aspects*. Philadelphia: Saunders; 1969.)

79.1). During development, α- and β-type globin gene clusters are activated sequentially from the 5′ (embryonic) end to the 3′ (adult) end. The α-type globin genes, ζ-globin, α_1-globin, and α_2-globin, are located on chromosome 16 with the ζ gene 5′ to a pair of duplicated α-globin genes. The β-type genes on chromosome 11 are oriented 5′ to 3′ as ε-, $^{G}\gamma$, $^{A}\gamma$, δ, and β (see Fig. 79.2). The protein products of the $^{A}\gamma$- and $^{G}\gamma$-globin genes are functionally similar and differ by a single amino acid residue. Globin gene expression is controlled by cis-elements of individual globin gene promoters, proximal and distal enhancer regions, and positively acting transcription factors, such as GATA1, GATA2, NFE2, MYB, EKLF, RBTN2, and SCL. Other mechanisms that also regulate globin switching are silencers, DNA conformational changes, and DNA methylation.[58,135] In fact, discovery of the ability to chemically demethylate CpG residues in the silenced γ-globin gene promoter launched translational research efforts to enhance fetal hemoglobin production in patients with β-globin defects such as β thalassemia and sickle cell anemia.

During yolk sac hematopoiesis, RBCs produce the embryonic hemoglobins (see Table 79.1). Hb F is the predominant hemoglobin in the fetus and neonate. Production of the major adult hemoglobin (Hb A) increases significantly between birth and 6 months of age, as Hb F production declines. Synthesis of HbA_2, a minor adult globin, also increases gradually over the first months of life (see Fig. 79.2). After 6 months of age, Hb F usually constitutes less than 1% of the total hemoglobin and is unevenly distributed among red blood cells. Each of the different types

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TABLE 79.2 Hematopoietic Growth Factors

Factor	Source	Receptor	Target Cells	Effects
Erythropoietin (EPO)	Kidney, hepatocytes	EPO-R	E, Meg	Stimulates growth and differentiation of erythroid precursors
Stem cell factor (SCF) (also known as steel factor [SF], KIT ligand [KL], and mast cell growth factor [MCGF])	Ubiquitous	KIT	E, mast cells, melanocytes, germ cells	Stimulates growth and differentiation of erythroid and myeloid precursors; enhances growth of mast cells
Granulocyte colony-stimulating factor (G-CSF)	Stromal cells, macrophages	G-CSF-R	N	Stimulates growth and differentiation of neutrophil precursors; activates phagocytic function of mature neutrophils
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Stromal cells	GM-CSF-R (α and β chains)	M, N, Eo, Endo	Stimulates growth and differentiation of neutrophils, eosinophils, and monocytes; activates endothelial cells; induces cytokine expression by monocytes
Macrophage colony-stimulating factor (M-CSF)	Mesenchymal cells	FMS	M	Stimulates growth and differentiation of monocytes; induces phagocytic function in monocytes and macrophages; is involved in bone remodeling
Interleukin 1 (IL-1)	Ubiquitous	IL-1RI, IL-1RII	T, E, B, M, S	Induces production of cytokines and prostaglandins by stromal cells, T cells, and many other cell types; induces fever
Interleukin 2 (IL-2)	T cells	P55, P75	B, T, NK	Induces proliferation and activation of T, B, and NK cells; induces IL-1 expression by monocytes
Interleukin 3 (IL-3)	T cells	IL-3Rα, GM-CSF-Rβ	M, N, Eo, Meg	Stimulates growth and differentiation of myeloid and erythroid precursors, induces cytokines
Interleukin 4 (IL-4)	T cells, mast cells, basophils	IL-4R	M, Ba, B, T	Induces proliferation and activation of B and T cells
Interleukin 6 (IL-6)	Ubiquitous	IL-6R/GP130	B, N	Induces activation of neutrophils; induces B-cell maturation, synergistic with IL-3
Interleukin 7 (IL-7)	Stromal cells	IL-2R	B, T, meg	Stimulates T cells; induces monocytes
Interleukin 8 (IL-8)	Stromal cells, macrophages, T cells	IL-8R	T, N	Induces neutrophils and chemotaxis
Interleukin 10 (IL-10)	T cells, macrophages	IL-10R	Meg, E	Induces B and mast cells; inhibits T cells
Interleukin 11 (IL-11)	Stromal cells	IL-11R, GP130	Meg	Stimulates megakaryocytes
Interleukin 12 (IL-12)	Neutrophils, monocytes	IL-12R	T, NK	Induces differentiation of cytotoxic T cells
Thrombopoietin (TPO)	Unknown	MPL	Meg	Stimulates megakaryocytes

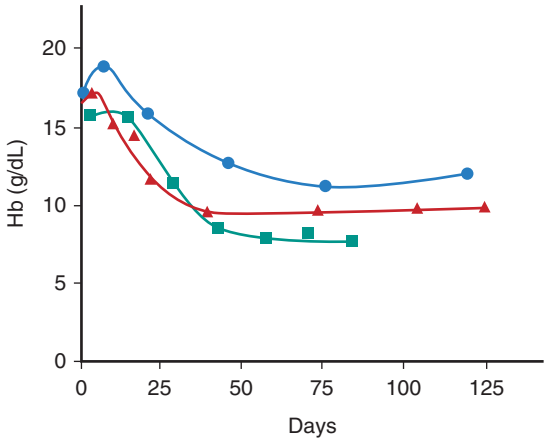
B, B cells; Ba, basophil; E, erythroid precursors; Endo, endothelial cell; Eo, eosinophil; M, monocyte; Meg, megakaryocyte; N, neutrophil; NK, natural killer cell; S, stroma cell; T, T cell.
Adapted from Bagby CC. Hematopoiesis. In: Stamatoyannopoulos G, et al., eds. *The molecular basis of blood diseases.* Vol 2. Philadelphia: Saunders; 1994:76.

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TABLE 79.3 Serum Erythropoietin Levels during Infancy

Postnatal Age (Days)	Serum EPO Level (mU/Ml)	Sample Size
0-6	33.0 ± 31.4	11
7-50	11.7 ± 3.6	7
51-100	21.1 ± 5.5	13
101-150	15.1 ± 3.9	5
151-200	17.8 ± 6.3	6
>200	23.1 ± 9.7	10

Data from Yamashita H, Kukita J, Ohga S, et al. Serum erythropoietin levels in term and preterm infants during the first year of life. *Am J Pediatr Hematol Oncol.* 1994;16:213-218.



• **Fig. 79.4** Hemoglobin concentrations in full-term and premature infants. (●) Full-term infants; (▲) premature infants, birth weight 1200-2350 g; (■) premature infants, birth weight less than 1200 g. (Adapted from Oski F. The erythrocyte and its disorders. In: Nathan D, et al., eds. *Hematology of infancy and childhood.* 4th ed. Philadelphia: Saunders; 1993:18.)

of globin exhibits distinctive functional properties. Fetal erythrocytes, which contain mostly Hb F, have a higher oxygen affinity than adult red blood cells. This allows the transport of oxygen from maternal Hb A–containing erythrocytes across the placenta to fetal red blood cells. The increased O_2 affinity of fetal hemoglobin has been ascribed to the diminished interactions of Hb F with red blood cell 2,3-BPG. Embryonic erythrocytes also display a greater affinity for oxygen than adult cells.

Erythropoietin, Erythropoiesis, and the Physiologic Anemia of Infancy

Erythropoietin (EPO), the essential glycoprotein growth factor for erythropoiesis, binds to erythropoietin receptors on early erythroid progenitor cells and via the JAK2 signaling pathway regulates RBC production by protecting them from apoptosis. Erythropoietin is produced primarily in the fetal liver and later in the cortical peritubular cells of the kidney, so that in adults renal production of EPO is the most important. Erythropoiesis is highly responsive to blood oxygenation. Hypoxia inducible factors (HIFs), constitutively expressed EPO transcription factors, are destroyed in the presence of oxygen. Under hypoxic conditions, EPO production increases. Levels of EPO in cord blood are higher than in adult blood samples (Table 79.3), but there is a dramatic decrease after birth in response to higher levels of tissue oxygenation. By 1 month of age, serum levels in healthy term infants reach their nadir. This is followed by a rise to maximal levels at 2 months of age and then a slow drift down to adult values.

The postnatal changes in tissue oxygenation and erythropoietin production result in a physiologic anemia of infancy with a mean minimal hemoglobin concentration in healthy term infants of about 11 g/dL at 8-12 weeks of life (Fig. 79.4; Table 79.4). Because of the shorter life span of RBCs in preterm infants with low EPO levels, the nadir is noted by 6 weeks of age and ranges from 7-10 g/dL. In very low birth weight (VLBW) and extremely low birth weight (ELBW) infants, the nadir is more than 20% below the value of the Hb at birth. In ELBW infants whose nadir falls below 7 g/dL, this so-called physiologic anemia of prematurity can be associated with pallor, tachypnea, tachycardia, poor feeding, and poor weight gain.[2,97] Other causes of blood loss and suppression of erythropoiesis in the ill neonate can contribute to more severe and earlier anemia. Although preterm infants will respond to hypoxia with a rise in EPO levels, the increase is lower than that expected for term infants. The suboptimal EPO response may be because of developmental changes in transcription factors or to the site of fetal EPO production. The use of recombinant EPO in premature and sick newborn infants is discussed later.

Red Blood Cell Indices during Prenatal and Postnatal Development

The RBC count, Hb concentration, and hematocrit (Hct) increase throughout gestation, as shown in Table 79.5. In term infants, the mean capillary hemoglobin at birth is 19.3 g/dL (see Table 79.4). The capillary Hct has a mean of 61 g/dL. Premature infants have lower Hb levels than do full-term infants. In addition to gestational age, Hb levels are influenced by a variety of factors that must be kept in mind when analyzing the neonate with anemia or polycythemia. One important determinant is the site of sampling: Capillary Hb values are higher than peripheral venous samples, and umbilical venous Hb results are the lowest. The interval between delivery and clamping of the umbilical cord and the height of the baby relative to the placenta can significantly affect a newborn's blood volume and total RBC mass. The placenta contains about 100 mL of blood. The mean blood volume of a full-term infant is about 85 mL/kg. Early or delayed clamping of the umbilical cord alters this mean blood volume by about 10% lower or higher,

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TABLE 79.4 Red Blood Cell Values (Capillary Samples) for Term Infants during the First 12 Weeks of Life

Age	Hb (g/dL) ± SD	RBC ($\times 10^{12}$/L) ± SD	Hematocrit (%) ± SD	MCV (fl) ± SD	MCHC (g/dL) ± SD	Reticulocytes (%) ± SD
Days						
1	19.3 ± 2.2	5.14 ± 0.7	61 ± 7.4	119 ± 9.4	31.6 ± 1.9	3.2 ± 1.4
2	19.0 ± 1.9	5.15 ± 0.8	60 ± 6.4	115 ± 7.0	31.6 ± 1.4	3.2 ± 1.3
3	18.8 ± 2.0	5.11 ± 0.7	62 ± 9.3	116 ± 5.3	31.1 ± 2.8	2.8 ± 1.7
4	18.6 ± 2.1	5.00 ± 0.6	57 ± 8.1	114 ± 7.5	32.6 ± 1.5	1.8 ± 1.1
5	17.6 ± 1.1	4.97 ± 0.4	57 ± 7.3	114 ± 8.9	30.9 ± 2.2	1.2 ± 0.2
6	17.4 ± 2.2	5.00 ± 0.7	54 ± 7.2	113 ± 10.0	32.2 ± 1.6	0.6 ± 0.2
7	17.9 ± 2.5	4.86 ± 0.6	56 ± 9.4	118 ± 11.2	32.0 ± 1.6	0.5 ± 0.4
Weeks						
1-2	17.3 ± 2.3	4.80 ± 0.8	54 ± 8.3	112 ± 19.0	32.1 ± 2.9	0.5 ± 0.3
2-3	15.6 ± 2.6	4.20 ± 0.6	46 ± 7.3	111 ± 8.2	33.9 ± 1.9	0.8 ± 0.6
3-4	14.2 ± 2.1	4.00 ± 0.6	43 ± 5.7	105 ± 7.5	33.5 ± 1.6	0.6 ± 0.3
4-5	12.7 ± 1.6	3.60 ± 0.4	36 ± 4.8	101 ± 8.1	34.9 ± 1.6	0.9 ± 0.8
5-6	11.9 ± 1.5	3.55 ± 0.4	36 ± 6.2	102 ± 10.2	34.1 ± 2.9	1.0 ± 0.7
6-7	12.0 ± 1.5	3.40 ± 0.4	36 ± 4.8	105 ± 12.0	33.8 ± 2.3	1.2 ± 0.7
7-8	11.1 ± 1.1	3.40 ± 0.4	33 ± 3.7	100 ± 13.0	33.7 ± 2.6	1.5 ± 0.7
8-9	10.7 ± 0.9	3.40 ± 0.5	31 ± 2.5	93 ± 12.0	34.1 ± 2.2	1.8 ± 1.0
9-10	11.2 ± 0.9	3.60 ± 0.3	32 ± 2.7	91 ± 9.3	34.3 ± 2.9	1.2 ± 0.6
10-11	11.4 ± 0.9	3.70 ± 0.4	34 ± 2.1	91 ± 7.7	33.2 ± 2.4	1.2 ± 0.7
11-12	11.3 ± 0.9	3.70 ± 0.3	33 ± 3.3	88 ± 7.9	34.8 ± 2.2	0.7 ± 0.3

Hb, Hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cells.
Data from Matoth Y, Zaizov R, Varsano I. Postnatal changes in some red cell parameters. *Acta Paediatr Scand.* 1971;60:317-323.

respectively. The average Hb at birth is relatively unchanged; however, 48 hours later, after redistribution of plasma volume, Hb values will reflect the lower or higher red cell mass. Racial differences also occur. One study reported significantly higher Hb, Hct, and MCV in white infants compared with black infants of similar gestational ages.[4] Reticulocyte counts in the cord blood of infants average 4%-5%, and nucleated RBCs are evident in most cord blood samples (40,000/μL). These findings are presumed to reflect high EPO production secondary to low oxygen retention in utero. Infants who experience placental insufficiency and intrauterine growth restriction have higher than normal EPO production and an even greater degree of erythrocytosis. The mean MCV of RBCs in the newborn is increased. The RBCs of the neonate have an increased Hb content, but the mean corpuscular hemoglobin concentration (MCHC) is comparable to that of adults.

Delayed (30-90 seconds) cord clamping (DCC) has been shown to prevent hypotension, raise hematocrit, and decrease the need for transfusions in preterm infants.[102] In addition, term infants who have had delayed cord clamping have reduced iron deficiency anemia in the first year of life but have an increased risk of early jaundice.[79] Thus, it has been recommended that both preterm and full-term infants undergo routine delayed cord clamping.

A new population that has also shown benefit is the neonate who has needed in utero transfusion because of red cell alloimmunization. Garabedian et al. studied a series of 72 neonates who needed in utero transfusion because of alloimmunization. Thirty-six of the neonates had DCC, and 36 neonates did not have DCC. More infants without DCC Hb had anemia at birth. The rate of transfusion, maximum level of bilirubin, the rate of intensive phototherapy, and the total duration of phototherapy were similar in the two groups. Postnatal exchange transfusions (ET) were more likely performed in the group without DCC than in the group with DCC. The interval between birth and the first transfusion was higher in the group with DCC. The authors recommended DCC with duration of 30 seconds in infants at risk for neonatal anemia because of red blood cell alloimmunization, provided that the management of jaundice is optimized.[44]

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TABLE 79.5 Red Blood Cell Values (Arterial Samples) on First Postnatal Day at Different Gestational Ages*

Variables	Group 1 23-25 Wk (*N* = 40)	Group 2 26-28 Wk (*N* = 60)	Group 3 29-31 Wk (*N* = 88)
Hematocrit (%)	43.5 ± 4.2† (36.0, 43.8, 51.0)	45.0 ± 4.5‡ (37.5, 45.0, 54.3)	48.0 ± 5.0‡† (39.4, 47.6, 56.0)
Hemoglobin (g/dL)	14.5 ±1.6 (12.0, 14.7, 17.4)	15.1 ± 1.6‡ (12.5, 15.0, 18.3)	16.2 ± 1.7‡† (13.2, 16.1, 18.8)
Mean corpuscular hemoglobin (pg)	38.6 ± 2.2† (35.0, 38.6, 43.0)	38.3 ± 2.0 (33.4, 38.4, 43.2)	37.3 ± 2.5† (32.0, 37.5, 40.6)
Mean corpuscular volume (fl)	115.6 ± 5.6† (107.0, 114.5, 125.7)	114.0 ± 7.6‡ (98.4, 114.0, 126.6)	110.4 ± 6.6†‡ (97.3, 111.2, 120.0)
Mean corpuscular hemoglobin concentration (g/dL)	33.4 ± 0.9 (32.3, 33.3, 34.6)	33.6 ± 0.6 (32.3, 33.6, 34.6)	33.7 ± 0.7 (32.5, 33.6, 34.9)
Red cell distribution width	15.9 ± 1.4 (14.2, 15.6, 18.5)	16.5 ± 1.9 (14.5, 16.0, 21.0)	16.4 ± 1.5 (14.6, 16.0, 19.4)

*Values are reported as mean ± standard deviation and 5th, 50th, and 95th percentiles in parentheses.
†*P*-value of <.01 between groups 1 and 3.
‡*P*-value of <.01 between groups 2 and 3.
Data from Alur P, Devapatla SS, Super DM, et al. Impact of race and gestational age on red blood cell indices in very low birth weight infants. *Pediatrics.* 2000;106:306-310.

Red Blood Cell Survival

The normal life span of adult RBCs is about 120 days. The life span of RBCs in newborns at term is 60-80 days and 30-50 days in ELBW infants. In general, red blood cell survival is affected by changes related to aging (senescence) and by random hemolysis of red blood cells, or portions of red blood cells, in the spleen and the rest of the reticuloendothelial system. Some of the changes in neonatal RBCs compared with adult RBCs listed in Table 79.6 affect survival. Aging erythrocytes with declining RBC enzyme activity become progressively less tolerant of oxidative challenges during the transportation of oxygen molecules and exposure to circulating oxidants. Any additional deficiencies in the enzymatic pathways of the RBC may affect the ability of the erythrocyte to tolerate oxidative challenges and further reduce red blood cell survival. With transit through the kidneys and lungs, the RBCs experience cycles of osmotic swelling and shrinkage. Shear forces in high-pressure areas of the circulation buffet the erythrocytes. Each passage through the cords of Billroth within the spleen requires the RBCs to deform and squeeze through tiny slits in the walls of the cords or face destruction if they cannot. Congenital or acquired defects in membrane stability or decreases in the ratio of surface area to red blood cell volume will also decrease erythrocyte survival. Alterations in the deformability of neonatal erythrocytes and relative intolerance to oxidative challenges result in shorter survival for neonatal red blood cells. Random hemolysis can be increased with splenic enlargement or activation of the phagocytic system. Infants with hemolysis may have exaggerated anemia because of decreased erythropoiesis, enhanced splenic filtration, and activation of phagocytes.

Red Blood Cell Disorders

Anemia

Anemia is defined by a hemoglobin or hematocrit value that is more than two standard deviations below the mean for age. In the neonate, the causes of anemia can be divided into two broad categories: anemia resulting from accelerated loss or destruction of red blood cells and anemia caused by a defect at some stage of red blood cell production (Box 79.1). The defects may be congenital or acquired, and the abnormality may be intrinsic to the RBCs or extrinsic. Anemias also may be categorized on a morphologic basis. Using the normal range of the MCV for age and gestation, the anemia may be characterized as microcytic, normocytic, or macrocytic (Box 79.2). Hypochromicity, abnormal RBC shapes (poikilocytes), polychromasia, and cell inclusions (e.g., basophilic stippling or Howell-Jolly bodies) also provide clues to the etiology of the anemia (Table 79.7).

Evaluation of Anemia

The clinician begins the evaluation of anemia by taking a thorough history. Appropriate data vary with the patient's age but often include the medical and dietary history of the pregnancy, the estimated gestational age at birth, the chronologic age, the infant's diet, and details of any previous anemia, blood loss, transfusions, medications, and illnesses, as well as the family history of anemia. The physical

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TABLE 79.6 Differences in Neonatal Red Blood Cells Compared with Adult Red Blood Cells

MCV (mean corpuscular volume)	↑
RBC count	↑
MCHC (mean corpuscular hemoglobin concentration)	↑
Surface area	↑
Reticulocyte count	↑
Resting cell diameter	↑
Hemoglobin F content	↑
Whole cell deformability	↔
Suction pressure for complete aspiration	↑
Sensitivity to osmotic lysis	↑
ATP utilization	↑
Glucose utilization	↑
Catalase glutathione peroxidase	↓
Susceptibility to oxidant injury	↑
Phospholipid, lipid, cholesterol content	↑
Loss of volume, surface area, and deformability with age	↑
Permeability to sodium and potassium	↑
I antigen expression on cell surface	↑
A, B, H blood group antigens on cell surface	↓
Life span	↓

↑, Increased; ↓, decreased; ↔, same.
Adapted from Linderkamp O, Nash GB, Paul YK, et al. Deformability and intrinsic material properties of neonatal red blood cells. *Blood*. 1966:67:1244-1250.

• BOX 79.1 Anemias by Etiology

Accelerated Loss

- Hemorrhage
  - Fetal
  - Fetal–maternal
  - Placental
  - Traumatic delivery
  - Coagulation defects
- Early umbilical cord clamping
- Twin–twin transfusion
- Excess phlebotomy losses

Accelerated Destruction

- Hemolytic anemia
  - Immune
    - Alloimmune: Rh, ABO, minor blood group
    - Autoimmune
  - Nonimmune
- Hemoglobinopathy
- Thalassemia
- Unstable hemoglobin
- Red blood cell enzyme defect
- Structural defect of red blood cell membrane
- Mechanical destruction
- Microangiopathic hemolytic anemia
- Infection
- Vitamin E deficiency

Diminished Red Blood Cell Production

- Congenital
  - Diamond-Blackfan anemia
  - Pearson syndrome
  - Fanconi anemia
  - Congenital dyserythropoietic anemias
  - Anemia of prematurity
- Acquired
  - Parvovirus B19
  - Transient erythroblastopenia of childhood
  - Human immunodeficiency virus
  - Syphilis
  - Iron deficiency
  - Lead toxicity
  - Infection

examination should evaluate the infant's general health, growth, and development. Identification of any dysmorphic features, abnormal masses, or skin lesions can aid the diagnosis (Table 79.8). The patient also should be assessed for jaundice, hepatosplenomegaly, vascular malformations, cardiovascular function, and lymphadenopathy.

The initial laboratory evaluation includes a complete blood count (CBC) with RBC indices, a reticulocyte count, and evaluation of the peripheral blood smear (Fig. 79.5). The results of the preliminary laboratory testing, combined with information from the history and physical examination, should dictate the need for further tests, such as hemoglobin analysis of the infant or parents, CBCs and blood smears of the parents, analysis of hepatic or renal function, direct or indirect antiglobulin (Coombs) testing, cultures or titers to identify infectious agents, a bone marrow aspirate or biopsy, osmotic fragility tests, and quantitative or qualitative testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The neonatal patient presents the diagnostician with a number of unique challenges. Because of the small total blood volume of the infant, who already is anemic, testing must be limited. Major pediatric medical centers can perform many of the necessary tests on very small quantities of blood, especially if the tests are appropriately batched when they are submitted. Because of the many morphologic and biochemical differences in neonatal and adult RBCs (see Table 79.6), some diagnoses are best made by testing the parents for evidence of disease or carrier states. At times, a definitive diagnosis can be made only with repeat testing later in infancy, when the infant would be expected to have a much higher percentage of adult-type RBCs or when the infant has recovered from an acute hemolytic crisis that may have destroyed the older, more biochemically or morphologically abnormal cells.

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• BOX 79.2 Classification of the Anemias According to Mean Corpuscular Volume

Macrocytic Anemia

- Reticulocytosis
- Folic acid deficiency
- B_{12} deficiency
- Bone marrow failure syndromes
  - Diamond-Blackfan anemia
  - Pearson syndrome
  - Fanconi anemia
- Down syndrome
- Myelodysplastic syndrome
- Liver disease
- Drugs (phenytoin, mercaptopurine)
- Hypothyroidism

Microcytic, Hypochromic Anemia

- Iron deficiency
- Thalassemia
- Chronic infection
- Hb E trait
- Sideroblastic anemia
- Copper deficiency
- Defects of iron metabolism
- Lead poisoning

Normocytic Anemia

- Low reticulocyte count
  - Acute blood loss
  - Infection
  - Parvovirus B19
  - Transient erythroblastopenia of childhood
  - Chronic disease
  - Drugs
  - Leukemia
  - Bone marrow infiltration
  - Liver disease
  - Renal failure
  - Aplastic anemia, acquired
- Normal or high reticulocyte count
  - Blood loss
  - Sequestration
  - Red blood cell enzyme defects
  - Immune hemolytic anemia
  - Mechanical hemolytic anemia
  - Red cell membrane defects
  - Unstable hemoglobin
  - Hemoglobinopathy

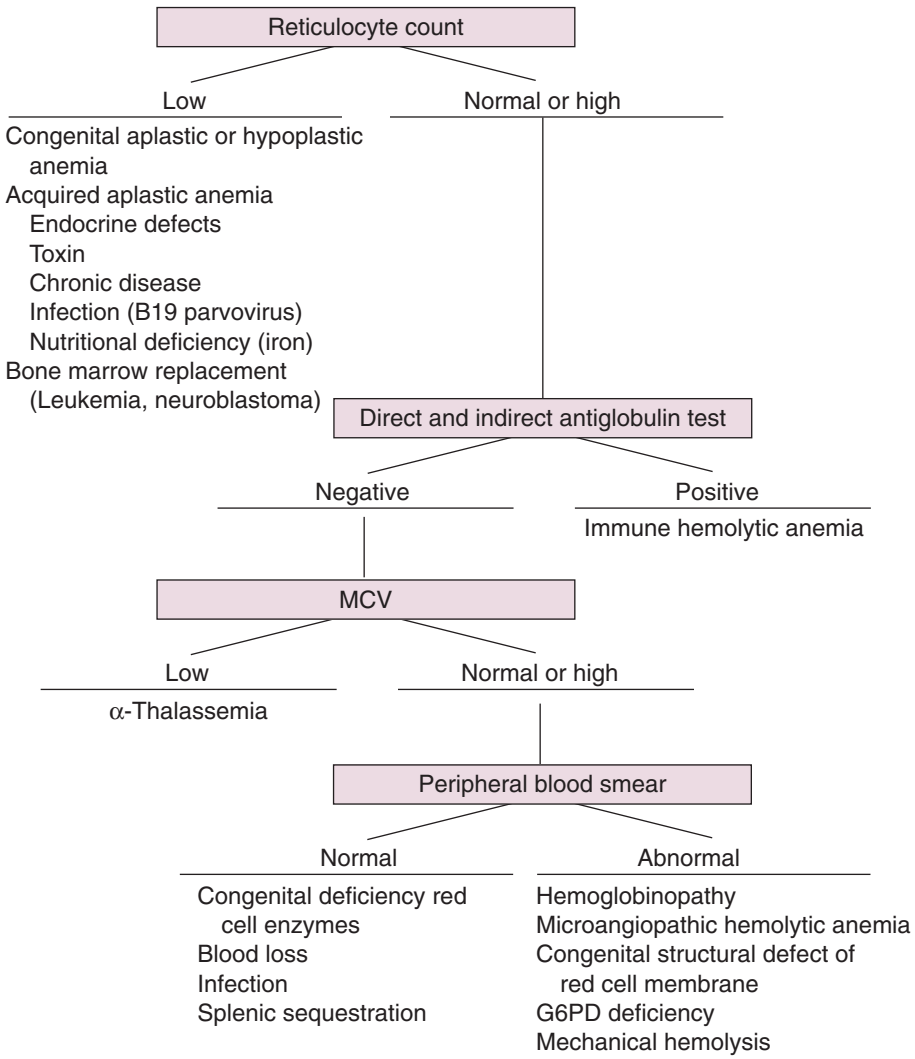
TABLE 79.7 Morphologic Findings on Peripheral Blood Smears

Morphologic Abnormality	Etiology
Acanthocytes	Alteration of lipid bilayers Liver disease Abetalipoproteinemia
Blister cells	G6PD deficiency
Basophilic stippling	Ineffective erythropoiesis: iron deficiency, lead poisoning, thalassemia, nonimmune hemolytic anemias
Elliptocytes	Structural defects of red cell membrane: hereditary elliptocytosis
Heinz bodies	Precipitated hemoglobin: normal in newborn; nonimmune hemolytic anemias
Howell-Jolly bodies	Splenic hypofunction or post splenectomy
Hypochromia	Iron deficiency, thalassemias, lead poisoning
Nucleated red blood cells	Normal in newborn; hemolytic anemias, semi-acute blood loss
Polychromasia	Normal in newborn; reticulocytosis
Pyropoikilocytosis	Neonates with hereditary elliptocytosis, hereditary pyropoikilocytosis, thermal injury of red cells (burn)
Rouleaux	Increased fibrinogen, inflammation
Schistocytes	Microangiopathic hemolytic anemias
Sickle cells	Hemoglobin SS and sickle variants
Spherocytes	Decreased cell membrane: volume—IgG+ hemolytic anemia, hereditary spherocytosis, artifact of area of blood smear
Target cells	Increased red blood cell surface: volume ratio Alteration in lipid structure of red blood cell membrane Hemoglobin C, hemoglobin S, thalassemias, liver disease, abetalipoproteinemia

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TABLE 79.8 Physical Findings in Neonatal Anemia

Physical Finding	Etiology
"Blueberry muffin" spots	Extramedullary hematopoiesis, replacement of bone marrow by tumor, congenital infection
Cardiac disease/mechanical heart valve	"Waring blender" syndrome
Congestive heart failure	Chronic anemia
Dysmorphic features	Bone marrow failure syndromes: Diamond-Blackfan anemia, Fanconi anemia, Shwachman-Diamond syndrome, Pearson syndrome Down syndrome Myelodysplastic syndrome
Failure to thrive	Pearson syndrome Shwachman-Diamond syndrome
Hepatosplenomegaly	Congenital infection, storage disorder, malignancy, hypersplenism, hemangioma, hemolytic anemia, transient abnormal myelopoiesis
Jaundice	Hemolytic anemia
Kaposiform hemangioendothelioma	Kasabach-Merritt syndrome
Microcephaly	Congenital infection Bone marrow failure syndrome
Short stature	Congenital bone marrow failure syndrome



• **Fig. 79.5** Algorithm for diagnosis of anemia in the neonate. MCV, Mean corpuscular volume.

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Rationale for Transfusion Therapy

See Chapter 80 for discussion of liberal versus restrictive transfusion practices in preterm infants. Because the primary function of the RBC is to transport oxygen from the pulmonary bed to other tissues for release, anemia diminishes oxygen-carrying capacity and can compromise tissue oxygenation. Tissue oxygenation is a complex concept involving not only the Hb concentration but also the oxygen affinity of the Hb in the patient's red blood cells, blood viscosity, and the patient's cardiorespiratory status. The only absolute indications for rapidly correcting anemia by RBC transfusion are to restore tissue oxygenation and to expand blood volume after severe, acute loss. In most pediatric centers, the sicker patients, especially those with cardiopulmonary dysfunction, receive transfusions to maintain the Hb closer to normal for age. Neonatal exchange transfusions are also performed with the goal of replacing "doomed" infant RBCs with healthy adult RBCs, which have superior oxygen-transporting ability. This has the triple benefit of limiting hyperbilirubinemia and other byproducts of RBC breakdown, reducing the body load of maternal antibodies, and supplementing with cells that contain Hb A.

Anemia Caused by Blood Loss

Blood loss can occur in the fetus, at birth, or in the postnatal period. The bleeding can be acute or chronic. Anemia caused by chronic blood loss generally is better tolerated because the neonate will at least partly compensate for a gradual reduction in RBC mass. Chronic blood loss can be diagnosed by identifying signs of compensation. Doppler assessment of the fetal middle cerebral artery peak systolic velocity is a noninvasive method for determination of fetal anemia, independent of the etiology. The infant may be pale and may exhibit signs and symptoms of congestive heart failure. Anemia will be present, often with reticulocytosis, hypochromia, and microcytosis.

An infant with acute blood loss may not be anemic if blood sampling is done soon enough after the acute event so that hemodilution has not yet occurred. Anemia usually develops within 3-4 hours after blood loss; repeat testing 6-12 hours after the event should reveal the true extent of the loss. In acute blood loss, the infant may exhibit signs and symptoms of hypovolemia and hypoxemia (e.g., tachycardia, tachypnea, hypotension). The RBCs should be morphologically normal. With either kind of hemorrhage, infants tend to have fewer problems with hyperbilirubinemia, because they have a reduced RBC mass. Jaundice can result if entrapped RBCs in a hematoma break down.

Internal bleeding can occur if the fetus has anatomic abnormalities or defects in the hemostatic system or with interventional obstetric procedures. A surprisingly large amount of blood can be lost within a cephalohematoma, and even greater bleeding can occur in the subaponeurotic area of the scalp (subgaleal hemorrhage), where bleeding is not limited by periosteal attachments. Traumatic or assisted deliveries and vitamin K deficiency are commonly associated with such bleeding. Full-term infants may have intracranial bleeding, which usually occurs in the subarachnoid or subdural regions. Full-term infants with intracranial hemorrhage should be evaluated for hemostasis abnormalities, because this type of bleeding is associated with qualitative and quantitative platelet defects and with abnormalities of several of the coagulation proteins. Hemorrhage into the adrenals, kidneys, liver, spleen, or retroperitoneum also can occur after difficult or breech deliveries. Splenic or hepatic rupture can occur after trauma, especially if the organs are enlarged as a result of extramedullary hematopoiesis. Occult or superficial vascular tumors can bleed and sequester large volumes of red blood cells and platelets.

Maternal factors can cause prenatal blood loss. Maternal history of vaginal bleeding, placenta previa, abruptio placentae, nonelective cesarean delivery, and cord compression are associated with anemia. Hemorrhage from the umbilical cord may be the result of intrinsic vascular abnormalities, inflammation of the cord, velamentous insertion of the cord, coagulation defects, or an unusually short cord. A normal cord can rupture during a precipitous or assisted delivery or if it becomes tangled around the infant. Accidental incision of the placenta during delivery also can result in bleeding.

Fetal–Maternal Hemorrhage

Fetal cells may be found in the maternal circulation in about half of all pregnancies. At 20 weeks' gestation, the fetoplacental volume is 30 mL, and it is rare for transplacental hemorrhage to exceed 1 mL of fetal red blood cells. By term, fetal–maternal hemorrhage (FMH) during delivery can exceed 30 mL of fetal blood, although in only 0.3% of pregnancies.[61] Fetal–maternal hemorrhage is associated with procedures such as external cephalic version or traumatic amniocentesis. The diagnosis is made by demonstrating fetal RBCs, which contain mostly Hb F, in a maternal blood sample; therefore, the analysis must be done before the fetal cells are cleared from the maternal circulation. The test usually is performed within the first few hours after delivery. In cases of ABO blood group incompatibility, the red blood cells may be cleared more rapidly, and the test may be falsely negative.

The prevention of maternal Rh D alloimmunization requires accurate detection and quantification of fetal blood cells in the maternal circulation. If a D-negative mother has evidence of FMH, Rh immune globulin (Rh IgG) can reduce D-sensitization and the resultant hemolytic disease of the newborn. Vaginal or peripheral blood samples from women with vaginal bleeding late in pregnancy may also be evaluated for the presence of fetal blood cells. The rosette screen is a sensitive, FDA-approved screening test for FMH when the mother is D-negative. Maternal red blood cells are incubated with anti-D and then washed. Indicator D-cells are added, and in the presence of fetal D-positive cells, aggregates or rosettes will be seen by light microscopy. Confirmation of a positive screening test is performed with a quantitative method. The acid elution

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technique, or Kleihauer-Betke test, is the most widely available quantitative test for FMH. This method exploits the stability of Hb F–containing RBCs in acid solution relative to cells containing Hb A. False-positive test results are seen in women with any condition (including many of the hemoglobinopathies) that elevates their own Hb F level. The Kleihauer-Betke test suffers from problems with standardization and is labor intensive. Some centers now offer flow cytometry–based quantification of FMH by detecting either Hb F or Rh D or a combination. Flow cytometry can distinguish adult F cells from fetal RBCs.[61]

Twin–Twin Transfusion Syndrome

In monochorionic diamniotic multiple gestations, twin–twin transfusion syndrome (TTTS) (see Chapter 21) can be diagnosed by ultrasound-demonstrating oligohydramnios in the donor sac and polyhydramnios in the recipient sac. Twin–twin transfusion syndrome occurs in 8%-10% of twin pregnancies with monochorionic diamniotic placentation and accounts for about half of the perinatal deaths.[87,118] Twin anemia polycythemia sequence (TAPS) is defined as the presence of anemia in the donor and polycythemia in the recipient twin. Prenatal middle cerebral artery peak systolic velocity criteria have been established for diagnosis in the absence of oligohydramnios–polyhydramnios. Blood can be exchanged unequally between the fetuses through placental vascular interfetal connections. Transfusion can be problematic for the hypovolemic donor who develops oligohydramnios, but the recipient often experiences greater difficulties with hyperbilirubinemia, hypervolemia, and hyperviscosity that arise from the increased RBC mass. Cardiac, neurologic, and developmental disorders have been associated with TTTS.[87,118]

Hemolytic Anemia: Accelerated Red Blood Cell Destruction

Accelerated destruction of RBCs is the end point of a number of intrinsic, extrinsic, congenital, and acquired RBC abnormalities. Because the RBCs of premature infants and newborns have a shorter life span, *hemolysis* is defined as a process that shortens the survival of the RBCs relative to the expected life span for the infant's gestational and postnatal age. In contrast to anemia caused by blood loss, most infants with hemolysis have some evidence of indirect hyperbilirubinemia and elevated lactate dehydrogenase for age. Reticulocytosis should accompany the hemolysis, although in conditions complicated by bone marrow suppression (congenital infections, chronic illness, or nutritional deficiency) or decreased erythropoietin production, the reticulocyte count may be inappropriately low for the degree of anemia present. With maximal response, the bone marrow can compensate for RBC survival of 20-30 days without anemia. The bone marrow may show hyperplasia and a reversal of the usual myeloid-to-erythroid ratio of 3 : 1. Because optimal conditions for bone marrow response are not present in the newborn, hemolysis with anemia and hyperbilirubinemia may be evident in the neonate. In chronic hemolytic states, compensatory hypertrophy of the bone marrow may result in bony changes and other evidence of extramedullary hematopoiesis. Intrinsic hemolytic anemias are caused by inherited abnormalities of the RBC membrane, hemoglobin, or RBC intracellular enzymes. Some intrinsic hemolytic anemias also result in extrinsic damage to the RBC membrane. Extrinsic factors cause hemolytic anemia by damaging the RBC chemically, physically, or immunologically. Extrinsic hemolysis can be divided into immune and nonimmune etiologies (see Box 79.1); the most common causes of immune hemolytic anemia are discussed first.

Immune Hemolytic Anemia

Alloimmune Hemolytic Anemia

Alloimmune hemolytic disease of the newborn (HDN) (see Chapter 23) is caused by the destruction of fetal or neonatal RBCs by maternal immunoglobulin G (IgG) antibodies. Alloimmune HDN involves the major blood group antigens of the Rhesus (Rh) and the A, B, AB, and O systems, but minor blood group incompatibilities (Kell, Duffy, MNS, and P systems) can also be associated with clinically significant disease. Particularly for Rh (D), anti-c, anti-E, and anti-K (Kell) antibodies, intrauterine or direct fetal transfusion may be indicated prenatally, and exchange transfusion may be necessary postnatally. Maternal IgG antibodies can cross the placenta, enter the fetal circulation and cause hemolysis, anemia, hyperbilirubinemia, and hydrops fetalis. In utero, the process is called *erythroblastosis fetalis*, whereas postnatally it is called *hemolytic disease of the newborn* (HDN). Maternal sensitization occurs through a prior transfusion of incompatible RBCs after fetal–maternal hemorrhage of incompatible fetal RBCs or from production of a pre-existing antibody developed against antigens from bacteria, viruses, or food. Transfer of antibodies across the placenta depends on the F_c component of the IgG molecule. Because both IgM and IgA antibodies lack this component, only IgG antibodies cause hemolytic disease of the newborn. Immunoglobulin G_1 antibodies cross the placenta earlier and are responsible for more prenatal hemolysis. Immunoglobulin G_3 antibodies cross the placenta later in gestation and are responsible for more severe hemolysis postnatally.

Rh Hemolytic Disease. The original description of HDN was caused by Rh D incompatibility, and it remains the most severe cause. The spectrum of clinical problems caused by Rh HDN ranges from mild, self-limited hemolytic anemia to hydrops fetalis. With the widespread use of antenatal and postpartum Rh immunoglobulin administration, Rh D sensitization is less common in pregnancies when prenatal care is received. Most cases today are caused by failure to administer Rh immunoglobulin when indicated, lack of identification of a large FMH, and chronic transplacental hemorrhage.

The Rh antigens are inherited as a linked group of two genes, *RHD* and *RHCE*, located on chromosome 1. Persons are typed as Rh negative or positive based on the expression

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TABLE 79.9 Prevalence of Rh-Negative Genotype (CDE/cde) by Population

Population Group	Percent Affected
European whites	11-21
US whites	14.4
Indians (India)	8
US African Americans	5.5
Native Americans	0
Chinese	0
Japanese	0

Adapted from Prokop O, et al. *Human blood and serum groups.* Barking, UK: Elsevier; 1969.

of the major D antigen on the RBC, and their RBCs will also express C or c and E or e antigens. Rarely, Rh deletions of D, C/c, and E/e loci can occur. Anti-c and anti-E are emerging as the most frequent causes of HDN as the incidence of Rh(D) disease decreases. The incidence of Rh disease depends on the prevalence of Rh-negative antigens in the population studied (Table 79.9). Even in white populations, only a small percentage of pregnancies are affected because not all women who are Rh negative develop antibodies, Rh immunization of the mother does not usually occur during the first pregnancy, and some of the second infants will be Rh negative.

Because the interaction of the anti-D IgG with a D-positive RBC does not usually involve complement, hemolysis is extravascular. Hyperbilirubinemia and jaundice can occur in the first day of life when the placenta is no longer available to clear bilirubin from hemolyzed RBCs. The peripheral blood smear may show anemia, reticulocytosis, and macrocytosis. Microspherocytes are usually not seen in Rh disease. A direct antiglobulin (Coombs) test should demonstrate anti-D IgG. Partial or total exchange transfusions may be necessary to reduce the load of antibody and remove the antibody-coated cells. Management of hyperbilirubinemia is discussed in Chapter 91.

ABO Hemolytic Disease. Although the incidence of blood group O mothers delivering babies of blood group A or B is about 15%, ABO hemolytic disease is estimated to occur in only 3% of pregnancies and requires treatment with exchange transfusion in less than 0.1% of pregnancies. In contrast to Rh hemolytic disease, ABO hemolytic disease tends to be less severe, and the severity does not depend on birth order. Most anti-A and anti-B antibodies are IgM molecules, which do not cross the placenta. However, maternal anti-A or anti-B IgG antibodies, which may have been raised against A or B substances occurring in food or on bacteria or in response to fetal–maternal hemorrhage, can cross the placenta and react with the sparsely distributed A or B antigens on the neonatal RBCs. Hemolysis is primarily extravascular. Infants may develop anemia, reticulocytosis, and hyperbilirubinemia within the first 24 hours of life. The hallmark of ABO hemolytic disease (in contrast to Rh disease) is the presence of microspherocytes on the peripheral blood smear. The direct antiglobulin test (DAT), or Coombs test, should be at least weakly positive for anti-A or anti-B; however, because of the sparse distribution of antigenic sites on a newborn's RBCs, ABO hemolytic disease may be present even without a positive result on the DAT. The maternal serum should have high titers of IgG directed against A or B (positive indirect antiglobulin test or IAT, which is the indirect Coombs test). In the absence of clinical hemolytic disease, laboratory evidence of erythrocyte sensitization should not be considered HDN.

Minor Blood Group Hemolytic Diseases. The incidence of HDN for minor blood group antigens is related to the antigenicity of the particular blood group antigen and the expression of that antigen on fetal RBCs. Maternal antibodies against minor blood group antigens develop after exposure from a transfusion or prior pregnancy or from contact with bacteria or viruses that express the antigen. Hemolytic disease of the newborn has been associated with the minor group antigens Kell, Duffy, MNS system, and P system. Most clinically significant HDN not attributed to ABO or Rh incompatibility is caused by anti-Kell, anti-E, and anti-c. Kell HDN may require intrauterine intervention. The severity of anti-Kell HDN is owing both to hemolysis and suppression of erythropoiesis in progenitor cells. Screening for minor group antibodies is recommended for all women in the 34th week of pregnancy: Routine screening with cells containing only high-frequency antigens would not detect antibodies to low-frequency antigens. The diagnosis and treatment of hemolytic disease are identical to those for Rh hemolytic disease. Identification of low-frequency antibodies associated with HDN is especially important for mothers who plan additional pregnancies. The role of IVIG in treatment of neonatal hemolytic disease, especially ABO incompatibility, is discussed in Chapter 91.

Natural History of Hemolytic Diseases of the Newborn. Hydrops fetalis is the most severe consequence of hemolysis, but anemia generally is less problematic than hyperbilirubinemia in the acute phase of illness. Hyperbilirubinemia may be evident within the first 24 hours of life. Anemia can occur in the first few weeks in both those who received exchange transfusions and those who required only phototherapy for management of hyperbilirubinemia. The anemia can be caused by ongoing hemolysis, hypersplenism, inadequate replacement by transfused red blood cells, and shortened survival of transfused red blood cells. Because the half-life of IgG molecules is about 28 days, hemolysis should resolve within the first 3 or 4 months. Resolution often occurs sooner if the antibodies are cleared by adhering to RBCs or by exchange transfusion. Thrombocytopenia and bleeding can complicate hemolytic disease. Usually, thrombocytopenia without other laboratory evidence of disseminated intravascular coagulation (DIC) is noted, but DIC can be triggered by massive hemolysis or shock and acidosis.

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Other Immune Hemolytic Anemias

The other immune hemolytic diseases of early childhood are relatively rare. Autoimmune hemolytic anemia occurs, as do anemias associated with infections, drugs, and immunodeficiency syndromes. IgG antibodies, with or without complement, are often directed against one of the Rh erythrocyte antigens. These antibodies are most active at 37°C and often are called *warm autoantibodies*. The IgG-coated cells, with or without the assistance of complement, are cleared by the spleen and, to a lesser extent, by the liver. Congenital infections (syphilis, cytomegalovirus, rubella, toxoplasmosis, herpes, HIV, hepatitis) and acquired infections can cause hemolytic anemia and bone marrow suppression with reticulocytopenia (see Chapters 48, 49, and 50). Immunoglobulin M autoantibodies can cause disease and are usually referred to as *cold agglutinins*, because they are most active at between 0°C and 30°C. These antibodies, with complement, coat RBCs and are usually cleared in the liver. Intravascular hemolysis is less common. The best-known causes of cold hemagglutinin disease are *Mycoplasma pneumoniae*, adenovirus, and Epstein-Barr virus. Immunoglobulin A–mediated hemolysis is quite rare but is remarkable for its severity (Table 79.10).

The natural history of autoimmune hemolytic disease in infancy is that of a rapid onset of anemia with hyperbilirubinemia, splenomegaly or hepatomegaly, and hemoglobinuria (with intravascular hemolysis). Initially, reticulocytopenia may be noted, especially if antibodies are directed against RBC progenitors in the bone marrow, but a brisk reticulocytosis usually follows. Resolution within 3-6 months is common. Anemia with reticulocytosis and spherocytosis may be seen on the peripheral blood smear, but the diagnosis depends on demonstration of antibody-coated cells, with or without complement, in the DAT and antibodies in the serum by the IAT. Therapy includes treatment of underlying infection, removal of the offending drug, and supportive measures to limit hyperbilirubinemia. Response to corticosteroids is common, as is complete recovery. Steroids are less effective in IgM-mediated disease. A subset of patients younger than 2 years, and with a slower onset of disease at presentation, develops chronic hemolytic anemia. Difficulties with identifying compatible blood during a hemolytic crisis, as well as the usually self-limited nature of the disease, restrict blood transfusions to cases in which severe anemia impairs tissue oxygenation.

TABLE 79.10 Acute Hemolytic Anemia: Causative Mechanisms and Representative Infectious Agents

Mechanism	Infectious Agent
Hemolysin production	*Clostridium perfringens*
Direct invasion of RBCs	Malaria
Alteration of RBC surface:	
Adherence to RBCs	*Bartonella* organisms
Neuramidase alters antigenic phenotype	Influenza virus
Cold agglutinin	Epstein-Barr virus
Absorption of capsular polysaccharide	*Haemophilus influenza*
Microangiopathy	Any agent causing disseminated intravascular coagulation or hemolytic-uremic syndrome
Enhanced oxidative stress	*Campylobacter jejuni* enteritis in neonates with a diminished cytochrome-b_5 reductase system

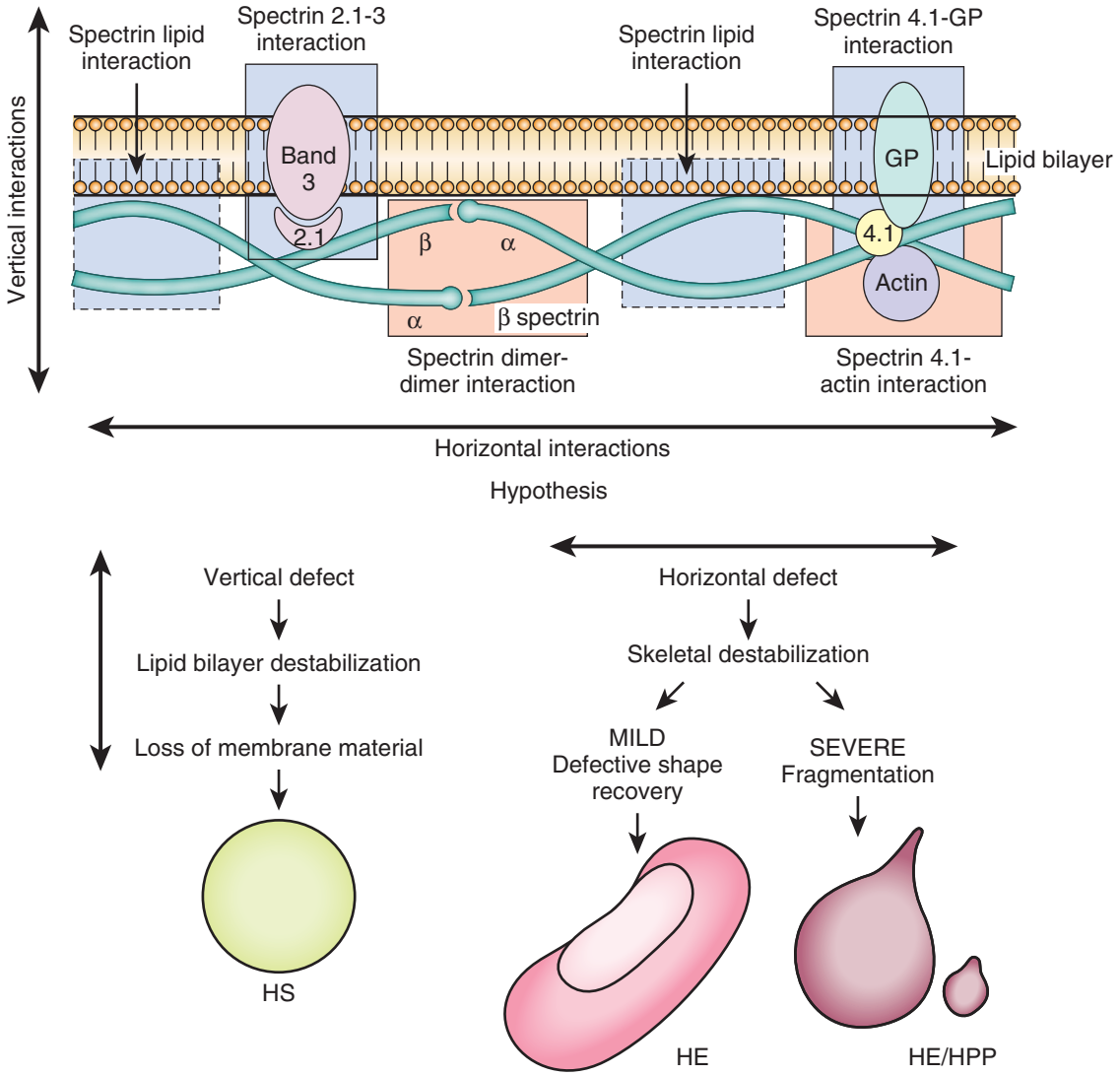
From Ritchey AK, et al. Hematologic manifestations of childhood illness. In: Hoffman R, et al., eds. *Hematology: basic principles and practice.* 2nd ed. New York: Churchill Livingstone; 1995:1722.

Nonimmune Hemolytic Anemia

Erythrocyte Structural Defects

During its lifetime, a normal RBC traverses the circulation thousands of times, enduring tremendous mechanical and metabolic stress with each passage. The smallest capillaries have an internal diameter that is smaller than the diameter of the RBC; thus the blood cells must deform to squeeze through the capillaries and then return to their normal shape as they enter distal venules. During their rapid transit, the RBCs must endure tremendous fluctuations in pH, Po_2, and osmotic pressure. The lipid bilayer that forms the cell membrane is the site of numerous biologic functions mediated by integral proteins. It also is the attachment site for the proteins of the cytoskeleton, which confer the shape and stability necessary for proper membrane function. Some abnormalities in the membrane-cytoskeleton unit result in morphologic defects of RBCs (Fig. 79.6). Because abnormally shaped RBCs are removed from the circulation by the reticuloendothelial system, many of these defects cause some degree of hemolytic anemia. Analysis of these congenital defects has led to an understanding of the erythrocyte membrane and cytoskeleton. The more common erythrocyte cytoskeletal defects originally were described by morphologic and clinical criteria. With better understanding of the cytoskeleton at a molecular level, it became clear that various mutations in genes coding for a few structural proteins are responsible for a family of inherited hemolytic anemias with overlapping morphologic, clinical, and genetic features. Mutations in the genes encoding α-spectrin, β-spectrin, ankyrin, protein 4.1, glycophorin C, protein 4.2, and band 3 have been reported in patients with hereditary defects of the red blood cell membrane/cytoskeleton.[17,91] Inherited hemolytic anemias caused by RBC membranopathy, enzymopathy, and hemoglobinopathy are generally diagnosed by using conventional methods, including RBC morphology, membrane protein analysis, Hb electrophoresis, and measurement of RBC enzyme levels. In the genetic era, Sanger sequencing has been useful for detecting genetic mutations that cause inherited hemolytic anemias. Sanger

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• **Fig. 79.6** Molecular origins of hereditary spherocytosis (HS) and hereditary elliptocytosis-pyropoikilocytosis (HE/HPP) based on the hypothesis of vertical and horizontal defects. Vertical interactions are those needed to stabilize the attachment of the spectrin lattice to the lipid bilayer. Abnormalities in this attachment result in destabilization of the lipid bilayer, membrane loss during splenic conditioning, and HS. Horizontal interactions reversibly hold spectrin dimers and tetramers together, allowing stretching and distortion of the red blood cell membrane during circulation. Weakening of these interactions results in loss of elasticity. GP, Glycoproteins. (Adapted from Palek J. Red cell membrane disorders. In: Hoffman R, et al., eds. *Hematology: basic principles and practice*. New York: Churchill Livingstone; 1991:472.)

sequencing is widely applied to identify disease-causing mutations in cases where traditional testing has failed or when a patient has been extensively transfused, leading to confounding biochemical and other testing findings caused by mixed RBC populations. Recent advances in genetic technology using next generation sequencing have enabled better identification of various genetic mutations that can cause these conditions.[60]

Membrane defects associated with hemolytic anemia may present in the neonate with hepatosplenomegaly, hyperbilirubinemia, and hemolytic anemia. Aplastic crisis, attributed to drugs or an infectious agent such as parvovirus B19, or splenic sequestration, may cause life-threatening anemia in patients with hemolytic anemia. The more severe cases of hemolytic anemia can require splenectomy, although surgery generally is delayed beyond the first few years of life.

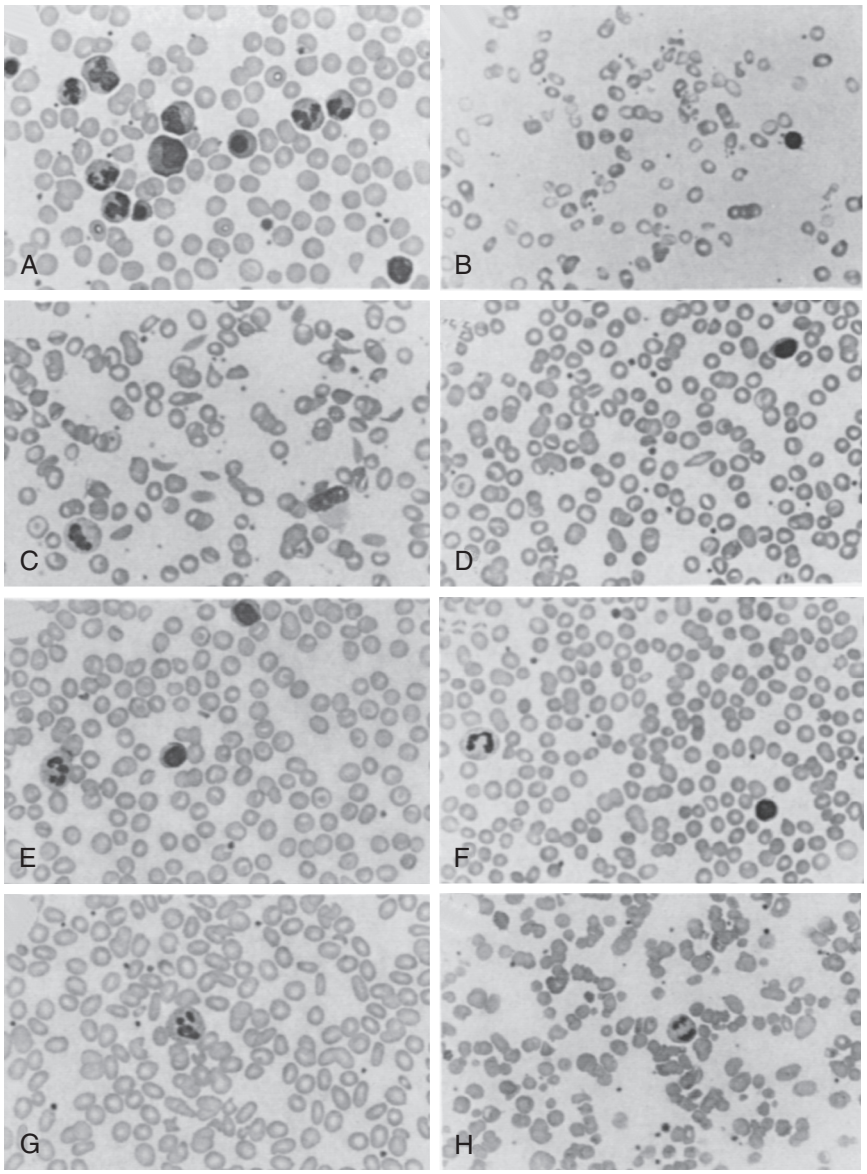
Hereditary Spherocytosis. Hereditary spherocytosis (HS) is characterized by the appearance of spherocytes on the peripheral blood smear, accompanied by a hemolytic anemia of varying severity and splenomegaly. Hereditary spherocytosis occurs predominantly in those of Northern European ancestry. Inheritance usually is autosomal dominant, but autosomal recessive and autosomal dominant inheritance with reduced penetrance also have been reported. Spontaneous mutations account for about one-fourth of HS. The defects alter the vertical stability of the cytoskeletal attachment to the lipid bilayer so that pieces of untethered membrane are removed in the spleen. Defects

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or deficiency in ankyrin are the most common, although defects in spectrin, band 3, and protein 4.2 also occur. Nondeformable spherocytes with a decrease in the surface area are more susceptible to lysis with exposure to the metabolic and deformation stresses of the splenic sinuses or with incubation in hyposmolar solutions. The osmotic fragility test exposes the suspected cells and normal control cells to progressively more hypotonic solutions and compares their ability to resist lysis.[16,18]

Hereditary Elliptocytosis and Hereditary Pyropoikilocytosis. The findings on the peripheral blood smears in hereditary elliptocytosis and hereditary pyropoikilocytosis are distinct (Fig. 79.7). Hereditary elliptocytosis (HE) is an autosomal dominant condition characterized by elliptical RBCs called ovalocytes, which is more common in people of African and Mediterranean origin. In hereditary pyropoikilocytosis (HPP), the RBC morphology is bizarre, marked by fragments, elliptocytes, and spiculated cells. The disorders are caused by defects in cytoskeletal proteins, most commonly α- or β-spectrin, which weaken the horizontal interactions necessary for cytoskeletal stability and reversible deformability (see Fig. 79.6). The deformed RBCs are prematurely cleared by the reticuloendothelial system. Hemolysis in HE generally is milder than in hereditary spherocytosis. The majority of those with HE are symptomatic. Hereditary pyropoikilocytosis is caused by homozygous or compound heterozygous defects.[16,18] Some neonates with HE may exhibit hemolysis with HPP morphology on blood smear, but later in life their red blood cells will appear as typical elliptocytes. Hereditary pyropoikilocytosis is associated with more severe hemolysis and hyperbilirubinemia, often requiring exchange transfusion or phototherapy in the neonatal period. Examination of blood smears from each parent may be helpful in making this diagnosis.

Southeast Asian ovalocytosis (SAO), or stomatic elliptocytosis, is a mild hemolytic variant of HE, which is common



• **Fig. 79.7** Peripheral blood smears. **A,** Premature newborn of 26 weeks' gestation. **B,** Iron deficiency. **C,** Hemoglobin SS. **D,** Hemoglobin SC. **E,** Hemoglobin CC. **F,** Hereditary spherocytosis. **G,** Hereditary elliptocytosis. **H,** Hereditary pyropoikilocytosis.

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in Southeast Asia, likely because it confers malaria resistance. Defects in band 3 are the most common.[16,18]

Spherocytic elliptocytosis, characterized by spherocytes and elliptocytes and a mild hemolysis, occurs in those of European ancestry.[16,18]

Membrane Lipid Defects

Membrane lipid abnormalities can be inherited but most often are acquired. Their presence, detected by morphologic abnormalities on the peripheral blood smear, is most important as the signal of an underlying disease. Target cells form when the surface-to-volume ratio of the red blood cell increases, either because of poorly hemoglobinated cells (iron deficiency, thalassemias, Hb C) or because lipids are added to the RBC membrane (liver disease with intrahepatic cholestasis, lecithin-cholesterol acyltransferase deficiency). Acanthocytes form when the membrane lipid composition between the inner and outer leaflets of the bilayer is altered, as in liver disease and abetalipoproteinemia.

Inherited Enzymatic Defects

The mature RBC, lacking a nucleus, polyribosomes, and mitochondria with which to carry out protein synthesis, must circulate through extremes of pH, Po_2, and osmotic gradients while maintaining deformability and integrity. Red blood cells metabolize glucose through the Embden-Meyerhof pathway and hexose monophosphate shunt to provide energy for maintaining ionic pumps, to reduce methemoglobin, and to synthesize small molecules such as adenine, guanine, pyrimidine nucleotides, glutathione, and lipids. The most commonly defective enzyme, glucose-6-phosphate dehydrogenase (G6PD), has been extensively evaluated at the clinical, biochemical, and molecular level. Many other enzymatic defects have been reported, but the rarity of the disorders has hindered investigation. Enzymatic defects of the RBC known to be associated with hemolytic anemia are listed in Box 79.3. A few of the enzyme deficiencies cause abnormalities in other tissues. The end result of these defects is hemolytic anemia of varying severity, sometimes called *hereditary nonspherocytic anemia*. The RBCs may be morphologically normal and usually produce normal results on osmotic fragility testing, but they have a shorter life span. The milder cases cause little difficulty in the neonatal period. Some defects are associated with chronic and/or severe hemolysis, necessitating intermittent or chronic blood transfusions.

Glucose-6-phosphate dehydrogenase deficiency is the only common defect of RBC enzymes and can be associated with severe hemolysis, anemia, and hyperbilirubinemia in the neonate, although many are asymptomatic. This enzymatic defect is common in infants with bilirubin encephalopathy. Occasionally, the hyperbilirubinemia is severe, because of an interaction of G6PD deficiency with the $(TA)_7$ promoter polymorphism of the UDP-glucuronosyltransferase 1A1 (UGT1A1) bilirubin-conjugating enzyme.[57] The prevalence among some ethnic groups suggests a selective advantage, because deficient cells are resistant to malaria. As an enzyme in the pentose phosphate pathway, G6PD supplies NADPH, and by producing hydrogen ions, promotes reduction of glutathione. Deficiency limits the cell's ability to recover from oxidative stress. The gene is inherited as an X-linked recessive. Males are affected most commonly. Females may also be affected, either because of homozygosity or compound heterozygosity, or in cases in which X-inactivation is unbalanced. In the United States, African-American males are the most commonly affected. The A-minus variant, common in Africans, results in a mild reduction in both catalytic activity and stability. The B variant, common among Mediterranean, some Asian, and Ashkenazi Jewish populations, involves a severe reduction of enzyme activity, resulting in chronic, moderate-to-severe hemolytic anemia that could prove fatal in the face of severe oxidant challenge. In affected patients, the oldest RBCs are most deficient, resulting in a normal or minimally shortened erythrocyte life span, but exposure to oxidant drugs and toxins or a febrile episode can precipitate severe hemolysis. Hemolysis occurs within 24-48 hours of exposure and is accompanied by abdominal pain, vomiting, diarrhea, low-grade fever, jaundice, splenomegaly, hemoglobinuria, and anemia.

Neonates may present with hemolytic anemia and hyperbilirubinemia within 24 hours of life and are susceptible to developing methemoglobinemia. Management involves

• BOX 79.3 Red Blood Cell Enzymatic Defects Associated with Hemolysis

Pentose Phosphate Pathway

- Glucose-6-phosphate dehydrogenase*

Glycolytic Pathway

- Pyruvate kinase†
- Hexokinase
- Glucose phosphate isomerase
- Phosphofructokinase
- Aldolase
- Triose phosphate isomerase
- Glyceraldehyde-3-phosphate dehydrogenase
- Phosphoglycerate kinase
- 2,3-Diphosphoglycerate mutase
- Enolase

Hexose Monophosphate Pathway

- Glutathione synthetase
- γ-Glutamyl cysteine synthetase
- Glutathione reductase
- Glutathione S-transferase
- Glutathione peroxidase

Erythrocyte Nucleotide Metabolism

- Elevated adenosine deaminase levels
- Pyrimidine 5′-nucleotidase
- Adenylate kinase

*Most common defect worldwide.
†Second most common defect.

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avoidance of precipitating agents, hydration, phototherapy and, if needed, transfusion (partial volume exchange or simple). Common drugs to be avoided or used with caution in this disorder include antimalarials, sulfonamides and sulfones, nitrofurans, anthelminthics, ciprofloxacin, methylene blue, acetaminophen, aspirin, and vitamin K analogues. An excellent resource for complete food and drug lists, as well as family education, is at https://www.g6pd.org (accessed May 4, 2018). Enzyme levels are highest in younger cells. Evaluation immediately after a hemolytic episode could be inconclusive because the older, abnormal cells have been destroyed. Repeat quantitative testing at a later time, as well as evaluation of maternal enzyme levels, can be useful. Some states and countries include GPD deficiency screening as part of their newborn screening program, using biochemical qualitation, biochemical quantitative assays, and DNA-based PCR screening for common mutations.[57,93]

Vitamin E Deficiency

Vitamin E is a fat-soluble antioxidant that reduces the peroxidation of polyunsaturated fatty acids by reactive oxygen species during oxidative enzyme activity. Preterm infants and infants with low birth weight have low serum and tissue levels of this vitamin. Patients who have chronic fat malabsorption are the most likely to develop symptomatic vitamin E deficiency. A deficiency state in preterm infants and those with very low birth weight has been described, characterized by hemolytic anemia, reticulocytosis, thrombocytosis, chronic lung disease, intracranial hemorrhage, and retinopathy of prematurity. However, present evidence does not support routine supplementation with intravenous or high-dose vitamin E in neonates.

The Thalassemias

The thalassemias are a group of hereditary anemias that arise from quantitative defects in the synthesis of globin chains. In their milder forms, thalassemias are among the most common heritable disorders. The α-thalassemias are most common in the Chinese subcontinent, Malaysia, Indochina, and Africa. β-Thalassemia is common in Mediterranean and African populations but also has a higher incidence in China, Pakistan, India, and the Middle East. Hemoglobin E is common in Southeast Asia. The four α-thalassemia syndromes (silent carrier, α-thalassemia trait, Hb H disease, and hydrops fetalis) are caused by diminished production of α-globin protein because of deletion in one, two, three, or four of the α-globin genes, respectively. Although only two genes for β-globin production are inherited, there are four clinical classifications for β-thalassemia: silent carrier, β-thalassemia trait, thalassemia intermedia, and thalassemia major. The blood smear shows hypochromic microcytes, target cells, and nucleated RBCs. Bizarre RBC shapes and fragments are seen in more severe disease. The clinical outcome in this disease is a result of complex interactions involving the type of genetic defect, the degree of β-globin production, and the ratio of α-globin chains produced relative to the number of β-globin chains (Table 79.11). Abnormal hemoglobin tetramers can accumulate in the bone marrow and reticuloendothelial system, resulting in ineffective erythropoiesis. Mutant hemoglobins can precipitate to form inclusion bodies that adhere to cell membranes, promote oxidative damage to the membrane, diminish cell deformability, and shorten RBC survival. Coinheritance of α- and β-globin defects may result in a less severe thalassemia, because the ratio of α- to β-globin chains is rebalanced.

Prenatal diagnosis strategies are available for both α- and β-thalassemia. If evaluation of the parents' RBCs provides evidence of thalassemia, molecular detection strategies can be used. Fetal tissue from chorionic villus sampling (10-12 weeks' gestation) or amniocentesis (15-20 weeks) can be analyzed by a number of DNA-based methodologies (see Chapter 10). After 18-20 weeks' gestation, fetal reticulocytes may be tested for globin chain biosynthetic ratios, although sampling carries higher risks.

α-Thalassemia

Because the production of α-globin chains predominates from midgestation onward, defects in synthesis can be

TABLE 79.11 Effects of Thalassemia Mutations

Thalassemia Defect	Product	Result	Outcome
Absent or reduced globin production	α:β Globins ratio altered	Precipitation of excess globins RBC membrane damage	Abnormal hemoglobin pattern Hemolysis Thrombosis
		Ineffective erythropoiesis	Basophilic stippling Hypochromia Microcytosis Reticulocytosis
		Anemia	Bone marrow expansion Extramedullary hematopoiesis Iron hyperabsorption

RBC, Red blood cell.

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detected at birth. Before the debut of molecular analysis, the various α-thalassemia syndromes were assigned according to clinical criteria (Table 79.12). Hydrops fetalis, the most severe and rarest form of α-thalassemia, occurs when an infant inherits deletions of both α-globin genes from each of the parents (see Chapter 23). Such an infant produces small quantities of Hb Portland to maintain in utero viability. The excess γ and β chains form tetramers with themselves, resulting in functionally useless Hb Barts (γ_4), present in the newborn, and Hb H (β_4) present in the older infant. The fetus with four α-globin gene defects experiences congestive heart failure in utero secondary to severe anemia and, in the absence of fetal transfusion, becomes grossly hydropic (hydrops fetalis). There is evidence of extensive extramedullary hematopoiesis and placental hypertrophy. Most are stillborn at 30-40 weeks' gestation or die shortly after delivery. Infants with hepatosplenomegaly, jaundice, and a moderate hypochromic, microcytic hemolytic anemia should be evaluated for deletion of three α-globin genes, Hb H disease. At birth, large amounts of Hb Barts may be seen as well as some Hb H. Incubation of the RBCs with brilliant cresyl blue reveals many small inclusions. Treatment is supportive and includes supplementation with folic acid, avoidance of oxidant drugs, transfusion of RBCs, and attention to iron hyperabsorption and transfusional iron overload. Hypersplenism,

TABLE 79.12 The Thalassemias

α-Thalassemia Genotype	Number of α Genes Deleted	Phenotype
αα/αα	0	Normal
αα/α–	1	Silent carrier
α–/α– αα/– –	2	Alpha thalassemia trait, trans Alpha thalassemia trait, cis
α–/– – – –/$\alpha^{cs}\alpha$	3	Hemoglobin H Hemoglobin H-Constant Spring
– –/– –	4	Hydrops fetalis
β-Thalassemia Genotype	**Phenotype**	**Clinical Implications**
β/β	Normal	Normal
β/β^+ β/β^0	β-Thalassemia minor (trait)	Microcytosis Hypochromia Increased Hb F, Hb A2 Basophilic stippling Occasional target cells
$\beta^{+/}\beta^+$ β^+/β^0 β^E/β^+ β^E/β^0	β-Thalassemia intermedia	Moderate microcytosis Moderate-severe anemia Moderate hypochromia Basophilic stippling Target cells Increased Hb F, Hb A2 Variable transfusion dependence Hepatosplenomegaly variable Iron hyperabsorption
β^0/β^0	β-Thalassemia major	Severe microcytosis, hypochromia, target cells Increased Hb F, Hb A2 Transfusion dependence Hepatosplenomegaly Iron hyperabsorption Transfusional iron overload
Hemoglobin E Genotype	**Phenotype**	**Clinical Features**
β/ε	Hb E Trait	Microcytosis
ε/ε	Hb E Disease	Microcytosis Mild anemia
ε/β^+	Hb E/β^+-Thalassemia	Moderate microcytosis Moderate anemia
ε/β^0	Hb E/β^0-Thalassemia	Moderate-severe microcytosis β-Thalassemia intermedia

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characterized by leukopenia, thrombocytopenia, and worsening anemia, may necessitate splenectomy, although this usually is deferred beyond the first few years of life and is associated with infectious risk as well as increased thrombosis.

α-Thalassemia trait is characterized by a mild anemia with microcytosis, hypochromia, and erythrocytosis. Hemoglobin Barts is mildly elevated at birth. After the neonatal period, there is no simple laboratory evaluation that is diagnostic for α-thalassemia trait. Alpha globin gene analysis can be ordered to confirm clinical suspicion. The diagnosis usually is made in an iron-replete patient with a normal hemoglobin electrophoresis and appropriate family history for α-thalassemia. As the name implies, silent carriers of α-thalassemia could have slightly microcytic RBCs but usually are asymptomatic. Several states now use molecular testing for *HBA1* and *HBA2*, the genes coding for α_1- and α_2-globin, respectively.

β-Thalassemia

β-Thalassemia is not usually diagnosed at birth unless blood loss or RBC destruction has created an unusually high demand for replacement of fetal RBCs with adult. The disease generally manifests after 6 months of age, when a microcytic anemia persists beyond the time course for physiologic anemia. The more severe manifestations of the disease traditionally were called *Cooley anemia*, but these have been separated into *thalassemia major* and *thalassemia intermedia* (see Table 79.12). Affected patients exhibit splenomegaly, poor growth, microcytic hemolytic anemia with ineffective erythropoiesis, target cells on the peripheral blood smear, and extramedullary expansion of erythropoiesis. An abnormal hemoglobin analysis reveals elevations of Hb F and Hb A_2 and a decrease in Hb A.

Patients are categorized as having thalassemia intermedia if they are able to maintain a hemoglobin level greater than 7 g/dL without routine transfusion. Thalassemia major patients require regular transfusions and iron chelation therapy to maintain a hemoglobin value adequate for growth and development. Iron overload is a significant cause of morbidity and mortality starting in the second decade of life. Evidence of hypersplenism may necessitate splenectomy. Bony deformities from expansion of extramedullary hematopoiesis occur in incompletely transfused patients.

β-Thalassemia trait is characterized by abnormalities on the blood smear: microcytosis, hypochromia, erythrocytosis, and the appearance of elliptocytes and target cells. Hemoglobin analysis reveals a mild elevation of Hb A_2 and Hb F, although this is not observed if the genetic mutation also interferes with production of δ- or γ-globin or if Hb A_2 and Hb F production are depressed because of coexistent iron deficiency anemia. The silent carrier state of β-thalassemia is associated with normal findings on the peripheral blood smear and hemoglobin electrophoresis and usually is identified through family studies of patients with a more severe β-thalassemia syndrome.

Hemoglobin E

Hemoglobin E causes one of the most common hemoglobinopathies in the world. This thalassemia syndrome, characterized as a qualitative and quantitative hemoglobinopathy, is particularly abundant among people of Southeast Asian ancestry, especially individuals from Laos, Cambodia, and Thailand. Hemoglobin E is generated by a single nucleotide substitution, Glu26Lys, in the coding region of the β-globin gene. The β-globin monomers associate normally with a pair of α-globin proteins to form a functional hemoglobin tetramer with essentially normal stability and oxygen-dissociation characteristics. Persons with Hb E are anemic because the mutation creates a cryptic splice site in the β-globin message. During RNA processing, a portion of the message is spliced into an abnormal, unstable transcript. Consequently, the total level of β-globin messenger RNA is reduced, resulting in a thalassemia phenotype. Hemoglobin E trait results in mild microcytosis. Those who are homozygous for Hb E have chronic, mild to moderate, microcytic anemia but are otherwise well; however, co-inheritance of an Hb E allele from one parent and a β-thalassemia allele from the other produces a moderate to severe anemia that can be transfusion dependent. Hemoglobin levels in these patients range from 2-7 g/dL, and children with this condition can develop hepatosplenomegaly and growth failure. Hemoglobin E-β^0 thalassemia disease now is the most common form of transfusion-dependent thalassemia in the United States and other parts of the world. Hemoglobin E co-inherited with Hb S results in a sickle phenotype.

Inefficient erythropoiesis is the main mechanism underlying the complications in thalassemia major, such as anemia, splenomegaly, bone malformations, and pulmonary hypertension. New knowledge has become available on pathways that contribute to the pathogenesis and clinical manifestations of this disease. Clinical trials with JAK2 inhibitors (ruxolitinib) and TGF-β family member inhibitors, sotatercept and luspatercept, are currently studying the benefits of these agents in decreasing ineffective erythropoiesis and splenomegaly.[7,88,130]

Another modality of treatment for hemoglobinopathies is gene therapy, which is showing its safety and potential efficacy in both preclinical and early clinical studies. Gene therapy is now a reality, with seven patients cured of their β0/βE thalassemia or with significant amelioration from β0/β0 thalassemia and one patient with SCD, while others are showing modest transgene expression.[42,47,73,103]

Qualitative Defects in Hemoglobin: Hemoglobin Variants

In the fetus, switching from one type of globin chain expression to another occurs several times (see Fig. 79.2), and during the first few months of the postnatal period, the final switch to the adult-type hemoglobin occurs. Some hereditary defects in fetal globin gene products can produce a hemolytic anemia that resolves as β-globin gene expression predominates. Similarly, a neonate who is asymptomatic at birth can develop a hemolytic anemia over the subsequent

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months as production of β-globin–containing hemoglobin assumes major importance. Because α chains are produced from the fetal period onward, defects in α-globin are present at birth. If the combination of the mutant α- and the γ-globin is more unstable than that of α- and β-globin or α- and δ-globin, the infant experiences a transient hemolytic anemia that resolves as Hb A predominates.

More than 500 structurally different hemoglobin variants have been reported. The clinically important variants are listed in Box 79.4. Most involve a single amino acid substitution in one of the globin polypeptide chains owing to a single nucleotide change in DNA. Other variants are the result of gene deletions or duplications caused by unequal crossover.

Unstable Hemoglobins

Most mutations causing unstable hemoglobin affect β-globin and involve amino acid substitutions in hydrophobic residues around the heme pocket. These amino acid replacements alter the hydrophobic interior of the molecule, predisposing the hemoglobin to instability and precipitation as small round inclusions known as Heinz bodies. Because the amino acid substitutions often involve replacing one neutral amino acid with another, the hemoglobin electrophoretic mobility may not change. Patients usually develop anemia and jaundice in late infancy as β-globin synthesis increases. Mutations in fetal or embryonic globins can cause symptoms at birth but not later in life. The diagnosis is confirmed by supravital staining for Heinz bodies, which are usually present, and hemoglobin analysis after isopropanol precipitation.

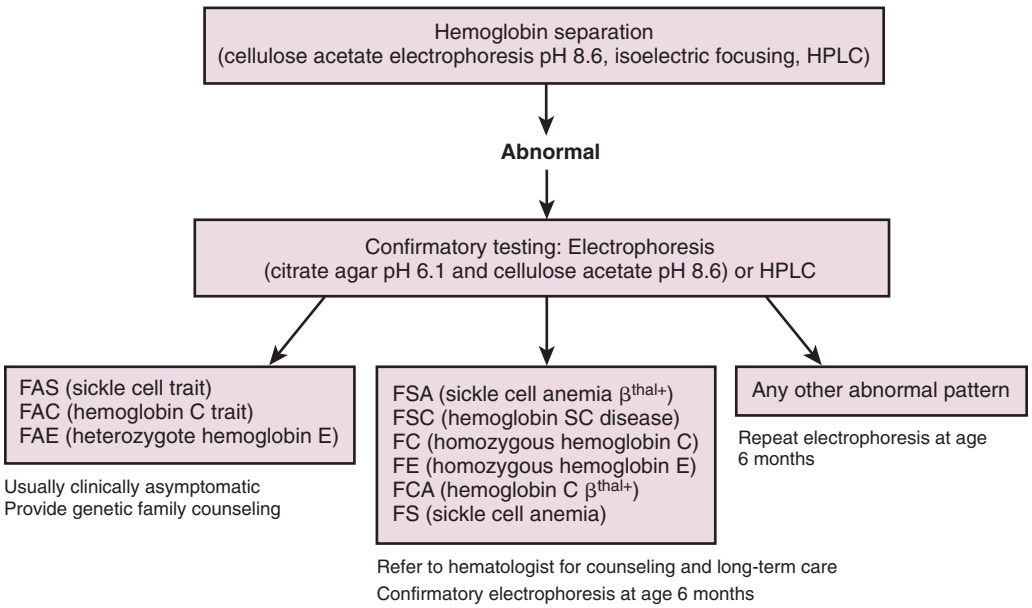
• BOX 79.4 Qualitative Hemoglobin (Hb) Variants

Alteration in Hb Function	Example
Increased oxygen affinity	Hb F, Hb Syracuse
Decreased oxygen affinity	Hb Kansas
Increased heme iron oxidation	Hb M, methemoglobin
Unstable	Hb Hasharon
Decreased solubility	Hb S, Hb C

Sickle Cell Anemia

Sickle cell disease is a common medical problem in the United States, where 1 in 400 newborns is affected. By definition, *sickle cell anemia* refers to the doubly heterozygous inheritance of abnormal genes that code for the substitution of valine in place of glutamic acid at position six in the β chain of hemoglobin (Hb SS). There are also a number of sickle hemoglobinopathies in which one gene coding for Hb S is inherited along with a second abnormal β-globin gene coding for other hemoglobins, such as Hb C, D, O^{Arab}, or β-thalassemia. The clinical course of affected patients may be indistinguishable from, or milder than, those of Hb SS disease. As with the thalassemias, prenatal diagnostic techniques are available. Newborn screening programs have been instituted in many parts of the world, including most of the United States. Samples of cord or capillary blood are subjected to testing, usually hemoglobin electrophoresis, high pressure liquid chromatography, or isoelectric focusing. Infants with abnormal results on the newborn screen are referred for confirmatory testing and disease counseling (Fig. 79.8; Box 79.5).

The clinical hallmark of Hb SS disease is hemolytic anemia with reticulocytosis and the appearance of irreversibly sickled cells on the peripheral blood smear. The onset of signs and symptoms correlates with the decrease in Hb



• Fig. 79.8 Algorithm for investigating abnormal results on hemoglobinopathy screening tests in newborns. FAC, FAE, FAS, FC, FCA, FE, FS, FSA, FSC are all sickle-cell traits; HPLC, high-performance liquid chromatography.

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• BOX 79.5 Common Newborn Screen Hemoglobin Patterns

Hemoglobin Pattern	Interpretation
FA	Normal
FAS	Sickle cell trait
FSC	Sickle C disease (Hb SC)
FS	Sickle cell disease or sickle β^0-thalassemia
FSA	Sickle β^+-thalassemia
FVA	Hb variant with β^+-thalassemia
FAV	Heterozygous or trait variant 2%-8% Barts—α-thalassemia trait 25%-50% Hb Barts—hemoglobin H disease
FV	Hb variant with β^0-thalassemia
FVV	Double heterozygous variant
FSV	Sickle Hb and variant Hb SO^{arab} and Hb SD are sickle hemoglobinopathies FS and Hb Barts—sickle cell disease with α-thalassemia
F	Very premature infant Absence of β globin production

F levels and increasing expression of the mutant β-globin gene products during the first year of life. Neonates generally are asymptomatic, although older infants are at risk for several disease-related complications. Because of splenic dysfunction, infections with certain bacteria, such as pneumococcus, are a major cause of mortality and morbidity in infants and young children. A suddenly pale, listless infant may be experiencing life-threatening anemia caused by hepatic or splenic sequestration. Aplastic crisis, triggered by infection or drugs, also may occur. Vaso-occlusive crisis of the infant's hands and feet, the hand–foot syndrome (dactylitis), manifests with pain, warmth, and swelling of the hands and/or feet.

Identification of affected newborns through newborn screening programs with enhancements in parent education and supportive care such as penicillin prophylaxis, immunization against *S. pneumoniae* and *H. influenzae*, and early identification of hepatic or splenic sequestration have decreased the death rate for infants and children. The natural history of sickle cell anemia includes painful vaso-occlusive events, acute and chronic lung disease, stroke, overwhelming sepsis from splenic dysfunction, avascular necrosis of joints, retinopathy, and transfusion-related iron overload. The National Heart, Lung and Blood Institute (NHLBI) issued management guidelines for sickle cell disease in 2002, which are available at https://www.nhlbi.nih.gov/files/docs/guidelines/sc_mngt.pdf. Treatment of the sickle hemoglobinopathies has been largely supported using penicillin prophylaxis; vaccinations; blood transfusions with extended RBC phenotyping; cross-matching to decrease the incidence of transfusion-associated alloimmunization; and hydration, narcotics, and nonsteroidal anti-inflammatory drugs for painful crises. Hydroxyurea decreased the number and severity of vaso-occlusive pain events in infants and young children with Hb SS and Hb SB^0 thalassemia in the randomized, placebo-controlled BABY HUG study.[131] Stem cell transplantation, the only established cure for sickle cell anemia, has been limited by the availability of suitable donors and the uncertainty in predicting which children will express a more severe phenotype. Ongoing studies using reduced intensity conditioning regimens and alternative donor options, as well as risk stratification of sickle cell patients, may allow larger number of patients to undergo stem cell transplantation in the future.

Sickle Cell Trait

Heterozygotes for Hb S (sickle cell trait) were thought to be clinically unaffected, but there are reports of hematuria, decreased urinary concentrating ability, and occasional reports of sudden death related to high altitude and extreme exercise. Associations have been made between sickle cell trait and venous thrombosis, renal medullary carcinoma, and a more severe course of diabetes mellitus.

When to Use Molecular Testing for Patients with Hemoglobin Disorders

Patients suspected of having hemoglobin disorders are screened with a CBC and hemoglobin analysis. Depending on the results and whether there are genetic counseling issues to consider, molecular testing for globin abnormalities may be indicated. Patients with ambiguous hemoglobin results or unusual phenotypes are candidates for DNA testing. Couples seeking genetic counseling should be offered DNA testing when both prospective parents are suspected of having *cis* α-globin deletions or both have β-thalassemia traits. In addition, individuals with β-thalassemia trait or hemoglobin E trait may have coincident α-thalassemia trait that is masked by the microcytosis associated with these β-globin disorders. In such cases α-globin DNA testing might be advised to evaluate risk to offspring of hemoglobin Bart's hydrops fetalis. Prenatal genetic testing should be offered to couples at risk for having an offspring with clinically severe hemoglobin disorders.[111]

Anemia Caused by Inefficient Production of Red Blood Cells

Iron Deficiency Anemia

Although the prevalence of iron deficiency anemia is decreasing in the United States, it remains a major cause of anemia in infants and children, and it has been associated with adverse neurocognitive outcomes. Factors associated with the declining rates of iron deficiency anemia include the increasing number of infants receiving breast milk, the use of standard iron-supplemented infant formulas and iron-supplemented baby cereals during the first year of life, and the delay of the introduction of cow milk into the infant diet until after 1 year of age.

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Iron is an essential nutrient. Most iron is bound to the heme proteins, hemoglobin, and myoglobin. The storage proteins ferritin and hemosiderin contain most of the rest of the iron. A small percentage is bound in enzyme systems such as cytochromes and catalase. In healthy adults, most of the body's iron is recycled from the breakdown of RBCs. Little iron needs to be absorbed from the intestines, and little is lost through fecal or urinary excretion. Because neonates must rapidly expand muscle mass and blood volume, they require a much higher percentage of dietary iron intake. The amount of iron stored in the neonate's body is proportional to birth weight. Eighty percent of a term infant's iron is acquired during the third trimester.[11] For a full-term infant, this should be sufficient for the first 4-6 months of life. Preterm infants and those born small for gestational age have a much faster rate of postnatal growth and are at risk for iron deficiency within the first 3 months of life (Box 79.6). Infants born anemic and those who have accelerated iron losses from repeated laboratory testing, trauma, surgery, or anatomic abnormalities may also become deficient. Although both breast milk and cow milk contain iron, the bioavailability of the iron in breast milk is much superior. The American Academy of Pediatrics (AAP) Committee on Nutrition updated its recommendations for diagnosing and preventing iron deficiency and iron deficiency anemia in 2010 (Table 79.13).[11] Full-term infants who are breastfed should not require iron supplementation until 4-6 months of age. At 4 months of age, human milk–fed infants should receive iron supplementation until they are eating iron-containing foods. Two daily servings of an iron-fortified cereal will meet this requirement. Infant cereal fortified with iron should be one of the earliest solid foods introduced. After 6 months of age, one daily serving of a vitamin C–rich food should be introduced. Because the protein in cow milk can cause occult gastrointestinal bleeding in the neonate and because of the poor bioavailability of iron in cow milk, it is recommended that babies avoid cow milk until after 1 year of age. In general, preterm infants who are fed human milk require iron supplementation after 1 month of age, either by a supplement added to the breast milk or iron given directly to the infant. An exception may be made for infants who have received multiple blood transfusions and are thus at risk for iron overload rather than deficiency. A thought-provoking, randomized, placebo-controlled trial of daily oral iron supplementation in very low birth weight infants (<1500 g) of less than 32 weeks' gestational age, who were managed on a liberal transfusion strategy, did not demonstrate an increase in the hematocrit, reticulocyte count, or transfusion requirements at week 36 postmenstrual age.[124]

With improved survival in the smallest patients, additional knowledge gaps and opportunities for investigation are identified in diagnosing, treating, and preventing iron deficiency and iron deficiency anemia (Box 79.7). Although severe iron deficiency in children is fairly simple to

• BOX 79.6 Risk Factors for Iron Deficiency Anemia in Infants

- Prematurity
- Small for gestational age
- Anemia at birth
- Fetal–maternal hemorrhage
- Twin–twin transfusion
- Perinatal hemorrhage
- Iatrogenic or other ongoing blood loss
- Insufficient dietary intake or malabsorption
- Early introduction of cow milk
- Erythropoietin use
- Maternal conditions: severe iron deficiency, diabetes

TABLE 79.13 Guidelines for Iron Supplementation for Infants in the First Year of Life

Birth Status	Intake	Minimum Daily Recommendation	How Supplied
Term, healthy	Human milk	1 mg/kg per day after 4 mo of age until addition of complementary iron-rich foods	Iron supplement until addition of complementary iron-rich foods
Term, healthy	>Half human milk	1 mg/kg per day after 4 mo of age until addition of complementary iron-rich foods	Iron supplement until addition of complementary iron-rich foods
Term, healthy	Standard infant formula	1 mg/kg per day after 4 mo of age	Supplied by standard infant formula and/or addition of complementary iron-rich foods
Preterm	Human milk	2 mg/kg per day beginning at 1 mo of age and until 12 mo of age	Supplement added to human milk or given separately until addition of complementary iron-rich foods
Preterm	Standard infant formula	2 mg/kg per day beginning at 1 mo of age and until 12 mo of age	Supplied by full feeds of standard infant formula and/or complementary iron-rich foods

Adapted from Baker RD, Greer FR, Committee on Nutrition American Academy of Pediatrics. Clinical report—diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics.* 2010;125:1040-1050.

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• BOX 79.7 Challenges in the Diagnosis and Treatment of Iron Deficiency and Iron Deficiency Anemia in Neonates

- Optimal lab testing for premature infants
- Optimal formulation of iron supplementation
- Optimal iron preparation
- Optimal dose and interval of supplementation
- Duration of iron supplementation
- Incidence and proper management of adverse effects of iron supplementation

Adapted from Buchanan GR. Paucity of clinical trials in iron deficiency: lessons learned from study of VLBW infants. *Pediatrics*. 2013;131:e582-e584.

diagnose, milder deficiency may not yet have caused anemia or may be difficult to distinguish from other causes of microcytic anemia, especially in patients with chronic or acute illness. The AAP recommends that testing for anemia by hemoglobin estimation should occur at approximately 12 months of age. In addition, there should be an assessment of risk factors for iron deficiency/iron deficiency anemia at that time. Earlier and/or more frequent assessments should occur in situations of high concern. A careful dietary history should be taken, and consideration should be given to special circumstances such as ongoing blood loss, malabsorption, early or excessive cow milk intake, and birth history. In early iron deficiency, the bone marrow stores are depleted and the RBC distribution width increases. Subsequently, the iron transporter levels fall, resulting in lower serum levels of iron, ferritin, and transferrin in the term infant. Finally, erythrocyte production is affected. A hypochromic, microcytic anemia becomes apparent. Screening test results such as serum iron, total iron-binding capacity, ferritin, and transferrin saturation may be inconclusive because of acute or chronic illness. It is unclear what testing is optimal in the premature infant. The AAP favors the reticulocyte Hb concentration (CHr) and the serum transferrin receptor 1 (TfR1), because these tests are not affected by inflammation or infection, but these tests are not widely available. A therapeutic trial of iron for presumptive iron deficiency anemia is a cost-effective strategy. Ferrous sulfate, in a dose of 2-6 mg/kg per day of elemental iron, may be given for 1 month. If the hemoglobin rises by at least 1 g/dL (in the absence of ongoing blood loss), the diagnosis of iron deficiency is made, and the iron supplementation is usually continued for 2-3 more months or until 1-2 months after the hemoglobin is in the normal range. Screening for lead exposure should be done as part of routine well-baby care and particularly considered if a hypochromia and microcytosis are detected.

Iron Transport Proteins and Iron Homeostasis

Our knowledge of iron biology has been enriched substantially by the recent discovery of mammalian iron transport proteins (DMT1, ferroportin, mitoferrin 1, and ZIP14), heme transporters (HRG1and FLVCR1), iron chaperones (PCBPs), ferrireductases and ferroxidases (DCYTB, STEAP3, PrPc, and hephaestin), and the iron-regulatory hormone hepcidin. The physiologic function of these proteins has been studied to a great extent and the implications of their up-and-down regulation.

We have learned in depth the mechanisms through which iron is transported in the gut. Iron is transported out of the enterocyte and into portal blood via ferroportin (SLC40A1) located on the basolateral membrane. Ferroportin transports only Fe2+, whereas transferrin in portal blood will bind only Fe3+. Efficient transfer of iron to portal blood transferrin is thought to involve an oxidation step catalyzed by a ferroxidase. The best characterized intestinal ferroxidase is hephaestin, a membrane-anchored homologue of the plasma ferroxidase, ceruloplasmin.

Iron Metabolism in Erythrocyte Precursors

Greater than 95% of iron in plasma is bound to its circulating transport protein transferrin, which delivers most of its iron to erythrocyte precursors (i.e., erythroid progenitor cells of the bone marrow that differentiate into mature RBCs). Each day, ~25 mg of iron is taken up into these cells to support the daily production of 200 billion new RBCs. Erythrocyte precursors take up iron nearly exclusively from transferrin via transferrin receptor 1 (TFR1). The quantitative importance of this uptake is illustrated by the fact that an estimated 80% of total body cellular TFR1 is located in the erythroid marrow of an adult human. When transferrin binds to TFR1 at the cell surface, the complex is internalized into endosomes, which become acidified, causing iron to dissociate from transferrin. The endosomal ferrireductase STEAP3 (six-transmembrane epithelial antigen of the prostate 3) reduces the liberated Fe3+ to Fe2+, which is subsequently transported into the cytosol via DMT1.[62,96] Despite being the most avid consumers of iron in the body, erythrocyte precursors abundantly express ferroportin at the plasma membrane and are therefore able to export nonheme iron. Systemic iron depletion has been shown to increase ferroportin expression in erythrocyte precursors, leading to the hypothesis that upregulation of ferroportin in iron deficiency serves to provide iron to nonerythropoietic tissues.[63]

The hepatically produced peptide, hepcidin, is an important regulator of iron homeostasis. It inhibits the transport of iron across the gut mucosa as well as the transport of iron out of macrophages. Hepcidin is an acute-phase reactant: in inflammation, increased hepcidin results in decreased iron absorption. Overexpression of hepcidin in genetically modified mice results in iron deficiency anemia. This has led to interest in human defects of hepcidin overexpression that may result in the inability to absorb iron (i.e., refractoriness to oral iron).[69] Conversely, the intestinal hyperabsorption of iron in thalassemias is associated with low hepcidin levels.

Physiologic Anemia of Infancy and Physiologic Anemia of Prematurity: The Role of Erythropoietin

The physiologic anemia of infancy can be exaggerated in the sick or premature infant by frequent blood sampling: the

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smaller the infant, the proportionally greater the volume of blood that is withdrawn for laboratory testing. Most RBC transfusions in neonates occur within the first 3-4 weeks of life, with the majority being in the first 2 weeks. Physiologically lower levels of EPO in neonates provided the rationale for the pharmacologic use of erythropoietin to reduce the volume and risks of blood transfusions. Recombinant erythropoietin products are commercially available and have been used for decades in the treatment of adults with renal disease and in cancer-associated anemia. The Food and Drug Administration (FDA) mandated black box warnings for EPO because of increased risks of death, myocardial infarction, stroke, venous thrombosis, and cancer progression in adult patients. These complications have not been seen in neonates. Two approaches to EPO therapy have been systematically reviewed in neonates and reported in a 2017 Cochrane database systematic review.[2,97] The early approach, defined by the use of EPO before day 8 of life, has been shown to reduce (but not eliminate) RBC transfusions and donor exposures but did not impact morbidity and mortality measures. The later use of EPO (on day 8 of life or after) resulted in a reduction in the number of blood transfusions but not the total volume of blood, per infant, so that meaningful clinical outcomes were not affected by the use of EPO. Because most infants received RBC transfusions very early and before being enrolled in the clinical trials evaluating this question, the authors concluded that the critical effort should be aimed at preventing donor exposures in the very first few days of life.[2,97] Stable and larger preterm infants have a better response to EPO therapy when compared with ELBW infants. Erythropoiesis requires iron. Even though EPO administration has been shown to reduce hepcidin levels, thereby increasing intestinal iron absorption, ferritin levels have been reported to drop with EPO use. Supplementation of between 1 mg/kg per day and 10 mg/kg per day elemental iron has been used to lessen the risk of iron deficiency.[2,97]

Transient Erythroblastopenia of Childhood

Transient erythroblastopenia of childhood (TEC) is an acquired, transient, normocytic, hypoplastic anemia with a peak incidence at ages 2-3 years. It is exceedingly rare in neonates. The etiology of TEC is unknown but may be the result of viral injury to erythroid precursors. Familial cases have been reported. The degree of anemia can range from moderate to severe. Transient erythroblastopenia of childhood is a diagnosis of retrospect. Treatment consists of supportive measures, including RBC transfusion if needed, until bone marrow recovery. Most patients recover in 1-2 months. The condition may be confused with Diamond-Blackfan anemia and parvovirus-induced anemias.

Parvovirus-Induced Anemia

Parvovirus B19, which proliferates in human erythroid precursors, causes several diseases. The majority of adults in the United States have antibodies to the virus. The virus produces fifth disease. The rash and joint symptoms associated with this generally minor illness are caused by vascular deposition of antibody complexes generated in response to the infection. In patients with underlying hemolytic anemias, parvovirus infection can cause a transient, severe aplastic crisis. It can also cause chronic anemia from a persistent infection in erythroblasts in immunocompromised hosts. Chronic parvovirus anemia responds to administration of intravenous immunoglobulin. The virus binds to blood group P-antigen on the surface of erythroid precursors, is internalized, and then replicates, disrupting normal erythroid differentiation. Endothelial cell P-antigen is postulated to participate in placental transmission of the virus. This antigen is also found on fetal cardiomyocytes, a finding consistent with the fact that the fetus infected with parvovirus can develop myocarditis. Infection rate during pregnancy is estimated to be in the 3% range. Parvovirus infection during pregnancy can result in anemia, hydrops fetalis, fetal loss, or congenital infection. The rate of transplacental transmission of the virus has been estimated at 33%. Initial reports of high rates of stillbirth and fetal loss have been modified; it is recognized that most of the mortality occurs during the first 20 weeks of gestation.[40] Severe thrombocytopenia occurs in more than one-third of cases and can complicate intrauterine transfusion. Parvovirus-induced hydrops can be detected by ultrasound, and treatment of suspected hydropic infants includes intrauterine RBC transfusion. Parvovirus infection of the fetus may persist after birth as a cause of congenital RBC aplasia.

Diamond-Blackfan Anemia

Diamond-Blackfan anemia (DBA) is a rare, autosomal dominant bone marrow failure syndrome of congenital macrocytic anemia with reticulocytopenia. Bone marrow examination reveals normal cellularity with decreased numbers of erythroid precursors and abnormal erythroid maturation. Serum EPO levels are elevated as a compensatory response to inefficient RBC production by the marrow. Erythrocyte adenosine deaminase (eADA) levels are elevated, as is fetal hemoglobin. Patients with DBA often have one or more physical anomalies, such as low birth weight, short stature, abnormal facies, skeletal abnormalities (including abnormal thumbs), and visceral anomalies. The median age of diagnosis is 2 months. Although the phenotypes of DBA and Fanconi anemia overlap, several features distinguish these syndromes. Patients with DBA are usually anemic from birth, whereas those with Fanconi anemia generally develop reticulocytopenia later in life. Laboratory evaluation reveals increased chromosome fragility in Fanconi lymphocytes but not in DBA. The other macrocytic bone marrow failure syndrome that presents at birth is Pearson syndrome (Table 79.14). Several genes have been identified whose mutations together account for about 45% of patients with DBA. All mutations identified affect proteins of the small (RPS) or large (RPL) ribosomal subunit, suggesting that this is a disorder of ribosome biogenesis. Heterozygous mutations in *RPS19* are evident in 25% of cases.[129]

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TABLE 79.14 Bone Marrow Failure Syndromes in the Neonate

Inherited Bone Marrow Failure Syndrome	Inheritance	Genetics	Testing	Treatment
Diamond-Blackfan anemia	Autosomal dominant	RPS19 RPS24, RPS17, RPL35A, RPL5, RPL11, RPS10, RPS26, RPS7 Many unknown	Erythrocyte adenosine deaminase high	20% improve by adulthood Prednisone ± Stem cell transplant
Fanconi anemia	Autosomal recessive X-linked	FANCA, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM, FANCN FANCB	Chromosomal breakage assay	Stem cell transplant, reduced intensity conditioning regimen Transfusion Androgens
Pearson syndrome	Maternal inheritance	Mitochondrial DNA deletion	Mitochondrial DNA sequencing	Pancreatic enzyme replacement Vitamins ADEK Transfusion
Shwachman-Diamond syndrome	Autosomal recessive	SBDS	Serum trypsinogen low, pancreatic isoamylase low, fecal elastase low, fatty pancreas by ultrasound	Pancreatic enzyme replacement Vitamins ADEK, G-CSF Transfusion Stem cell transplant, reduced intensity conditioning regimen

About two-thirds of patients with Diamond-Blackfan anemia respond to glucocorticoid therapy with an increase in Hb concentration and the reticulocyte count. Nonresponders to steroids are managed with chronic RBC transfusion therapy, with the long-term complication of iron overload. Stem cell transplantation from an HLA-matched unaffected sibling is a consideration for transfusion-dependent patients, but this is complicated by the fact that about 20% of patients will enter remission by adulthood and also that the sibling donor may have a mutation not detectable by current genetic screening. Despite advances in medical therapy, patients with Diamond-Blackfan anemia have a shortened expected life span. As is true for other congenital bone marrow failure syndromes, Diamond-Blackfan anemia is associated with an increased risk for aplastic anemia, myelodysplastic syndrome, acute leukemia, and other malignancies later in life.[129]

Fanconi Anemia

Although Fanconi anemia (FA) is not a cause of pure anemia in the neonate, this congenital bone marrow failure syndrome is discussed here in the context of congenital morphologic abnormalities and bone marrow failure syndromes. Originally characterized as familial aplastic anemia with birth defects, the condition has been extended to include patients with characteristic chromosome fragility, with or without aplastic anemia and with or without birth anomalies. Hematologic abnormalities other than macrocytosis usually are not evident in infants with FA. The condition often is not recognized until the onset of aplastic anemia, at a mean age of 8 years, or after diagnosis of a rare cancer at an early age. Many physical anomalies associated with FA have been reported. Only a minority of Fanconi patients have radial ray anomalies, the birth defect traditionally associated with this condition. A high incidence of cancers is associated in affected patients. Lymphocytes from patients with FA exhibit increased chromosome breakage in response to certain alkylating agents, and this now is the basis of diagnostic testing for this condition.

Pearson Syndrome

Pearson syndrome is characterized by early-onset cytopenias, macrocytosis, exocrine pancreatic dysfunction, acidosis, sepsis, and hepatic and renal failure with early death. A sideroblastic anemia is present in most patients in the first 6 months of life, but it often resolves. The bone marrow will show vacuolated precursor cells and ringed sideroblasts. This maternally inherited disorder of mitochondrial DNA is diagnosed by mitochondrial DNA sequencing. Fatty replacement of the pancreas on ultrasound is found in Pearson syndrome but also in Shwachman-Diamond syndrome.

Congenital Dyserythropoietic Anemias

Patients with these rare disorders have congenital anemia with ineffective, morphologically abnormal erythroid production. The degree of anemia can range from moderate to severe and can be macrocytic, normocytic, or microcytic. Type II is the most common of the three described types. Bone marrow examination shows multinucleated RBC precursors and asynchrony in the maturation of erythroid nuclei and cytoplasm. Defects in glycosylation of erythroid

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precursor surface glycoproteins and glycolipids have been associated with some cases. Congenital dyserythropoietic anemias (CDA) often remain undiagnosed in the neonatal period, although many patients are noted to have anemia and jaundice early on. Dysmorphic features can be associated with the anemia. Management includes transfusion and chelation of iron excess. Stem cell transplantation has been attempted in severe cases.[54,55]

Other Erythrocyte Disorders

Methemoglobinemia

Methemoglobinemia results when methemoglobin production is increased or when the ability to reduce methemoglobin is decreased. For hemoglobin to reversibly bind oxygen, the heme iron must be in the ferrous (Fe^{2+}) state. As the RBC circulates and is exposed to various oxidants, the oxyhemoglobin is slowly oxidized to methemoglobin in the ferric (Fe^{3+}) state. Partial oxidation of hemoglobin markedly increases the oxygen affinity of the other hemes in the tetramer and decreases oxygen delivery to tissues. Reduction of methemoglobin in the RBC depends largely on two electron carriers, cytochrome-b_5 and nicotinamide adenine dinucleotide (NADH), as well as the enzyme cytochrome-b_5 reductase. An alternate pathway using G6PD to generate nicotinamide adenine dinucleotide phosphate (NADPH) in the hexose monophosphate shunt can be driven by the addition of electron carriers such as methylene blue. It is estimated that methemoglobin accumulates in adults at a rate of 2%-3% per day, but RBCs with an intact cytochrome-b_5 reductase system contain less than 0.6% methemoglobin.[77] Neonates and premature infants have a transient enzymatic deficiency and lower cytochrome-b_5 levels for the first few months of life. Ingestion of nitrates, usually from contaminated well water, and their subsequent conversion to oxidizing nitrites by gut bacteria is the leading cause of acquired methemoglobinemia in infants. There is an association between diarrheal illness in infants and methemoglobinemia even when toxin exposure has not been detected. Xylocaine and its derivatives and dapsone are the most common drugs precipitating methemoglobinemia.

Congenital methemoglobinemia is due either to a defect in the cytochrome-b_5 reductase system or to inheritance of one of the M hemoglobins (Hb M), which have an alteration in either the α or β chain, resulting in preferential binding of ferric iron. Inheritance of the Hb M variants is autosomal dominant, whereas defects in the cytochrome-b_5 reductase system are inherited in an autosomal-recessive fashion. Homozygotes and compound heterozygotes usually are affected, but heterozygotes can become symptomatic after exposure to oxidant drugs or toxins. Patients with congenital methemoglobinemia may be cyanotic but otherwise asymptomatic. Similarly, patients with chronic methemoglobinemia, with methemoglobin levels of up to 40% or 50%, may be physiologically well compensated and exhibit minimal symptoms. Acute methemoglobinemia with levels above 20% produces the signs and symptoms of hypoxia. Levels greater than 70% can result in coma and death, although there are reports of neonates who survived levels as high as 85%. The onset of symptoms in patients with one of the M hemoglobins corresponds with expression of the affected globin chains. Patients with cytochrome-b_5 reductase deficiency type I are asymptomatic other than cyanosis; the more rare type II disease presents with cyanosis, failure to thrive, and a severe neurologic phenotype. Many with type II disease die in infancy.[77] The cyanosis is unresponsive to oxygen therapy. Blood is a characteristic chocolate-brown color. A fresh sample of blood is analyzed by co-oximetry to detect absorbance in the 630-nm range. False-positive test results may be caused by the presence of other pigments that absorb near the same wavelength, such as sulfhemoglobin and methylene blue. Confirmatory testing of positive results should be performed. Both quantitative and qualitative tests are available for evaluating defects in the cytochrome-b_5 reductase system.[59,77]

Therapy is initiated for symptomatic patients with cytochrome-b_5 reductase deficiency and those with methemoglobin levels greater than 40%. The usual treatment is oral methylene blue. If the patient does not show a good response within 1 hour, the treatment may be repeated, although consideration should be given that the patient could be deficient in G6PD. Patients with G6PD deficiency should not be treated with methylene blue, because it is often not beneficial, and it also causes oxidant stress and hemolysis. Alternative therapy with ascorbic acid may be used with caution because of concerns about calcium kidney stone formation. High-dose ascorbic acid also has oxidant potential and can trigger hemolysis in G6PD-deficient patients. No treatment exists for those with Hb M variants.

Polycythemia

Polycythemia is defined as an increase in RBC mass more than two standard deviations above the mean for age and gestation. For a term infant, polycythemia occurs when a peripheral venous blood sample has an Hb greater than 22 g/dL or a hematocrit greater than 65%. Capillary blood samples are generally higher than those drawn from peripheral blood; central venous values are lower still. The real issue is viscosity, which has a linear relationship to the hematocrit up to about 60%. Blood viscosity increases more rapidly at greater than 60% hematocrit but less predictably. Laboratory testing for hyperviscosity is not generally available, so decisions are made using the hematocrit or hemoglobin and clinical symptoms. Symptoms include listlessness, irritability, plethora, acrocyanosis, poor feeding, hypoglycemia, respiratory distress, and systemic thrombosis. Persistent pulmonary hypertension of the newborn can be caused by increased pulmonary vascular resistance. Renal vein thrombosis and cerebral sinovenous thrombosis have been associated with polycythemia. The increased load of RBCs also contributes to hyperbilirubinemia. Symptoms often appear at or after 2 hours of life, when the hematocrit is highest because of fluid shifts. Some patients with excessive

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extracellular fluid losses may become symptomatic on day 2 or 3 of life, and although most symptoms are transient, there is concern about effects on neurodevelopmental outcome.

Polycythemia is estimated to occur in 2%-5% of term infants. Conditions that result in transfusion to the fetus such as twin–twin or maternal–fetal transfusion or delayed clamping of the umbilical cord can cause polycythemia. It can also be caused by a compensatory response to intrauterine hypoxia, placental insufficiency, maternal toxemia, or postmaturity. Maternal smoking has been associated with symptomatic polycythemia in infants. Several endocrine conditions are associated with increased RBC production and polycythemia, including maternal diabetes, hyperthyroidism or hypothyroidism, and congenital adrenal hyperplasia. Excessive EPO production and polycythemia also are seen in infants with Down syndrome, some other trisomies, and Beckwith-Wiedemann syndrome. Less commonly, hemoglobin with increased oxygen affinity can cause polycythemia, but most of the cases described involved β-chain defects that would be expected to manifest later in infancy. Hereditary defects in the EPO receptor associated with polycythemia also have been reported.[36] Management remains supportive for most infants, because exchange transfusion is associated with the usual transfusion risks as well as increased risk for necrotizing enterocolitis. There is no evidence of long-term neurodevelopmental benefit from partial exchange transfusion; rather, outcome is postulated to be associated with the underlying cause of the polycythemia.[36]

White Blood Cells

Human myelopoiesis begins in the embryo at about 8 weeks. Hematopietic stem cells (HSCs) develop during embryogenesis. This process takes places in different anatomical sites: the yolk sac and the aorta-gonad-mesonephros region. HSCs colonize the bone marrow at birth.[81] By 20 weeks of gestation, neutrophils demonstrate partial functional activity. Neutrophils are derived from a common stem cell progenitor, which also gives rise to mature erythrocytes, megakaryocytes (and ultimately platelets), eosinophils, basophils, and monocytes (see Fig. 79.1). Leukocytes serve as major effector cells for host defense against invading organisms. Neutrophils circulate in the blood until they encounter specific chemotactic signals that promote adhesion to the vascular endothelium and migration through (diapedesis) and movement to the sites of microbial invasion (chemotaxis). Mononuclear phagocytes (monocytes, macrophages) function primarily as cells resident within certain tissues, such as the spleen, lungs, and peritoneum, where they interact closely with lymphocytes to generate a local immune response. Both neutrophils and mononuclear phagocytes, as members of the innate immune system, take up opsonized targets (internalization, phagocytosis). The targets are then destroyed within intracellular vacuoles by the release of hydrolytic enzymes and reactive oxygen intermediates (respiratory burst activity).

Neonatal leukocytes demonstrate impaired adhesion and chemotaxis. Defects in phagocytosis are debated. Neutrophil survival appears to be decreased. A variety of recently identified growth factors and cytokines regulate proliferation and differentiation along neutrophilic lineage (see Table 79.2). Granulocyte colony-stimulating factor (G-CSF) has been used in patients with low neutrophil counts.

Number and Kinetics of Phagocytes

The circulating blood neutrophil pool reflects a dynamic equilibrium among several compartments. Within the bone marrow are the dividing (or mitotic) pool, the differentiation (or maturation) pool, and the storage pool. Outside the bone marrow are the circulating pool, the vascular marginated pool, and the peripheral tissue pool. Neutrophils transit the circulating pool only during a brief 5- to 6-hour period before arrival in tissues. Thus, changes in the WBC count or differential reflect rapid changes in a relatively small yet highly fluctuant pool. Estimates suggest that the peripheral blood neutrophil count represents less than 5% of total neutrophils. About 20% are in the marrow neutrophil precursor pool, 75% are in the marrow storage pool, and 3% are in the marginated vascular pool (Table 79.15). Neutrophils have a residence time of 9 days in marrow, 5-6 hours in blood, and 1-4 days in peripheral tissues.

Neutrophil counts at birth depend on birth weight and gestational age. For term and near-term infants absolute neutrophil count (ANC) increases at birth, followed by sharp three- to fivefold increase (up to ANC of 1500) in next 18 hours of life and later. It gradually decreases after this but is elevated for the first 2 months of life (Table 79.16).[76] ANC values are lower in very low birth weight infants.[89] ANC is the product of the total white blood cell (WBC) count and the percentage of mature neutrophils plus bands:

$$\text{ANC} = \text{WBC} \times (\%\ \text{neutrophils} + \%\ \text{bands}) \times 0.01$$

Neutropenia is defined as ANC value that is two standard deviations below the mean or lower than the fifth percentile. Based on Manroe et al., such value is an ANC less than 1800/μL, whereas Mouzinho charts would suggest an ANC less than 1000/μL.[71]

Neutrophilia is an elevation of the blood neutrophil count greater than two standard deviations above the mean or value above the 95th percentile.[92]

Phagocyte Abnormalities

Neutropenia

Neutropenia is a common finding in the NICU, particularly during the first week of life and in lower birth weight and ill infants. Neutropenia results from a decline in neutrophil production or from accelerated destruction, as well as from changes in the relative distribution of neutrophils between the circulating pool and the marrow and peripheral tissue pools. Most cases are caused by acquired defects,

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TABLE 79.15 Adult Blood Neutrophil Pools and Kinetics

Pool	Definition/Calculation	Mean Pool Size ($\times 10^7$/kg)	95% Limits
Total blood neutrophil pool (TBNP)	All neutrophils in the circulation	70	14-160
Circulating neutrophil pool (CNP)	Blood neutrophil concentration multiplied by blood volume	31	11-46
Marginal neutrophil pool (MNP)	Total blood neutrophil pool less circulating pool (MNP = TBNP – CNP)	39	0-85
Kinetics	**Definition/Calculation**	**Mean Value**	**95% Limits**
$t_{1/2}$ (Blood clearance half-time)	Disappearance time of half of the labeled neutrophils from circulation	6.7 hr	4-10 hr
Neutrophil turnover rate (NTR)		163 × 10^7/kg per day	50-340 × 10^7/kg per day

Adapted from Beutler E, et al. *Williams' hematology.* 5th ed. New York: McGraw-Hill; 1995.

TABLE 79.16 Polymorphonuclear Leukocyte and Band Counts in the Newborn during the First 2 Days of Life*

Age (hr)	Absolute Neutrophil Count (per µL)	Absolute Band Count (per µL)	Band-to-Neutrophil Ratio
Birth	3500-6000	1300	0.14
12	8000-15000	1300	0.14
24	7000-13000	1300	0.14
36	5000-9000	700	0.11
48	3500-5200	700	0.11

*Normal values were obtained from the assessment of 3100 separate white blood cell counts obtained from 965 infants; 513 counts were from infants considered to be completely normal at the time the count was obtained and for the preceding and subsequent 48 hours. There was no difference in the normal ranges when infants were compared by either birth weight (whether more or less than 2500 g) or gestational age.
Data from Manroe BL, Rosenfeld CR, Weinberg AG, et al. The differential leukocyte count in the assessment and outcome of early-onset neonatal group B streptococcal disease. *J Pediatr.* 1977;91:632-637.

• BOX 79.8 Etiologies of Early-Onset Neutropenia

- Congenital infection
- Prematurity
- Sepsis
- Birth asphyxia
- Maternal hypertension
- Intrauterine growth restriction
- Bone marrow failure syndromes
- Bone marrow infiltration
- Congenital neutropenias

many of which are transient. Persistent neutropenia, particularly in an infant with dysmorphic features, should be investigated (Box 79.8). Laboratory investigation begins with a CBC and evaluation of the peripheral blood smear, looking for defects in the other cell lines as well as leukocyte morphology. Serial CBCs are often appropriate before bone marrow aspiration and biopsy. Strong consideration should be made as to whether the neutropenia could be part of an immunologic defect such as severe combined immunodeficiency disorder; absolute lymphocyte count, lymphocyte subsets, serum immunoglobulins, and specific testing of B and T lymphocyte function may be needed. Bone marrow morphologic examination and assessment of cellularity, myeloid maturation, and presence of fibrosis can be performed. Bone marrow cytogenetics, FISH for suspected genetic defects or myelodysplasia, and iron staining can also be performed. Rarely, ancillary testing such as electron microscopy of the bone marrow, fetal hemoglobin levels, and pancreatic enzymes may be ordered.

Severe neutropenia is defined by an ANC less than 500/µL. *Very severe neutropenia* requires ANC less than 200/µL. *Moderate neutropenia* occurs at ANC less than 1000/µL. Neutropenia can be central or peripheral depending on whether or not the bone marrow is depleted in mature progenitors. Central neutropenia carries a higher infection risk.[39] Infectious risk depends on the duration of neutropenia and on whether the remaining neutrophils function normally. Bacterial and fungal infections are most common in neutropenia. Typical organisms include staphylococci, streptococci, enterococci, pneumococci, *Pseudomonas*, gram-negative bacilli, *Candida*, and *Aspergillus*. The skin, mucous membranes, nasopharyngeal region, and lungs are most commonly infected.

Extrinsic Defects of Phagocyte Function

Sepsis and Postinfectious Neutropenia. Infection is the most common cause of neutropenia in the neonate.

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Neutropenia is a risk factor for infection and sepsis, but it can also occur as a result of overwhelming sepsis. Neonates are particularly at risk for this complication, because their neutrophil storage pools are smaller. Neutrophil counts are sometimes unmeasurable in the peripheral blood if the bone marrow neutrophil pool is exhausted. Both increased vascular neutrophil margination and vascular-to-tissue neutrophil movement are associated with circulating neutropenia during sepsis. Among hospitalized infants, neonatal sepsis continues to be a major cause of morbidity and mortality. Neonates with very low birth weight are most vulnerable and are prone to early- and late-onset sepsis.[43] Cytokines such as G-CSF have been used without clear benefit in preventing or treating sepsis in neonates. They are used more commonly, empirically, in neutropenic neonates with serious infection or sepsis. Granulocyte transfusions are discussed in Chapter 80.

Neonatal Alloimmune Neutropenia. Neonatal alloimmune neutropenia (NAN) is a rare cause of neutropenia with an incidence between 0.1% and 0.81%.[1,24,136] However, it can present as severe infection with a mortality rate up to 5%.[136] The cause is analogous to Rh hemolytic disease of the newborn. The neutropenia, which can be severe, is caused by maternal sensitization to paternally inherited human neutrophil antigens (HNA). If maternal IgG crosses the placenta and coats the fetal neutrophils, they will be destroyed by opsonization. Isolated neutropenia (<1000/μL) with normal maternal neutrophil count should trigger suspicion. The diagnosis depends on detection of maternal antineutrophil antibodies in the serum of mother and baby. Most common antibodies are directed against HNA-1 antigens 1a, 1b, and 1c. Human neutrophil antigen typing of the mother and father confirms the diagnosis. If the father is homozygous, the risk for future alloimmune neutropenia is 100%. Affected newborns often develop fever in the first few days of life with associated cutaneous infections, omphalitis, pneumonia, otitis media, necrotizing enterocolitis, and sepsis. Treatment consists of supportive care with antibiotics and sometimes G-CSF or IVIG. As expected for the half-life of maternal IgG, infant neutrophil counts generally return to normal within the first 1-3 months of life.[1]

Autoimmune Neutropenia of Infancy (Chronic Benign Neutropenia). In this case, antibodies are developed by the infant against his own neutrophils. Antineutrophil antibodies have been detected in the serum of infants in the first months of life, although very rarely. It is usually diagnosed between the ages of 5 and 15 months, often discovered during evaluation of fever or infection. A peripheral monocytosis or eosinophilia may be present. Most common is the primary autoimmune neutropenia (not associated with an underlying disorder), severe infection is uncommon, but central neutropenia raises the risk. Secondary neutropenia that is associated with autoimmune disease, infections, or drugs may be more severe.[41] Because neutropenia masks signs and symptoms of severe infection and also increases infectious risk, medical evaluation is recommended for moderate to high fever, and empiric antibiotic coverage is often instituted when the ANC is less than 500/μL. Autoimmune neutropenia is self-limited, with resolution in the first 2-3 years of life. Confirmatory testing demonstrates antineutrophil antibodies in the serum most often against the FcRγIIIb receptor or CD16.[41] If a bone marrow analysis is performed, there may be a paucity of neutrophils and myeloid progenitor cells depending on the specificity of the antibody for mature or progenitor cell antigens. The overall bone marrow cellularity may be normal or hypercellular.[39] Therapy for autoimmune neutropenia depends on the severity of the neutropenia-associated symptoms (e.g., recurrent fevers requiring frequent medical evaluations and/or severe infection). Often no treatment is needed. Supportive care with antibiotics either for brief empiric coverage in the setting of severe neutropenia or to treat infection is important. Granulocyte colony-stimulating factor has been used in the setting of severe infection with neutropenia and also for prevention of recurrent symptomatic severe neutropenia.[41]

Neonatal Iso-immune Neutropenia. This is noted in infants whose mothers have autoimmune disease with passive passage of maternal antineutrophil antibodies to the fetus. In such cases, both mother and infant are neutropenic. Usually neutropenia is transient and asymptomatic.[72]

Drug-Induced Neutropenia. An enormous number of agents have been implicated as causes of neutropenia (Box 79.9). The mechanisms include direct bone marrow suppression or immune-mediated destruction. Anti-inflammatory drugs, semisynthetic penicillins, antiseizure medications, and a host of other drugs commonly used in the newborn nursery can cause neutropenia. Recovery from marrow toxic effects generally begins within several days after the offending agent is discontinued. As with recovery from chemotherapy-induced neutropenia, recovery of peripheral neutrophil counts is ushered in by a rise in circulating monocytes and immature neutrophils in the peripheral blood.

Therapeutic Uses of Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor

The cytokines granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are members of a family of hematopoietic growth factors that stimulate production of mature WBCs in the bone marrow. These two cytokines also enhance neutrophil and monocyte functions, such as neutrophil oxidative metabolism, chemotaxis, and phagocytosis. Both are normally present at low concentrations in serum. Granulocyte colony-stimulating factor levels are about threefold higher in the cord blood of premature infants than in term infants in the first 3 days of life. Granulocyte colony-stimulating factor levels peak at 7 hours of life, followed by a rise in the neutrophil count at about 13 hours of life.[45] Whether preterm and full-term infants are capable

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• BOX 79.9 Some Common Drugs Associated with Idiosyncratic Neutropenia

Analgesics and Anti-inflammatory Agents
- Indomethacin*
- Acetaminophen

Antibiotics
- Cephalosporins
- Chloramphenicol*
- Clindamycin
- Gentamicin
- Isoniazid
- Penicillins and semisynthetic penicillins*
- Rifampin
- Streptomycin
- Sulfonamides*
- Tetracyclines
- Trimethoprim-sulfamethoxazole
- Vancomycin

Anticonvulsants
- Carbamazepine
- Mephenytoin
- Phenytoin
- Valproate

Antihistamines (H_2 Blockers)
- Cimetidine
- Ranitidine

Antimalarials
- Amodiaquine
- Chloroquine
- Dapsone
- Pyrimethamine
- Quinine

Cardiovascular Drugs
- Captopril
- Disopyramide
- Hydralazine
- Methyldopa
- Procainamide
- Propranolol
- Quinidine
- Tocainide

Diuretics
- Acetazolamide
- Chlorothiazide
- Chlorthalidone
- Ethacrynic acid
- Hydrochlorothiazide

*More often reported to cause neutropenia in epidemiologic studies.
Adapted from Beutler E, et al. *Williams' hematology*. 5th ed. New York: McGraw-Hill; 1995.

of mounting an appropriate cytokine response to infection or sepsis and whether neonatal cells respond adequately to cytokines are still under investigation. The first randomized trial reported 5-year follow-up outcomes of children who received GM-CSF as very small-for-gestational-age preterm babies. It reported that GM-CSF raised neonatal neutrophil counts but did not reduce the prevalence of neonatal sepsis or other neonatal morbidities, nor affected neurodevelopment later in childhood.[78] The utility of these growth factors in the treatment and prevention of sepsis in non-neutropenic infants, however, has not been clearly demonstrated.[25,43] However, based on limited studies there might be utility of growth factor use when systemic infection is accompanied by severe neutropenia as it may reduce mortality.[25] On the other hand, clinical trials using pharmacologic doses of G-CSF have shown benefit in patients with congenital neutropenia by reducing infectious morbidity and mortality and improving quality of life.[33] It is also effective in correcting immune-mediated neutropenias when patients present with infections and an ANC less than 500/μL.

Inherited Disorders Associated with Neutropenia

Congenital Neutropenias

The congenital neutropenias are a group of disorders that persist at least 3 months, whether intermittent or permanent, severe or mild, with or without extrahematopoietic findings, and that are caused by a constitutional genetic defect. About half of the genetic defects reported in neutropenia registries are in the neutrophil elastase gene *ELA2*, which can cause permanent or intermittent (cyclic) neutropenia. The risk of infection correlates with the severity of the neutropenia and increases with dysfunction of the neutrophils or other components of the immune system. Treatment is supportive, with antibiotics and antifungal prophylaxis and sometimes G-CSF. Stem cell transplantation is indicated for some syndromes.[39]

Congenital Neutropenia with Primarily Hematopoietic Abnormalities

Severe Congenital Neutropenia. Kostmann syndrome was the first severe congenital neutropenia described. In the first several months of life, infants manifest severe neutropenia (ANC <200/μL) with recurrent infections (e.g., omphalitis, skin abscesses, respiratory tract infections, sepsis). Bone marrow examination reveals a paucity of myeloid cells and arrest at the promyelocyte or myelocyte stage. Defects are in the *ELA2*, *HAX-1*, and less commonly, in the genes coding for the G-CSF receptor. Inheritance may be autosomal dominant, autosomal recessive, or sporadic. Antibiotic and antifungal prophylaxis, aggressive treatment of infections, and high-dose G-CSF treatment in responsive

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patients has improved morbidity and mortality, but early death is still common. Patients who survive early childhood are at risk for myelodysplastic syndrome and acute myeloid leukemia. Stem cell transplantation is an option for selected patients. Later neurologic manifestations of developmental delay and seizures are seen in patients with *HAX-1* mutations.[39]

Cyclic Neutropenia and ELA2 Mutations. Cyclic neutropenia is diagnosed later than Kostmann syndrome, often in the second year of life or later. Patients present with fevers, mouth ulcers, and infections during the nadir of the ANC, which is documented by two to three CBCs per week for 6 weeks, to cycle neutrophil counts approximately every 21 days plus or minus 3 days. Autosomal dominant *ELA2* mutations are the most common and severe. Sporadic inheritance is also described. Supportive care for fevers and infection and possible use of G-CSF to modulate the nadir are common management strategies.[39]

Congenital Neutropenia with Extrahematopoietic Abnormalities

The most common congenital neutropenias with extrahematopoietic defects in neutropenia registries are *HAX-1* mutations, Shwachman-Diamond syndrome, and the glucose-6-phosphatase complex disorders. Many rare congenital neutropenia syndromes have been described clinically, and some have associated genetic defects identified. Deficits in neutrophil function as well as a myriad of dysmorphic defects are associated with these syndromes, although it is important to realize that not all defects are present in the neonatal period, and not all defects appear in a particular patient. The reader is referred to an excellent review of congenital neutropenia by Donadieu and co-workers for more details.[39]

Shwachman-Diamond Syndrome (SDS). Once believed rare, but now accounting for about one-fourth of patients in neutropenia registries, Shwachman-Diamond syndrome (SDS) is characterized by pancreatic exocrine dysfunction, failure to thrive, neutropenia of varying degrees, neutrophil chemotactic dysfunction, and many other dysmorphic features presenting at various times over the life of the patient. Bony abnormalities, rash, cytopenias, mental retardation, and failure to thrive are among the most common features. Shwachman-Diamond syndrome is often included as part of the differential diagnoses with Pearson syndrome and cystic fibrosis. Hematologic manifestations include intermittent neutropenia, cytopenias, aplastic anemia, myelodysplastic syndrome (mutations in chromosome 7), and leukemic transformation. Autosomal recessive inheritance is described, often with defects in the *SBDS* gene on 7q11 with resultant defect in ribosomal function affecting multiple organ systems.[20] Diagnostic testing may include radiographic demonstration skeletal abnormalities, evidence of pancreatic insufficiency (decreased fecal elastase and low serum trypsinogen), as well as hematologic changes. Finding of typical mutation is diagnostic. Supportive care with pancreatic enzyme replacement, G-CSF for neutropenia or severe infection, antibiotics, and antifungals are recommended. Monitoring for malignant transformation is important. Hematopoietic stem cell transplantation is indicated for severe cytopenia, myelodysplastic syndrome, or acute myeloid leukemia.[33]

Glucose-6-Phosphatase Complex Disorders: Glycogen Storage Disease Type 1b and G6PC3. Hepatic glycogen can be dephosphorylated by G-6-P to produce glucose as an energy source. Two of the three proteins that comprise the G-6-P complex on the endoplasmic reticulum are associated with congenital neutropenia: the translocase SLC37A4 and the catalytic protein G6PC3. G6PC3 disorders are characterized by severe, permanent neutropenia with myeloid arrest, thin skin, genitourinary abnormalities, cardiac disease, and myopathy.[39]

GSD1b is characterized by hypoglycemia at birth, lactic acidemia, hepatomegaly with hepatic glycogen accumulation, Crohn-like colitis, neutropenia, and variable neutrophil dysfunction. Diagnosis is based on constellation of symptoms and genetic testing. Patients respond to G-CSF, although in GSD1b, patients may develop worsening splenomegaly. AML has been reported in GSD1b.[33]

Congenital Neutropenia with Defective Immune System

As part of the innate immune system, neutrophils participate in development of the adaptive immune system, and there are some shared receptors and proteins among lymphocytes and neutrophils. Neutropenia may be an early presenting feature of a more global and lethal immunologic defect, with or without autoimmune phenomena. Young age at presentation, failure to thrive, lymphopenia, eczema, and serious infections should be signals that a comprehensive evaluation of innate and adaptive immunity should be undertaken.

X-linked Neutropenia/Myelodysplasia

An X-linked mutation of the Wiskott-Aldrich syndrome gene protein presents with neutropenia but without the classic WAS phenotype.

Cartilage-Hair Hypoplasia. Cartilage-hair hypoplasia is a rare autosomal recessive disorder characterized by short-limbed dwarfism, fine hair, hyperextensible digits, increased susceptibility to infection, lymphopenia, impaired cellular immunity, and chronic neutropenia. This autosomal recessive disease is caused by mutations in *RMRP*, a noncoding RNA gene involved in mitochondrial DNA replication, ribosome biogenesis, and ribosomal RNA processing.[39]

Dyskeratosis Congenita. Dyskeratosis congenita is characterized by neutropenia (and other cytopenias), abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia. Other features include immunodeficiency, fragile bones, tooth decay, short stature, alopecia or premature graying, gonadal hypoplasia, urethral abnormalities, pulmonary fibrosis, liver cirrhosis, esophageal strictures, mental retardation, and a predisposition to cancers of the skin, gastrointestinal tract, and other sites.

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Other Related Syndromes Discussed under Immune Deficiencies

Bone Marrow Failure Syndromes

See Diamond-Blackfan anemia, Fanconi anemia, and Shwachman-Diamond syndrome.

Congenital Neutropenia with Inborn Errors of Metabolism

Isovaleric, methylmalonic, and propionic acidemias; hyperglycinemia; and tyrosinemia are associated with neutropenia.

Neutrophilia

Neutrophilia is the specific elevation of the ANC more than two standard deviations above the mean. Infection is the most common. Other causes include stress, birth asphyxia, and hypoxia.

Leukemoid Reaction

Newborns sometimes mount an exaggerated response to infection. As in older children, the circulating neutrophil count increases, and a left shift occurs (band forms, myelocytes, and metamyelocytes increase in the peripheral circulation). A significant increase in early neutrophil precursors in the peripheral blood, as well as an increase in the white blood cell count (generally exceeding 50,000/μL), is considered a leukemoid reaction. A normal newborn in the first 2 days of life displays a neutrophilia. Immature myeloid forms and even blasts can be seen in the first day or two, and these are especially common in premature infants. A leukemoid reaction associated with severe infection in the newborn often is accompanied by neutrophil cytoplasmic vacuoles and toxic granulations. A rare, autosomal dominant hereditary neutrophilia has been described. Infants with Down syndrome can have a type of leukemoid reaction or even a leukoerythroblastic picture called transient abnormal myelopoiesis.

Down Syndrome Hematologic Abnormalities and Transient Abnormal Myelopoiesis. Hematologic abnormalities are common in Down syndrome (Table 79.17). The American Academy of Pediatrics recommends ordering a CBC for newborns with Down syndrome to screen for hematologic problems. About 10% of infants who have Down syndrome develop a transient clonal myeloproliferative disorder now called *transient abnormal myelopoiesis* (TAM). This process also sometimes occurs in a phenotypically normal child with trisomy 21 mosaicism, including an isolated clone of trisomy 21 bone marrow cells. Transient abnormal myelopoiesis is characterized by a leukoerythroblastic picture with megakaryoblasts in the peripheral blood, variable thrombocytopenia, and hepatosplenomegaly.[110] Abnormalities of all three hematopoietic cell lineages have been described. It is believed that mutations in the megakaryocyte transcription factor GATA1 occur during the period of fetal liver hematopoiesis. There are no clinical, hematologic, or cytogenetic parameters that can predict if the newborn has TAM, which resolves, or acute leukemia. The median age at diagnosis of TAM is 3-7 days. Almost all cases are diagnosed by 2 months of age and resolve by 3-6 months. Transient myeloproliferative disorder can be life threatening or fatal from complications of hepatic fibrosis/liver failure, hydrops fetalis, or hyperleukocytosis (Box 79.10).[38] At least half of infants with TAM show no associated clinical symptoms (silent TAM). About 10%-20% of infants with TAM will develop myeloid leukemia of Down syndrome (ML-DS). Somatic mutations in *GATA1* have been reported in nearly all cases of TAM and ML-DS. In the absence of leukocytosis greater than 100,000 WBC/μL, refractory DIC, massive organomegaly, respiratory compromise, renal dysfunction, or impending liver failure from hepatic fibrosis, pediatric oncologists adopt a wait-and-see approach in managing TAM. Infants with organ infiltration or a severe leukocytosis can be managed with low-dose cytarabine.[13]

TABLE 79.17 Hematologic Manifestations of Down Syndrome

Cell	Defect
Red Blood Cell	Macrocytosis Anemia Polycythemia
White Blood Cell	Transient abnormal myelopoiesis Leukocytosis Neutropenia Acute leukemia
Platelets	Thrombocytosis Thrombocytopenia

Adapted from Dixon N, Kishani PS, Zimmerman S. Clinical manifestations of hematologic and oncologic disorders in patients with Down syndrome. *Am J Med Genet.* 2006;142C:149-157.

• BOX 79.10 Transient Abnormal Myelopoiesis: High-Risk Features

- WBC >100 × 10^9/L
- Disseminated intravascular coagulation
- Failure to clear blasts
- Prematurity
- Ascites/pleural effusion
- Hepatic or renal dysfunction
- Respiratory compromise

WBC, White blood cells.
Adapted from Roy A, Roberts I, Vyas P. Biology and management of transient abnormal myelopoiesis (TAM) in children with Down syndrome. *Semin Fetal Neonatal Med*. 2012;17:196-201.

Neutrophil Functional Defects

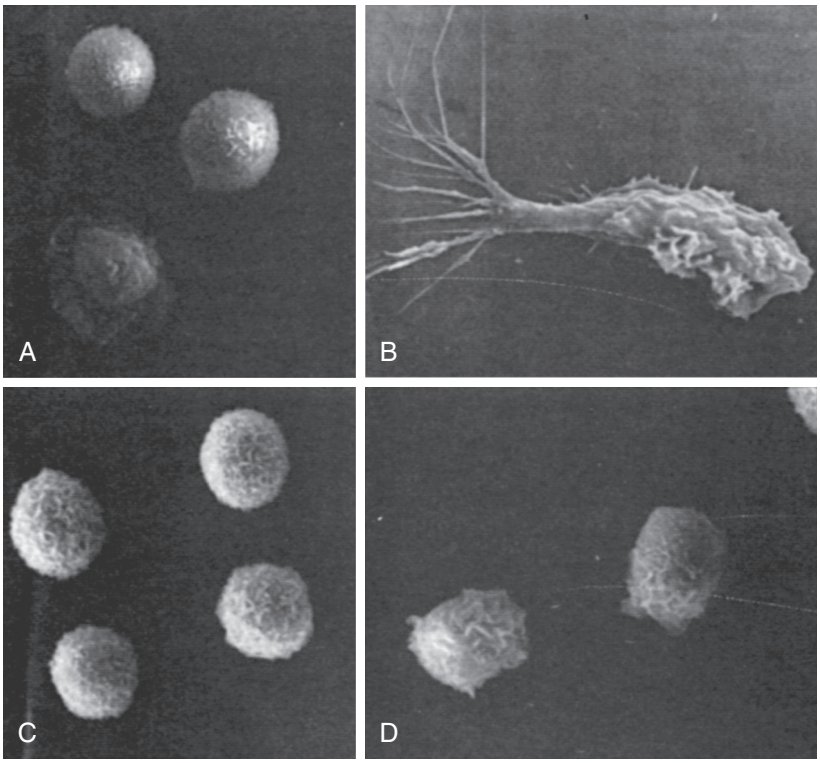
These conditions are rare; however, neonatologists need to be aware. Below are conditions most commonly seen in infancy.

Oxidative Killing Disorder: Chronic Granulomatous Disease. Chronic granulomatous disease (CGD) is a rare, genetically heterogeneous disorder characterized by

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inherited defects in generation of the respiratory burst by NADPH oxidase in neutrophils, monocytes, and macrophages. Some patients are mildly affected, whereas others develop severe, recurrent bacterial and fungal infections of skin, mucous membranes, liver, lung, spleen, and lymph nodes in the setting of increased or normal neutrophil counts. Catalase-positive bacteria and *Aspergillus* species are common pathogens. Most patients manifest symptoms within the first year of life. Inadequate neutrophil killing or ingestion is associated with a chronic inflammatory response that culminates in the formation of macrophage-containing granulomas throughout the gastrointestinal and urinary tracts. Because four distinct gene products are required for functional NADPH oxidase activity, defects in any one of these components can lead to this disorder. Chronic granulomatous disease is usually X-linked in inheritance, associated with the gp91 protein, gp91phox, but autosomal recessive forms are associated with defects in p22phox, p47phox, and p67phox. Diagnosis is made by spectrophotometric measurement of superoxide production or by measurement of reactive oxygen species production by flow cytometry, fluorometry, or chemiluminescence. Genetic analysis of affected patients can identify the specific genetic defect. Therapy involves prophylactic antibiotics and antifungal agents. Recombinant interferon-γ-1b prophylaxis has also been effective in reducing the incidence of infections. Hematopoietic stem cell transplantation is an option for severe disease.[116]

Adhesion Disorders: Leukocyte Adhesion Deficiencies Types I and II. Leukocyte adhesion deficiency (LAD) includes a rare group of autosomal recessive disorders characterized by persistent leukocytosis, delayed separation of the umbilical cord, and recurrent infections. LAD-I is characterized by the impairment of the respiratory burst generation of complement-opsonized microorganisms and is associated with defects in neutrophil adhesion and chemotaxis (Fig. 79.9). The clinical picture varies depending on the relative deficiency of CD18, the β2 subunit of integrin. Leukocyte adhesion deficiency should be suspected in any infant who has unusually severe bacterial infections accompanied by normal to increased blood leukocyte counts. There is a striking absence of pus at the site of infection, because neutrophils do not migrate from the vasculature to sites of inflammation within tissues. Diagnosis is made by flow cytometric analysis demonstrating deficiency of CD18 or CD11b/CD18. Carriers can be identified by the expression of about 50% normal CD18 on circulating neutrophils. In addition to persistent leukocytosis and recurrent bacterial infections, the autosomal recessive clinical syndrome LAD-II (Rambam-Hasharon syndrome) described in a few Israeli patients includes short stature, severe mental retardation, and the hh (Bombay) RBC phenotype. The



• **Fig. 79.9** Attachment and spread of leukocyte adhesion deficiency (LAD) **(A)** and control **(B)** neutrophils through cell surface integrins, as visualized through scanning electron microscopy. Orientation and movement of LAD **(C)** and control **(D)** neutrophils to a chemotactic gradient (from the right), as visualized by means of scanning microscopy. (Adapted from Anderson D, et al. Abnormalities of polymorphonuclear leukocyte function associated with a heritable deficiency of high-molecular-weight surface glycoproteins [GP 138]: common relationship to diminished cell adherence. *J Clin Invest*. 1985;74:536.)

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molecular defect in these patients is a defect of fucosyl transferase, the enzyme responsible for carbohydrate linkages associated with the AB blood groups, specifically the sialyl-Lewis X structure. Sialyl-Lewis X is necessary for the formation of the neutrophil cell surface ligand recognized by the endothelial cell surface E- and P-selectin receptors. Neutrophils from these patients exhibit markedly diminished chemotaxis in vitro but have normal levels of C18.[39]

LAD-III results from mutation in FERMT3, which encodes kindling-3, a protein that binds β integrin tails. Clinically, it is similar to LAD-1; however, patients are also as at risk for bleeding as patients with Glanzmann thrombasthenia. Hematopoietic stem cells are recommended for LAD-1 and LAD-3. LAD-2 patients require supportive care such as fucose supplementation.[37]

Chediak-Higashi Syndrome and Griscelli Syndrome Type 2

Chediak-Higashi syndrome, caused by a defective *CHS1* gene, is an autosomal recessive syndrome featuring oculocutaneous albinism, nystagmus, photophobia, neurodegeneration, neutropenia, giant red inclusions in leukocytes, NK cell dysfunction, recurrent infection, and progression to lymphoproliferative and hemophagocytic disorders. Griscelli syndrome type 2 shares many of these features but lacks the leucocyte inclusions.[39]

Neonatal Immune Deficiencies

It is important for neonatologists to understand primary immune deficiencies, as failure to recognize them early can result in delayed treatment and worse outcomes for these patients. Severe combined immune deficiency (SCID) newborn screen (NBS) using T-cell receptor excision circle (TREC) assay has allowed early detection of T-cell lymphopenia in newborns. As of 2015, this assay is performed in 27 states in the United States, as well as the District of Columbia and the Navajo Nation. Affected infants are reliably being detected and promptly referred to centers that provide immune system restoring treatments. Bone marrow transplantation (BMT) has success rates that vary from 50%-100%.[67] Patients with SCID transplanted within first 3 1/2 months of life have a superior outcome. Population-based screening has determined the incidence of SCID to be 1 in 58,000 births, higher than previous estimates.[68] An infant with recurrent infections and an ALC less than 3000/cmm should warrant immediate referral and further testing of immune system.[80] Absence of a thymic shadow on x-ray is another hint of SCID. Family history is important as well. SCID patients are at risk to succumb to opportunistic life-threatening infections (bacterial, fungal, viral, and mycobacterial). They are also at risk of developing graft-versus-host disease (GVHD) secondary to maternally derived T cells as well as transfusions with nonirradiated blood products. IVIG has a role if B-cell function is impaired.

Primary immune deficiencies can be classified based on immune cells involved (T cell, B cells, NK cells). The majority have an alteration in more than one cellular compartment (combined immune deficiencies). Table 79.18 summarizes most immune deficiencies and defects involved.[67] Below is a brief review of the most recognized diseases.

Humoral Immune Defects

Transient Hypogammaglobulinemia of Infancy. This is caused by a delay in maturation of immunoglobulin production and presents with prolonged hypogammaglobulinemia but is rarely symptomatic. It resolves by 3-4 years of age.[67]

X-linked Agammaglobulinemia. Most common of the agammaglobulinemias, these patients are protected by maternal antibodies in the first months of life. Recurrent infections with encapsulated bacteria or viruses occur later. There is a lack of IgA conjunctivitis; otitis may occur earlier. The mainstay of treatment is IVIG.[67]

Hyper IgM syndrome. This is caused by defects in a CD40 ligand/CD40 interaction. It results in very low levels of IgG, IgA, and IgE but normal or elevated levels of IgM. The immunoglobulin class switch is impaired. Patients can present early in infancy and have neutropenia as well as typical infections characteristic for combined immune deficiencies. BMT is treatment of choice. IVIG infusions are given as well.[67]

Combined Immune Deficiencies

Severe Combined Immunodeficiency (SCID)

Common γ Chain Deficiency (X-linked SCID). Should be considered a pediatric emergency that is fatal if untreated. Patients present within the first few months of life with recurrent sinopulmonary, skin infections, and diarrhea. The infection is bacterial, fungal, viral, and mycobacterial. GVHD from maternally acquired T cells can occur. These patients sometimes present with complete absence of functional lymphocytes. B cells are preserved. The treatment is bone marrow transplantation.[67]

Adenosine Deaminase Deficiency. Adenosine deaminase deficiency is the most common autosomal recessive SCID. Lack of ADA activity allows toxic metabolites to accumulate in immune cells. In addition to complications listed under X-linked SCID, these patients also have ribcage anomalies and osseochondral dysplasia.[67] The treatment is bone marrow transplantation.

Omenn Syndrome (Leaky SCID). Caused by partial deficiency of RAG1 or RAG2, this CID is characterized by splenomegaly, diarrhea, hypereosinophilia, erythroderma, and increased IgE in newborns.

Innate Immune Defects

Wart Hypogammaglobulinemia Immunodeficiency Syndrome

This autosomal dominantly inherited syndrome of bcl-x overexpression is characterized by severe neutropenia with myeloid hyperplasia and degraded precursor cells (myelokathexis) in the bone marrow, recurrent warts, hypogammaglobulinemia, and recurrent infections.[39]

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TABLE 79.18 Genetic Defects Linked to Common Immune Deficiencies

Immune Deficiency Group	Condition	Inheritance	Genetic Defect	Affected Cells	Most Common Symptoms
Humoral deficiencies	X-linked agammaglobulinemia	X-linked	BTK	B cells with decreased production in all immunoglobulins	Recurrent infections with encapsulated bacteria, absent lymphoid tissue on exam
	Hyper IgM heavy chain defect	AR	IGHM	B cells with decreased production in all immunoglobulins	Recurrent infections, lymphoid hyperplasia
	Transient hypogammaglobulinemia of infancy	Unknown	Unknown	Low IgA and IgG	Recurrent bacterial and viral infections that resolve by age of 4 years
	CVID	AR, some unknown	ICOS, TNFRSF13B, still learning about new mutations	B cells with decreased production in all immunoglobulins	Chronic sinusitis, bronchiectasis, autoimmune disorders
	Selective IgA deficiency	Unknown		Low IgA	Gastrointestinal, respiratory, urogenital infections
	Immunodeficiency, centromeric instability, facial anomaly (ICF) syndrome	AR	DNMT3B	B cells limited to naïve B cells	Facial anomalies: low set ears, epicanthal folds, flat nasal bridge, hypertelorism, macroglossia Sinopulmonary infections
T-cell and NK-cell deficiencies with intact humoral system	Interferon-γ/IL-12 axis disorders	AR, AD	IL12B IL12RB1 IFNGR1 IFNGR2 STAT1	Macrophages+/- T cells, NK cells	Mycobacterial and Salmonella infections *IFNGR1* gene defects predisposes to atopy, vasculitis, positive rheumatoid factor
	CD16 deficiency	FCGR3A	Unknown	NK cytopenia	Viral (HSV) Abnormal BCG response
T-cell deficiency with B cells present, but not functional	X-linked SCID	IL2RG	X-linked	T-cell lymphopenia, B cells present but nonfunctional, hypogammaglobulinemia	First few months of life: sinopulmonary, skin infections, FTT, diarrhea. Bacteria, viruses, fungals, mycobacteria, and opportunistic organisms. GVHD risk.
	IL-2 receptor α (IL2R α) deficiency	IL2RA	AR	T-cell lymphopenia, B cells present but nonfunctional, hypogammaglobulinemia	Same as X-linked SCID
	IL-7 receptor α (IL7R α)	IL7R	AR	T-cell lymphopenia, B cells present but nonfunctional, hypogammaglobulinemia	Same as X-linked SCID
	Janus kinase-3 (Jak3) deficiency	JAK3	AR	T-cell lymphopenia, B cells present but nonfunctional, hypogammaglobulinemia	Same as X-linked SCID
	CD3δ deficiency	CD3D	AR	T-cell lymphopenia, B cells present but nonfunctional, hypogammaglobulinemia	Same as X-linked SCID
	CD45 deficiency	PTPRC	AR	T-cell lymphopenia, B cells present but nonfunctional, hypogammaglobulinemia Normal γδ T cells	Same as X-linked SCID

Continued

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TABLE 79.18 Genetic Defects Linked to Common Immune Deficiencies—cont'd

Immune Deficiency Group	Condition	Inheritance	Genetic Defect	Affected Cells	Most Common Symptoms
T-cell deficiency with B-cell deficiency	Adenosine deaminase deficiency	ADA	AR	T-cell and B-cell lymphopenia NK cells present	Same as X-linked SCID May have rib cage anomalies and osseochondral dysplasia
	Recombinase activating gene (RAG) deficiency	RAG1/2	AR	T-cell and B-cell lymphopenia NK cells present	If partial deficiency of RAG1 and RAG2, it will result in Omenn syndrome (see below).
	Artemis deficiency	DCCRE1C	AR	T-cell and B cell lymphopenia NK cells present	Similar to Omenn syndrome. Radiation sensitivity
	Reticular dysgenesis	Unknown	Likely AR	T-cell and B-cell lymphopenia plus neutropenia	Infections characteristic of SCID, plus neutropenia and thrombocytopenia. Deafness reported.
Immunodeficiencies with various T-cell abnormalities	X-linked hyper IgM	TNFSF5		Normal T-cell number, but low IgG, IgA, IgE and high IgM neutropenia	Can present in early infancy with abscesses, autoimmune cytopenias, hepatoma.
	Omenn syndrome	RAG1/2	AR	T-cell oligoclonal, B cells low, hypogammaglobulinemia	Hypereosinophilia, erythroderma, increased IgE, diarrhea in newborns
	MHC I deficiencies	TAP-1, TAP-2, TAPBP	AR	Low CD8, CD4 preserved Normal B cells.	Milder form
	MHC II deficiencies	RFX5, RFXAP, RFXANK, CIIA, ZAP70, p46Lck	AR	Very low CD4 count, CD8 preserved Normal B cells. ZAP70 causes low CD8 and normal but dysfunctional CD4.	More severe than MCH I deficiencies
DNA repair defects	Ataxia-telangiectasia	ATM	AR	Impaired T cells and immunoglobulin production	Oculocutaneous telangiectasia, cerebellar ataxia, bronchopulmonary infections, sensitivity to ionizing radiation and susceptibility to cancer.

AD, Autosomal dominant; AR, autosomal recessive; CVID, common variable immune deficiency; FTT, failure to thrive; GVHD, graft vs host disease; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; SCID, severe combined immunodeficiency.

Adapted from Kumar A, et al. Current perspectives on primary immunodeficiency diseases. *Clin Dev Immunol.* 2006;13(2-4):223-259.

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IRAK 4 Mutation

Defective expression of the *IRAK 4* gene results in impaired innate immunity caused by defective interleukin 1 receptor-associated kinase 4. Staphylococcal and pneumococcal infections are especially common with moderate neutropenia, which may normalize during infection. Inheritance is autosomal recessive.[39]

Nonmalignant Disorders of Histiocytes

Dendritic Cell Disorders: Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH), the most common disorder of dendritic cells, is defined by accumulation of dendritic cells similar to Langerhans cells in various organs. The disease may be unifocal or multiorgan in involvement. Any organ can be affected, most commonly skeleton, skin, and pituitary. BRAF mutations have been identified in more than half of LCH cases. Diagnosis is made by biopsy of involved tissues and demonstration of Birbeck granules as well as positivity for S-100, CD1a, and Langerin (CD207). Langerhans cell histiocytosis can occur in the perinatal period. The estimated incidence in neonates is one to two per million. The majority (59%) of infants present with multisystem disease (two or more organs involved).[82] The skin is the predominant organ to be involved in infants. The extent of treatment (from observation to systemic chemotherapy) depends on disease status and should be risk adapted according to LCH guidelines.[51]

Congenital Self-Healing Reticulohistiocytosis with Spontaneous Regression

This variant of LCH typically appears at birth or in the neonatal period as multiple crusted papular skin lesions. These lesions tend to resolve spontaneously within weeks to a few months leaving residual hypo- or hyperpigmentation. Extracutaneous presentation is rare. This is diagnosed by skin performing histology of skin lesions.[98]

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a condition characterized by persistent fever, cytopenia, splenomegaly, hypertriglyceridemia, elevated serum ferritin, elevation in the soluble IL-2 receptor CD25, and hypofibrinogenemia. Familial HLH, a form of primary HLH, is an autosomal recessive disorder that most often presents in infancy. Familial HLH has five subtypes described based on genes involved: one to five correspond to defects in *HPLH1*, *PRF1*, *UNC13D*, *STX11*, and *STXBP2* genes, respectively.[53] Demonstration of a genetic defect is diagnostic but often lags behind fulfillment of clinical criteria and the need to initiate treatment. Management of primary HLH consists of immunomodulatory therapy followed by hematopoietic stem cell transplantation. SCID-associated HLH in neonates has been described. Neonates can also succumb to herpes simplex virus–associated HLH; therefore, prompt initiation of acyclovir is needed.[122]

The Hemostatic System

Overview of Normal Hemostasis

The strategic elements of the hemostatic system are vascular endothelium, platelets, and coagulation proteins. The immediate response to vascular injury is transient arteriolar vasoconstriction caused by reflex neurogenic mechanisms and local secretion of vasoactive factors. This is followed by activation of platelets and coagulation proteins. Finally, once bleeding is controlled, blood vessel patency is restored by the fibrinolytic system. Hence the normal hemostatic response can be viewed to occur in the following three phases (Fig. 79.10):

1. Initiation and formation of the platelet plug (primary hemostasis)
2. Propagation of the clotting process by the coagulation cascade followed by termination of clotting by antithrombotic control mechanisms (secondary hemostasis)
3. Removal of the clot by the fibrinolytic system (tertiary hemostasis)

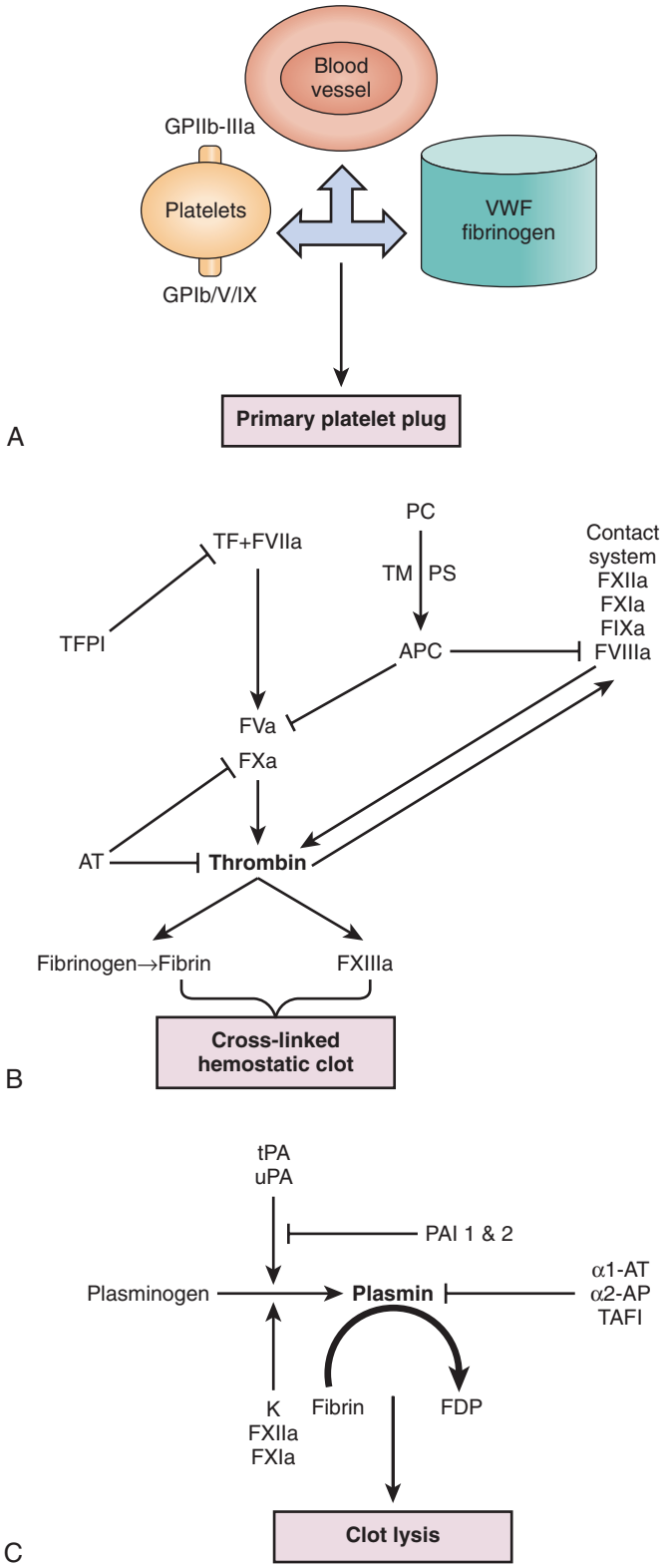
Vitamin K Physiology in Neonates

Vitamin K is present in a variety of dietary sources and is also produced by intestinal bacteria. Vitamin K is a cofactor for γ-glutamyl carboxylase, an enzyme that performs post-translational carboxylation, converting glutamate residues in proteins to γ-carboxyglutamate residues (Fig. 79.11). These residues facilitate membrane interactions mediated by calcium ions and are necessary for proper function of procoagulant factors (coagulation factors II, VII, IX, and X) and natural anticoagulants (proteins C and S). The newborn infant has a particularly fragile vitamin K status because of limited hepatic stores at birth, limited placental transfer of vitamin K, variable and limited content of vitamin K in breast milk, and an initially sterile gastrointestinal system.[127]

Developmental Hemostasis in the Neonate

Proteins required for hemostasis do not cross the placenta and are synthesized by the fetus. Distinctive, quantitative and qualitative, gestational age–dependent differences involving various components of hemostasis have been well characterized in neonates (Table 79.19).[5,6] These differences are more pronounced in premature infants. Although neonatal platelets are hyporeactive, the concentration and function of von Willebrand factor (VWF) are increased in neonates because of the presence of ultra-large hemostatically potent VWF multimers.[55] Vitamin K–dependent factors II, VII, IX, and X, and contact factors XI and XII, are reduced to about 50% of normal adult values, whereas the levels of the factors V, VIII, and XIII are similar to adult ranges. Although fibrinogen concentration is within normal adult ranges, it exists in a "fetal" form in the first 3 weeks of life. Fetal fibrinogen has a different composition compared to adult fibrinogen (increased sialic acid and phosphorus content) and shows decreased rates of fibrin polymerization,

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• **Fig. 79.10** Overview of the three phases of hemostasis. **A,** Primary hemostasis is dependent on interactions among platelets, the vascular endothelium, and coagulation proteins (von Willebrand factor [VWF] and fibrinogen). VWF associated with collagen in the exposed subendothelial matrix interacts with platelet GPIb/V/IX complex to mediate "platelet adhesion," whereas VWF and fibrinogen bind platelet GPIIb-IIIa to mediate "platelet aggregation." **B,** Secondary hemostasis involves sequential activation of coagulation factors. Formation of F (factor) VIIa-tissue factor (TF) complex is the major initiating event, which results in the generation of small amounts of thrombin (initiation phase or intrinsic pathway). These amounts of thrombin activate platelets and additional coagulation factors (amplification phase or extrinsic pathway), which results in a burst of thrombin formation so that a stable fibrin clot can be formed. This process is subsequently terminated by three types of natural anticoagulants: antithrombin (AT), which inhibits the activity of thrombin and factors (IXa, Xa, XIa, and XIIa); protein C, which is activated by thrombomodulin (TM), thrombin, and its cofactor protein S, which inhibits factors Va and VIIIa; and TF pathway inhibitor (TFPI), which inhibits FXa and TF/FVII. **C,** Tertiary hemostasis (fibrinolysis) functions to remove formed clots after hemostasis is secured. α1-AT 1 and 2, α1-antitrypsin 1 and 2; FDP, fibrin degradation products; PAI 1 and 2, plasminogen activator inhibitor 1 and 2; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator.

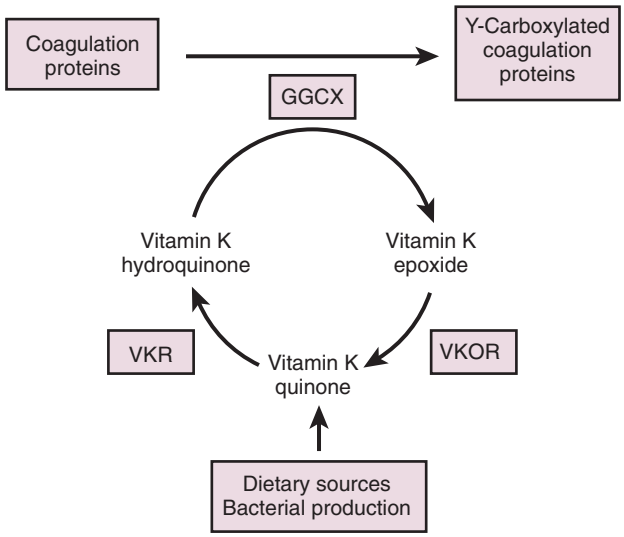
which results in prolonged thrombin clotting time (TCT) in normal neonates.[141] Similarly, concentrations of antithrombin, protein C, and protein S are significantly lower at birth, and the overall fibrinolytic capacity is decreased in neonates. On the other hand, despite significantly reduced total protein S antigen levels in neonatal plasma, the difference in the concentration of the anticoagulant, active, free form of protein S between infants and adults is much less pronounced, owing to low or undetectable C4b-binding protein in the neonatal period.[115] As a result of all these counterbalanced differences, the neonatal hemostatic system remains physiologically intact in the healthy neonate but lacks adequate reserve under stress conditions. Therefore, the risk of both bleeding and thrombosis is increased in sick neonates and is further increased in premature infants.

General Approach to Neonatal Bleeding Disorders

Bleeding disorders in neonates can be inherited but are more often acquired. It is clinically useful to classify bleeding disorders into those affecting primary hemostasis (blood vessels, VWF, and platelets) and those affecting secondary hemostasis (coagulation proteins). Disorders involving tertiary hemostasis (fibrinolytic system) are exceedingly rare. Acquired bleeding disorders can affect multiple components in the hemostatic system, and these can result in complex hemostatic abnormalities. The evaluation of bleeding disorders in neonates can be challenging because of subtle or nonspecific clinical presentations and difficulties in both obtaining adequate specimen for coagulation testing and interpreting the results of these tests in the context of developmental hemostasis. A systematic approach and the involvement of a pediatric hematologist are vital to

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establishing the diagnosis and planning the therapeutic approach to a neonate with a suspected bleeding disorder. A complete history and physical examination is an essential first step that directs further laboratory work-up (Table 79.20). The laboratory evaluation of neonates with suspected bleeding disorders is best carried out in a rational, stepwise fashion (Fig. 79.12). An initial hemostatic screen is performed, and this is followed by additional testing if an abnormality is identified on the initial screen. Additional testing is also indicated if the clinical suspicion remains high despite a normal hemostatic screen. Screening tests do not exclude several less common or milder bleeding disorders



• **Fig. 79.11** The vitamin K cycle. GGCX, Vitamin K γ-glutamyl carboxylase; VKOR, vitamin K epoxide reductase; VKR, vitamin K reductase.

TABLE 79.19 Hemostatic Parameters in the Newborn

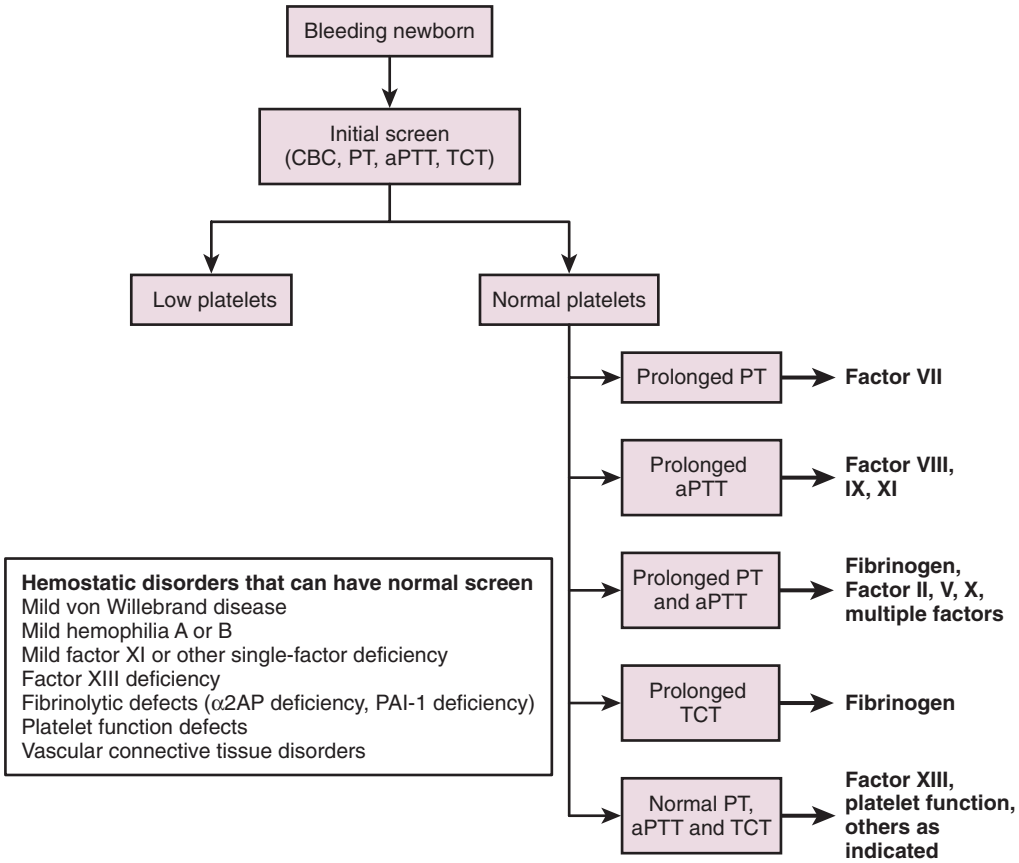
Decreased Compared with Adult Reference Ranges	Within Normal Adult Reference Ranges	Increased Compared with Adult Reference Ranges
Factor II	Fibrinogen	Factor VIII (mildly)
Factor VII	Factor V	VWF*
Factor IX	Factor XIII	α2-Macroglobulin
Factor X	α2-antiplasmin	
Factor XI	tPA	
Factor XII	PAI-1	
Pre-kallikrein		
HMWK		
Antithrombin		
Heparin cofactor II		
Protein C		
Protein S		
TFPI		
Plasminogen		

Platelet count and mean platelet volume vary with gestational and postnatal ages with wider intervals than adult reference ranges, prothrombin time (PT) is minimally prolonged, and activated partial thromboplastin time (aPTT) is markedly prolonged. Thrombin clotting time (TCT) is also prolonged. Platelet function studies show shorter bleeding times; shorter closure times by the platelet function analyzer (PFA-100); and decreased platelet aggregation in response to thrombin, ADP, and epinephrine.
HMWK, High molecular weight kininogen; PAI-1, plasminogen activator inhibitor-1; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; VWF, von Willebrand factor.
*VWF concentration and function are both increased, and ultra-large molecular weight multimers are present in neonatal plasma.
Data from Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. *Blood.* 1987;70:165-172; Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the healthy premature infant. *Blood.* 1988;72:1651-1657.

TABLE 79.20 Pertinent History and Physical Examination Findings in Neonatal Bleeding Disorders

History	• Presentations suggestive of neonatal bleeding disorders include diffuse purpura/ecchymoses, oozing from the umbilical stump, excessive bleeding from peripheral puncture/heel stick sites, large cephalohematomas without significant birth trauma history, prolonged bleeding following circumcision, intracranial hemorrhage in a term or late-preterm infant without history of birth trauma, and unexplained bleeding in a very low birth weight infant. • Bleeding in a well neonate is suggestive of an inherited coagulation disorder or an immune-mediated thrombocytopenia, whereas a sick preterm neonate is more likely to have acquired hemostatic disorder. • Vitamin K administration. • Maternal and obstetric history, including history of prior pregnancies and their outcomes, maternal medications (e.g., anticonvulsants can cause neonatal vitamin K deficiency), and maternal immune thrombocytopenia, which can cause neonatal thrombocytopenia. • Family history, including parental ethnic background and consanguinity, and family history of bleeding.
Physical examination	• The finding of purpura, petechiae, ecchymoses, and mucosal bleeding in neonates is suggestive of a primary hemostatic defect. • The presence of dysmorphic features/congenital anomalies may suggest an underlying genetic defect as some genetic syndromes are associated with a congenital bleeding tendency, most commonly involving platelets.

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• **Fig. 79.12** Approach to laboratory evaluation of coagulation in neonates. aPTT, Activated partial thromboplastin time; CBC, complete blood count; PT, prothrombin time; TCT, thrombin clotting time.

(see Fig. 79.12). Moreover, several potential pitfalls should be kept in mind regarding laboratory evaluation of hemostasis in neonates (Table 79.21).[84] Although many of these issues can be overcome, the major challenge in hemostatic testing in neonates remains the establishment of appropriate neonatal reference values that are analyzer- and reagent-specific and, at the same time, are clinically relevant (i.e., reference ranges that can accurately distinguish "disease" from "normal").[84]

Neonatal Platelet Disorders

This group of disorders results when platelets are either decreased in number (thrombocytopenia), functionally defective (thrombocytopathy), or both. Typical manifestations include petechiae (singly or in crops), bruising, and hemorrhage from mucosal surfaces. Bleeding from a heel stick puncture is often the first clinical indicator of an issue. Although generally rare, serious bleeding can complicate some of the more severe platelet defects.

Neonatal Thrombocytopenia (Quantitative Platelet Disorders)

Thrombocytopenia in a neonate of any viable gestational age was traditionally defined as a platelet count of less than 150×10^9/L.[108,109] However, recently, gestational and postnatal age-specific reference intervals for platelet counts have been described that should be considered when investigating thrombocytopenia in premature neonates.[134] Thrombocytopenia is one of the most frequent hematologic disorders encountered in the sick neonate.[108,109] This is evidenced by a fairly high incidence among neonates admitted to the neonatal intensive care unit (NICU) (22%-35%) compared with a relatively low overall incidence (0.7%-0.9%).[120] The incidence is inversely proportional to gestational age and/or birth weight.[30,31] Severe thrombocytopenia (platelet count $<50 \times 10^9$/L) is less common, affecting 5%-10% of all neonates and 14% of extremely low birth weight (ELBW) infants.[9,109] The predisposition of neonates to develop thrombocytopenia in response to illness is likely a result of the limited ability of the neonatal megakaryopoietic axis to increase platelet production in response to platelet consumption.[119] Although a large number of disease processes have been associated with thrombocytopenia in neonates, impaired platelet production is the prevailing mechanism in most cases of neonatal thrombocytopenia; consumption and/or sequestration underlie thrombocytopenia in 25%-35% of cases.[107] The differential diagnosis, and consequently diagnostic evaluation, of neonates with thrombocytopenia is usually based on onset (early onset ≤72 hours and late onset >72 hours), overall presentation, and

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TABLE 79.21 Special Considerations in Neonatal Hemostatic Laboratory Testing

Variable	Sources of Error	Possible Solution(s)
Preanalytical	Insufficient sample volume and underfilling of collection tubes Heparin contamination (sample collected from indwelling catheters or into a preheparinized syringe) Specimen activation	Establishment of standard protocols, techniques for specimen collection, and transport and microtization of assays
	High hematocrit at birth (required citrate-to-blood ratio of 9:1 may not be achieved using standard collection tubes)	When the hematocrit exceeds 0.55 (55%), the reduced plasma volume requires a decrease in the volume of anticoagulant used to maintain the ratio of 9:1 using the following formula: $C\ (mL) = 1.85 \times 10^{-3} \times (100 - Hct\ [\%]) \times V\ (mL)$ C = mL of 3.2% sodium citrate anticoagulant; Hct (%) = hematocrit of the patient in %; and V = mL of whole blood in tube
Analytical	Elevated levels of bilirubin or lipids and hemolysis in neonates can interfere with optical density measurements used to determine end points of some coagulation tests.	Additional centrifugation of the sample
Postanalytical	Defining appropriate reference ranges for neonates	Use of age-related reference ranges specific for analyzer-reagent combination used in the coagulation laboratory

natural course (Table 79.22). Although the most common identifiable causes are chronic fetal hypoxia in early-onset thrombocytopenia and sepsis and necrotizing enterocolitis (NEC) in late-onset thrombocytopenia, no etiology is identified in a significant proportion of thrombocytopenia among ELBW neonates.[31]

Neonatal Thrombocytopenic Disorders Requiring Special Attention

Immune-Mediated Thrombocytopenias

Fetal and Neonatal Alloimmune Thrombocytopenia

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the most common cause of severe neonatal thrombocytopenia and of intracranial hemorrhage (ICH) in term neonates.[21,23] Fetal and neonatal alloimmune thrombocytopenia occurs at an estimated incidence of 1/1000 to 2000 live births.[34] Fetal and neonatal alloimmune thrombocytopenia results from transplacental passage of maternal antibodies, which adhere to fetal platelets expressing paternal antigens that the mother lacks. Fetomaternal incompatibility involving certain human platelet antigens (HPAs) specifically expressed by fetal platelets leads to the production of a maternal IgG alloantibody in response to exposure to fetal blood. Maternal IgG crosses the placenta, often in early pregnancy, and binds to fetal platelets. The fetal platelets are cleared in the reticuloendothelial system, resulting in fetal and neonatal thrombocytopenia. Genetic incompatibility to platelet antigens is necessary but not sufficient for FNAIT, because the observed frequency of the clinical syndrome is far lower than what would be expected based on genetic frequency alone.[21,23] Thus other factors, including genetic immune response modifiers and HLA alleles, must be important in the pathophysiology.[139] The frequency of significant bleeding in FNAIT is striking compared with other thrombocytopenic disorders such as immune thrombocytopenia (ITP). Alloantibody-mediated secondary effects, such as platelet dysfunction and megakaryocytic damage resulting in prolonged thrombocytopenia and endothelial injury, may be responsible for the high incidence of severe bleeding (e.g., HPA-1a antigen is expressed by endothelial cells).[8,10] Human platelet antigen frequencies vary among different ethnic groups; the severity of FNAIT can correlate with the specific HPA incompatibility identified.

Fetal and neonatal alloimmune thrombocytopenia should be strongly considered in one of two clinical scenarios: (1) in an otherwise healthy neonate, born after an uneventful pregnancy and delivery, exhibiting petechiae or widespread purpura within 24-48 hours of birth associated with severe thrombocytopenia (platelet count $<50 \times 10^9$/L); or (2) in cases in which intracranial hemorrhage (ICH), porencephaly, or ventriculomegaly is discovered during fetal life. About 10%-20% of clinically recognized cases have ICH, which is asymptomatic (discovered radiographically) or symptomatic. Fifty to seventy-five percent of ICH occurs in utero. It can be fatal in one-third of cases, and in the rest can result in significant neurologic sequelae. Confirmation of a clinical diagnosis of FNAIT requires two laboratory approaches: (1) platelet antigen incompatibility is demonstrated by genotyping (PCR techniques) and phenotyping (flow cytometry, various immunoassay methods), and (2) there is evidence of maternal alloantibody directed against the identified alloantigen (various immunoassays such as ELISA and using maternal serum tested against paternal

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TABLE 79.22 Causes of Neonatal Thrombocytopenia

Classification	Causes	Presentation
Early-onset (≤72 hours)	Chronic fetal hypoxia/placental insufficiency (PIH, IUGR, diabetes)	Slowly evolving, mild–moderate thrombocytopenia, nadir at days 4-7; resolution by day 10
	Aneuploidy (trisomies 18, 13, 21, isochromosome 18q, triploidy, Turner syndrome)	Dysmorphism, congenital anomalies
	Perinatal asphyxia	Sick neonate with severe thrombocytopenia
	Early neonatal sepsis (*E. coli*, GBS, *H. influenza*)	
	DIC	
	Immune-mediated thrombocytopenias (FNAIT, autoimmune thrombocytopenia from maternal ITP)	Well full-term neonate with severe thrombocytopenia
	Kasabach-Merritt syndrome	Severe thrombocytopenia, DIC, enlarging cutaneous or visceral vascular tumor
	Thrombosis (renal vein thrombosis, aortic thrombosis, portal vein thrombosis, CSVT)	Unexplained thrombocytopenia, clinical features of organ dysfunction (e.g., renal insufficiency in renal vein thrombosis, seizures in CSVT)
	Thrombotic microangiopathies (congenital TTP, familial atypical HUS)	Hemolysis, hyperbilirubinemia, multiorgan dysfunction
	Congenital infections (CMV, toxoplasma, others)	Stigmata of congenital infections
	Bone marrow failure syndromes or replacement (congenital leukemia, metastatic neuroblastoma, storage disorders)	Pancytopenia, additional systemic manifestations
	Inborn errors of metabolism (organic acidemia)	Associated clinical features
	Inherited thrombocytopenias	Persistent unexplained thrombocytopenia, associated congenital anomalies
Late-onset (>72hours)	Late-onset sepsis (bacterial/fungal)	Rapid onset severe thrombocytopenia with slow recovery
	NEC	
	Autoimmune thrombocytopenia from maternal ITP	History of maternal thrombocytopenia/SLE
	Congenital infection (CMV, toxoplasma, others)	As above
	Kasabach-Merritt syndrome	
	Inborn errors of metabolism	
	Inherited thrombocytopenias	
	Drug-induced thrombocytopenia (β-lactams, vancomycin, indomethacin, ibuprofen, H_2-blockers, heparin)	Resolution upon withdrawal of offending drug

CMV, Cytomegalovirus; CSVT, cerebral sinovenous thrombosis; DIC, disseminated intravascular coagulation; FNAIT, fetal and neonatal alloimmune thrombocytopenia; GBS, group B Streptococcus; HUS, hemolytic uremic syndrome; ITP, immune thrombocytopenia; IUGR, intrauterine growth restriction; PIH, pregnancy-induced hypertension; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.
Data from Roberts I, Stanworth S, Murray NA. Thrombocytopenia in the neonate. *Blood Rev.* 2008;22:173-186.

platelets and/or platelets from normal donors with known platelet alloantigen phenotypes).[21,23] Neuroimaging of all neonates with suspected FNAIT is recommended, because some will have asymptomatic central nervous system bleeding requiring more aggressive treatment measures.

Autoimmune Thrombocytopenia in Infants Born to Mothers with Immune Thrombocytopenic Purpura

Neonatal ITP caused by transplacental passage of maternal IgG antiplatelet autoantibodies occurs in up to 25% of mothers who develop primary or secondary (owing to systemic lupus erythematosus) ITP during pregnancy.[109,132] The risk of severe thrombocytopenia and ICH in affected neonates is significantly lower compared with FNAIT (<15% and <2%, respectively). Maternal platelet counts during pregnancy cannot reliably predict the risk of neonatal thrombocytopenia; however, a maternal platelet count less than 50×10^9/L at delivery and a history of severe thrombocytopenia in a previous neonate may be useful indicators of the likelihood of significant neonatal thrombocytopenia complicating the current pregnancy.[56,126] Typically, the nadir platelet count in affected neonates is observed between days 2 and 5 after birth with resolution by day 7; however, some neonates may continue to have thrombocytopenia secondary to maternal ITP for months, necessitating long-term monitoring. Evaluation of affected neonates should include serial platelet counts and screening transcranial ultrasonography (if platelet count is $<50 \times 10^9$/L).

Inherited Thrombocytopenias

Inherited thrombocytopenias are a rare, heterogeneous group of disorders with highly variable bleeding tendency (Table 79.23). Although far less common than acquired forms, inherited thrombocytopenias should be considered in neonates with persistent unexplained thrombocytopenia

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TABLE 79.23 Inherited Thrombocytopenic Syndromes that Can Present in the Neonatal Period

Syndrome	Genetics	Hemostatic Features	Additional Findings
Large/Giant Platelets, MPV >11 fl			
MYH9-related thrombocytopenia (May-Hegglin anomaly and Fechtner, Epstein, and Sebastian syndromes)	AD (22q11)	Mild bleeding tendency Mild–moderate thrombocytopenia with mild platelet dysfunction	Neutrophil inclusions, ± sensorineural hearing loss, ± nephritis, ± cataracts
Bernard-Soulier syndrome	AR (17pter-p12; 22q11.2; 3q21)	Severe bleeding tendency Variable thrombocytopenia with defective platelet adhesion	None
X-linked thrombocytopenia with dyserythropoiesis	XL (Xp11.23)	Severe bleeding tendency Severe thrombocytopenia with defective platelet function	Microcytic anemia, dyserythropoiesis, thalassemia, splenomegaly
11q terminal deletion disorder (Paris-Trousseau thrombocytopenia/ Jacobsen syndrome)	AD (11q23)	Mild bleeding tendency Severe neonatal thrombocytopenia that resolves over time, and persistent platelet dysfunction	Developmental delay, growth restriction, dysmorphism, and multiple congenital anomalies (Jacobsen syndrome)
Normal-Sized Platelets, MPV 7-11 fl			
Congenital amegakaryocytic thrombocytopenia	AR (1p34)	Severe bleeding tendency Severe neonatal thrombocytopenia	Marrow failure during second decade
Thrombocytopenia and absent radii	AR (?)	Severe bleeding tendency Severe neonatal thrombocytopenia	Shortened/absent radii bilaterally. Bleeding tendency and thrombocytopenia improve after infancy.
Thrombocytopenia and radial synostosis	AD (7p15-p14.2)	Severe bleeding tendency Severe neonatal thrombocytopenia	Fused radius, incomplete range of motion, other skeletal defects, and sensorineural hearing loss Thrombocytopenia usually does not improve with time.
Small Platelets, MPV <7 fl			
Classic Wiskott-Aldrich syndrome	XL (Xp11.23-p11.22)	Severe bleeding tendency with significant risk of bleeding Severe neonatal thrombocytopenia	Immunodeficiency, autoimmunity, eczema, lymphoma
X-linked thrombocytopenia	XL (Xp11.23-p11.22)	Severe bleeding tendency with significant risk of bleeding Severe neonatal thrombocytopenia	Manifestations besides microthrombocytopenia are uncommon.

AD, Autosomal dominant; AR, autosomal recessive; MPV, Mean platelet volume; XL, X-linked.

since birth; bleeding tendency disproportionate to the platelet counts; family history of thrombocytopenia; typical congenital anomalies/dysmorphism; or suggestive blood smear abnormalities (consistently large or small platelets, abnormal platelet granules, or neutrophil inclusions called Döhle bodies). Except for Wiskott-Aldrich syndrome and X-linked thrombocytopenia (XLT), in which increased consumption of platelets in addition to defective production is implicated, thrombocytopenia in these disorders is caused by impaired production. Platelet dysfunction, identified in many inherited thrombocytopenias, is responsible for the significant bleeding tendency that is out of proportion to the measured platelet count and is characteristic of some of these disorders (e.g., Bernard-Soulier syndrome). The diagnostic evaluation of these disorders can be challenging. Testing should be conducted by a clinician with expertise and directed by clinical manifestations, physical examination findings, and initial lab results. Platelet function testing is imperfect, labor intensive, and requires relatively large volumes of blood for immediate processing. Some tests are available only in research laboratories. Genetic and/or molecular studies are needed to confirm the diagnosis in some inherited platelet disorders (such as Wiskott-Aldrich syndrome/X-linked thrombocytopenia).

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Platelet Function Disorders (Qualitative Platelet Disorders)

Qualitative platelet disorders include a large number of abnormalities, which are either inherited or acquired (Box 79.11). These disorders pose diagnostic challenges, because the tests needed to fully evaluate platelet function can be complex, requiring a great deal of expertise, and are often restricted to specialized coagulation and/or research laboratories. As a group, these disorders present as primary hemostatic defects of variable severity characterized by mucocutaneous bleeding (bruising, petechiae). Although congenital platelet function defects rarely cause pathologic bleeding in the neonatal period, the severe platelet function disorders such as Glanzmann thrombasthenia and Bernard-Soulier syndrome can present in neonates (Table 79.24). Some of these congenital disorders are associated with thrombocytopenia, while others cause isolated platelet dysfunction with normal platelet counts. For more information about these disorders, the reader is referred to excellent reviews by Bolton-Maggs and co-workers and Nurden et al.[17,95]

Management of Platelet Disorders in Neonates

Besides treating the underlying cause, platelet transfusions are the mainstay therapy for most neonates with platelet disorders. In neonatal thrombocytopenia, platelet transfusions can be given therapeutically in those with active bleeding or, in most cases, prophylactically to prevent serious bleeding events, particularly intracranial hemorrhage and intraventricular hemorrhage (IVH) in preterm infants. Although the correlation between platelet count and the risk of a clinical hemorrhage is poor, the risk of bleeding is likely higher in neonates with FNAIT, sepsis, or

• BOX 79.11 Causes of Platelet Function Defects

Acquired

- Uremia
- Liver disease
- Extracorporeal membrane oxygenation and cardiopulmonary bypass
- Disseminated intravascular coagulation
- Medications (indomethacin, ibuprofen, nitric oxide, others)
- Hypothermia

Inherited

- Primary platelet function defects
- Defective platelet adhesion (platelet-type VWD, Bernard-Soulier syndrome)
- Defective platelet aggregation (Glanzmann thrombasthenia)
- Defective receptor interactions and abnormal signal transduction
- Receptor defects (thromboxane A2 receptor defect, purinergic receptor defects for ADP and ATP, collagen receptor defects)
- Arachidonic acid pathway defects (cyclooxygenase-1 deficiency and thromboxane synthase deficiency)
- Signal transduction defects (defects in G-protein activation, defects in phosphatidylinositol metabolism, defects in calcium mobilization, and defects in protein phosphorylation)
- Defective granule storage and secretion
- Deficiency of α granules (Gray platelet syndrome, Quebec platelet disorder, arthrogryposis-renal dysfunction-cholestasis syndrome)
- Deficiency of δ granules (idiopathic δ-storage pool disease, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome)
- Deficiency of α and δ granules (11q terminal deletion disorder)
- Defective procoagulant function (Scott syndrome)
- Secondary platelet function defects
- VWD
- Congenital afibrinogenemia

ADP, Adenosine diphosphate; ATP, adenosine triphosphate; VWD, von Willebrand disease.

TABLE 79.24 Glanzmann Thrombasthenia versus Bernard-Soulier Syndrome

	Glanzmann Thrombasthenia	Bernard-Soulier Syndrome
Epidemiology	International frequency data are unknown. Increased incidence in certain ethnic groups (South Indian Hindus, Iraqi Jews, French gypsies, and Jordanian nomadic tribes) and families with consanguinity	Estimated prevalence <1 in 1,000,000
Pathophysiology	Defective platelet aggregation caused by quantitative or qualitative defect of platelet GpIIb/IIIa (fibrinogen receptor)	Defective platelet adhesion due to quantitative or qualitative defects of platelet GPIb-IX-V receptor complex (von Willebrand factor receptor)
Inheritance	Autosomal recessive	Autosomal recessive
Thrombocytopenia	No	Yes (of variable severity)
Aggregation studies	Absent platelet aggregation in response to all agonists except ristocetin	Failure to aggregate with ristocetin, normal aggregation response to other agonists
Diagnosis	Flow cytometric studies of platelet surface glycoprotein expression, GpIIb/IIIa	Flow cytometric studies of platelet surface glycoprotein expression, GpIb/IX

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TABLE 79.25 Platelet Transfusion Thresholds in Neonates (Platelet Counts $\times 10^9$/L)

	Nonbleeding					
	Preterm					
Published Guidelines	Stable	Unstable	Term	Bleeding	Before Invasive Procedure	ECMO
Most restrictive	<20	<30	<20	<50	<50	<100
Least restrictive	<50	<100	<30	<100	<100	

ECMO, Extracorporeal membrane oxygenation.
Data from Blanchette VS, Hume HA, Levy GJ, et al. Guidelines for auditing pediatric blood transfusion practices. *Am J Dis Child.* 1991;145:787-796; Gibson BE, Todd A, Roberts I, et al. Transfusion guidelines for neonates and older children. *Br J Haematol.* 2004;124:433-453.

necrotizing enterocolitis, particularly those with extreme prematurity.[29,35,143] Because of the paucity of evidence-based guidelines, considerable variability exists in practice as well as in published guidelines (Table 79.25).[14,46] Some recommendations are, however, more restrictive, accepting lower platelet triggers for transfusions because of recognition that the clinical condition is an important determinant of the risk of bleeding and because of concerns regarding the risks of platelet transfusions (e.g., transfusion-related acute lung injury, bacterial contamination, alloimmunization).

Treatment of infants with suspected FNAIT should be initiated promptly and without awaiting definitive test results. The mainstay of therapy is platelet transfusions, which should be given in nonbleeding, well neonates if the platelet count is less than 30×10^9/L and in neonates with intracranial hemorrhage or other major bleeding events if the platelet count is less than 50 to 100×10^9/L.[21,46] Human platelet antigen-1a/5b negative platelets are compatible in greater than 90% of cases with FNAIT, or washed, irradiated maternal platelets are used as the platelet products of choice because they result in higher and longer-lasting platelet count increments.[21] If, however, matched platelets are not immediately available, random donor platelets should be given instead.[8] Intravenous immunoglobulin (IVIG) and corticosteroids can also be used as adjuvant therapies.[21] Antenatal management of pregnancies at risk for FNAIT is complex, requiring a multidisciplinary approach. Standard medical treatment consists of weekly IVIG in early pregnancy with or without systemic corticosteroids. Intrauterine platelet antigen-negative platelet transfusions are reserved for medical treatment failures and for prophylaxis of acute hemorrhage at the time of fetal blood sampling.[22] Early cesarean delivery has also been advocated to decrease the risk of intracranial hemorrhage, although evidence is lacking.

Recommended management of neonatal ITP consists of close observation in those with platelet counts between 20 and 50×10^9/L at delivery and IVIG in neonates with clinical hemorrhage or platelet counts less than 20×10^9/L.[101] Cesarean section, unless otherwise indicated for obstetric reasons, and intrapartum fetal platelet count measurements are not recommended.[94]

In neonates with significant bleeding because of congenital platelet disorders or acquired platelet dysfunction, fibrinolytic inhibitor drugs (epsilon aminocaproic acid and tranexamic acid), and recombinant activated factor VII can be used as adjuvant to or, in some cases, in place of platelet transfusions. Patients with Bernard-Soulier syndrome or Glanzmann thrombasthenia are at increased risk of isoimmunization and/or alloimmunization from platelet transfusion therapy, which can result in platelet transfusion refractoriness rendering future platelet transfusions largely ineffective.[117] For certain inherited platelet disorders, such as congenital amegakaryocytic thrombocytopenia and Wiskott-Aldrich syndrome, hematopoietic stem cell transplantation from suitable donors can be curative.

Neonatal Coagulation Disorders

This group of disorders results in impairment of secondary hemostasis resulting in bleeding that is typically delayed and in deep tissues. As for platelet disorders, inherited or, more commonly, acquired mechanisms are involved. In this section, coagulation disorders are described that can present in neonates.

Inherited Coagulation Disorders

Inherited coagulation disorders usually present with abnormal bleeding in an otherwise healthy neonate. Although a positive family history can confirm the diagnosis, an inherited bleeding disorder in the absence of family history is still possible in cases arising as a result of new mutations or inherited in an autosomal recessive fashion.

Hemophilia

Hemophilia, the most common inherited bleeding disorder to present in the neonatal period, is caused by deficiency of factor VIII (hemophilia A) or, less commonly, factor IX (hemophilia B). Hemophilia is classified according to severity on the basis of plasma procoagulant concentrations. Patients are categorized as having mild hemophilia (>5% but <40% normal factor [<0.05-<0.40 IU/mL]); moderately severe hemophilia (1%-5% normal factor

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[0.01-0.05 IU/mL]); and severe hemophilia (<1% normal factor [<0.01 IU/mL]). The annual incidences of hemophilias A and B in the United States are 1 in 5000 and 1 in 30,000 male births, respectively. In all, 60% and 44% of these new cases, respectively, have severe phenotype. In both disorders, thrombin generation is markedly decreased, which leads to delayed formation and poor stability of the hemostatic clot.

Both are X-linked recessive disorders caused by a variety of gene mutations. It is estimated that up to thirty percent of mutations in hemophilia A are de novo (new) mutations. Hemophilia A and B are clinically indistinguishable, and clinical manifestations early in life are almost always confined to boys. Greater than 50% of hemophilia patients are diagnosed as neonates, of whom up to one-third have clinically significant bleeding.[32] The pattern of bleeding in newborns with hemophilia differs significantly from that in older children and adults. Iatrogenic bleeding is the most common hemorrhagic manifestation, typically presenting as significant oozing or hematoma formation following venous or arterial puncture, heel stick, intramuscular vitamin K injection, or circumcision. Extracranial hemorrhage (ECH) including subgaleal hemorrhage and cephalohematomas, as well as ICH, can also occur in neonates with hemophilia. The incidence of ICH in neonates with severe hemophilia is 1%-7%.[64,65,123] Intracranial hemorrhage is more common than ECH, and the most frequent site of hemorrhage is subdural.[66] Risk factors for cranial bleeding include forceps/vacuum instrumentation during delivery, severe phenotype, and preterm delivery. Intracranial hemorrhage can have dramatic (seizures, focal deficits) or subtle presentations or can be asymptomatic or "silent." Extracranial hemorrhage also demands attention because it can cause massive blood loss in neonates with hemophilia. Finally, umbilical, musculoskeletal, and GI and other organ bleeding are infrequently encountered in hemophilic neonates.[27,28]

The diagnosis of hemophilia in neonates requires laboratory confirmation. Isolated prolongation of the aPTT is usually found on routine coagulation testing. The definitive diagnosis of hemophilia requires measurement of factor levels in uncontaminated cord blood or neonatal venous blood samples. Although it is usually possible to confirm a diagnosis of hemophilia A of any severity in the neonatal period, irrespective of the gestational age, confirmation of mild hemophilia B is problematic. Unlike factor VIII, factor IX levels are reduced at birth and are further reduced in preterm infants. It is, therefore, possible to make a diagnosis of severe and moderate hemophilia B at birth, but for mildly affected neonates, confirmation requires repeat testing at 6 months of age or molecular analysis if the genetic defect is known.[27,28] Controversy exists regarding role, timing, and optimal technique for radiologic assessment of ICH in neonates with hemophilia. The British Committee for Standards in Hematology has published guidelines that recommend screening cranial ultrasound in all neonates with severe or moderate hemophilia before discharge and cranial MRI or CT scan in symptomatic neonates even if the ultrasound is normal, owing to the low sensitivity of ultrasound for the detection of subdural bleeding.[26]

The management of neonatal hemophilia can be summarized as follows.[26]

Management during Delivery

The optimal mode of delivery remains unclear and may be best determined on an individual basis, taking into account obstetric and hemostatic factors.[70] Vacuum extraction, forceps, and invasive monitoring procedures, such as placement of fetal scalp electrodes and fetal scalp blood sampling, should be avoided.

Management in the Postnatal Period

Intramuscular vitamin K should be withheld until hemophilia is excluded. Oral vitamin K can be given instead if there is a delay in diagnosis or if hemophilia is confirmed. Following confirmation of diagnosis, short-term prophylactic replacement therapy (with specific factor concentrates) may be given to neonates following traumatic, instrumented, or preterm delivery or a prolonged second stage of labor. The benefits of factor replacement must be weighed against the risk of inhibitor development, although a recent report from the CDC demonstrated no difference in inhibitor rates with neonatal factor exposure.[65]

Management of Clinically Significant Bleeding in Neonates

Before confirmation of diagnosis, fresh frozen plasma (15-25 mL/kg) should be given. After confirmation of diagnosis, recombinant factor VIII or IX concentrates should be given with close monitoring, as neonates may require higher doses to achieve desired factor levels and may demonstrate a shortened factor half-life. Although extended half-life factors are now available for use in hemophilia, use in neonates and previously untreated patients is not yet recommended outside of a clinical trial.[74]

von Willebrand Disease

Despite being the most common inherited bleeding disorder overall, initial presentation and identification of most forms of von Willebrand disease (VWD) in neonates is rare, owing to physiologically increased VWF concentration and function in neonates compared to adults. The classification of VWD consists of type 1 disease, which is a partial quantitative deficiency in VWF; type 2 disease, which is characterized by various qualitative (functional) defects in VWF; and type 3 disease, which is owing to a total quantitative deficiency of VWF. More recently, a subtype of type 1 VWD, Vicenza variant, with features of increased clearance of VWF has been identified.[104] Although most types of VWD are inherited in an autosomal dominant fashion, type 3 is recessively inherited as homozygous or compound heterozygous. Laboratory tests in VWD usually include measurements of plasma VWF antigen (VWF:Ag), VWF function by VWF ristocetin cofactor assay (VWF:RCo),

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FVIII coagulant activity (FVIII:C), and assessment of the circulating plasma VWF (VWF multimers). Two types of VWD can present in neonates.

Type 2B VWD is characterized by increased affinity for VWF to platelets leading to the formation of circulating platelet aggregates that are reversibly sequestered in the microcirculation. Neonates with this type can present with moderate thrombocytopenia and bleeding. This rare type of VWD should be considered in the differential diagnosis of unexplained neonatal thrombocytopenia.

VWD type 3, the most severe form, represents less than or equal to 1% of all VWD cases but is the type most likely to present in neonates. Bleeding manifestations are variable. Mucosal bleeding is more common than in hemophilia A, whereas ICH is almost unheard of in type 3 VWD. This may be attributed to low, but residual, factor VIII activity.[133] On coagulation testing, type 3 VWD is characterized by prolonged aPTT, undetectable VWF:Ag and VWF:Rco, very low factor VIII:C (<1 IU/mL), and absent VWF multimers.

Because of the clinical and laboratory overlap with severe hemophilia A, testing for type 3 VWD should be considered in neonates with suspected severe hemophilia A, particularly when the gender, clinical course, or laboratory data are not typical. Management of bleeding in VWD requires factor replacement using plasma-derived VWF-containing factor VIII concentrate for moderate to severe bleeding. In older children who present with mild VWD (type 1 and some type 2), desmopressin (DDAVP) is used to increase VWF levels. Because of the risk of hyponatremia, desmopressin (DDAVP) should not be used in the treatment of neonatal VWD.[137]

Rare Inherited Coagulation Disorders

Rare inherited coagulopathies comprise less than 5% of all inherited deficiencies of coagulation. They are generally transmitted as autosomal-recessive traits. Unlike hemophilia, causative mutations, identifiable in 80%-90% of patients, are private (i.e., unique for each affected kindred).[75] Because of their rarity, data on clinical manifestations and management are relatively limited, but it is clear that a number of these disorders are associated with a severe bleeding tendency, which may manifest itself in neonates (Table 79.26).[27] Typical manifestations in neonates include soft tissue bleeding, umbilical stump bleeding, and post-circumcision bleeding. Intracranial hemorrhage is also a relatively common feature of these disorders.[27] These disorders should be suspected in neonates with bleeding tendency and prolonged clotting times. A prolonged PT with a normal aPTT is indicative of factor VII deficiency, whereas a prolonged aPTT with a normal PT is indicative of factor XI deficiency, provided that VWD and hemophilia have been ruled out. The prolongation of both tests should point to the possible deficiencies of factor X, factor V, prothrombin, or fibrinogen; dysfibrinogenemia; or combined factor deficiencies. Factor XII, prekallikrein, and high molecular weight kininogen, if deficient, will prolong the aPTT but are not associated with clinical bleeding. Factor XIII deficiency is an exception in that both PT and aPTT are normal. Quantitative factor XIII assays are preferred over the urea clot stability assay for diagnosis of this factor deficiency. Confirmation of diagnosis is achieved by specific factor coagulant activity assays and, rarely, antigen assays. Although DNA mutation analysis is rarely performed, results can be useful for prenatal diagnosis.[75]

TABLE 79.26 Rare Inherited Coagulation Disorders that Can Present in the Neonatal Period

Disorder	Estimated Prevalence*	Treatment
Afibrinogenemia†	1	Cryoprecipitate and fibrinogen concentrates
Factor II deficiency	0.5	FFP and PCC
Factor V deficiency	1	FFP
Factor VII deficiency	2	FFP and rVIIa
Factor X deficiency	1	FFP and PCC
Factor XI deficiency	1	FFP and FXI concentrate
Factor XIII deficiency‡	0.5	Cryoprecipitate, FFP, and FXIII concentrate
Combined FV and FVIII deficiency	0.5	FFP
Combined vitamin K–dependent coagulation factor deficiency§	0.5	Vitamin K (oral or parenteral), FFP

*Per 1 million population.
†Inherited fibrinogen disorders can manifest as quantitative defects (afibrinogenemia and hypofibrinogenemia) or qualitative defects (dysfibrinogenemia). Neonatal presentation is usually seen in afibrinogenemia, which is characterized by the complete deficiency of plasma fibrinogen.
‡In addition to bleeding tendency, affected neonates can have impaired wound healing.
§Severely affected neonates may also exhibit features that resemble "warfarin embryopathy," including nasal hypoplasia, distal digital hypoplasia, epiphyseal stippling, and mild conductive hearing loss attributed to dysfunction of other vitamin K–dependent proteins (osteocalcin and matrix Gla proteins).
FFP, Fresh frozen plasma; PCC, prothrombin complex concentrate.
Data from Bolton-Maggs PH, Perry DJ, Chalmers EA, et al. The rare coagulation disorders—review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia.* 2004;10:593-628.

Acquired Coagulation Disorders

Acquired deficiency or impairment of coagulation is a frequent complication in sick neonates. In the next section, three important acquired coagulopathies in neonates are reviewed: vitamin K deficiency, DIC, and coagulopathy of liver disease.

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Vitamin K Deficiency

As discussed, vitamin K is a critical cofactor required for posttranslational modification of coagulation proteins II, VII, IX, and X. In the absence of vitamin K, these proteins are dysfunctional and are released into the circulation in a decarboxylated form known as proteins induced by vitamin K absence (PIVKA). The presence of PIVKA without coagulation deficit indicates subclinical vitamin K deficiency.[127] The recommended dietary intake of vitamin K is 1 μg/kg body weight/day.[127] Vitamin K deficiency can be idiopathic or secondary. Secondary causes include the following:

1. Inadequate intake, which can occur in infants exclusively receiving unsupplemented breast feedings, infants on broad-spectrum antibiotics that eliminate intestinal vitamin K–producing bacteria, or infants who are receiving total parenteral nutrition without vitamin K supplementation.
2. Poor absorption or fat malabsorption state caused by cholestatic liver disease, pancreatic insufficiency, or intestinal disorders (e.g., short bowel syndrome).
3. Poor utilization, as seen in significant liver disease.
4. Vitamin K antagonism due to warfarin therapy.

Vitamin K deficiency bleeding (VKDB) is a rare but potentially life-threatening bleeding disorder, which presents in three different patterns (Table 79.27). Isolated prolongation of the PT is the earliest laboratory evidence of vitamin K deficiency, followed by prolongation of the aPTT. The diagnosis is confirmed by correction of these parameters by vitamin K administration or by assays of the specific factors. Other confirmatory tests, such as measurement of decarboxy prothrombin (PIVKA-II) and measurement of vitamin K concentrations, are rarely able to return a result in real time, limiting their clinical utility for routine laboratory use.[137]

Treatment of VKDB requires parenteral vitamin K administration by slow IV infusion or subcutaneously if venous access cannot be established. For neonates who are bleeding, fresh frozen plasma should also be given. Prothrombin complex concentrates (PCC) should be considered in the presence of life-threatening hemorrhage or ICH when it is necessary to rapidly normalize the levels of the depleted coagulation factors.[137] In the United States, prevention of VKDB by administration of a single intramuscular injection of vitamin K soon after birth is the current standard practice and has been almost universally effective. A single oral dose of vitamin K is ineffective for long-term protection.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a clinicopathologic syndrome that is characterized by systemic activation of coagulation and fibrinolysis, consumption of platelets and coagulation factors, and generation of fibrin clots that can lead to ischemic organ damage or failure. Disseminated intravascular coagulation represents a continuum in severity with definable phases characterized by initial localization and compensation (nonovert or compensated DIC) that progresses into widespread dysregulation of coagulation and fibrinolysis (overt or decompensated DIC).

Although the risk of developing DIC is believed to be highest in neonates, accurate data on the epidemiology of DIC in neonates are lacking because of difficulties in establishing the diagnosis and, consequently, underestimation of the true frequency of this disorder.[128] Disseminated intravascular coagulation in neonates can be triggered by a variety of pathologic conditions (Box 79.12). The cardinal manifestations of overt DIC are caused by excessive bleeding and microvascular thrombosis. Hemorrhagic symptoms include petechiae and bruising, oozing from venipuncture sites, bleeding from traumatic and surgical wounds, and in severe cases, bleeding involving internal organs. Thrombosis typically manifests as biochemical and/or clinical evidence of end-organ dysfunction. Kasabach-Merritt syndrome (KMS) represents a localized form of DIC seen in association with cutaneous or occasionally visceral congenital vascular lesions such as kaposiform hemangioendothelioma and tufted angiomas.[50] The pathophysiology of KMS is

TABLE 79.27 Vitamin K–Deficiency Bleeding Presentations in Neonates

Presentation	Bleeding Sites	Etiologies
Early (first 24 h)	Scalp, subperiosteal, skin, intracranial, intrathoracic, intra-abdominal	Maternal drugs (e.g., warfarin, anticonvulsants)
Classical (days 1-7)	Gastrointestinal, umbilical, skin, nose, circumcision	Mainly idiopathic, breastfeeding (low milk intake)
Late (≥day 8; peak 3-8 weeks)	Intracranial, skin, gastrointestinal	Idiopathic or secondary, exclusive breastfeeding in the absence of vitamin K administration, undiagnosed cholestasis often present. Secondary cases from malabsorption resulting from underlying disease (e.g., biliary atresia, α-1-antitrypsin, cystic fibrosis) or chronic diarrhea. Antibiotic therapy sometimes implicated.

Data from Van Winckel M, De Bruyne R, Van De Velde S, et al. Vitamin K, an update for the paediatrician. *Eur J Pediatr.* 2009;168:127-134.

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• BOX 79.12 Common Causes of Disseminated Intravascular Coagulation in Neonates

- Sepsis
- Perinatal hypoxia-ischemia (perinatal asphyxia, placental abruption)
- Necrotizing enterocolitis
- Severe hepatic dysfunction
- Respiratory disorders (RDS, MAS)
- Metabolic disorders (galactosemia, others)
- Vascular anomalies (Kasabach-Merritt syndrome)
- Hematologic disorders (purpura fulminans caused by protein C or S deficiency, erythroblastosis fetalis)

MAS, Meconium aspiration syndrome; RDS, respiratory distress syndrome.

generally presumed to be that of platelet trapping by abnormally proliferating endothelium within the vascular anomaly. This results in the activation of platelets with a secondary consumption of clotting factors. The diagnosis of DIC, particularly in the early stages, can be problematic because there is no single laboratory test that can establish or rule out DIC. Hence, the diagnosis is often made on the basis of an appropriate clinical suspicion supported by laboratory evidence of procoagulant and fibrinolytic system activation coupled with anticoagulant consumption. Laboratory abnormalities seen in DIC include thrombocytopenia, elevated fibrin degradation products (FDP) or D-dimers, prolonged PT, prolonged aPTT, prolonged thrombin clotting time, and a low fibrinogen. Serial testing may be necessary for the diagnosis, given the dynamic nature of DIC and that fibrinogen is an acute-phase reactant; plasma fibrinogen can remain well within the normal range despite ongoing consumption.

Successful treatment of DIC relies largely on reversal of the underlying condition and supporting adequate blood flow and oxygen delivery. Blood component transfusions (platelets, fresh frozen plasma, and cryoprecipitate) are an important part of supportive treatment in DIC. In cases of DIC in which thrombosis predominates, such as arterial or venous thromboembolism or severe purpura fulminans, therapeutic anticoagulation with unfractionated heparin may be considered. Except for the use of protein C concentrates in purpura fulminans owing to protein C deficiency, anticoagulant concentrates (protein C, antithrombin), recombinant factor VIIa, and recombinant tissue plasminogen activator are not generally indicated for the routine treatment of DIC.

Coagulopathy of Acute Liver Disease

Acute liver disease affects hemostasis in several different ways. Hemostatic abnormalities associated with acute liver failure include thrombocytopenia and thrombocytopathy, decreased production of coagulation factors, vitamin K deficiency, reduced vitamin K-dependent γ-carboxylase activity, acquired dysfibrinogenemia, decreased fibrinolytic activity, and DIC. The net result is a complex bleeding diathesis of variable severity. Although spontaneous bleeding is rare, serious bleeding after invasive procedures can occur.

Coagulation testing often shows prolonged PT and aPTT, thrombocytopenia, decreased fibrinogen level, and decreased concentrations of factors VII and V. A normal or elevated factor VIII concentration distinguishes primary liver disease from DIC. Conventional coagulation assays do not fully reflect the hemostatic status and do not predict risk of bleeding. Hence, there is no benefit to correcting coagulopathy in nonbleeding neonates. Treatment of active hemorrhage includes blood product transfusions (FFP, cryoprecipitate, platelets) and vitamin K administration. Recombinant factor VIIa has also been used successfully to maintain hemostasis, although there is an increased risk of thrombosis in this setting.[113,140]

Neonatal Thrombotic Disorders

Neonates, particularly those who are critically ill, have a significantly increased risk of developing thrombotic events. This increased risk can be explained by the presence of risk factors unique to this period of time that can promote thrombosis (sepsis, inflammation, hypotension, hypoxia, and the use of intravascular catheters in small-caliber vessels), as well as the developmental hemostatic differences in neonates discussed earlier.[105] Acquired and inherited prothrombotic conditions including factor V Leiden and prothrombin gene mutation; deficiencies of protein C, protein S, and antithrombin; elevated factor VIII, lipoprotein (a), and homocysteine; and antiphospholipid antibodies are known risk factors for thrombosis. However, the contribution of neonatal, and especially maternal, prothrombotic conditions in the causation of thrombosis in neonates is not well characterized. Data from various registries, which likely underrepresent the true frequency of thrombotic complications in newborns, have reported incidences of up to 5.1 per 100,000 live births and 2.4 per 1000 NICU admissions with 45%-55% of these events affecting preterm infants.[12] Common neonatal thrombotic events include thrombosis of upper/lower venous system, portal veins, renal veins, or cerebral venous sinuses, as well as peripheral and CNS arterial thrombosis. The most common trigger for neonatal thrombotic events is an indwelling vascular access device.

Neonatal Deep Vein Thrombosis of the Upper/Lower Venous System

Almost all cases of deep vein thrombosis (DVT) of the upper and lower venous system in neonates are associated with indwelling central venous lines such as an umbilical venous catheter (UVC), peripherally inserted central catheter (PICC), or Broviac catheter. Manifestations are highly variable and include catheter dysfunction, limb or face swelling, discoloration of the skin and/or distention of the superficial veins, persistent chylous effusion, and superior vena cava (SVC) syndrome. Some cases are asymptomatic and are identified incidentally on radiologic studies.

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Diagnosis is most commonly established by compression Doppler ultrasound. For thrombosis involving the upper central venous system (proximal subclavian vein, brachiocephalic vein, SVC), Doppler ultrasound has lower sensitivity, and other imaging modalities such as echocardiography or venography (magnetic resonance, computed tomography, or conventional) are often required to make the diagnosis of DVT in this location. In general, the recommended management of acute and symptomatic central venous line–related DVT includes anticoagulation therapy, usually with low molecular weight heparin (LMWH), for a total of 6-12 weeks. The central venous line should be removed if no longer required or if it is nonfunctioning. Anticoagulation therapy 3-5 days before the central venous line removal is recommended. If the central venous line is still required and is functioning, it may be left in place. If the central venous line is still in place on completion of therapeutic anticoagulation, a prophylactic dose of LMWH should be given to prevent recurrent thrombosis until such time as the central venous line is removed. The management of radiologically detected asymptomatic central venous line–related DVT is less clear. If central line access is still required, management options include either anticoagulation in the absence of contraindications or close clinical and radiologic monitoring.[106]

Neonatal Portal Vein Thrombosis

Neonatal portal vein thrombosis (PVT) is an underrecognized thrombotic event that is most commonly encountered in association with UVC placement. The reported incidence of UVC-related PVT is highly variable, ranging from 1.3% up to 43%.[138] A large, single-center retrospective study reported an overall estimated incidence of at least 3.6 per 1000 NICU admissions.[86] Risk factors include both UVC-related factors, such as inappropriate UVC placement (low or intrahepatic), and prolonged catheterization and transfusion through the UVC, as well as patient-related factors, including low birth weight, low-flow state, hypoxia, infection, sepsis, congenital malformations, and gestational diabetes mellitus. Portal vein thrombosis is often associated with subtle, nonspecific, or absent clinical and laboratory signs. Unexplained thrombocytopenia may be an initial manifestation in a proportion of cases.[86] Diagnosis is usually established by Doppler ultrasound. Management is similar to any central venous line–related DVT, although it is not clear if anticoagulation improves outcome. Long-term complications of PVT include portal hypertension and hepatic lobar atrophy, which is usually asymptomatic. As such, PVT is the major cause of extrahepatic portal hypertension and gastrointestinal bleeding in childhood.[138]

Neonatal Renal Vein Thrombosis

Neonatal renal vein thrombosis (RVT) is the most prevalent non-catheter-related thrombotic event during the neonatal period, accounting for up to 20% of all thrombotic events in newborns.[19] Risk factors include a history of perinatal asphyxia, gestational diabetes mellitus, prematurity, dehydration, infection, and congenital heart disease.[19] Involvement of renal veins may also be seen in the context of central venous line–related thrombosis of the inferior vena cava (IVC). Males are more commonly affected than females, representing 67.2% of cases.[19] Approximately 70% of neonatal RVT cases are unilateral, with a left-sided predominance. Most neonates with RVT will manifest with one or more of the three cardinal clinical features of macroscopic (or microscopic) hematuria, palpable flank mass, and thrombocytopenia.[19] Other manifestations include acute renal injury, which can be present in a significant number of cases, distant embolization, and hypertension. Diagnosis is confirmed by Doppler ultrasonography. Current management guidelines recommend either supportive care with radiologic monitoring for extension of thrombosis or anticoagulation for 6-12 weeks for unilateral RVT in the absence of renal impairment or extension into the IVC; anticoagulation for 6-12 weeks for unilateral RVT that extends into the IVC; and anticoagulation alone for 6-12 weeks or initial thrombolytic therapy with tissue plasminogen activator, followed by anticoagulation for 6-12 weeks for bilateral RVT with evidence of renal impairment.[83] Acute complications of RVT include adrenal hemorrhage and distant embolization. Long-term complications include chronic renal insufficiency and hypertension.[19]

Neonatal Arterial Thrombosis

The majority of cases of arterial thrombosis in neonates are caused by indwelling arterial catheters. Neonatal aortic thrombosis is a potentially life-threatening arterial thrombotic event that is most commonly associated with use of umbilical arterial catheters but has been reported to occur spontaneously. Affected neonates can be asymptomatic or present with irritability, absent/diminished peripheral pulses, and coldness or duskiness of extremities. Additional manifestations include catheter dysfunction, hypertension, acute renal injury, mesenteric ischemia, and signs of heart failure.[90] Diagnosis is confirmed by Doppler ultrasound. Management typically includes immediate removal of the indwelling arterial catheter and anticoagulation therapy for 5-7 days. Thrombolytic therapy or surgical thrombectomy should be considered for limb, organ, or life-threatening arterial ischemia.[83]

Neonatal Stroke

See Chapter 53.

Neonatal Purpura Fulminans

Neonatal purpura fulminans (PF) describes a clinicopathologic entity characterized by dermal microvascular thrombosis, DIC, and perivascular hemorrhage, occurring in the

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newborn period.[100] Inherited cases are most commonly caused by homozygous deficiency of protein C or S. Acquired causes are more common and often are associated with severe infection, most commonly group B streptococcus causing a consumptive coagulopathy and a relative deficiency of protein C and/or S.[100] Neonatal PF usually presents with a rapid onset of cutaneous purpuric lesions shortly after birth and DIC. The skin lesions initially appear dark red and then become purple-black and indurated. They occur at previous sites of trauma (e.g., intravenous cannula insertion sites), and they may initially be mistaken as bruising. There is a predilection for the limbs, although buttocks and thighs are often affected. In time, the areas may become necrotic and gangrenous, resulting in loss of extremities.[100] Other manifestations include thrombosis of the cerebral vasculature, vitreous hemorrhage, and retinal detachment that may result in partial or complete blindness, and large vessel venous thromboses such as RVT.[100] Diagnosis is based on typical clinical presentation. Confirmation of inherited forms requires demonstration of undetectable levels of protein C or protein S, a heterozygous state in the parents, and, if possible, identification of the molecular defect.[100] Treatment should be initiated promptly and includes replacement therapy with fresh frozen plasma (or protein C concentrate for patients with protein C deficiency), followed by indefinite anticoagulation for inherited cases. For acquired cases, the mainstay of therapy is aggressive treatment of the underlying cause and supportive therapy.[100]

Neonatal Antithrombotic Therapy

Antithrombotic agents, which include anticoagulants and thrombolytics, are increasingly used in neonates for treatment of thromboembolism and for prevention of thrombosis in neonates with congenital heart disease and those requiring mechanical circulatory support. The immaturity of the hemostatic system in neonates leads to differences in the pharmacokinetics of commonly used antithrombotic agents and increased risk of bleeding.[142]

Anticoagulants

In neonates, unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the two most commonly utilized anticoagulants. Both agents function as an anticoagulant by potentiating the inhibitory effects of antithrombin on thrombin and factor Xa. Low molecular weight heparin, which is derived from UFH, has a more profound inhibitory effect on factor Xa than on thrombin.[142] Because antithrombin levels are significantly decreased in neonates, higher initial doses are required to achieve the target anticoagulation levels. Low molecular weight heparin has more stable pharmacokinetics and thus more predictable responses than UFH.[142]

Unfractionated heparin is most often used for the treatment and prevention of thromboembolic events, prevention of thrombosis during cardiac catheterization, and for maintaining the patency of venous and arterial catheters and extracorporeal circuits in cardiopulmonary bypass and extracorporeal life support. Unfractionated heparin in pediatrics is administered as an intravenous infusion. The therapeutic dose recommended for treatment of thromboembolic events in neonates is 28 units/kg per hour, administered as a continuous intravenous infusion and titrated to a target aPTT or antifactor Xa activity level. A bolus dose of 75 units/kg IV, administered over 10 minutes, may be given immediately before initiating the maintenance infusion to accelerate achievement of target anticoagulation.[83] The prophylactic dose of UFH is 10 units/kg per hour, administered as continuous intravenous infusion.[83] The standard concentration for UFH infusion in neonates is 50 units/mL, and it is important that this concentration be stocked for the NICU and for use in infants to avoid dosing errors.

The activated partial thromboplastin time (aPTT) and the antifactor Xa activity are the two assays commonly used to monitor UFH. Target levels for therapeutic anticoagulation for thromboembolic events are an aPTT of 1.5-2.5 times the control aPTT, usually 60-85 seconds, or an antifactor Xa activity of 0.35-0.7 units/mL.[83] Although the antifactor Xa assay, which is generally considered a more reliable measure of the anticoagulant effect, may be preferred to the aPTT in neonates, neither test is ideal. Monitoring of UFH in neonates remains challenging, with a high degree of inter- and intrapatient variability in dosing, leading to difficulty in maintaining target levels.[142] Antithrombin supplementation, either with fresh frozen plasma or antithrombin concentrate, is sometimes used for neonates in whom therapeutic heparinization has been difficult to achieve despite dose escalation.

The most important adverse effect of anticoagulation is bleeding. Heparin-induced bleeding in neonates as a result of accidental overdose, owing to drug error in which a higher heparin infusion concentration is erroneously dispensed and administered, is a common serious and avoidable problem in hospitals. Because UFH is used for a variety of clinical indications other than therapeutic and prophylactic infusions (e.g., line flushes), a variety of heparin concentrations are available on hospital formularies, potentially leading to these kinds of errors.[83] Treatment of bleeding owing to UFH includes immediate termination of the infusion and administration of protamine sulfate (if rapid reversal is required). Heparin-induced thrombocytopenia, a very serious adverse event that can lead to severe thrombotic complications, can affect up to 1% of neonates, particularly those with congenital heart disease.[142]

The most frequently used LMWH in pediatrics is enoxaparin. In neonates, LMWH (enoxaparin) has replaced UFH as the anticoagulant of choice in the initial treatment of thromboembolism because of more predictable pharmacokinetics and ease of administration and monitoring. Low molecular weight heparin is also the preferred agent for long-term anticoagulation in neonates. Nevertheless, in neonates at risk for bleeding, UFH is still preferred because of its

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shorter half-life and complete reversibility with protamine sulfate. The traditionally recommended therapeutic dose of enoxaparin for treatment of thromboembolic events in neonates is 1.5 mg/kg per dose, administered subcutaneously every 12 hours.[83] However, a higher initial dose (1.8-2 mg/kg/dose) administered subcutaneously every 12 hours is commonly employed at major pediatric thrombosis centers, based on data that suggest a higher final dose requirement in this patient population, especially in preterm infants.[83] The recommended prophylactic dose of enoxaparin in neonates is 0.75 mg/kg per dose, administered subcutaneously every 12 hours.[83] Low molecular weight heparin is monitored by the anti-factor Xa assay. A common ordering error occurs when providers request a factor X activity assay rather than the antifactor Xa activity assay. Some laboratories have renamed the antifactor Xa activity assay as a LMWH activity assay to avoid this problem. The target antifactor Xa activity, measured 4-6 hours after dose administration, is 0.5-1 units/mL for therapeutic anticoagulation and 0.1-0.3 units/mL for prophylactic anticoagulation.[83] Adverse effects such as bleeding and heparin-induced thrombocytopenia are infrequent. Protamine sulfate can be administered in serious bleeding but does not completely reverse the anticoagulant effects of LMWH.

Thrombolytics

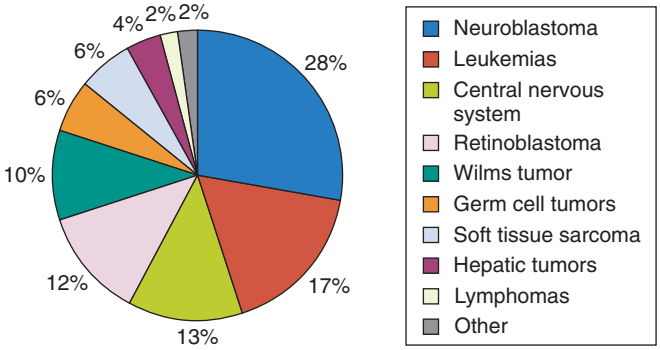
Alteplase, recombinant tissue plasminogen activator (tPA), is the thrombolytic agent of choice. The main indication for thrombolysis is life-, organ-, or limb-threatening thromboembolism. An important consideration in neonates is that plasminogen levels are significantly lower in newborn infants, which may result in reduced clinical efficacy. Plasminogen supplementation with fresh frozen plasma infusion should be considered before administration of alteplase in neonates to enhance the thrombolytic effect. Thrombolytic therapy is contraindicated in any clinical situation with serious bleeding or increased bleeding risk, including prematurity (<32 weeks' gestation).[83] The recommended dose of alteplase is 0.5 mg/kg per hour, infused for 6 hours. Lower doses of 0.06-0.1 mg/kg per hour have also been successfully used and may be associated with lower bleeding risk. Prophylactic UFH (i.e., 10 units/kg per hour) is typically administered concurrently with alteplase infusion, which is then followed by therapeutic heparinization after discontinuation of thrombolytic therapy.[83] Close clinical and laboratory monitoring (PT, aPTT, fibrinogen, D-dimer, and platelet counts) is required. In patients receiving thrombolytic therapy, fibrinogen levels should be kept greater than 100 mg/dL and platelets should be kept at 100,000/μL to reduce bleeding risk.[83] A screening head ultrasound, CT scan, or brain MRI is commonly obtained in neonates before initiation of thrombolytic therapy to confirm the absence of intracranial hemorrhage (ICH) at baseline. The major adverse event is bleeding, including serious and life-threatening hemorrhages. Intracranial hemorrhage has been reported in up to one-fourth of neonates receiving thrombolytic therapy.[83] Major bleeding is treated by stopping the infusion of the thrombolytic agent and anticoagulant; administering cryoprecipitate (usual dose of 1 unit/5 kg or 5-10 mL/kg), an antifibrinolytic agent (e.g., aminocaproic acid or tranexamic acid), or both; and administering other blood products as indicated.[83]

Neoplasms in the Neonate

Infant Cancer

The annual incidence of cancer in the first year of life, 234 per million infants, is the highest for all of childhood (<15 years of age) according to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) statistics for the years 1992-2007. This represents 10% of all childhood malignancies. The first year of life is the only period in childhood when the incidence of cancers is not higher in males than females.[99] Neonatal tumors comprise 2% of all childhood malignancies.[85] The majority of neonatal tumors are solid and can be picked up by a perinatal ultrasound. Teratoma, a germ cell tumor presenting most often on prenatal ultrasound in the sacrococcygeal area, is the most common neoplasm in infancy but is usually surgically excised as a nonmalignant (i.e., noncancerous) tumor. Fig. 79.13 provides a graphic summary of infant cancer incidence by common types.

In adults, cancer is thought to occur after a long interplay between environmental triggers and genetic predisposition. In infancy, especially in the neonatal period, the normal, genetically programmed protections against unregulated growth of cells fail very early. In infancy, embryonal tumors such as neuroblastoma, Wilms tumor, medulloblastoma, hepatoblastoma, and retinoblastoma are more common compared to older ages. The association between congenital abnormalities and certain tumors is well established.[85] The 5-year overall survival for all neonates (age <1 month) was 60.3%. Neonates with solid tumors had the highest 5-year overall survival (71.2%), followed by leukemia (39.1%) and CNS tumors (15%). Except for neuroblastoma, all of the neonatal tumors showed significantly inferior outcomes



• **Fig. 79.13** Comparative incidence of infant cancers. (Data from Pereira GA, Ribeiro KB, Rodriguez-Galindo C, et al. Changes in incidence of infant cancer: analysis of SEER data 1992-2007. *J Clin Oncol.* 2011;29[Suppl]; abstr 9542.)

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compared to that in older patients.[3] The inferior survival rates for similar histologic tumors is likely attributable both to differences in the tumor biology and also to altered drug metabolism and increased toxic effects of therapy in infancy.[49] Treatment protocols for infant cancers include elimination or reduction of radiation therapy and age- and weight-based decreases in chemotherapy doses.

Neuroblastoma

Neuroblastoma, an embryonal tumor of neural crest origin arising anywhere along the sympathetic chain, is the leading malignant tumor of the perinatal period and the second most common solid tumor in childhood. About half of infant neuroblastomas are diagnosed within the first 4 months of life, with many being detected as an adrenal mass in utero. Survival of infants with neuroblastoma detected before birth is better that those diagnosed after birth.[52] Other common sites of presentation are cervical and thoracic. Neurologic signs and symptoms of spinal cord compression prompt urgent diagnosis and management with steroids and chemotherapy in about 20% of neonatal neuroblastomas. Many neuroblastoma tumors secrete catecholamines. Urine homovanillic acid and vanillylmandelic acid levels are commonly used diagnostic tests. Mass infant screening programs using these urine tests in Japan, Quebec, and Europe have increased the detection of good-prognosis tumors but have failed to change the mortality rate from high-risk neuroblastoma. Familial neuroblastoma with germline mutations in *PHOX2B* or *ALK* account for 1% of childhood neuroblastoma.[94]

The most important prognostic variables for infant neuroblastoma are the patient age at diagnosis, the stage of the tumor, DNA index, and *MYCN* amplification. Tumor hyperdiploidy (DNA index <1) is a favorable prognostic indicator, whereas *MYCN* amplification is associated with more aggressive disease. Infants with neuroblastoma have a better prognosis than older children, with an overall 5-year survival of about 88% (versus 45% for those >1 year at diagnosis). Infants with localized tumors have a 5-year survival rate of 95%. Expectant observation of babies younger than 6 months of age with small adrenal masses has reduced surgical morbidity and mortality while maintaining excellent event-free survival rates.[94] Observation or surgery, with or without low-dose chemotherapy, is recommended for lower-risk neuroblastoma in infants. High-dose chemotherapy with peripheral blood stem cell rescue, radiation therapy, cis-retinoic acid, and immunotherapy are treatment modalities for infants with high-risk, *MYCN*-amplified disease.

A unique stage of neuroblastoma is 4s. These patients have to be less than 1 year of age, have localized primary tumor with disease dissemination to skin and liver, and have <10% of bone marrow involved with negative metaiodobenzylguanidine (MIBG) in bone marrow. Stage 4s accounts for 7%-10% of the cases of neuroblastoma.[114] This subgroup of infants has the unique, poorly understood characteristic of spontaneous tumor regression. Infants with 4S disease require chemotherapy only if they develop threatening symptoms or progressive disease.[114]

Leukemia

Leukemia is the second most common cancer in infancy. Infant leukemias tend to present toward the second half of the first year of life. Approximate incidence rates per million infants include acute lymphoblastic leukemia (ALL) 20 per million, acute myelogenous leukemia (AML) 10 per million, and juvenile myelomonocytic leukemia (JMML) at 2 per million. Neonatal or congenital leukemia, estimated to occur in 1-5 per million infants, is diagnosed in the first 30 days of life and carries a particularly grave prognosis. Acute myelogenous leukemia is more common than ALL in neonatal leukemia. Rearrangements of the mixed lineage leukemia (*MLL*) gene at chromosome 11q23, MLL-r, are common in congenital and infant ALL and AML. Prenatal MLL-r events promote rapid development of additional mutations or "hits" resulting in early leukemia presentation. If a monozygotic twin is diagnosed with leukemia in the first year of life, intrauterine transfer of the mutation results in an almost 100% concordance for the other twin, with a brief lag time of weeks until the other twin's leukemia diagnosis.[125]

There are many genetic syndromes associated with increased leukemia risk. Bone marrow failure syndromes, primary and secondary immunodeficiencies, defects in DNA repair, and genetic defects impacting tumor suppressor genes are associated with leukemogenesis as well as oncogenesis. Down syndrome (ALL, AML), Noonan syndrome (JMML, AML), and neurofibromatosis type 1 (ALL, AML, JMML) have strong associations and early leukemia presentations.

The differential diagnosis for congenital leukemia includes transient abnormal myelopoiesis, leukemoid reaction, congenital infections, hypoxia or hemolysis, hemophagocytic lymphohistiocytosis, and stage 4s neuroblastoma. Langerhans cell histiocytosis can also present in infants with pancytopenia, organomegaly, and cutaneous extramedullary hematopoiesis.

Infant Acute Lymphocytic Leukemia

A number of clinical features that have been associated with a poorer prognosis are common in neonates and infants with acute lymphocytic leukemia (ALL): a large tumor cell burden (hyperleukocytosis), massive hepatosplenomegaly, involvement of the central nervous system, leukemic skin infiltrates (leukemia cutis), and hypogammaglobulinemia. The leukemic blasts in infant ALL often are CD10 negative, express myeloid antigens, and have cytogenetic abnormalities involving the *MLL* gene, which carries worse prognosis. Strategies to intensify therapy have improved survival for infants with ALL but not for the ones with *MLL* rearrangement.[48] A small percentage of these leukemias are biphenotypic (i.e., express characteristics of both ALL and AML). Neonates experience significant toxicities both from

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chemotherapy and central nervous system irradiation. The especially poor prognosis for infant ALL is owing to the high incidence of bone marrow and extramedullary relapse. Infants <90 days of age at diagnosis have worse outcomes.[48] Progressively more intensive chemotherapeutic regimens and bone marrow transplantation have been used in these patients, but the event-free survival rate at 5 years is only in the 30% range.[125]

Infant Acute Myelogenous Leukemia

Neonates with acute myelogenous leukemia (AML) have similarly poor remission and disease-free survival rates indistinguishable from those for older children. Distinctive features of AML in the infant include very high incidences of cutaneous involvement (leukemia cutis) and central nervous system disease, hepatosplenomegaly, hyperleukocytosis, and an unusually high number of cases with blasts of the monoblastic (M5%-50%) or myelomonocytic (M4%-10%) type. Leukostasis syndrome, a complication of severe hyperleukocytosis more commonly seen in AML than in ALL, is characterized by white blood cell plugs in the microvasculature, causing central nervous system events such as stroke and respiratory and cardiac failure. Cytogenetic abnormalities in the blasts are exceptionally common and usually involve *MLL* gene rearrangement, such as t(11;19)(q23;p13) and t(9;11)(p21;q23). Infants with Down syndrome who are diagnosed with AML have a superior survival rate compared with others with AML, because they tend to develop the acute megakaryocytic leukemia subset of AML (AMKL or M7) and have a very high response rate to therapy. Approximately one-third of infants who experience transient abnormal myelopoiesis will develop AMKL. Most other infants with AMKL have a t(1;22)(p13;q13) aberration, which confers a poor prognosis.[125]

Juvenile Myelomonocytic Leukemia

Juvenile myelomonocytic leukemia (JMML, formerly juvenile chronic myelogenous leukemia) is classified as a myeloproliferative neoplasm/myelodysplastic syndrome that accounts for less than 1% of pediatric leukemias. Ten percent of cases are diagnosed before 3 months of age, and the majority are diagnosed by 2 years of age. Clinical manifestations include splenomegaly, rash, lymphadenopathy, failure to thrive, leukoerythroblastosis, monocytosis, thrombocytopenia, and elevated fetal hemoglobin. The abnormal growth of JMML cells has been linked to a dysregulated transduction signal through the pathway that involves GM-CSF, the GM-CSF receptor neurofibromin, and Ras.

About 10% of children with JMML have neurofibromatosis type 1 (NF1). Neurofibromatosis type 1–activating mutations and *RAS* family oncogene mutations are seen in the leukemic cells of JMML patients. Patients with Noonan syndrome, a disorder associated with gain-of-function mutations in *PTPN11*, the gene encoding the protein tyrosine phosphatase SHP-2, are at increased risk for developing JMML. SHP-2 mutations are present in the leukemia cells of one-third of JMML cases. Mutations of the E3 ubiquitin ligase CBL are now identified in up to another 10%. Monosomy 7 is also seen in a subset of JMML. Patients diagnosed before 3 years of age and those with Noonan syndrome have a better prognosis. Although a variety of therapies have been employed to treat JMML, allogeneic bone marrow transplantation is the only curative treatment.[125]

Many entities (e.g., retinoblastoma [see Chapter 95], Wilms tumor [see Chapter 93], and sacrococcygeal teratoma [see Chapter 13]) are discussed elsewhere.

Teratomas and Other Germ Cell Tumors

Most infant germ cell tumors (GCTs) are diagnosed before the age of 2 months. GCTs comprise a wide range of benign and malignant tumors. They originate from preinvasive precursors that transform into overt tumors during infancy, adolescence, or young adulthood. Whereas 90% of GCTs diagnosed during adult life are gonadal, two-thirds of neonatal and childhood GCTs are extragonadal, with sacrococcygeal teratoma being most prevalent.[112] Serum markers used to help in diagnosis of GCTs are α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-hCG). It is important to note that AFP levels are high at birth and decrease to adult values only by 812 months of age.[112] See Table 79.28 for age-adjusted AFP values.

Most neonatal germ cell tumors, irrespective of location, are benign. The term *teratoma* describes both benign and malignant tumors composed of haphazardly intermixed tissues that originate from pluripotent stem cells and that are foreign to the anatomic site in which they arise. Traditionally, tissue components from all three embryonic germ layers—endoderm, mesoderm, and ectoderm—should be represented in a teratoma. However, it is now generally accepted that tumors that are foreign to the site where they arise and consist of more than one embryonic layer can be classified as teratomas. Sacrococcygeal teratomas are frequently detected prenatally or at birth as a mass in the region of the sacrum or buttocks, sometimes accompanied by obstruction of the rectum or urinary tract. Vertebral anomalies can be seen in patients with sacrococcygeal teratomas. The mainstay of therapy for germ cell tumors is surgical resection. Typically, teratomas have an excellent outcome. Immature teratomas have a prognosis comparable to mature teratomas, provided the tumor can be totally excised. In the case of sacrococcygeal teratomas, prematurity, perioperative hemorrhage, and other postoperative events result in a 10%-20% risk for mortality. Endodermal sinus tumors of the infant testis have a better prognosis than those at later ages and other locations, including the ovary.

Soft Tissue Sarcomas

Infant soft tissue sarcomas account for about 7% of infant cancers and are the fifth most common malignancy in the first year of life. About one-third of these are rhabdomyosarcoma. Rare non-rhabdomyosarcoma tumors of soft tissue

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TABLE 79.28 Postnatal Serum Concentrations of α-Fetoprotein in Preterm and Term Infants

Age	α-Fetoprotein Concentration (μg/L)* 10th Percentile	Median	90th Percentile
Preterm Infants (27-35 Weeks' Gestational Age)			
Birth	149,700	252,125	335,375
1 wk	43,825	96,510	234,500
1 mo	21,825	41,975	66,460
2 mo	3,100	16,000	36,900
3 mo	560	1,250	10,140
4 mo	75	162	621
6 mo	22	67	170
9 mo	6	20	54
12 mo	5	10	28
Term Infants (38-42 Weeks' Gestational Age)			
Birth	17,200	30,875	44,350
2 mo	88	206	412
4 mo	16	77	127
6 mo	11	30	67
9 mo	5	12	27
12 mo	4	7	17

*1 μg/L AFP = 1.09 IU/mL.
Data from Lahdenne P, et al. Biphasic reduction and concanavalin A binding properties of serum alpha-fetoprotein in preterm and term infants. *J Pediatr.* 1991;118:272.

that have increased incidence in infancy include infantile fibrosarcoma (25%), malignant rhabdoid tumor (15%), and infantile hemangiopericytoma (4%). Although the prognoses for infantile fibrosarcoma and infantile hemangiopericytoma are excellent, in general, infantile soft tissue sarcomas have a worse outcome than in older children. Radiation therapy is less likely to be used in infants, and vulnerability to acute and late effects of chemotherapy requires dose reductions and careful monitoring for toxicity.[121]

Rhabdomyosarcoma

Rhabdomyosarcoma is a tumor of striated muscle accounting for about half of infant soft tissue sarcomas. Neonatal rhabdomyosarcoma commonly occurs in the genitourinary area or trunk rather than appearing as masses in the head and neck region, as in older infants, and in head/neck and extremities, as in older children. The prognosis depends on both the histologic type (embryonal or alveolar in best to worst order of prognosis) and the extent of tumor resection. Both radiation therapy and chemotherapy are important adjuvants to surgical resection, with infants being less likely to receive radiation and more likely to have local recurrence.[121]

Infantile Fibrosarcoma

Infantile fibrosarcoma is a spindle cell tumor of the soft tissues. It usually presents before the age of 2 years. Surgery is the mainstay of therapy, which, coupled with good response to chemotherapy, results in excellent prognosis. A novel chromosomal translocation, t(12;15)(p13;q25), which gives rise to an *ETV6-NTRK3* fusion transcript, is present in these tumors as well as in congenital mesoblastic nephroma.[121]

Neonatal Brain Tumors

The incidence of neonatal brain tumors is low, accounting for <1% of pediatric CNS malignancies. Histology differs from older children: teratomas, astrocytomas, embryonal tumors, gangliogliomas, etc. It can be diagnosed using antenatal ultrasonography (macrocephaly, hydrocephaly, or other changes suggestive of intracranial tumor). Postnatally infants present with increased head circumference, signs of increased intracranial pressure, bulging fontanelles, hypotonia, irritability, seizures, and neurologic deficits. MRI is the choice of imaging.[15] For infants with suspected germ-cell tumors, checking the AFP and β-hCG values may help in diagnosis. Treatment is reserved to surgical resection and chemotherapy if indicated. Radiation should not be used. Survival in neonates with CNS tumors is poor because of inability to perform aggressive resection, avoidance of radiation, and high-grade pathology. Also, these patients have a very high incidence of endocrine, neurologic, and cognitive deficits later in life.[15]

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Key Points

- Hematopoiesis is a complex process tightly regulated by a multitude of growth factors and chemokines.
- Red blood cell disorders are common in the neonatal period, and their management differs depending on the inheritance pattern and severity of manifestations.
- DNA-based tests are readily available for diagnosis of inherited red blood cell defects when conventional tests have failed, or there is concern for confounding biochemical results caused by previous transfusions.

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- Our knowledge and experience have expanded significantly in the recent years in several areas such as iron metabolism, regulation of erythropoiesis, and gene therapies for hemoglobinopathies.
- Gene therapy is emerging as a treatment for hemoglobinopathies and is showing its safety and potential efficacy in both preclinical and early clinical studies. Gene therapy is now a reality, with seven patients cured of their β0/βE thalassemia or with significant amelioration from β0/β0 thalassemia and one patient with SCD, while others are showing modest transgene expression.
- Supplementation of between 1 mg/kg per day and 10 mg/kg per day elemental iron is a clinically important strategy used to lessen the risk of iron deficiency.
- Neutropenia is a common finding in the NICU, particularly during the first week of life and in lower birth weight and ill infants, but persistent neutropenia, particularly in an infant with dysmorphic features, should be investigated.
- About 10% of infants who have Down syndrome develop a transient clonal myeloproliferative disorder now called *transient abnormal myelopoiesis* (TAM).
- An infant with recurrent infections, an absolute lymphocyte count less than 3000/cmm, should warrant immediate referral and further testing of the immune system.
- Hemophilia is the most common inherited bleeding disorder to present in the neonatal period.

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80

Blood Component Therapy for the Neonate

CYRIL JACQUOT, YUNCHUAN DELORES MO, AND NAOMI L. C. LUBAN

Special Considerations for Transfusion Therapy in the Neonate

Neonates constitute one of the most heavily transfused patient groups in the hospital. In a Canadian study, over 50% of infants at less than 30 weeks' gestation and more than 80% of infants with a birth weight of less than 1000 grams received at least one red blood cell (RBC) transfusion during their initial hospitalization.[86] Neonatal transfusion practices differ substantially from adult and pediatric transfusion practices because of unique differences in neonatal physiology. Neonates have small blood volumes when compared with older children and adults but high blood volume per body weight. Their immature organ system function predisposes them to metabolic derangements from blood products and additive solutions and to the infectious and immunomodulatory hazards of transfusion such as transfusion-transmitted cytomegalovirus (TT-CMV) infection and transfusion-associated graft-versus-host disease (TA-GVHD). Neonates undergo rapid growth but have a limited capacity to expand their blood volume. In addition, passive transfer of maternal antibodies to the immunologically naïve newborn creates unique compatibility scenarios not commonly seen in children or adults. Their responses to stresses, including hypothermia, hypovolemia, hypoxia, and acidosis are dependent on gestational age, birth weight, and co-morbidities. These considerations necessitate special approaches to transfusion therapy in the neonate.[98,196,197]

Risks of Transfusion Therapy

Advances in donor recruitment, blood screening, and processing have decreased the risks associated with blood transfusion. As part of patient blood management, current transfusion considerations and guidelines focus on reducing both transfusion number and donor exposures. Nevertheless, hematologic, immunologic, infectious, cardiovascular, and metabolic complications can occur. Many of these risks exist for transfusion recipients of any age, whereas others pose a greater threat to the neonatal recipient. These potential risks affect the choice and processing of blood products. Parents must be advised of the risks, benefits, and alternatives to transfusion, and informed consent should be documented in the medical record along with the indications for, and results of, the prescribed transfusion.

Metabolic Complications

Neonates, especially extremely premature infants, are more susceptible to metabolic alterations caused by the immaturity of many of their organ systems. Glucose imbalances, hyperkalemia, and hypocalcemia are the most common metabolic derangements related to transfusion, owing to the inability of the infant to efficiently metabolize and/or excrete elements intrinsic to blood and blood components, including anticoagulants, preservative solutions, and other solutes that accumulate during refrigerated storage.

Hypoglycemia

Hypoglycemia (see Chapter 86) can result from the combination of decreased glucose infusion rates during transfusion and impaired glycogenolysis and gluconeogenesis within the liver of the preterm neonate. Continuous glucose infusion rates of greater than 3-4 mg/kg per minute are often required in preterm infants; if maintenance fluids are suspended during transfusion, glucose infusion rates can decrease to approximately 0.2 mg/kg per minute for citrate-phosphate-dextrose-adenine (CPDA-1) preserved RBCs and 0.5 mg/kg per minute for the RBC additive Adsol® (AS-1) preserved RBCs. In neonatal intensive care units, holding feeds during blood transfusions, particularly for premature infants, has become a common practice to decrease the risk of neonatal enterocolitis (NEC).[39] In a previous report of 31 fresh (<5 days old) small-volume RBC transfusions in 16 preterm infants (mean birth weight and gestational age: 863 grams and 26 weeks, respectively), 15% of infants receiving AS-1-preserved RBCs and 64% of infants receiving CPDA-1-preserved RBCs required supplemental dextrose infusions during the transfusion owing to hypoglycemia (blood glucose <40 mg/dL or symptoms of

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Abstract

Neonates constitute one of the most heavily transfused patient groups in the hospital. Neonatal transfusion practices differ substantially from adult and pediatric transfusion practices because of unique differences in neonatal physiology. Neonates have small blood volumes when compared with older children and adults but high blood volume per body weight. Their immature organ system function predisposes them to metabolic derangements from blood products and additive solutions and to the infectious and immunomodulatory hazards of transfusion such as transfusion-transmitted cytomegalovirus (TT-CMV) infection and transfusion-associated graft-versus-host disease (TA-GVHD). Of recent concern has been the emergence of Zika virus (ZIKV), which can be transmitted by blood products and is associated with abnormalities in fetal development. Neonatal responses to stresses, including hypothermia, hypovolemia, hypoxia, and acidosis, are dependent on gestational age, birth weight, and co-morbidities. These considerations necessitate special approaches to transfusion therapy in the neonate. This chapter also discusses transfusion thresholds and indications for different blood components.

Keywords

neonatal transfusions
transfusion risks
blood components
transfusion indications
factor concentrates
pathogen reduction

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hypoglycemia).[62] Subsequent analysis has shown similar frequency of transfusion-associated hypoglycemia when older (5-21 days old) AS-1-preserved units were used. Furthermore, reported incidences of hypoglycemia in neonates either during or after exchange transfusions range from 1.4%-3.6% with no difference in incidence when group O whole blood or reconstituted whole blood was used. Hypoglycemia occurring after exchange transfusion is believed to be caused by intraprocedural hyperglycemia, which causes rebound hypoglycemia from insulin secretion.[55] Preventive measures for transfusion-associated hypoglycemia include recognizing those infants at risk for developing glucose homeostatic imbalances, continuing the infusion of maintenance fluids rich in dextrose (albeit at a slower rate) to maintain an adequate glucose infusion rate during simple transfusions and close monitoring of blood glucose during both small and large volume transfusions. To minimize the risk of RBC hemolysis and/or agglutination, dextrose-rich fluids should be infused in a separate intravenous line from the blood transfusion.[84]

Hyperkalemia

The risk of transfusion-induced hyperkalemia is directly related to the magnitude of the K^+ load delivered with RBC transfusion, which depends on the age, plasma volume, and plasma concentration of K^+ of the unit, and the rate at which K^+ is delivered (potassium infusion rate). Potassium infusion rates greater than 0.01 mEq/kg per minute may pose a potential risk of transfusion-associated hyperkalemia and have been shown to result in cardiac arrhythmia/arrest in neonates.[55] As stored red blood cells age, potassium leaks out into the plasma and raises the extracellular potassium level within the component. Units of RBCs in extended-storage media (AS-1, AS-3, AS-5) have a hematocrit (Hct) of approximately 60%, and RBCs stored in CPDA-1 have an Hct of approximately 70%. Furthermore, some pediatric transfusion centers centrifuge RBC aliquots before transfusions for neonates to further reduce the plasma component to 20% (e.g., RBC unit: Hct >80%). Such an approach helps reduce the content of potassium, mannitol, and RBC microvesicles in irradiated RBC aliquots stored up to 21 days.[157] After 42 days of storage, K^+ levels in the plasma of an AS-1-preserved RBC unit approximate to 0.05 mEq/mL. Therefore, infusing 15 mL/kg over 3 hours would yield a potassium dose of 0.33 mEq/kg and a potassium infusion rate of 0.002 mEq/kg per minute (e.g., 1-kg infant receiving 15 mL RBC and 6 mL plasma). Conversely, after 35 days of storage of CPDA-1-preserved RBCs, potassium levels in the plasma approximate to 0.08 mEq/mL. Transfusing 15 mL/kg of the CPDA-1-stored product over 3 hours would yield a potassium dose of 0.36 mEq/kg (e.g., 1-kg infant receiving 15 mL RBC and 4.5 mL plasma) at a potassium infusion rate of 0.002 mEq/kg per minute.[55] Given that daily potassium requirement is approximately 2-3 mEq/kg, simple RBC transfusions infused slowly over 2-4 hours (2-5 mL/kg per hour) do not pose a threat for hyperkalemia (Table 80.1).

It has been shown in multiple studies that transfusing dedicated RBC units to their expiration dates does not cause hyperkalemia even in extremely preterm infants.[55,76,100,178]

TABLE 80.1 Dose and Infusion Rate for Potassium in Small-Volume and Large-Volume Transfusion

	CPDA-1 (35-Day)	Additive Solution* (42-Day)	Additive Solution* (20-Day)
Unit hematocrit	70%-75%	57%-60%	57%-60%
Plasma (K+)	0.080 mEq/mL	0.050 mEq/mL	0.030 mEq/mL
15 mL/kg over 3 hours (0.08 mL/kg/min)			
K^+ dose	0.36 mEq/kg	0.33 mEq/kg	0.20 mEq/kg
K^+ infusion rate	0.002 mEq/kg/min	0.002 mEq/kg/min	0.001 mEq/kg/min
25 mL/kg over 3 hours (0.14 mL/kg/min)			
K^+ dose	0.60 mEq/kg	0.54 mEq/kg	0.32 mEq/kg
K^+ infusion rate	0.003 mEq/kg/min	0.003 mEq/kg/min	0.002 mEq/kg/min
25 mL/kg over 1 hour (0.42 mL/kg/min)			
K^+ dose	0.60 mEq/kg	0.54 mEq/kg	0.32 mEq/kg
K^+ infusion rate	0.01 mEq/kg/min†	0.009 mEq/kg/min	0.005 mEq/kg/min
25 mL/kg over 30 min (0.84 mL/kg/min)			
K^+ dose	0.60 mEq/kg	0.54 mEq/kg	0.32 mEq/kg
K^+ infusion rate†	0.02 mEq/kg/min†	0.018 mEq/kg/min†	0.011 mEq/kg/min†

*AS-1, AS-3, or AS-5 RBC units.
†Potassium infusion rate may pose a potential risk of transfusion-associated hyperkalemia, which may result in cardiac arrhythmia/arrest, especially if given through a central line.
Data from Fasano RM, Paul WM, Pisciotto P. Complications of neonatal transfusion. In: Popovsky MA, ed. *Transfusion reactions*. 4th ed. Bethesda, MD: AABB Press; 2012:471-518.

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Therefore, the routine practice of washing older RBCs is unnecessary for most small-volume RBC transfusions (10-20 mL/kg) in infants, including those with birth weights less than 1.5 kg.[55] Irradiation of RBC components damages the erythrocyte membranes, causing K^+ leakage and a linear increase in plasma potassium concentration over time. Irradiation substantially increases plasma K^+ compared with nonirradiated RBC components, both within the first 24 hours after irradiation (twofold increase) and for the life of the RBC component. The difference was detectable as early as 2 hours after irradiation.[189,194]

Large-volume RBC transfusions (>25 mL/kg), particularly if infused rapidly, may pose a significant risk to the neonate. There have been reports of hyperkalemia-induced electrocardiac abnormalities and cardiac arrest when RBC transfusions (fresh and old) have been administered via rapid infusion (10-20 mL/kg over 10-15 minutes) to neonates with concurrent low cardiac output states when the RBCs were irradiated more than 24 hours prior to infusion and/or when they were given via central line directly into the inferior vena cava.[13,164,189] Whenever possible, fresh RBC units (<7-10 days) should be issued for large-volume RBC transfusions. When fresh RBC units are unavailable, they should be volume reduced or washed and transfused as soon as possible after washing to minimize K^+ re-accumulation. Previously irradiated and stored (≥24 hours) units may have plasma K^+ levels unsafe for large-volume transfusion to neonates, especially if administered rapidly. Therefore, they should be issued immediately postirradiation or volume-reduced or washed to remove extracellular K^+ that accumulates after processing.[100,196] In emergent circumstances of unexpected massive bleeding, when neither fresh nor washed nor volume-reduced RBC units are available, infusion rate should not exceed 0.5 mL/kg per minute.[176]

Special considerations should be taken when RBCs need to be transfused rapidly and should be coordinated with the transfusion center so that proper preparation can be performed to avoid hyperkalemia. Measures to reduce the risk of transfusion-associated hyperkalemia leading to cardiac arrest include anticipating and replacing blood loss before significant hemodynamic compromise occurs, using larger-bore (>23-gauge) peripheral intravenous catheters rather than central venous access, checking and correcting electrolyte abnormalities frequently, and using fresher RBCs for massive transfusion.[97] For patients on extracorporeal membrane oxygenation, prebypass ultrafiltration helps normalize the electrolyte balance of the circuit prime and may reduce the risk of hyperkalemia-related cardiac arrest.[45] In-line potassium adsorption filters have been shown to remove extracellular K^+ in stored AS-3 RBC units to minimal levels *in vitro*.[199] A small randomized clinical trial in adults (>18 years of age) showed that the transfusion of one irradiated RBC unit with a potassium filter was as safe and efficacious as transfusion of one irradiated RBC unit with a standard blood infusion set.[38] However, the use of potassium filters in neonatal RBC transfusions requires more extensive study.

Hypocalcemia

Infants, especially premature infants, are particularly susceptible to hypocalcemia (see Chapter 87) within the first week of life, owing to multiple factors. Because of the immaturity in neonatal liver and kidney function, and small skeletal muscle mass, transfusion of citrate-enriched blood can result in hypocalcemia from citrate toxicity. The amount of citrate infused into a neonate during a small-volume transfusion (10-15 mL/kg) is very unlikely to cause hypocalcemia; however, the citrate load during an exchange transfusion can reach very high levels and lead to symptomatic hypocalcemia. In a retrospective review of neonatal exchange transfusions, symptomatic hypocalcemia was one of the most common side effects along with bleeding associated with thrombocytopenia, catheter-related complications, apnea, bradycardia, and other metabolic disturbances. Adverse events were generally higher among ill neonates (i.e., presence of co-morbidities besides indication for exchange) when compared to healthy ones and complication frequency increased with decreasing birth weights.[112] Because clinical manifestations of hypocalcemia are often subtle and/or variable in premature infants, many recommend monitoring ionized calcium levels and/or QT intervals throughout exchange transfusion procedures, in addition to minimizing potentiating factors such as hypomagnesemia, hyperkalemia, alkalosis, and hypothermia in high-risk (ill) patients. Insufficient evidence is currently available in the literature to support or reject the continual use of prophylactic intravenous calcium infusions in neonates receiving exchange transfusions.[123]

Effect of Plasticizers *(See Also Chapter 14)*

The toxicity associated with the use of the plasticizer di-(2-diethylhexyl) phthalate (DEHP) in blood storage bags has been debated in the transfusion medicine community for over 50 years. DEHP is added to polyvinylchloride plastic storage blood bags to increase bag flexibility, RBC survival, and oxygen permeability for platelet storage. DEHP also stabilizes RBC membranes, which prevents hemolysis and alteration during refrigerated storage. Because of its desirable structural properties, it is also widely used in medical plastics as well as in food storage and household products.[159] Critically ill neonates exposed to endotracheal tubes, orogastric tubes, intravenous tubing, and blood products can have DEHP exposures that exceed safe levels by 3-5 orders of magnitude.[101]

However, there is evidence that DEHP exerts detrimental effects on the endocrine system by acting as an androgen antagonist and an estrogen agonist. While DEHP is broken down in the gastrointestinal tract to some extent, transfusions bypass this protection. At particular risk for toxicity are neonates receiving high-volume transfusions, such as neonatal RBC exchange, during extracorporeal membrane oxygenation (ECMO), and during massive transfusion.[151]

Manufacturers have attempted to find suitable alternatives to DEHP. For example, butyrul-n-trihexyl-citrate

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leaches from the plastic at a slower rate, exhibits lower toxicity, and provides similar antihemolytic effects.[167] Other DEHP-free storage containers are at various stages of development throughout the world. However, a recent survey identified barriers to widespread implementation, including decreased quality of blood products stored in non-DEHP plastics, higher price, shorter shelf-life, and ongoing debate about the evidence of DEHP toxicity.[185]

Immunologic Complications

Transfusion Reactions

Transfusion reactions are less common in neonates than in older children or adults. Nevertheless, whenever a patient is transfused, he/she should be closely monitored for symptoms and signs of a reaction. Often, potential reactions are noted by a change in vital signs or a rash early in the transfusion, but they may occur at any point. The Joint Commission recommends that vital signs be measured pretransfusion, within 15 minutes of initiation and within 1 hour of transfusion end.[48] Hospital policies are based on these guidelines but may differ with respect to each other. In addition to vital signs, it is important to also assess the patient for cutaneous changes (e.g., rash, hives), respiratory distress, discomfort, or pain.

When an acute transfusion reaction occurs, it is crucial to discontinue the transfusion immediately, maintain intravenous access, and verify that the correct unit was transfused while treating the patient's symptoms. Notifying the transfusion service for further laboratory evaluation of the reaction is essential to properly classify the reaction so that the patient can be managed appropriately.[47] Since a single blood donation often results in several different blood products, there may be untransfused co-components that must be quarantined until the investigation is complete.

Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions occur when RBCs are transfused to a recipient with preformed antibodies to antigens on the transfused RBCs. Almost all acute hemolytic transfusion reaction fatalities are the result of transfusion of ABO-incompatible blood because of clerical errors and misidentification; however, nonimmune causes of acute hemolysis may also occur. These include hemolysis from shear and/or heat stress imposed on erythrocytes by extracorporeal circuits, infusion devices, filters, blood warmers, or phototherapy light exposure. These reactions are characterized by fever, chills, diaphoresis, abdominal pain, hypotension, and hemoglobinuria with potential progression to disseminated intravascular coagulation (DIC) and acute renal failure. When a hemolytic transfusion reaction is suspected, the transfusion should be immediately stopped, blood cultures (from patient and blood component[s]) should be obtained, and the transfusion service should be notified. A clerical check of all labels, blood component inspection, posttransfusion hemolysis check, and direct antiglobulin test (DAT) should be completed by the transfusion service. The patient's hemoglobin/hematocrit, serum bilirubin, lactate dehydrogenase (LDH), and urobilinogen should be monitored, and intravenous fluids should be administered to offset hypotension and ensure adequate urine output. Mannitol may be administered to force diuresis, but osmotic diuresis in neonates is controversial because of concerns about alterations in cerebral microcirculation and risk of intraventricular hemorrhage. Although infants less than 4 months old have an absence of A and B hemagglutinins and other RBC alloantibodies, maternal IgG antibodies can cross the placenta, causing hemolysis of transfused RBCs and, therefore, should be considered when transfusing infants.[44]

Delayed hemolytic transfusion reactions (DHTRs) occur 3-10 days following RBC transfusion and manifest as unexplained anemia, hyperbilirubinemia, and abdominal pain. As with acute hemolytic reactions, the diagnosis is confirmed by a positive DAT, identification of a new RBC antibody, hyperbilirubinemia, and a reduction in hemoglobin.[29] DHTRs are extremely rare in neonates because of the immaturity of the immune system. Even though there have been case reports of anti-E and anti-Kell formation in infants as young as 18 days of life, the majority of reports have supported the infrequency of RBC alloimmunization and DHTRs in infants less than 4 months of age.[55] A cohort study of 1641 neonates and children up to the age of 3 years found no alloimmunization cases within the first 6 months of life. The authors conclude that after initial testing, repeat antibody screening and cross-matching during the first 4 months of life can be safely omitted.[184]

Febrile Nonhemolytic Transfusion Reactions

Febrile nonhemolytic transfusion reactions (FNHTRs) are characterized by fever, chills, and diaphoresis. These reactions are believed to result from the release of pyrogenic cytokines by leukocytes within the plasma during storage. The incidence of FNHTRs has decreased dramatically since the implementation of prestorage leukoreduction of RBCs and platelet products in 1999. Whereas FNHTRs occurred in approximately 10% of transfusions in the past, the incidence for all products since the introduction of leukoreduction is now 0.1% to 3% (approximately 0.2% for prestorage leukoreduction).[89,130] When FNHTR is suspected, the transfusion should be stopped and more serious reactions ruled out. A sample of blood from the patient may be sent for DAT, plasma hemoglobin quantification, serum lactate dehydrogenase, and bilirubin level to ensure that the patient is not experiencing a hemolytic transfusion reaction. The transfusion service may repeat the crossmatch between the RBC unit and a post-transfusion patient sample to ensure there is no new unexpected incompatibility. Bacterial contamination should be assessed via cultures of the transfused product and the patient's blood; empiric antibiotic therapy may be warranted. Most FNHTRs respond to antipyretics, and meperidine may be used for rigors.[87,154]

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Allergic Transfusion Reactions

Allergic transfusion reactions (ATRs) are marked by urticaria and itching but can include flushing, bronchospasm, and anaphylaxis in severe cases. For mild or localized cases, transfusion can be continued once symptoms have subsided; however, severe allergic reactions (anaphylactoid or anaphylactic reactions) may require treatment with corticosteroids and/or epinephrine. The same blood unit should never be restarted in severe cases, even after symptoms have abated. Leukoreduction does not decrease the incidence of ATRs as it has for FNHTRs.[130] Premedication with antihistamines with or without steroids is recommended for ATRs. Because these reactions are caused by an antibody response in a sensitized recipient to soluble plasma proteins within the blood product, washed RBCs and platelets may be used for severe or recurrent ATRs nonresponsive to medication. Severe ATRs leading to anaphylaxis can be caused by the development of anti-IgA antibodies in recipients who are IgA-deficient. In these instances, IgA-deficient plasma products may be obtained but require the use of rare donor registries.[188] In patients of Asian descent, haptoglobin deficiency may also be associated with severe ATRs.[160]

The use of platelets in additive solution (PAS) resulted in decreased incidence of ATRs and FNHTRs in one adult study, presumably because of decrease in donor plasma content in the blood products.[40] Since neonates represented only 1.8% of the study population, the effect of PAS platelets in neonates requires further study.

Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when an immunosuppressed or immunodeficient patient receives cellular blood products, which contain immunologically competent lymphocytes.[95] The transfused donor lymphocytes are able to proliferate and engraft within the immunologic incompetent recipient because the recipient is unable to detect and reject foreign cells. The degree of similarity between human leukocyte antigens (HLA) of donor and recipient also increases the likelihood of developing TA-GVHD. As an example, in the setting of directed donation from a first-degree relative, donor lymphocyte homozygosity for an HLA haplotype for which the recipient is haploidentical predisposes to recipient tolerance, donor lymphocyte engraftment, and alloreaction leading to TA-GVHD.[54]

The clinical signs and symptoms of TA-GVHD include fever; generalized, erythematous rash that may progress to desquamation; watery diarrhea; mild hepatitis to fulminant liver failure; respiratory distress; and pancytopenia, which is unusually severe because hematopoietic progenitor cells are preferentially affected. Onset is from 3-30 days following transfusion of lymphocyte-replete cellular blood components in older children and adults; however, there may be a longer latency period before the onset of clinical manifestations of TA-GVHD and a longer course of disease before death in neonates. In a literature review of 27 cases of TA-GVHD in neonates in Japan, the median interval of clinical manifestations was 28 (fever), 30 (rash), and 43 (leukopenia) days, and death occurred in all affected patients at a median interval of 51 days. Prolonged latency of clinical manifestations and death is believed to result from thymic and/or extrathymic semi-tolerance for allogeneic cytotoxic T lymphocytes.[127]

Neonates at "high risk" for TA-GVHD include those with impaired cellular immunity, such as severe combined immunodeficiency (SCID) or Wiskott-Aldrich syndrome, those receiving intrauterine transfusions and/or neonatal exchange transfusion, and those receiving cellular blood components from family members or those who are genetically similar to the recipient. Extremely premature neonates are also considered by many to be at significant risk for TA-GVHD.[74,175]

No effective therapy is available to treat TA-GVHD except for hematopoietic stem cell transplantation, and owing to bone marrow hypoplasia, the mortality rate is 90% in the pediatric population. Fortunately, this complication can be prevented by pretransfusion gamma or X-ray irradiation of cellular blood components at a dose of 2.5 Gy, which effectively abolishes lymphocyte proliferation.[95] The shelf life of irradiated red blood cells is 28 days; however, no data currently exist on the safety in the neonatal population of gamma-irradiated or X-ray-treated RBCs that are stored for this amount of time. Because potassium and free hemoglobin increase after irradiation and storage of RBCs, it is preferable to irradiate cellular blood products close to administration time for neonates, who may not be able to tolerate high potassium loads.[194] Irradiation of RBCs also fosters the release of cell membrane microparticles, which may be associated with thrombotic risk.[30] There exists no "standard of care" regarding irradiation of blood products for otherwise non-high-risk infants. Many transfusion services irradiate all cellular blood products given to preterm infants born weighing 1.0-1.2 kg or less, whereas some irradiate all cellular blood products for infants less than 4 months of age, citing the lack of clinical studies on the incidence of TA-GVHD in the neonatal population and the concern for failure to recognize an infant with an undiagnosed congenital immunodeficiency. When an infant requires irradiated blood components, all cellular blood components for that infant should be irradiated; however, it is not necessary to irradiate acellular blood components, such as fresh frozen plasma (FFP) and cryoprecipitate. The known and presumed indications for irradiation of blood components for neonates are listed in Box 80.1.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is an uncommon, potentially fatal acute immune-related transfusion reaction, which typically occurs within 4-6 hours of transfusion and presents with respiratory distress caused by noncardiogenic pulmonary edema (normal central venous pressure and pulmonary capillary wedge pressure), hypotension, fever, and severe hypoxemia.[29] Differentiation from transfusion-associated circulatory overload (TACO), an

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• BOX 80.1 Indications for Administering Irradiated Blood Components to Neonates

- Transfusion to a premature infant with birth weight <1200 g
- Intrauterine transfusion
- Known or suspected congenital cellular immunodeficiency
- Hematologic malignancies or solid tumors
- Significant immunosuppression related to chemotherapy, radiation, or immunosuppressive treatment
- Transfusion of a cellular blood component obtained from a blood relative
- Transfusion of an HLA-matched or platelet-cross-matched product
- Granulocyte components

Modified from Wong ECC, Punzalan RC. Neonatal and pediatric transfusion practice. In: Fung, MK, ed. *Technical manual of the American Association of Blood Banks*. 19th ed. Bethesda, MD: American Association of Blood Banks; 2017;613-640; Savage WJ, Hod EA. Noninfectious complications of blood transfusion. In: Fung, MK, ed. *Technical manual of the American Association of Blood Banks*. 19th ed. Bethesda, MD: American Association of Blood Banks; 2017;569-597; and Roseff SD, Luban NL, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion*. 2002;42:1398-1413.

acute, nonimmune transfusion reaction that presents with respiratory distress, cardiogenic pulmonary edema, and hypertension caused by volume overload, is important because treatments differ. Furthermore, transient leukopenia, which is commonly seen with TRALI but is absent in TACO, can aid in differentiation of these reactions. Symptoms of TRALI usually improve within 48-96 hours; however, three-fourths of patients require aggressive respiratory support. Treatment is mainly supportive, including fluid and/or vasopressor support in the face of hypotension. Whereas aggressive diuresis is often required in TACO, this should be avoided in TRALI.[94]

Although the exact mechanism of TRALI remains uncertain, it is generally believed to be caused by the passive transmission of HLA and/or neutrophil antibodies directed against recipient leukocyte antigens. These antibodies activate and sequester recipient neutrophils within the endothelium of the lungs, ultimately leading to the production of vasoactive mediators and capillary leak. Plasma products (such as FFP, plasma frozen within 24 hours of collection [FP24], and apheresis platelets) account for the majority of severe TRALI cases, and multiparous women are the most commonly implicated donors.[94,152] Because of these findings, various preventative measures have been adopted in the United States and elsewhere. These include the use of male-only, high-volume plasma products (FFP, FP24, platelets), or the selection of donor products from donors who have a low likelihood of being alloimmunized via pregnancy or prior transfusions or who are negative on HLA antibody screen.[129] Although there have been no definitive cases of TRALI documented in the neonatal population, TRALI has been well-documented in the pediatric population. A case has been reported of a 4-month-old girl who experienced respiratory distress, hypoxemia, hypotension, and fever within 2 hours of completion of an RBC transfusion from her mother. HLA antibodies were identified in the mother's serum, demonstrating the possible role of HLA antibodies in the pathogenesis of TRALI in the setting of a designated blood transfusion between mother and infant.[152,202]

T-Antigen Activation

"T-activation" is a phenomenon that can cause immune-mediated hemolysis in neonates, ranging from minor to fulminant and fatal. Removal of N-acetyl neuraminic (sialic) acid residues from the O-linked oligosaccharides on glycophorins (A, B, and C) on RBC membranes by neuraminidase-producing bacteria, particularly *Clostridium bacteroides* and *Streptococcus pneumoniae*, results in exposure of the normally masked Thomsen-Friedenreich (T) cryptantigen on the RBC surface of the neonate. Transfusion of adult blood products containing plasma with naturally occurring anti-T antibodies into neonates with T-activation can produce intravascular hemolysis following transfusion or unexplained failure to achieve an expected post-transfusion hemoglobin increment. Alternatively, T-activation may be detected in the laboratory without any evidence of clinical hemolysis, making broad-based screening impractical. T-activation has been reported mainly in neonates with necrotizing enterocolitis, especially in those with severe disease requiring surgical intervention but also in septic infants with other surgical problems.[146]

The incidence of T-activation has been reported in 5%-35% of infants with necrotizing enterocolitis (NEC).[107] The rate of T-activation is higher in infants with more severe disease (e.g., multiple cultures positive for Clostridia, presence of intestinal perforation, need for surgical intervention). In a retrospective report, laboratory evidence of T-antigen activation was detected by lectin agglutination testing in 9% of 43 Taiwanese infants with stage II/III NEC but did not result in hemolysis regardless of whether washed or unwashed RBC units were administered or contribute to an increase in NEC-related mortality.[191] A more recent publication reported that transfusion-associated hemolysis is often not seen in T-activated infants when transfused with donor anti-T-containing plasma. The authors concluded that the use of plasma-containing blood products is not contraindicated in NEC patients with coagulopathy or requiring hemostatic factors, even if T-activation is present.[107] However, others have shown that infants with confirmed NEC and laboratory evidence of T-activation had more frequent and severe hemolysis, hyperkalemia, renal impairment, and hypotension than those without T-activation.[128]

Routine cross-matching techniques may not detect the polyagglutination owing to T-activation when monoclonal ABO antiserum is used. Minor cross-matching of neonatal T-activated red blood cells with donor anti-T-containing serum may show agglutination, but this is not performed routinely. Infants with discrepancies in forward and reverse blood typing and those with evidence of hemolysis on smear

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should be suspected of T-activation. The diagnosis is confirmed by specific agglutination tests using peanut lectin *Arachis hypogea* and *Glycine soja*. Further hemolysis may be prevented by using washed RBCs and platelets and low-titer anti-T plasma if available.[55] Exchange transfusion with plasma-reduced components may be necessary for infants with severe ongoing hemolysis. Alternatively, hemolysis associated with T-activation may occur independently of transfusion with anti-T-containing serum, and may be the result of sepsis or disseminated intravascular coagulation and cannot be prevented.

Transfusion-Associated Dyspnea (TAD)

TAD is defined as acute respiratory distress occurring within 24 hours of cessation of transfusion. Diagnosis requires ruling out other types of transfusion reactions associated with respiratory symptoms such as ATR, TACO, and TRALI.[29] In some cases, TAD may represent allergic reactions without the full complement of cutaneous and hemodynamic manifestations.

Transfusion-Related Sepsis

Septic transfusion reactions generally present with fever, hypotension, shock, and acutely ill appearance. Platelets are most frequently implicated since their storage at room temperature can foster growth of bacterial contaminants. Based on the inoculum of the pathogen, the onset may be earlier or later in the transfusion. However, the diagnosis can be challenging since such symptoms may also present as part of other transfusion reactions or as a manifestation of the patient's underlying disease.[138]

If a septic transfusion reaction is suspected, the transfusion should be stopped immediately. It is important to maintain venous access by running normal saline through the intravenous line. The remaining blood bag should be sent to the transfusion service for visual inspection, clerical check, possible culture, and placement of co-components into quarantine. If the clinical suspicion for sepsis is high, antibiotic therapy should be started immediately. Cultures of the patient and/or blood product may take some time to turn positive.

Transfusion-Related Necrotizing Enterocolitis (NEC)

NEC is a devastating gastrointestinal emergency that primarily afflicts premature infants but can occur in at-risk term gestation infants as well. Severity and treatment can range from full recovery with conservative medical management to intestinal perforation and bowel necrosis requiring surgical intervention. NEC-related morbidity and mortality remains quite high, with up to 30% of affected infants succumbing to the disease, many with an acute presentation followed by rapid deterioration and death. For full description of clinical presentations, pathophysiology, diagnosis, and treatment of NEC, refer to Chapter 85.

Although the exact mechanism of NEC is not completely elucidated, ischemic insult to the gastrointestinal tract has been proposed as one major contributor to NEC. Some hypothesize that even subtle reductions in blood flow and subsequent reperfusion occurring in response to hypoxia may contribute to bowel injury. It has been demonstrated that high vascular resistance of the superior mesenteric artery determined by Doppler flow velocity on the first day of life in preterm infants is associated with an increased risk of NEC.[111] Furthermore, the stressed newborn has been shown to exhibit abnormal regulation of intestinal vasomotor mediators (i.e., nitric oxide, endothelium, substance P, norepinephrine, and angiotensin), resulting in compromised intestinal flow.[24,121] It has been proposed that anemia may impair blood flow to the intestine, with subsequent transfusion of RBCs leading to reperfusion injury. This phenomenon may be exacerbated by abnormalities associated with stored RBCs, including reduced erythrocyte deformability, increased erythrocyte adhesion/aggregation, and decreased nitric oxide stores.[147] This last effect may predispose to vasoconstriction and further ischemic insult owing to transfused RBCs acting as a nitric oxide sink within the intestinal microvasculature.[32] Similarly, stored platelets accumulate proinflammatory factors over time. One of these, neuropeptide Y, has splanchnic vasoconstrictor effects, enhances neutrophil adhesion to endothelial cells, induces histamine release, and stimulates macrophage phagocytosis.[131a] The use of near-infrared spectroscopy has gained popularity in recent years with its ability to measure regional tissue saturations. A prospective study to examine potential alterations in mesenteric tissue oxygenation demonstrated wide fluctuations and decreases in mesenteric oxygenation patterns in infants who developed transfusion-related NEC.[104] Proposed, but unproven, pathologic mechanisms for transfusion-associated NEC include: a transfusion immunologic injury to the intestine similar to what is seen in transfusion-related acute lung injury (TRALI) and/or transfusion-related ischemia/reperfusion injury as described previously.

Several retrospective studies have demonstrated a temporal association between RBC transfusion and neonatal NEC. They report that 25%-38% of NEC cases occur within 48 hours of RBC transfusion and that the risk of transfusion-associated NEC increases with decreasing gestational age of the infant.[12,18,80,135] Blau et al. found a convergence of transfusion-associated NEC at 31 weeks' gestation,[18] the age of presentation of O_2 toxicity and other neovascularization syndromes. In another retrospective report, Singh et al. displayed a strong association of transfusion and NEC within 24 hours (OR = 7.60, $p = .001$), a significant albeit decreased association for transfusion within 48 hours (OR = 5.55, $p = .001$), and a statistically insignificant (absent) association for transfusion within 96 hours (OR = 2.13, $p = .07$) in their multivariate analysis.[163] Although attempts were made to minimize the confounding effects of multiple

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variables, the effect of infants' nadir hematocrit level on the risk of developing NEC remained statistically significant, making it impossible to separate the influence of hematocrit and RBC transfusion.

However, other studies suggest that RBC transfusions may be an epiphenomenon with respect to NEC rather than a contributor to the pathogenesis of disease. Bednarek et al. reported that there was no significant difference in the incidence of NEC between high versus low hematocrit threshold transfusion practices among six NICUs,[14] and the Premature Infants in Need of Transfusion (PINT) (NCT00182390) trial did not show a difference in the incidence of NEC between the low versus high hematocrit transfusion threshold groups.[90] In a meta-analysis of the published literature on transfusions and NEC, increased RBC transfusions were associated with lower rates of NEC; the direction of effect of RBC transfusions on NEC in randomized trials was opposite to that seen in observational studies.[91] Keir and colleagues performed a separate systematic review and did not find an association between transfusions and NEC.[85] One recent prospective study of 598 very low birth weight infants found that severe anemia (hemoglobin <8 g/dL), but not RBC transfusion, was associated with an increased risk of NEC. Thus, prevention of severe anemia may be more important than avoidance of RBC transfusion alone.[132] The temporal relationship observed between RBC transfusion and neonatal NEC may represent reverse causation, whereby clinical instability from evolving NEC leads to RBC transfusion prior to the formal diagnosis of NEC.

A prospective, multicenter observational cohort study of infants with birth weight less than or equal to 1250 g is underway to investigate the associations between RBC transfusion, product irradiation, anemia, intestinal oxygenation, and injury that lead to NEC.[104a]

Transfusion-Related Intraventricular Hemorrhage (See Also Chapter 53)

A newly postulated risk of transfusions among VLBW neonates has emerged based on an association between RBC transfusion and the development of, and progression to, severe intraventricular hemorrhage (IVH), which has been observed in retrospective case control reports. In a six-site prospective study, Bednarek et al. found a trend toward a higher incidence of severe IVH (adjusted for birth weight and illness severity) in NICUs administering RBC transfusions "liberally," compared with other NICUs using transfusions in a more restricted fashion.[14] Subsequently, a retrospective analysis of 155 VLBW neonates with normal head ultrasounds during the first week of life indicated an association between RBC transfusion and the risk of developing a severe IVH within the first month, independent of hemoglobin level, initial pH, sepsis, ventilation, coagulation studies, or severe thrombocytopenia. During the first 72 hours of life and when the head ultrasound was normal, 67% of those neonates who later developed severe IVH versus 31% who did not develop IVH received one or more RBC transfusions ($p < .001$).[10] Additionally, each subsequent RBC transfusion during the first week was determined to double the risk of a severe IVH (each transfusion increased relative risk 2.02; 95% CI 1.54-3.33). In another report by the same investigators, Baer et al. retrospectively compared 55 VLBW neonates in whom a grade I IVH evolved into a grade II or higher IVH to 362 VLBW neonates matched for demographic, level of illness, and coagulation parameters, who had a grade I IVH that resolved completely with no extension to a higher grade. On logistic (and Lasso-fit) regression analysis, an association was found between RBC transfusion up to and on the day of the grade I IVH and extension of the IVH (OR 2.92; 95% CI 2.19-3.90).[11]

However, these associations do not necessarily indicate a cause-and-effect relationship because of inherent limitations in retrospective studies such as failure to recognize confounding variables and susceptibility to bias. Furthermore, no difference in risk of IVH (all grades, or ≥ grade III) was seen in those infants randomized to liberal versus restrictive transfusion practices in either the multi-institutional Canadian PINT study[90] or the Bell study.[15] A meta-analysis similarly did not identify increased rates of IVH in association with transfusions.[85] Additional studies are needed to determine if early RBC transfusion plays any pathogenic role in IVH development or extension.

Infectious Complications

Many infectious agents can be transmitted by blood or blood component transfusion (Table 80.2). These include viruses, bacteria, protozoa, and other pathogens. Current transfusion-transmitted disease testing for allogeneic blood donation includes hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), anti-hepatitis C antibody (anti-HCV), antibody to HIV-1 and HIV-2 (anti-HIV-1/2), antibody to human T-lymphotropic virus (HTLV-I and HTLV-II), serology for syphilis and *Trypanosoma cruzi*, and nucleic acid testing (NAT) for HIV-1, HIV-2, HCV, HBV, West Nile virus (WNV), and Zika virus (ZIKV).[173,193]

Cytomegalovirus Infection

The prevalence of human cytomegalovirus (CMV) is 30%-70% in blood donors, varies based on demographic differences within areas of the United States, and increases with age. This DNA virus remains latent within the leukocytes of immune persons and can be transmitted by transfusion of cellular blood components into seronegative recipients. Primary CMV infection occurs in a seronegative recipient from a blood component from a donor who has either active or latent infection. There is wide variation in clinical sequelae from transfusion-transmitted CMV (TT-CMV), ranging from asymptomatic serologic conversion to significant morbidity and mortality from CMV-related pneumonia, cytopenias, and hepatic dysfunction.

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TABLE 80.2 Transfusion-Transmitted Infections[16,67,82,174,193,203]

Infectious Agent	Infectious Risk
Bacterial contamination risk	
Platelets	1 in 2500
RBCs	1 in 38,500
Septic transfusion reaction risk	
Platelets	1 in 100,000-200,000
RBCs	1 in 250,000
Hepatitis A	1 in 10 million
Hepatitis B	1 in 750,000-1 million
Hepatitis C	1 in 1.9 million
HIV	1 in 2.1 million
Cytomegalovirus	Unknown
Human T-lymphotropic virus	1 in 2,993,000
West Nile virus	Extremely low
Chagas disease (*T. cruzi*)	Extremely low
Syphilis	Virtually nonexistent
Malaria	1 in 4 million
Babesiosis (*Babesia microti*)	Extremely low*
Creutzfeldt-Jakob disease	No cases reported in United States
Zika virus	Approximately 1 in 93,000 tested donations†

*May be as high as 1 in 1800 in highly endemic areas (northeast United States and upper Midwest).
†Based on sample of 466,834 donations tested between September 19 and November 30, 2016.

Premature, seronegative neonates less than 1250 grams, fetuses receiving intrauterine transfusions, severely immunocompromised individuals, and recipients of hematopoietic stem cell and solid-organ transplants are recipient groups at increased risk for post-transfusion CMV-related morbidity and mortality.[98] Infants born to seropositive mothers apparently have decreased risk for acquiring TT-CMV, but perinatal infection with a different strain of CMV has been reported infrequently.

Because the prevalence of CMV seropositivity among blood donors limits the availability of seronegative components, supplementary strategies can be used to minimize the risk of TT-CMV infection in high-risk infants. Use of third-generation leukoreduction filters at the time of collection of cellular products has been recommended for recipients at risk for TT-CMV. The American Association of Blood Banks states that "leukoreduced" blood products must contain fewer than 5×10^6 total WBCs per unit.[169] Current third-generation leukocyte reduction filters consistently provide WBC reduction in accordance with these standards, with some filters yielding less than 1×10^6 per product. European standards maintain a more stringent definition of leukoreduced as less than 1×10^6 total WBCs per unit.[98]

Leukocyte reduction has been shown to be effective in preventing CMV infection in neonates, among other groups; however, whether leukocyte reduction is as efficacious as the use of CMV-seronegative blood has been disputed widely. In one study, equivalent rates of post-transfusion CMV infection in allogeneic hematopoietic stem cell transplant patients were found for CMV-seronegative units and leukoreduced units (1.4% vs. 2.4%, respectively).[20] A subsequent study demonstrated similar rates of TT-CMV for leukoreduced and CMV-seronegative platelet products but not for RBC products.[117] A prospective observational study of 23 allogeneic hematopoietic stem cell transplant recipients in CMV-negative donor-patient paired individuals were transfused a total of 1847 leukoreduced cellular blood products from CMV "untested" donors and demonstrated no CMV DNA within the blood or CMV-associated clinical complications in the patients greater than 100 days post-transplant despite anti-CMV IgG seroconversion in 17 of 23 patients.[181] These reports support the notion that leukoreduced blood products are "CMV safe" and some experts have argued that leukocyte-reduction alone is sufficient.[177] However, no formal consensus on the debate of equivalency has been developed,[1] leading many to advise against the elimination of "dual inventories" of blood products for CMV-seronegative and seropositive units. Nonetheless, variable strategies for preventing TT-CMV currently exist depending on the number of high-risk patients treated at a given center, the regional donor demographics, and product availability. A prospective multicenter birth cohort study revealed that transfusion of leukoreduced, CMV-seronegative blood products effectively prevented transmission of CMV to very low birth weight infants. In fact, acquisition of CMV in the patient population was primarily through maternal breast milk.[77]

Hepatitis A Virus

Post-transfusion hepatitis A infection is an infrequent complication of transfusion because of the short period of viremia and the lack of an asymptomatic carrier state associated with the hepatitis A virus.[51] The risk of hepatitis A transmission increases when the transfused product is derived from a pool of products, such as cryoprecipitate and plasma-derived clotting factors. Since they rely on solvent/detergent disruption of lipid membranes, purification processes used to treat derivatives of human plasma are ineffective against nonenveloped viruses such as hepatitis A.[71] The virus has demonstrated varying susceptibility to pathogen reduction technologies.

Hepatitis B Virus

Acute infection with hepatitis B virus (HBV) is symptomatic in about 50% of adults, and 5%-10% of those infected become chronic carriers.[51] In contrast, HBV infection acquired in infancy and early childhood is often asymptomatic, yet 70% of those infected become chronic

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carriers. Elimination of paid blood donors, uniform screening of blood donations for HBV surface antigen (HBsAg), and routine immunization for hepatitis B have reduced the estimated incidence of transfusion-transmitted HBV (TT-HBV) to 1 in 250,000-350,000 units transfused.[51] Initiating donor HBV nucleic acid testing (NAT) has further reduced the estimated incidence of TT-HBV to levels close to HIV and HCV by shortening the window period (time interval between infection and laboratory test positivity when viral markers are too low for detection).

Hepatitis C Virus

Hepatitis C virus (HCV) is a well-known cause of transfusion-associated hepatitis. Acute HCV infection is often asymptomatic and anicteric, but the likelihood of developing chronic hepatitis exceeds 60%. Approximately one-third of those with untreated chronic hepatitis will develop hepatic fibrosis and cirrhosis within 2 decades; those with cirrhosis have a 1%-5% risk of hepatocellular carcinoma 20 years after cirrhosis is diagnosed.[98] Long-term outcome is dependent upon the route of transmission, age when infected, gender, and coexisting morbidities. A retrospective study of 31 adults with transfusion-associated HCV acquired at birth (35 years earlier) described a milder disease with slower progression to hepatic fibrosis in perinatally acquired HCV than those who acquire HCV in early adulthood.[28,99] In a look-back study involving previously transfused infants and children, 88% of those with silent infection (positive anti-HCV enzyme immunoassay) had persistent HCV viremia at 10 years post transfusion. This is in contrast to previously reported pediatric HCV clearance rates of 45% and 42% at 19.5 and 35 years post-transfusion, respectively, which indicated that pediatric patients, unlike adults, may clear HCV over time.[99] The current standard treatment of chronic HCV infection in children ages 3 or older is pegylated-interferon-alpha and ribavirin. However, because of adverse effects (e.g., constitutional symptoms, bone marrow suppression, neuropsychiatric complications, hypothyroidism, and inhibited growth), therapy is often held until later in life. In adults, these medications have been largely supplanted by direct-acting antivirals (DAA) because of improved side effect profile and sustained virologic response. Pediatric clinical trials with DAA are underway.[201]

Since the advent of NAT for HCV in the late 1990s, the incidence of TT-HCV has decreased to 1 in 1.9 million within the United States. This is because of shorter window periods from time of acute infection to laboratory markers of infection (8 days) within the donor population.[98,203]

HIV-1 and HIV-2

The retroviruses HIV-1 and HIV-2 are the agents responsible for acquired immunodeficiency syndrome (AIDS). In the United States, the vast majority of AIDS cases are related to HIV-1. Approximately 1.9% of all reported cases of AIDS have been attributed to HIV-1 transmission by blood components, excluding factor concentrates.[51,98] Factor concentrates were responsible for an additional 0.75% of the more than 339,000 reported transfusion-transmitted AIDS cases. Virtually all of these transfusion-transmitted infections occurred before 1985, when serologic screening for HIV was initiated, and numerous effective methods of viral inactivation for plasma-derived clotting factor concentrates subsequently became available. Today, the risk of HIV transmission from blood transfusion is less than 1 in 2.1 million because of improved donor history screening and the advent of NAT testing in the late 1990s, which decreased the estimated window period to about 9 days.[203]

West Nile Virus

West Nile virus (WNV), a mosquito-borne, single-stranded RNA virus of the *Flaviridae* family, has become a major public health concern since its first detection in the United States in 1999. The first cases of transfusion-transmitted WNV occurred in 2002, with growing numbers of cases through 2004. Infection results in neuroinvasive disease (meningo-encephalitis, spastic paralysis) in roughly 20% of individuals, with more severe sequelae in the elderly and immunocompromised. Donors with WNV virus are commonly asymptomatic, meaning that the donor health questionnaire may fail to identify donors at risk. Despite implementation of pooled blood donor sample WNV NAT testing (with triggered individual donation testing when local disease activity exceeds preset thresholds) in 2003, sporadic cases of TT-WNV in immunosuppressed patients show that rare breakthrough transmissions may still occur in the United States.[173]

Zika Virus

Zika virus (ZIKV) is a flavivirus first discovered in the Zika Forest in Uganda in 1947. For many years, the virus caused sporadic outbreaks in Africa before gradually moving east. Several Pacific Islands were affected in 2013-2014. In 2016, the virus appeared in South America and rapidly spread. The virus is transmitted by the *Aedes* mosquito and, therefore, shows more activity during the summer months. Transfusion-transmitted infection has been documented.[137]

Unlike other flavivirus, ZIKV has been associated with microcephaly and other fetal abnormalities when placental transmission occurs in an acutely infected pregnant woman and is currently under intense study.[161] Of concern for blood supply safety, about 80% of infected patients are asymptomatic. Thus, there was a great risk of a viremic blood donation and transmission to a susceptible donor without suitable laboratory detection. Blood collections were temporarily halted in areas with local virus transmission (e.g., Puerto Rico). In the fall of 2016, NAT screening of all donations in the United States was implemented under an investigation new drug (IND) protocol. During a period of about 2 months, 5 of 466,834 donations tested for ZIKV RNA were found to be positive.[193] The FDA cleared the first approved ZIKV detection test based on viral RNA in the plasma of blood donors in October 2017.

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Emerging Pathogens

Transmission of babesiosis and malaria has been reported in neonates within endemic areas such as the northeast United States and Africa, respectively.[59,162] Healthy patients transfused with *Babesia microti*–contaminated blood often do not get sick; however, transfusion-transmitted Babesia can be a significant cause of transfusion-related morbidity and mortality, especially for premature infants. Neonatologists in endemic areas should have a high index of suspicion for babesiosis in premature infants exposed to blood transfusions, because infection is minimized but not eliminated through current blood bank practices.[162] At this time, blood products collected in United States regions with high prevalence of the disease (e.g., Minnesota, Wisconsin, Massachusetts, and Connecticut) are tested for Babesia by a nucleic acid detection test.[109] However, implementation of nationwide testing has not been mandated because of cost-effectiveness considerations.[60]

Continuous attention is being paid to emerging infections such as chikungunya, dengue fever, Ebola, *Trypanosoma cruzi*, variant Creutzfeldt-Jakob disease, and malaria, among others. Despite extensive donor screening and laboratory testing, infections can still be transmitted through blood products. Pathogen reduction/inactivation offers the advantage of eliminating the risk of infection with any nucleic acid–containing agent, which includes viruses, bacteria, protozoa, and fungi (prions excluded). However, current pathogen reduction/techniques using nucleic acid–inactivating agents are still under investigation, because no single technique has proved to be effective for all blood components.[141]

Pathogen Reduction

Current screening approaches are reactive in nature and depend on pathogen identification, characterization of infectious markers, and development of detection assays. While this iterative approach has provided very high blood supply safety, it does require some time to implement for each emerging pathogen.

Pathogen reduction (PR) is an all-encompassing term for a variety of methods (e.g., photochemical activation or solvent detergent treatment) that may be applied to blood following collection in order to confer broad protection against multiple infectious agents by countering proliferation and contamination.[141] Many of these technologies target DNA or cell membranes and are effective across different classes of pathogens (e.g., viruses, bacteria, and parasites), offering the ability to interdict agents that are known to be transfusion-transmissible as well as emerging pathogens that pose uncertain risks to the blood supply.

The appeal of pathogen reduction is that it is a proactive approach to blood safety that inactivates pathogens instead of only screening for their presence. Although developed to complement current testing, PR could ultimately prove to be an alternative to testing. If widely effective, PR could reduce the number of donor deferrals due to disease risk factors. Since PR inactivates white blood cells, it may provide additional benefits such as TA-GVHD prevention and alloimmunization reduction.[37,92] However, concerns remain that PR's detrimental effect on platelet and plasma function may lead to increased bleeding risk in susceptible patients such as trauma victims.[66]

Two different methodologies of photochemical activation that have been more extensively studied will be briefly described, but others are at various stages of development. Thus far, these technologies have been applied only to platelets and plasma. Platelets are of primary concern since their storage at 20-24°C heightens their risk of contamination. No photochemical activation process is currently in clinical use for RBCs; these present an obstacle due to hemoglobin's absorption.

INTERCEPT® and Mirasol® Systems

The only photochemical activation platform approved by the FDA at the time of this chapter is the INTERCEPT® system (Cerus, Concord, CA). This technique uses amotosalen, which can intercalate between DNA bases. In the presence of activation by UVA light, this molecule irreversibly crosslinks with the DNA, thus preventing DNA transcription and cellular reproduction.[81] After INTERCEPT® treatment, an adsorption step removes excess amotosalen; only a tiny quantity remains.[36]

INTERCEPT® is widely used for platelets and plasma and is approved in the United States and European Union for this purpose.[73,114] The technology is effective against viruses, bacteria, and protozoans. However, breakthrough transmission has been reported with hepatitis A virus (HAV), hepatitis E virus (HEV), parvovirus B19, poliovirus, and certain spore-forming and/or fast-growing bacteria.[64,133,155]

The Mirasol® (TerumoBCT, Lakewood, CO) system uses riboflavin as a photosensitizer compound with UVB light. Riboflavin readily traverses lipid membranes and then intercalates nonspecifically with nucleic acids. Upon exposure to UVB light, intercalated riboflavin-modified guanine residues promote the generation of oxygen radicals.[25,61] Since riboflavin and its byproducts are naturally occurring, no additional steps for removal following treatment are believed to be necessary.[136] Mirasol® has shown efficacy against a wide variety of pathogens that pose a risk of transfusion transmission.[9,61,141,183]

A Cochrane review that evaluated 10 randomized control trials (9 with INTERCEPT®, 1 with Mirasol®) showed no difference in clinically significant bleeding or severe bleeding between recipients of pathogen-reduced platelets compared to control platelets. When evaluated, all-cause mortality, product utilization, and adverse events were also not increased.[6,23] Clinical trials performed with INTERCEPT®-treated plasma have shown no difference in clinical efficacy when compared to standard FFP.[70] A European prospective hemovigilance study of INTERCEPT®-treated platelets

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following 19,175 transfusions in 2,441 patients demonstrated a low incidence of acute transfusion reactions and a safety profile in line with conventional platelet components. Forty-six of the patients were neonates (<28 days of age) who received a range of 1-9 platelet transfusions while 242 were children (<18 years of age) who received a range of 1-66 transfusions.[93] Thus, there is relative paucity of neonatal and pediatric safety data.

Donor-Specific Units

Autologous Red Blood Cell Transfusions

Collection of autologous umbilical cord blood was first reported in 1979. Depending on the gestational age of the infant, the umbilical cord contains 75-120 mL of fetal blood, which could serve as an alternative source of RBCs for transfusion. It has been shown that collection of placental blood in both vaginal and cesarean deliveries is possible and that the RBC component is able to be stored for short periods of time (21-28 days) in additive solutions (AS-3, SAGM). However, problems with obtaining sufficient volumes, with clotting or hemolysis within the stored unit, and with bacterial contamination are frequently reported, particularly in those who are most likely to benefit from autologous RBC transfusions (e.g., ELBW neonates).[22,34,179]

In most of the reports to date, autologous RBC transfusions have been shown to replace only a minority of allogeneic RBC transfusions needed by the infants, and the cost of collecting and storing autologous umbilical cord blood for subsequent RBC transfusion did not justify the limited benefits. For example, Khodabux et al. reported that of the 176 attempted autologous umbilical cord blood collections performed in neonates with gestational age less than 32 weeks, 101 (57%) yielded 15 mL/kg or greater, and only 64 (36%) yielded satisfactory units for transfusion.[88] Furthermore, only 17% of umbilical cord blood collections were available for autologous RBC transfusions in infants with birth weights less than 1000 grams, and in those infants who received autologous RBCs, their allogeneic RBC transfusion requirements were reduced by only 15%.[88] It is certainly possible that as better techniques are developed for harvesting, storing, and administering autologous RBCs from the umbilical cord, the benefits of using autologous RBC transfusions may outweigh the cost and risks as a means to reducing the need of allogeneic RBC transfusion in VLBW infants. Recent reports have demonstrated improved techniques for harvesting, storing, and administering autologous umbilical cord RBCs and shown the feasibility of using this autologous blood for open heart surgery and cardiopulmonary bypass priming.[31,56] These cord blood transfusions prevented or reduced the need for intraprocedural allogeneic RBC transfusion in infants undergoing cardiac surgery. However, additional large, randomized controlled clinical trials are needed to validate the safety and efficacy of this process before it can become routine NICU practice.[42]

Delayed Cord Clamping and Cord Stripping

Delayed clamping of the umbilical cord of premature infants has been reported as a successful variation of autologous transfusion. Meta-analysis of 738 preterm infants (analysis of 15 studies) showed that delayed cord clamping (30-180 seconds) is safe and is associated with higher circulating blood volumes during the first 24 hours of life, decreased immediate need of blood transfusions (RR 0.61, 95% CI 0.46-0.81), decreased incidence of intraventricular hemorrhage (RR 0.59, 95% CI 0.41-0.85), and decreased incidence of necrotizing enterocolitis (RR 0.62, 95% CI 0.43-0.90).[145] In a follow-up study from their randomized controlled trial (RCT) of immediate versus delayed cord clamping, Mercer et al. showed that delayed cord clamping at birth may be protective against motor disability in VLBW male infants at 7 months' corrected age.[106] However, in a meta-analysis by Rabe et al., there were no significant differences between groups in mean Bayley II scores at 7 months' corrected age. Additionally, it was found that the peak bilirubin concentration was higher for infants who had received delayed cord clamping compared to infants with immediate clamping.[143]

One limitation with delayed cord clamping is the required delay of 30 seconds or more in neonatal resuscitation during a VLBW delivery. As an alternative, "milking" or "stripping" the cord has been proposed. This is done by holding the placental end of the umbilical cord and gently moving blood within the umbilical vessels toward the neonate. This "stripping" is performed one to four times prior to clamping and cutting the cord. In a randomized controlled trial of 40 VLBW infants (stripping versus immediate clamping), Hosono et al. reported that those infants in the stripped group had higher hemoglobin values and blood pressures at NICU admission, shorter duration of ventilation, lower odds of requiring an RBC transfusion, and lower odds of developing an IVH.[69] Subsequently, Rabe et al. compared delayed cord clamping versus cord stripping in a randomized trial ($N = 58$) and found no differences between the two groups in hemoglobin values, number of RBC transfusions, or morbidities.[144] A Cochrane review in 2012 shows that delayed cord clamping up to 180 seconds or umbilical cord milking versus immediate cord clamping resulted in 39% fewer transfusions for anemia, 41% fewer patients with IVH, and 38% fewer patients with NEC.[33,143] Similarly, a randomized clinical trial in 2017 found that delayed cord clamping reduced anemia at 8 and 12 months in infants at high risk for iron deficiency.[83] The American College of Obstetricians and Gynecologists currently recommends a delay in umbilical cord clamping in vigorous term and preterm infants for at least 30-60 seconds after birth.[2]

A large, recent, randomized Australian study of preterm infants <30 weeks' gestation demonstrated no significant benefit of delayed cord clamping on the combined outcome of death or major morbidity or incidence of chronic lung disease or other major morbidities.[180] When this large trial

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was included among other available studies, meta-analysis revealed that delayed cord clamping did reduce overall hospital mortality in infants <37 weeks' gestation, although no differences in randomized groups were observed in major morbidities. Delayed cord clamping did increase peak hematocrit by about 3% and reduced the proportion of infants having a blood transfusion by 10%.[58]

Parental Blood Donation

Concern over transfusion-associated infections has encouraged directed-donor blood programs, including those that allow biologic parents to serve as directed donors for their neonates. No data exist to support the contention that directed-donor programs increase safety. Indeed, a retrospective review at a pediatric institution found that parental donors had higher rates of infectious-disease-testing positivity than community donors.[75] Furthermore, paternal blood products are a poor choice in neonates with immune-mediated hemolysis (hemolytic disease of the newborn, or HDN) or neonatal alloimmune thrombocytopenia (NAIT). In these cases, transfused paternal cells express the antigens to which the mother has been sensitized and are passively transferred via the placenta to the neonate. Maternal plasma may contain alloantibodies directed against paternal RBC, leukocyte, platelet, and HLA antigens. Antileukocyte and antiplatelet antibodies have been found in 16% and 12% of mothers, respectively.[53] Transfusion of any maternal blood component containing plasma exposes the infant to these antibodies, with the potential to cause significant hemolytic, thrombocytopenic, or pulmonary reactions. Given these concerns, when parental-directed donation is considered for an infant, the following recommendation should be reviewed with families and the provider[54]:

- All parental cellular blood components must be irradiated before transfusion to the neonate to prevent TA-GVHD.
- If maternal RBCs or platelets are transfused, they should be given as washed cells or should be plasma reduced and irradiated.
- Fathers are not recommended as RBC donors for their newborns.
- Fathers should not donate granulocytes or platelets to their infants unless maternal serum is shown to lack lymphocytotoxic antibodies.

Blood Products

Red Blood Cell Transfusion

In the first few days of life, full-term infants have an elevated hemoglobin concentration (14-20 gm/dL); however, because of physiologic decreases in erythropoietin (EPO) levels, hemoglobin concentration decreases to a nadir of 10-12 gm/dL at approximately 2-3 months before beginning to rise. This is referred to as the physiologic anemia of infancy. In preterm infants, this anemia is more significant, with mean nadirs of 8 gm/dL in VLBW infants (birth weight:1.0-1.5 kg) and 7 gm/dL in ELBW infants (birth weight: <1 kg). This is the result of lower hemoglobin concentrations at birth, frequent blood sampling, low total blood volume to blood sampling ratio, increased risk for other co-morbidities, and diminished capacity of the premature infant to increase EPO.[54] Normal ranges of hemoglobin and hematocrit have been established for full-term and premature infants; however, guidelines for red blood cell transfusion therapy remain controversial, because there are few randomized controlled studies that address appropriate neonatal transfusion triggers. Recent neonatal and pediatric guidelines recommend transfusion at varying hemoglobin or hematocrit thresholds stratified by postnatal age and clinical condition or in circumstances where the amount of blood loss or removal exceeds 10% of a neonate's total blood volume.[116,196] Infants with significant cardiac or respiratory disease generally receive more aggressive RBC transfusion therapy. Recommended guidelines for replacement transfusion therapy in neonates are given in Box 80.2. Two studies attempted to address high versus low threshold transfusion guidelines based on level of respiratory support in ELBW and VLBW infants. Although very different in design and outcome, neither study clearly established an appropriate hemoglobin target. While the multi-institutional Canadian PINT study[90] (enrolling 451 preterm infants) demonstrated no advantage for liberal transfusion practices, the Bell study[15] (enrolling 100 preterm infants) suggested that restrictive transfusion was associated with more apneic episodes, intraparenchymal brain hemorrhage, and periventricular leukomalacia. The disparate results may be a result of a greater hemoglobin difference in the restrictive/liberal transfusion groups (Bell study: 2.7 gm/dL versus PINT: 1.1 gm/dL) and a higher overall hemoglobin value in the liberal transfusion group in the Bell study compared to the PINT study.

Long-term neurodevelopmental assessments in the Bell study cohort demonstrated that those individuals in the

• BOX 80.2 Suggested Guidelines for Red Blood Cell Replacement in High-Risk Neonates†

- For severe cardiopulmonary disease*
  Maintain hematocrit 40%-45%
- For moderate cardiopulmonary disease
  Maintain hematocrit 30%-40%
- For major surgery
  Maintain hematocrit 30%-35%
- For infants with stable anemia
  Maintain hematocrit >20%-25%

Modified from Strauss RG. How I transfuse red blood cells and platelets to infants with anemia and thrombocytopenia of prematurity. *Transfusion.* 2008;48:209-217.

†There is a paucity of evidence-based guidelines for this practice.

*Severe cardiopulmonary disease defined as: requiring mechanical ventilation with >0.35 FiO_2.

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liberal transfusion group performed poorer than those in the restrictive group on visual memory, reading, and associative verbal fluency measures at school age, in accord with structural findings in a subgroup of the original newborn cohort.[105,120] Conversely, previously enrolled infants from the PINT study who were followed up at 18-21 months' corrected age showed a statistically significant advantage of the liberal transfusion group on post-hoc analysis of cognitive delay defined as Mental Development Index score (MDIC) <85; however, there was no significant difference in cerebral palsy, severe cognitive delay (MDIC <70), severe hearing or visual impairment, or death.[192]

Two currently active clinical trials, the Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO) (NCT01393496)[72] and the Transfusion of Prematures trial (TOP) (NCT01702805), seek to address the conflicting results of the Bell and PINT studies through enrollment of large, randomized cohorts (ETTNO: 920 neonates; TOP:1824 neonates).[118] These trials are aimed at examining the short- and long-term outcomes in extremely low birth weight infants randomized to liberal or restrictive RBC transfusion thresholds.[72,119]

The debate on whether to adopt liberal versus restrictive transfusion practices in neonates remains unresolved. Some argue for more restrictive transfusion practices because of concerns of a potential causative effect of RBC transfusion on NEC, IVH, retinopathy of prematurity (ROP), and chronic lung disease (CLD), although the largely retrospective nature of these observations leads to difficulty in definitive establishment of causation.[190] Others support a more liberal approach to RBC transfusion, owing to decreasing transfusion-transmitted infection risks and the ability to minimize donor exposures using aliquots from the same donor and a potential neuroprotective advantage with a more liberal transfusion approach. Keir and colleagues recently performed a systematic review of primary and secondary adverse clinical outcomes in neonates exposed to liberal versus conservative transfusion strategies and found no statistically significant differences between the two groups across both randomized and nonrandomized studies.[85] Results from the ongoing clinical trials will hopefully delineate the short- and long-term risks and benefits of each transfusion practice to better guide RBC transfusion support decisions.

Most RBC transfusions in newborns are administered to either replace blood loss or treat anemia of prematurity. Blood loss can result from hemorrhage or phlebotomy. Iatrogenic losses from phlebotomy can be considerable but can be minimized by judicious testing strategies, sampling from indwelling catheters, using microtainers for laboratory assays, and implementing point-of-care testing.

The use of recombinant human EPO has been proposed to decrease neonatal transfusion burden, donor exposure, and anemia of prematurity, as well as other co-morbidities. The 2014 Cochrane review assessing the effectiveness and safety of early initiation of EPO (<8 days of life) showed minimal benefits with regard to donor blood exposure, number of RBC transfusions, and volume of transfusions (mL/kg) in 2209 premature infants.[126] Unlike the previous review in 2012, a statistically significant increased risk of retinopathy of prematurity (ROP) (>stage 3) was not noted in neonates who received early EPO therapy. The most recent review is notable for inclusion of new studies using darbepoetin, an erythropoiesis stimulating agent with a longer half-life requiring less frequent dosing compared to EPO.[124] As in the previous review in 2012 (no new studies were included, although one study was reassigned from the early to late EPO review category), meta-analysis of late EPO use (>8 days of life) involving 1591 preterm infants also failed to demonstrate a clear benefit in terms of significantly decreased donor exposures, nor was there any effect on incidence of co-morbidities aside from a trend toward increased risk of ROP with EPO administration. A significant decrease in donor exposures was not demonstrated, because many infants had received one or more transfusions prior to receiving EPO at study entry.[4] Although late administration of EPO reduced the number of RBC transfusions per infant, the clinical impact of these results was likewise trivial with a reduction of <1 transfusion per infant, and the total volume (mL/kg) of RBCs transfused was not significantly reduced in the neonates who received EPO. Therefore, no conclusive evidence currently exists that either early or late EPO use offers any clear benefit in regard to donor exposure or improvement of morbidity and/or mortality in preterm infants, nor that early EPO use may increase risk of ROP in the VLBW neonatal population. Additional studies utilizing darbepoetin are also indicated to determine its risks and advantages compared to erythropoietin. The use of EPO as a neuroprotectant is currently under investigation in the Preterm Erythropoietin Neuroprotection (PENUT) Trial (NCT01378273).[139] Recent preliminary data are very encouraging for improved neurocognitive outcome.[125]

Pretransfusion Testing

Prior to red blood cell transfusion, a blood sample is obtained for ABO and Rh determination (blood group and type) and to screen for antibodies against blood group antigens. Because antibodies identified in the neonate's blood are most often of maternal origin, maternal blood can often serve as the source of serum/plasma for the antibody screen. A newborn's ABO group is assigned solely on the testing of the patient's RBCs for the A and B antigens (forward typing), because the isohemagglutinins anti-A and anti-B are not present in the serum at birth. The use of cord blood specimens for infant blood type determination is discouraged because of possible contamination with Wharton jelly and because of concerns about proper identification of the specimen.

If the newborn's antibody screen is negative, ABO- and Rh-specific RBCs may be transfused, and the antibody screen does not need to be repeated during the infant's hospitalization during the first 4 months of life. If the

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screening identifies passively acquired maternal blood group antibodies, as in Rh hemolytic disease of the newborn, then O-negative red blood cells should be transfused until repeat testing is negative for antibodies reacting against the ABO- or Rh-specific units. When antibodies to other RBC antigens other than D are detected, RBCs selected for transfusion should also be negative for the identified antibody. In cases when reconstituted whole blood is needed for large volume transfusion procedures (i.e., exchange transfusions, cardiopulmonary bypass, extracorporeal membrane oxygenation [ECMO]), the neonate may be given plasma that is ABO compatible with the neonate's RBCs but receive RBCs that are compatible with maternal serum. This may result in disparate ABO group of the RBC and plasma units. An alternative used by some transfusion centers entails the use of low isohemagglutinin titer, group-O whole blood, if available.[54] Infants whose Rh-negative mothers were treated with Rh immune globulin (RhIG) during pregnancy often have a positive DAT because of circulating anti-D antibody from the RhIG. The clinician must distinguish this situation from Rh hemolytic disease of the newborn.

In infants older than 4 months of age, repeat testing for blood group, Rh-type, and antibody screening is performed within 72 hours of each red blood cell transfusion if the patient has received a transfusion during the last 3 months or if the history is uncertain or unavailable. Reverse ABO blood group testing, which detects anti-A and anti-B antibodies, is frequently deferred for the first 4-6 months of life, because this testing is often weak or nonreactive in babies less than 1 year of age.

Red Blood Cell Preparations

Viability and functional activity of RBCs require that they be preserved in additive solutions that support their metabolic demands. All anticoagulant/preservative (AP) solutions contain citrate, phosphate, and dextrose (CPD), which function as an anticoagulant, a buffer, and a source of RBC metabolic energy, respectively. The addition of mannitol and adenine to existing additive solutions has increased the shelf life of RBCs from 21 days (CPD) to 35 days (CPDA-1) and to 42 days for newer AP solutions (Adsol® [AS-1], Nutricel® [AS-3], Optisol® [AS-5]) by stabilizing the RBC membrane and maintaining 2,3-diphosphoglycerate and adenosine triphosphate within erythrocytes. Studies have shown that extended-storage preservative solutions are safe and as efficacious as CPDA-1 RBCs in increasing the hematocrit for neonates receiving small-volume (10–15 mL/kg) RBC transfusions.[76,178] However, there are no clinical studies that have confirmed or refuted the effect of an AP on metabolic abnormalities in massive transfusion (>20 mL/kg) for the neonate. Of particular concern is the potential for adenine-induced nephrotoxicity[178] and intolerable fluid shifts secondary to the diuretic effects of mannitol (present in AS-1, AS-5, and AS-7 but not AS-3)[76] in neonatal patients with limited blood volumes.[196] Therefore, some experts recommend avoiding RBCs stored in extended-storage media (AS-1, AS-3, AS-5) for large-volume transfusions until such data have been published.

TABLE 80.3 Estimated Blood Volumes

Age	Blood Volume (mL/kg)
Premature infant	90-105
Term newborn	82-86
1-7 days	78-86
1-12 months	72-78

Data from Price DC, et al. In: Handmaker H, et al, eds. *Nuclear medicine in clinical pediatrics*. New York: Society of Nuclear Medicine; 1975:279.

Red Blood Cell Dose and Administration

The highest relative blood volumes (mL/kg) are found in neonates. Adult blood volumes on a per-kilogram basis are achieved by 3 months of age (Table 80.3). A typical replacement transfusion is 10-15 mL of RBCs per kilogram. Because infants are so small, many pediatric transfusion centers dispense small aliquots from one RBC unit (300-350 mL) to one or several neonates who require multiple transfusions to decrease donor exposure and to conserve RBC inventory. This practice requires sterile connecting devices to assure that the original RBC unit remains a closed system and transfer packs or syringe sets that permit multiple aliquots to be removed. Studies have shown that CPDA-1 and AS-3-preserved split RBC packs effectively limit donor exposures and are safe for use in neonatal small-volume transfusions after 35 days of storage.[102]

A few small studies have compared the consequences of RBCs on clinical outcomes; however, only one prospective study has been conducted in premature infants to evaluate whether fresh RBCs (≤7 days) decreased morbidity and mortality in VLBW infants compared with standard RBCs. In the Age of Red Blood Cells in Premature Infants (ARIPI) trial conducted in Canada, 188 infants provided with fresh RBC transfusions (mean age of transfused RBCs 5.1 days, SD 2.0 days) did not demonstrate an improvement in a composite outcome measure of major neonatal morbidities (NEC, IVH, bronchopulmonary dysplasia [BPD], and ROP) or death at 30 and 90 days compared with the 189 infants who received standard RBC products (mean age of transfused RBCs 14.6 days, SD 8.3 days) despite having 60% more donor exposures.[57] Although an unblinded, randomized control trial suggested an advantage in clinical outcomes in neonates with congenital heart disease receiving reconstituted fresh whole blood defined as less than 48 hours old when dispensed for cardiopulmonary bypass pump priming and postoperative transfusion support,[63] the role of fresh RBCs for routine transfusion support in premature infants has not shown a clear benefit. ARIPI has subsequently been criticized for insufficient separation of mean RBC storage time between its two cohorts (<2

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weeks) and for inadequately addressing the issue of storage lesion in the oldest additive solution units (35-42 days). The use of a relatively liberal transfusion strategy may also have contributed to better clinical outcomes than would be expected with restrictive practices.[118] Although the saline-adenine-glucose-mannitol (SAGM) additive solution used in the study is widely available in Canada and Europe, its restricted distribution in other regions may limit the relevance of its conclusions in countries like the United States where other types of additive solutions are utilized.[187] However, based on the results of this and other recent RCTs in older children and adults such as ABLE,[96] RECESS,[172] TOTAL,[49] and INFORM,[65] recent guidelines for neonatal transfusion do not recommend limiting the age of transfused RBCs to <10 days.[27,182]

Because red blood cell units are stored at 4°-6°C, hypothermia can develop after massive transfusion unless the blood products are first warmed to body temperature. Inline blood warmers should be used for RBC exchange transfusions, and radiant heaters should be avoided because they can result in hemolysis of the RBC component. When phototherapy is in progress, the blood component and tubing should be positioned so as to minimize exposure to phototherapy light, which may also cause hemolysis.[196]

Platelet Transfusion

Indications

As with older children and adults, platelet transfusions are administered to neonates therapeutically or prophylactically to prevent the hemorrhagic complications of thrombocytopenia. Neonates have different risks of bleeding given the same degree of thrombocytopenia. For example, thrombocytopenic neonates with neonatal alloimmune thrombocytopenia purpura (NAIT) have a high risk of major bleeding, whereas those with sepsis or NEC, and those with IUGR, have an intermediate and low risk of major hemorrhage, respectively. Differences in platelet function or concurrent coagulopathy are likely causes for these discrepancies.[17] A historic randomized controlled trial addressing whether platelet transfusions reduce major bleeding in neonates found no benefit of maintaining a normal platelet count (platelets >150,000/μL) in preterm neonates compared with those maintained at greater than 50,000/μL. However, this study did not address bleeding risk or transfusion benefit for neonates with platelet counts less than 50,000/μL.[7] More recent data comparing prophylactic platelet transfusion thresholds of 25,000/μL and 50,000/μL in terms of mortality and major bleeding complications in 660 premature infants (less than 34 weeks), reported results in 2018. Infants randomized to the higher transfusion threshold had higher occurrence of a new major bleeding episode or death than infants randomized to the lower threshold (26% versus 19%, $p = 0.02$).[43]

Neonatal platelet transfusion threshold policies vary widely, both nationally and internationally,[41,79] and are largely based on expert panel recommendations garnered from clinical experience because of the lack of randomized clinical trials addressing absolute bleeding risk in thrombocytopenic neonates caused by different etiologies. Because of the concern for IVH in the sick neonate, many physicians have traditionally adopted a fairly aggressive platelet threshold for transfusion (e.g., platelet count >100,000/μL in high-risk patients). Murray et al. retrospectively studied 53 neonates (44 preterm) with severe thrombocytopenia and concluded that a threshold of 30,000/μL without other risk factors or previous IVH is safe for the majority of neonates.[113] In a cross-sectional observational study of neonatal outcomes with severe thrombocytopenia, Stanworth et al. failed to show a clear relationship between nadir platelet count/degree of thrombocytopenia and major hemorrhage (IVH, pulmonary, intra-abdominal, hematuria). In the 169 neonates studied with severe thrombocytopenia (platelet count nadir <60,000/μL), 154 (91%) did not experience major hemorrhage. Of the 15 (9%) that experienced major hemorrhage, 12 patients (80%) had a platelet count nadir before the hemorrhage of greater than 20,000/μL,[170] and follow-up analysis revealed that thrombocytopenia alone was not a strong indicator of bleeding risk, whereas gestational age (<34 weeks), early onset of postnatal thrombocytopenia (<10 days after birth), and coexistence of NEC were strong clinical risk factors for bleeding in this population.[115] Retrospective studies have also failed to establish a link between the severity of thrombocytopenia and risk of IVH[187] across both liberal and restrictive transfusion practices.[19,186] A recent retrospective study of VLBW infants demonstrated that a restrictive platelet transfusion protocol using platelet count thresholds of 25,000/μL in clinically stable neonates and 50,000/μL in clinically unstable neonates, extremely premature neonates within the first week of life, or neonates at high risk of major bleeding was not associated with an increased risk for IVH compared with a more aggressive transfusion protocol.[19] Nevertheless, in their recent retrospective review, Sparger and colleagues found that a majority of neonatal platelet transfusions in the United States continue to be administered for pretransfusion platelet counts of ≥50,000/μL in VLBW infants despite evidence that platelet transfusion has little appreciable impact on the risk of IVH after adjustment for underlying clinical variables.[168]

Thus, a generally accepted transfusion trigger for platelet count less than 25,000/μL has been endorsed for healthy or stable term and preterm infants without other risk factors, whereas some experts propose a higher trigger (<50,000/μL) for VLBW neonates within the first week of life, clinically unstable neonates, and neonates with NAIT (using HPA-compatible platelet products).[149,150] Current recommended thresholds for neonatal platelet transfusion are listed in Box 80.3. Platelet transfusions are also indicated to treat hemorrhage associated with acquired (i.e., ECMO, cardiopulmonary bypass, uremia) or congenital qualitative platelet abnormalities (i.e., Glanzman thrombasthenia, Bernard-Soulier syndrome), even if the platelet count is within the normal range.

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• BOX 80.3 Recommended Thresholds for Neonatal Platelet Transfusion

- Platelet count <25 × 10^9/L
  No bleeding, including neonatal alloimmune thrombocytopenia (NAIT) without bleeding or family history of ICH
- Platelet count <50 × 10^9/L
  Bleeding, current coagulopathy, surgical prophylaxis, or NAIT with a family history of ICH in an affected sibling
- Platelet count <100 × 10^9/L
  Major bleeding or requiring major surgery (e.g., neurosurgery)

Modified from New HV, et al. Guidelines on transfusion for fetuses, neonates, and older children. *Brit J Haematol.* 2016;175:784-828.

Pretransfusion Testing

Platelets express intrinsic ABO antigens but not Rh antigens. They should be ABO-group specific whenever possible because of reports of intravascular hemolysis following transfusion of ABO-incompatible platelets in infants and children.[8] Platelets do not routinely require cross-matching. If ABO-incompatible platelets must be used, plasma removal via volume reduction or washing, or selecting low isohemagglutinin (anti-A, anti-B) titer units, are options.[78] Routine volume-reduction methods for all neonates should be avoided, because approximately 20% of platelets are lost in the final product, which is resuspended in either saline or compatible plasma. Although Rh matching does not affect post-transfusion platelet survival, RBCs are present in small amounts of whole blood–derived platelet concentrate and can cause Rh sensitization in an Rh-negative recipient. Administration of RhIG should be strongly considered for any Rh-negative neonate, especially females, within 72 hours of exposure to Rh-positive RBCs through a platelet transfusion. The recommended dose is 120 IU RhIG per mL of RBCs transfused, administered intramuscularly (90 IU RhIG per mL of RBCs intravenously).[46] When aliquots of apheresis platelets, which are relatively RBC free, are used, there should be limited to no concern for Rh sensitization.

Component Definition and Dosing

A standard unit of platelets, prepared from a single donation of whole blood, contains at least 5.5 × 10^{10} platelets in 50-70 mL of plasma.[169] Apheresis platelets, often called single-donor platelets, contain a minimum of 3 × 10^{11} platelets in approximately 250 mL (range: 200-400 mL) of plasma, the equivalent of an estimated 6 units of whole blood–derived platelets. There are two ways to calculate platelet doses in neonates, based on mL/kg or based on equivalent units/kg. An equivalent unit (EU) is the volume of a platelet aliquot that has a minimum platelet content of 5.5 × 10^{10}. Because one apheresis unit contains at least 3 × 10^{11} platelets, the content of an apheresis platelet unit is equivalent to approximately 6 units of whole blood–derived platelets. The standard dose based on this method is 1 EU/5 to 10 kg with a minimum dose of 1 EU. EU-based dosing offers the advantage of reducing platelet content variability in the transfused product because a minimum platelet content will be administered regardless of its volume. This may be clinically significant in sick neonates with thrombocytopenia.

Platelet components may be volume reduced to 15-20 mL for patients requiring significant volume restrictions, but this is associated with significant platelet loss of 15%-35% and may affect platelet function adversely. Rapid decreases in pH have also been observed for aliquots stored in syringes after volume reduction; for this reason, infusion of these products is recommended within 4-6 hours of processing to avoid induction or exacerbation of acidosis in transfusion recipients.[50] Platelets are stored at 20°-24°C under constant agitation and have a shelf life of 5 days after collection. Transfusion of 10-15 mL/kg of platelets for neonates, or 1 EU/5 to 10 kg for children over 5-10 kg, should yield a platelet increment of 50,000/μL to 100,000/μL if no predisposing risk factors for refractoriness exist. It is important to account for device-related dead space (10-30 mL) when issuing the product, as this can be considerable in relation to the overall platelet dose. The expected rise in the platelet count after transfusion may not be met because of destructive thrombocytopenia such as occurs with splenomegaly, fever, sepsis, DIC, bleeding, or antibiotic therapy. Immune-mediated causes of platelet refractoriness, such as alloantibodies to platelet-specific antigens (e.g., HPA-1a, 5b) in NAIT and autoantibodies to common platelet antigens in idiopathic thrombocytopenic purpura, require consideration in this population so that appropriate management can be initiated.[54]

Despite increasing availability of alternative products such as platelet additive solution (PAS)[40] or pathogen-reduced platelets[93] in the United States, their efficacy and safety in neonates or pediatric patients in general have not been widely published with a few exceptions.[68,200]

Granulocyte Transfusion

Neonates, particularly those with very low birth weights, are susceptible to overwhelming bacterial infection. Many factors contribute to this risk, including disruption of mucosal barriers, hypogammaglobulinemia, and qualitative neutrophil defects. Furthermore, preterm neonates may become neutropenic during sepsis because of a reduced capacity to increase myeloid progenitor cell proliferation with infections. Transfusion of granulocytes has been employed in the treatment of neonatal sepsis; however, the efficacy of such transfusions is controversial. Meta-analysis of the safety and efficacy of granulocyte infusion adjunctive to antimicrobial therapy in the treatment of septic neutropenic neonates failed to show that granulocyte infusions reduce mortality or morbidity, although a reduction in the latter approached statistical significance.[131] The Resolving Infection in Neutropenia with Granulocytes (RING) randomized clinical trial compared standard antimicrobial

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therapy alone against daily granulocyte transfusion from donors stimulated with GCSF and dexamethasone in addition to standard therapy and found no difference in survival or microbial response in the granulocyte arm,[140] although secondary analyses indicated that higher doses of granulocytes achieved through GCSF stimulation were associated with better outcomes than lower doses.[103] Although children (defined as <18 years of age) were included in this study, they comprised only a minority of the total number of subjects (6/49 in control arm, 4/48 in granulocyte arm).[140] In spite of the conflicting evidence, granulocyte transfusion may be considered in neonates with qualitative neutrophil defects with severe (or progressive) bacterial or fungal infection who have not responded to appropriate aggressive antimicrobial treatment.[150]

Granulocyte concentrates for neonatal transfusion are prepared by automated leukapheresis of healthy stimulated (dexamethasone ± granulocyte colony-stimulating factor [G-CSF]) donors, and contain 1 to 2×10^9 neutrophils per kilogram in a volume of 10-15 mL/kg. Treatment should be continued daily until clinical improvement or neutrophil count recovery (absolute neutrophil count >3000/μL in first week of life; >1500/μL thereafter). All granulocytes should be gamma or x-ray irradiated and CMV negative since leukodepletion is contraindicated. Because granulocyte concentrates have a significant amount of RBCs (hematocrit: 15%-20%), the component must be ABO/Rh and cross-match compatible with the intended neonatal recipient. Because granulocytes must be transfused within 24 hours of collection, FDA-mandated testing for blood products will not be completed before the product is released for administration; therefore, the risks and benefits of transfusing an untested blood product must be weighed by the medical team and the parents of the infant and documented accordingly in the medical record.[54]

There are unique risks to granulocyte transfusion. They include varying degrees of pulmonary reactions from mild transient respiratory distress to severe pulmonary edema, hypoxia, and acute respiratory distress syndrome (ARDS), as well as a high incidence of febrile transfusion reactions. Pulmonary complications have been reported in 4% of transfused infants,[108] and severe pulmonary reactions resembling TRALI have been reported.[122] Mild to moderate reactions occur in 25%-50% and severe reactions in about 1% of all granulocyte transfusions.[140] Administration of amphotericin B should not be done within 6 hours of granulocytes because of suspected increased risk of severe pulmonary reactions. Polycythemia secondary to granulocyte transfusion is an infrequently reported complication but may be especially relevant in neonates, owing to a relatively large volume of RBCs within the granulocyte product being transfused into an infant with a small blood volume. Given the relatively high RBC volume in granulocyte concentrates (hematocrit 15%-20%), a significant increase in the patient's hematocrit may be observed when granulocytes are given at doses of 15-20 mL/kg for several days in a row.[3]

Although granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have been used successfully to stimulate neutrophil numbers, and IVIG has been attempted to augment traditional antimicrobial therapy to support septic neonates, data on efficacy are inconclusive.[26,153] Because of the lack of clear consensus on their impact on improving host defense mechanisms and improving outcomes, these adjuncts to standard antimicrobial and antifungal therapy need further investigation.

Fresh Frozen Plasma Transfusion

Plasma can be prepared by either whole blood separation or by apheresis. When the plasma product is frozen to −18°C or colder within 8 hours of collection, it is labeled as fresh frozen plasma (FFP) (approximately 250-300 mL) and can be stored at this temperature for up to 1 year.[54] Plasma frozen within 24 hours of collection (FP24) has a similar shelf life and is considered essentially bioequivalent to FFP with the exception of ARIPI Factor VIII activity, which is typically 15%-30% lower.[52,156] To conserve plasma inventory and limit donor exposures for infants who receive only fractions of an adult-sized unit, plasma can be separated into a system of multiple satellite bags and frozen as aliquots. Once thawed, plasma components can be further subdivided into aliquots for multiple neonates via sterile connecting devices, stored at 1°-6°C for up to 5 days and transfused as "thawed plasma."[196] Although thawed plasma has approximately 40% Factor V and VIII (heat labile factors) activity, effective hemostasis is maintained at this level, making thawed plasma clinically similar to FFP and FP24.

Plasma is used primarily to treat acquired coagulation factor deficiencies as a result of DIC, liver failure, vitamin K deficiency from malabsorption, biliary disease, warfarin therapy, or dilutional coagulopathy from massive transfusion. It can also be used for specific factor replacement in congenital factor deficiencies (e.g., Factors V, X, XI) when specific factor concentrates or recombinant products are not manufactured or unavailable.[54,150,196] However, the optimal role of plasma in neonatal transfusion practice has not been established through evidence-based studies, and a majority of FFP transfusions in patients of all ages appear to be given for prophylactic purposes.[110,171] Recent transfusion guidelines do not recommend routine use of plasma for correction of coagulopathy in neonates without clinically significant bleeds. In contrast, plasma may be of use in neonates with significant bleeding, including those requiring massive transfusion or at high risk for bleeding because of an invasive procedure or significant coagulopathy as evidenced by markedly prolonged PT or aPTT.[66] Plasma is not indicated for volume expansion, enhancement of wound healing, or as first-line treatment for congenital factor deficiencies when either a virally inactivated, plasma-derived factor concentrate or recombinant factor is available.

Plasma transfusions should be ABO-compatible with the neonate's RBCs to avoid passive transfer of

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isohemagglutinins from ABO-incompatible plasma, which may result in hemolysis.[196] Because the freezing process renders the frozen-thawed plasma component free of viable leukocytes, plasma products are not screened for CMV antibody, nor are leukoreduction and irradiation necessary for the prevention of CMV reactivation and TA-GVHD, respectively. However, passive administration of antibody to CMV in plasma may cause CMV IgG testing to become positive in the transfused neonate. This does not represent CMV infection, and the antibody disappears in a time course consistent with the 21-day half-life of gamma-globulin.[98,181]

Plasma is typically dosed at 10-15 mL/kg. Assuming that 1 mL of plasma equates to 1 U of factor activity (definition of 100% activity), one can predict the amount of replacement of most factors following plasma transfusion. For example, for a *preterm* infant, the calculations are as follows:

1. 1 U of factor activity = 1 mL plasma
2. TBV (total blood volume) = weight × 100 mL/kg
3. TPV (total plasma volume) = TBV × (1 − Hct)
4. Unit of factor needed = TPV × (desired factor [%] − initial factor [%])

Example: 1-kg preterm infant, with Hct 55%; desired factor activity increment of 30%:

TBV = 100 mL, and TPV = 45 mL
Units of factor needed = 45 × (0.30) = 15 U
Amount of plasma needed = 15 mL (or 15 mL/kg)

Using these calculations for a *preterm* infant, it is evident that 10-15 mL/kg of plasma will replace approximately 10%-30% of most factors immediately following transfusion. It is important for the clinician to know the half-lives of the factor(s), because factor half-lives vary. Furthermore, vitamin K–dependent factors (Factors II, VII, IX, and X, as well as anticoagulant proteins C and S) are lower in neonates, thereby prolonging both the PT and aPTT. Correlation of lab values with gestational age and clinical status is, therefore, important when devising a plasma-dosing schedule for a coagulopathic infant. It is critical that appropriately collected specimens for evaluation of coagulation factors be obtained in advance of plasma transfusion.

Solvent/detergent (S/D) treatment shows great effect against enveloped viruses since it disrupts their lipid-containing membranes. Since the treatment also lyses cells, S/D can only be used for acellular products such as plasma (e.g., Octaplas) or coagulation factors. A limitation of the treatment is that non-enveloped viruses such as hepatitis A and parvovirus are relatively resistant. Octaplas received Health Canada approval in 2005 and FDA approval in January 2013. It has been available in Europe since 1992 and several countries (e.g., Norway, Ireland, and Finland) have entirely converted their plasma supply from FFP to Octaplas. Each lot is prepared from a pool of 630-1520 units of FFP, which provides a more consistent level of coagulation factors. The risk of allergic reactions and TRALI appears reduced because of the process of filtration to remove cellular debris as well as the dilution of individual donor plasma proteins. The product is available in 200-mL aliquots, but these cannot be divided into smaller portions, limiting their use in smaller patients. Octaplas preparation includes affinity ligand chromatography (to remove prions), several filtration steps, and S/D treatment with trinitrobutyl phosphate and Triton X-100. Through such preparation processes, Octaplas is associated with reduced risk of bacterial contamination.[148] In the United States, the shelf-life is 3 years when stored below −18°C (compared to 1 year for FFP or FP24).

Cryoprecipitate Transfusion

Cryoprecipitate is the cold-insoluble precipitate prepared from FFP that has been thawed slowly at 1°-6°C and refrozen at −18°C after removal of the supernatant. Each unit (bag) of cryoprecipitate is derived from a single whole-blood donation and has a shelf life of up to 1 year. A unit (10-15 mL) of cryoprecipitate contains a minimum of 80 units of Factor VIII activity and 150 mg of fibrinogen. There are no standards for the quantity of the other factors; however, there is approximately the same amount of von Willebrand Factor (vWF) and Factor XIII in one unit as 10-15 mL/kg of FFP.[54] Therefore, it is a useful product in infants who require higher concentrations of Factors VIII, XIII, vWF, or fibrinogen levels and who are volume restricted. Cryoprecipitate is indicated in the treatment of bleeding episodes associated with von Willebrand disease and/or hemophilia A only when FDA-licensed recombinant factor concentrates and/or viral-inactivated, pooled plasma-derived factor concentrates are not available. Cryoprecipitate is the treatment of choice for Factor XIII deficiency, congenital afibrinogenemia, dysfibrinogenemia, and severe hypofibrinogenemia (<150 mg/dL) associated with bleeding.[54] In general, an infant should receive 1 bag of cryoprecipitate per 5 kg, which increases the total fibrinogen by about 100 mg/dL.

Factor Concentrates

A variety of human plasma-derived and recombinant factor medications have become more widely available in the last several decades, including short- and long-acting Factor VIII and Factor IX concentrates indicated in the treatment of hemophilia A and B, respectively, and von Willebrand Factor concentrates for von Willebrand disease. Activated Factor VII (Novoseven) is indicated for congenital Factor VIII deficiency and hemophiliac patients with high titer inhibitors but is most commonly used for off-label treatment of refractory bleeding in neonates on cardiopulmonary bypass. There is conflicting evidence as to whether the risk of thrombosis is significantly higher in neonates compared to older children.[142] Prothrombin complex concentrates (PCC) containing three (Factors II, IX, X) or four (Factors II, VII, IX, X) factors are indicated for

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vitamin K deficiency, especially when plasma is contraindicated because of volume restriction, as well as congenital Factor X deficiency. Newer agents indicated for rare specific factor deficiencies include Factor XIII (Corifact), protein C (Ceprotin), and fibrinogen (RiaSTAP) concentrates. The use of antithrombin concentrates is discussed below under the Extracorporeal Membrane Oxygenation (ECMO) section.

Special Topics in Neonatal Transfusion

Exchange Transfusion

Exchange transfusion is the replacement of most or all of the recipient's RBC mass and plasma with appropriately compatible RBCs and plasma from one or more donors. The amount of blood exchanged generally is expressed in relation to the recipient's blood volume (e.g., as a partial, single, or double volume exchange).

Indications

Neonatal exchange transfusions are most commonly used in infants with hemolytic disease of the newborn (HDN). Double-volume exchange transfusions also are frequently used in newborns with severe jaundice from other causes to prevent kernicterus and other toxicities related to hyperbilirubinemia.[196] Bilirubin levels warranting exchange transfusion are discussed in Chapter 91.

Although a Cochrane meta-analysis demonstrated that IVIG administration (0.5-1 gm/kg) may prevent exchange transfusion for many term infants with HDN, a prospective, randomized control trial showed that prophylactic IVIG (0.75 g/kg) did not decrease the duration of phototherapy, maximum bilirubin levels, or need for RBC transfusion or exchange transfusion in Rh HDN.[5,166] Despite this, IVIG is often considered when serum bilirubin levels continue to rise despite aggressive phototherapy or when the bilirubin level is approaching the exchange level. Exchange transfusion can also be used, albeit infrequently, to remove exogenous (drugs) or endogenous (metabolic) toxins.

The efficiency of exchange transfusion diminishes exponentially as the procedure continues. The kinetics of exchange are very similar, regardless of whether a continuous technique (simultaneous withdrawal and replacement) or discontinuous technique (alternating withdrawal and replacement) is used. The effectiveness of exchange transfusion varies with the component being removed and its relative distribution within intravascular and extravascular compartments. The efficiency is highest for RBC exchange. A double-volume ET results in removal of approximately 85% of the neonate's RBCs; however, the amount of bilirubin or maternal alloantibody removed by exchange transfusion is significantly less (25%-45%) because of equilibrium between the intravascular pool and the extravascular tissues for bilirubin, antibodies, and similar substances.

The optimal volume for an exchange transfusion is twice the infant's blood volume. Little is gained by exceeding two blood volumes. When anticipating the volume needed for double-volume exchange, the total volume required depends on whether the infant is preterm. For example, using two times total blood volume (TBV):

$$2 - \text{volume exchange volume (preterm)} = 100\ \text{mL/kg} \times 2, \text{ or } 200\ \text{mL/kg}$$

$$2 - \text{volume exchange volume (term)} = 85\ \text{mL/kg} \times 2, \text{ or } 170\ \text{mL/kg}$$

To perform the exchange transfusion, aliquots of the reconstituted whole blood product are administered while equal amounts of the infant's blood are withdrawn, with careful attention not to exceed 5 mL/kg or 5% of TBV at a time (over 2-10 minutes).

Choice of Blood Components

Either stored whole blood, if available, or reconstituted whole blood (i.e., RBCs plus plasma) can be used for neonatal exchange transfusion. The RBC component should be group O-negative or ABO/Rh compatible to maternal serum for Rh HDN. Fresh (<5-7 days) CPDA-1 units should be used, because the safety of extended storage media has not been amply studied for neonatal large-volume transfusions. If only older CPD(A) units or extended-storage additive units are available, the RBC units can be washed or the supernatant removed. The RBCs are reconstituted with whole blood or compatible plasma to a final hematocrit of 40%-50%. Furthermore, components should be CMV risk reduced (leukodepletion), gamma irradiated, and sickle negative. Both whole blood and reconstituted whole blood are deficient in platelets. Platelets are not added to reconstituted blood during an exchange, because this could lead to increased microaggregate formation. Infants who are significantly thrombocytopenic (platelet count <30,000/μL) after an exchange transfusion or who are bleeding should receive a platelet transfusion. For infants with HDN caused by other RBC antibodies, the RBC product should be specifically selected to be negative for the offending antibody(ies).

Potential complications of exchange transfusion include: hypocalcemia, hyperglycemia (with subsequent rebound hypoglycemia), hypothermia (typically avoided with use of appropriate in-line blood warmers), dilutional thrombocytopenia, neutropenia, umbilical vein/arterial thrombosis, necrotizing enterocolitis, intracranial pressure fluctuations resulting in IVH, air embolization, and infection.[116,196] The majority of adverse events associated with exchange transfusions reported include hypocalcemia (3%-42%), metabolic acidosis (approximately 24%), hypernatremia (8%), severe thrombocytopenia defined as platelet count <50,000/μL (6%-44%; and up to 63% in neonates receiving exchange transfusion specifically for Rh HDN), and leukopenia/neutropenia (70%). These adverse events may occur as asymptomatic laboratory abnormalities or may be associated with significant exchange-transfusion–related morbidity. Adverse events are more frequent in exchanges

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done on preterm infants less than 32 weeks, infants with other significant co-morbidities, and when umbilical catheters are used (in particular, portal vein thrombosis). One unique risk factor associated with exchange transfusion in neonates is subsequent development of invasive bacterial infections, with reported incidence of exchange-transfusion-related sepsis ranging from 0%-11%. It is postulated that the increased risk may result from the use of umbilical vein catheters, the associated exchange-transfusion-related leukopenia, and potentially an immunomodulatory effect of blood transfusion.[74,134,165]

Partial Exchange Transfusion

Approximately 5% of all neonates are born with or develop polycythemia. Infants of diabetic mothers and small-for-gestational-age neonates are at higher risk. Neonatal polycythemia is defined as a venous hematocrit greater than 65% within the first week of life. Partial exchange transfusion effectively lowers the hematocrit and reduces whole blood viscosity in polycythemic neonates who have hyperviscosity. Partial exchange transfusion is also useful for correcting severe anemia without the risk of fluid overload and heart failure.

The long-term benefit of early partial exchange transfusion in polycythemic neonates is controversial, at least partly because the prognosis for such infants depends greatly on the etiology. A hematocrit greater than 65% is generally used as the stimulus for partial exchange transfusion because as the hematocrit rises over this level, blood viscosity significantly increases and oxygen transport diminishes.

A partial exchange is used to normalize the hematocrit to below 60% by removing infant whole blood and replacing with an equal volume of isotonic crystalloid solution. Crystalloid solutions are preferable to plasma to decrease exposure to plasma and because NEC has been associated with the use of plasma as replacement solution.[116] The volume of exchange required can be calculated with the following formula:

$$\text{Volume of exchange (mL)} = \text{TBV (mL)} \times \left[\frac{\text{Observed Hct} - \text{Desired Hct}}{\text{Observed Hct}}\right]$$

For example: 1-kg preterm infant with Hct 68%, desired postpartial exchange Hct 55%

$$\text{Volume of exchange (mL)} = 100\ \text{mL} \times \left[\left(\frac{(68-55)}{68}\right)\right] = \approx 20\ \text{mL of crystalloid exchanged with whole blood}$$

To correct severe anemia, RBCs are used as the replacement fluid for the whole blood withdrawn. The formula used to calculate the volume required for exchange is similar to the one above; however, the hematocrit of the RBC product used must be taken into account. RBCs in CPDA-1 usually have a hematocrit of approximately 70%; thus the formula is:

$$\text{Volume of exchange (mL)} = \text{TBV (mL)} \times \left[\frac{\text{Desired Hct} - \text{Observed Hct}}{\text{Hct of Unit} - \text{Observed Hct}}\right]$$

For example: 1-kg preterm infant with Hct 21%, desired postpartial exchange Hct 45%

$$\text{Volume of exchange (mL)} = 100\ \text{mL} \times \left[\frac{(45-21)}{(70-21)}\right] = \approx 49\ \text{mL of CPDA RBCs exchanged with whole blood}$$

If RBCs preserved in other solutions are used, the equation must be altered to take into account the average hematocrit of the product. The technique of partial exchange transfusion is similar to that used in larger volume exchange. A discontinuous methodology is most often used; aliquots of 5 mL/kg or less should be used for each withdrawal and infusion.

Extracorporeal Membrane Oxygenation

Because of the large volume of transfused red blood cells used for ECMO, RBCs used in the bypass circuit should be less than 7-14 days old to avoid high potassium levels in older blood.[100] In the infant with presumed or suspected cellular immunodeficiency, the blood products should undergo CMV risk reduction (CMV seronegative *or* leukoreduced) and gamma or x-ray irradiation. There is mounting anecdotal evidence that RBCs preserved in extended storage media (AS-1, AS-3) are safe for ECMO. Some ECMO centers use RBC products stored in CPD/CPDA preservatives or reduce the additive prior to use.[196] Hemolysis from mechanical damage and phlebotomy contributes to ongoing red blood cell transfusion requirements. Thrombocytopenia occurs in all patients undergoing ECMO as a result of accelerated platelet destruction. This, coupled with the need for systemic anticoagulation with heparin to prevent clotting within the extracorporeal circuit (see Chapter 79), places infants on ECMO at significant risk for hemorrhage.[21] Platelets should be maintained at greater than 50,000-150,000/μL or higher in infants undergoing major surgery such as diaphragmatic hernia repair while on ECMO. Activated clotting times and other coagulation tests such as thromboelastography, aPTT, and anti-Xa assays are used to measure coagulation parameters, and FFP and cryoprecipitate are often needed to correct laboratory abnormalities.

Management of ECMO Patients Using Factor Concentrates (e.g., Antithrombin III)

Although on-demand dosing of antithrombin concentrates (Thrombate, ATryn) for pediatric patients on ECMO increases antithrombin levels and decreases heparin

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requirements for at least 12 hours after dosing, no statistical differences in the number of circuit changes, in vivo clots or hemorrhages, transfusion requirements, hospital or ICU length of stay, or in-hospital mortality were identified compared to controls.[198] Similarly, studies of antithrombin supplementation in children on cardiopulmonary bypass have demonstrated decreased heparin doses without significant impact on clinical outcomes.[142]

Therapeutic Hypothermia

Infants presenting with neonatal encephalopathy as a result of a hypoxic insult are offered neuroprotective therapy with whole body or selective head cooling.[158] Often, these infants have suffered an ischemic insult involving several organs, including the liver. This may predispose the infant to liver dysfunction and result in clinical bleeding or disseminated intravascular coagulation. Hypothermia-associated bleeding has been hypothesized to result from dysregulation of enzymatic function, reduced platelet activity, and/or altered fibrinolysis.[35,195] Therapeutic (induced) hypothermia may worsen baseline coagulopathy in asphyxiated newborns through the above mechanisms. Patients undergoing hypothermia with prolonged INR and aPTT values and lower platelet and fibrinogen levels may have a higher incidence of clinical bleeding. Sites of bleeding may be intracranial, pulmonary, gastrointestinal, and/or genitourinary. These data suggest that maintaining an appropriate INR, platelet count, and fibrinogen level may be important in reducing the incidence of clinical bleeding among this vulnerable group of patients.

Future Directions

Neonatal transfusion practices remain highly variable across institutions because of a paucity of evidence-based guidelines. Cure and colleagues recently identified several key areas requiring additional research,[42] including ideal parameters for assessing the need for transfusion beyond cell counts as well as markers for assessing transfusion efficacy and long-term outcomes, methods of gathering and compiling epidemiologic data on neonatal transfusions, and blood management strategies for neonates, especially with regard to safety of pathogen-inactivated products. The authors propose that additional translational studies and clinical randomized controlled trials are needed to address these questions along with large, centralized repositories for collection and analysis of data.

Key Points

- Leukoreduction, donor selection criteria, and improved infectious disease screening have contributed to a very safe blood supply.
- Nevertheless, transfusions still carry infectious and noninfectious risks and should, therefore, be administered carefully and judiciously. Rapid, large volume transfusions, in particular, can lead to metabolic derangements.
- During all transfusions, patients must be closely monitored for signs and symptoms of transfusion reactions.
- Current neonatal transfusion practices are guided by the gestational age and clinical status of the patient but remain highly variable across institutions due to lack of evidence-based studies for many blood components.
- Recent clinical trials have contributed toward understanding of neonatal transfusion triggers and clinical outcomes, but ongoing and future trials are needed for further clarification of these parameters as well as identification of viable alternatives to blood products.
- Increasing availability of both plasma-derived and recombinant factor concentrates has led to replacement of plasma products in the treatment of certain clinical conditions and additional applications in the management of neonates on extracorporeal life support.

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Development of the Neonatal Gastrointestinal Tract

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The human gastrointestinal (GI) tract is a complex combination of organs whose primary function is to digest and absorb nutrients. Many important secondary functions are also performed, such as the endocrine function of the pancreas. In fact, what was once considered a simple system of digestion and absorption is now recognized as something much more complex and dynamic. Furthermore, as with the respiratory system, to perform its duties, the GI tract must be in continuity with the environment. This places the additional demand of having mechanisms in place to protect the host from toxins and pathogens. It is remarkable that this tube, open to the outside world at both ends and colonized by bacteria for a significant portion of its length, is tolerated so well and has relatively few complications associated with it. But troubles do occur, and in the neonate, most can be traced to developmental anomalies.

The Beginning

During gestation, the alimentary canal can be simply considered as the folding of endoderm and splanchnic mesoderm into a tube at the end of week 3 and the beginning of week 4.[8] As the head fold forms, the cranial part of the yolk sac becomes enclosed within the embryo and becomes the foregut. Shortly thereafter, the caudal portion of the yolk sac becomes enclosed and forms the hindgut. The midgut resides between the foregut and the hindgut, near the yolk sac, which remains outside the embryo. The midgut remains in communication with the yolk sac until the yolk stalk closes during the 10th week of gestation. Initially the digestive tube ends blindly—cranially at the oropharyngeal membrane and caudally at the cloacal membrane. These membranes, made up of endoderm and ectoderm, break down, with the oropharyngeal going first at the start of week 4 followed by the cloacal at the start of week 6.

Esophagus

The esophagus serves as a complex conduit between mouth and stomach and, at the gastroesophageal junction, functions to avoid reflux of stomach contents back up the esophagus. Although this task sounds simple, the esophagus performs its roles so well that no esophageal replacement has been found that does anywhere near as good a job. All efforts are made to keep a native esophagus, even a severely compromised one, rather than go with any replacement.

The fully developed esophagus extends from the pharynx and cricopharyngeal sphincter in the neck to the lower esophageal sphincter and gastroesophageal junction in the abdomen. The blood supply to the esophagus is segmental, which is a key concept to understand for surgical planning. The upper esophagus is supplied by branches descending from the inferior thyroid artery. The middle and lower thirds of the esophagus are supplied by branches arising directly from the bronchial vessels or the descending thoracic aorta. The abdominal and lower esophagus also receive blood supply from the left gastric and inferior phrenic arteries. The full-term newborn esophagus is 10 cm in length and up to 40 cm in adulthood. There are four areas of natural anatomic constriction of the esophagus: (1) at the level of the cricopharyngeal sphincter, (2) as the aortic arch crosses anteriorly, (3) as the left main stem bronchus crosses anteriorly, and (4) at the level of the lower esophageal sphincter. Foreign bodies in the esophagus tend to lodge at one of these areas of constriction, and burns from caustic ingestion tend to be more severe in these regions.[14]

The esophagus is differentiated from the primitive foregut during the 4th week of gestation.[10,11] A tracheoesophageal septum is evident at this time, initiating the division of the trachea anteriorly from the foregut posteriorly. The septum remains at about the same level in the fetus while the body grows cranially. This leads to elongation of the esophagus, primarily from "ascent" of the pharynx rather than "descent" of the stomach. It reaches its full length, relative to the size of the developing fetus, during the 7th week of gestation. Aberrations during this phase of development result in esophageal atresia and tracheoesophageal fistulas.[4]

The muscular wall of the esophagus is similar to that of the rest of the GI tract, with an outer longitudinal layer and a circular inner layer. The more highly developed longitudinal layer forms during the 9th week of gestation, whereas

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Abstract

This chapter reviews the embryology of the gastrointestinal tract with a focus toward clinically relevant information.

Keywords

GI embryology
stomach development
esophagus development
intestinal development

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the circular layer forms during the 6th week. There is no serosa on the esophagus except in the short abdominal portion. This is clinically important when considering the resection or repair of the esophagus.

The epithelial lining of the esophagus is derived from the primitive endoderm. At the 10th week of gestation, this is ciliated, but a stratified, nonkeratinizing, squamous epithelium begins replacing the ciliated epithelium at about the fourth month of gestation. Some ciliated epithelium along the length of the esophagus may persist until birth. The striated muscle of the upper third arises from mesoderm of the branchial arches, whereas the smooth muscle of the distal two-thirds is derived from splanchnic mesenchyme. Therefore diseases of smooth muscle tend to affect the lower esophagus only.

Small glands of mucus- and bicarbonate-secreting cells with ducts opening onto the surface of the epithelium are scattered throughout the length of the esophagus, particularly in the lower third.

By 8 weeks' gestation, immature neurons are identifiable within the wall of the esophagus. These nerves are derived from both parasympathetic and sympathetic fibers. The cervical sympathetic trunks send fibers along the inferior thyroid artery to the upper third of the esophagus, whereas the middle and lower thirds are supplied by branches from the greater splanchnic nerves. The thoracic esophagus is supplied by branches of the esophageal vagal plexus, arising directly from the vagus trunks in the chest.[8]

The act of swallowing is initiated by impulses from the swallowing center, an area in the reticular formation of the rostral medulla where the nuclei of cranial nerves IX and X are located. The initial event in esophageal peristalsis is stimulation of the longitudinal muscle layer, which is followed by the segmental activation of the circular muscle and relaxation of the lower esophageal sphincter. The peristaltic wave begins in the pharynx and continues through to the gastroesophageal junction without interruption. Whereas primary waves are initiated from the swallowing center, secondary peristalsis is mediated by local intramural pathways to return refluxed material in the lower esophagus to the stomach.

The upper esophageal sphincter corresponds to the cricopharyngeal muscle. There is no morphologic distinction in the muscular wall of the lower esophagus that would identify this sphincter, although clearly one functionally exists. The primary role of this sphincter is to prevent the reflux of gastric contents back into the lower esophagus. The lower esophageal sphincter relaxes as the primary peristaltic wave traverses the esophageal body, and it remains open until the peristaltic wave enters the sphincter and closes it. Disordered lower esophageal sphincter function is thought to be one of the mechanisms for pathologic gastroesophageal reflux.[4]

Stomach

The stomach first appears as a fusiform dilation of the caudal part of the foregut at the end of the 4th week of gestation.[7] At this time, the stomach is suspended between the posterior and anterior body walls by a ventral and dorsal mesentery. During weeks 6 through 10, the stomach undergoes rotation in two planes, as well as growth differentials that lead to the appropriate size and orientation of the organ as seen at birth. One rotation is 90 degrees counterclockwise (viewed from below upward) along the longitudinal axis of the stomach. This brings the dorsal aspect of the stomach toward the fetus' left side, and the ventral aspect now points to the right. The two mesenteries follow this rotation, with the ventral mesentery finally extending horizontally from the stomach to the liver as the lesser omentum. The cranial portion of the dorsal mesentery runs horizontally to the spleen laterally as the gastrosplenic ligament, and it contains the short gastric vessels. A second, lesser rotation, in conjunction with a growth differential favoring greater growth on the dorsal (now left lateral) side of the stomach, leads to the organ's final position. This rotation is clockwise around the body's anterior–posterior axis when viewed from the front and brings part of the now left lateral (formerly dorsal) side of the stomach to point caudally. This part of the stomach still has the caudal portion of the stomach's dorsal mesentery attached, which now grows quite quickly caudally, forming a two-layer fat pad that covers the bowel and extends to the pelvis. The two fat layers fuse to each other and to the colon and become the greater omentum. The space now created behind the stomach is called the lesser sac. It has one entrance, the epiploic foramen (foramen of Winslow), which is located beneath the free edge of the ventral mesentery that now extends from the area of the gastroduodenal junction to the liver.[8]

The final shape of the stomach along with the various epithelial cell types that constitute its mucosal lining create distinct areas: the cardia around the gastroesophageal (GE) junction; the fundus, which projects cephalad from the gastroesophageal junction; the body, which is the vast majority of the gastric reservoir; and the antrum, the portion of the stomach immediately before the pylorus. There are three muscle layers of the stomach: the outer longitudinal, the intermediate circular, and the inner oblique. The three layers permit complex mixing and churning movements that help begin the process of digestion.

The blood supply to the stomach is extremely rich and is derived principally from the celiac axis and superior mesenteric artery. Four major vessels are felt to provide the stomach with blood: the right and left gastric and the right and left gastroepiploic. Also important are the short gastric arteries off the splenic artery. Venous drainage is via the portal system, with the exception of the gastroesophageal junction, which can drain to the systemic system via esophageal veins (critical to the development of esophageal varices). The blood supply to the stomach is so redundant that the organ can survive if three of the four major arteries are divided, which is key in operative planning.

The gastric epithelium is made up of a diverse cell population distributed in a regionally specific manner. The early gastric mucosa is initially a stratified or pseudostratified

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columnar epithelium that later becomes cuboidal. This mucus-secreting cuboidal epithelium then becomes peppered with gastric pits that are first observed between gestational weeks 6 and 9. By 20 weeks, the mucosa of the stomach is mature in appearance. At the base of the gastric pits are the gastric glands, which contain the effector and regulator cells of gastric secretion.[8]

The different cell populations of the gastric glands in various regions of the stomach allow the stomach to be histologically and functionally compartmentalized. Parietal cells are found predominantly in the gastric fundus and body and less often in the proximal antrum and can be identified in gastric glands as early as week 10. They produce both hydrochloric acid and intrinsic factor under complicated regulatory control. Chief cells are found principally in the gastric fundus and body, first appearing in gestational week 12. They are located exclusively at the base of the gastric glands, where they synthesize, store, and secrete pepsinogen. Pepsinogen is hydrolyzed to the active proteolytic enzyme pepsin in the acid environment of the stomach.

Enteroendocrine cells are present throughout the stomach, duodenum, and distal intestine. Because of their ability to produce biologically active amines and peptides and to internalize certain precursor molecules, they are referred to as *amine precursor uptake and decarboxylation* (APUD) cells. There are many distinct types of enteroendocrine and neuroendocrine cells found in the gastric mucosa. These cells are among the first to populate the gastric glands, appearing at 8-9 weeks. The most common and well characterized are the G cells, which produce gastrin, and the D cells, which produce somatostatin and amylin. These cells predominate in the gastric antrum. Other enteroendocrine cells are ubiquitous both within the gastric glands and within the duodenal wall. They are responsible for producing such diverse amines and peptides as histamine (from the enterochromaffin-like cells), serotonin, dopamine, vasoactive intestinal peptide (VIP), glucagon, gastric-releasing peptide (GRP), motilin, and ghrelin. Interestingly, the A cells, which produce glucagon, are present only in fetal and neonatal glands. Considered along with the trophic effect of many GI hormones, this suggests a growth and differentiation role for these substances, along with the digestive and regulatory roles they are currently known to have.

All three components of the autonomic nervous system—sympathetic, parasympathetic, and enteric—innervate the stomach. The parasympathetic and enteric predominate. Sympathetic innervation is predominantly inhibitory to GI function and primarily uses the postganglionic neurotransmitter norepinephrine.[5] The parasympathetic pathways mediated by acetylcholine are generally stimulatory. The enteric nervous system (ENS), on the other hand, uses a variety of neurotransmitters, including dopamine, somatostatin, VIP, GRP, ghrelin, and cholecystokinin. The ENS is the largest and most complex compartment of the autonomic nervous system and comprises more than 10^9 resident neurons within the wall of the GI tract. The ENS is anatomically separate from the CNS (i.e., the sympathetic and parasympathetic systems).

Sympathetic innervation originates from cell bodies within the thoracic spinal cord and extends through presynaptic fibers in the greater splanchnic nerve to postsynaptic neurons in the celiac ganglion, whose axonal fibers follow blood vessels into the gastroduodenal wall. Parasympathetic presynaptic nerves originate in the brainstem and follow the vagus nerves to the stomach. ENS precursors differentiate from neuroblasts located in the vagal area of the neural crest and migrate with the vagus nerves to the developing GI tract. These ENS neurons then further differentiate, proliferate, and establish connections to each other, to other autonomic pathways, and to developing gastric secretory and muscle cells. There is significantly more ENS than CNS activity within the GI tract, suggesting a more powerful role for intrinsic (ENS) control than for extrinsic (CNS) control.

The stomach has two distinct functional zones based on motor activity differences. The proximal zone, which includes the fundus and the proximal third of the body of the stomach, serves as a reservoir in which an ingested meal is stored. Its ability to distend without increasing intraluminal pressure is important during bolus feeding. The proximal stomach generates slow, sustained tonic contractions under CNS control via the vagus. This action creates a constant pressure gradient that controls the passage of material through the stomach. Vagotomy significantly impairs this function, causing rapid emptying of fluids.[13]

Motor activity in the stomach distal to the proximal third of the body of the stomach is characterized by spontaneous depolarizations that result in phasic, directional contractions. This gives this portion of the stomach the ability to mix and grind solid food and to empty mixed food particles into the duodenum in a controlled fashion. During the fasting state, gastric activity follows a 90- to 120-minute repetitive pattern called the *interdigestive migrating motor complex*. This four-phase complex runs from mechanically silent to coordinated contractions that empty the gastric lumen of all indigestible materials. The fed state occurs when the migrating motor complex is interrupted by the arrival of ingested food. Now, the stomach begins forceful, nonpropagated contractions in the distal stomach coupled with coordinated contractions of the pyloric sphincter that churn food into small particles. A gastric pacemaker located along the greater curvature at the proximal boundary of the distal zone triggers these contractions at a rate of three to four cycles per minute. When the average particle size reaches 1 mm, chyme is allowed to empty into the duodenum. Complex CNS and ENS coordination permits adequate breakdown of the food and ensures that the rate of gastric emptying is adjusted to provide an isocaloric flow of nutrients into the duodenum over time.

Gastric secretory function evolves early in development. By 10 weeks' gestation, parietal and enteroendocrine cells have begun to differentiate, and by 12-13 weeks, gastrin, hydrochloric acid, pepsin, and intrinsic factor (IF) can all be detected. Mucus and bicarbonate secretion commences

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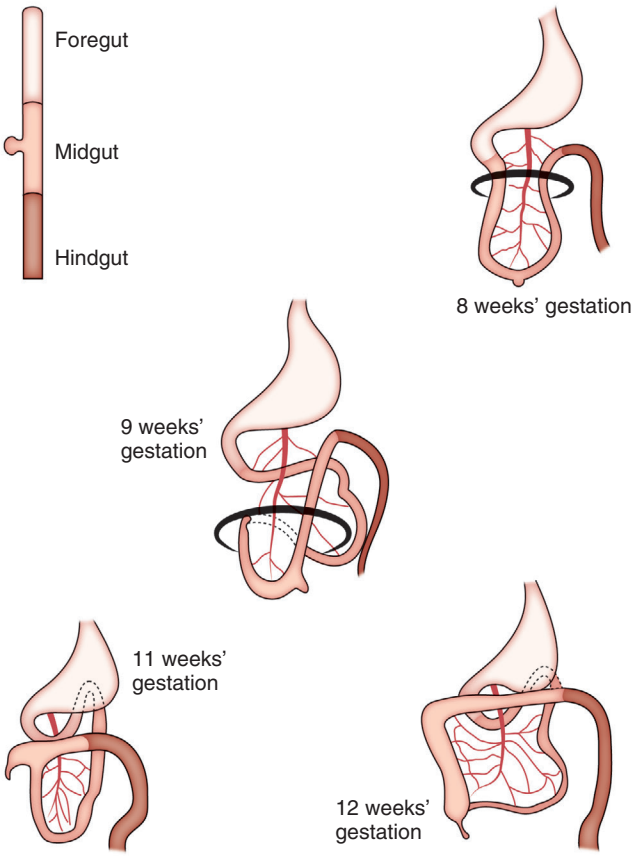
later, at about the 16th week. The gastric luminal pH of full-term newborns is neutral, but it is as low as 3.5 within a few hours. By 48 hours, the pH is between 1.0 and 3.0. Premature infants have a prolonged period of alkalinity—often many days—that is related to the degree of prematurity.

The production and secretion of hydrochloric acid by gastric parietal cells is governed by complex neurocrine, endocrine, and paracrine pathways, with little evidence for a final common pathway. The parietal cell can receive input and respond to a large variety of inputs, making its regulation by medical and surgical treatments difficult. Gastric acid has many functions. One is to facilitate protein digestion, but the lack of malabsorption problems in patients with achlorhydria indicates that this role may not be critical. Normal acid secretion does, however, play an integral role in initiating the digestive process. Gastric acid also creates a barrier to the entrance of bacteria into the GI tract. This not only protects the upper aerodigestive tract but also insulates the bacteria downstream from constant challenges from above. This is consistent with data that acid suppression therapy for gastroesophageal reflux may be associated with a higher incidence of lower respiratory tract infections.[9]

Duodenum, Pancreas, and Biliary System

The duodenum is the short retroperitoneal portion of the GI tract that connects the foregut to the midgut. At its proximal end, it connects to the outlet of the stomach, the pylorus, and it ends a short distance later at the ligament of Treitz, where the GI tract becomes an intraperitoneal organ once again and becomes the jejunum. Like the stomach, the duodenum undergoes a rotational process that brings it to its final C-loop configuration (Fig. 81.1). This 270-degree counterclockwise rotation swings the duodenum under the superior mesenteric artery. During this rotation, the duodenum's dorsal mesentery shortens, which allows the duodenum to become fixed in the retroperitoneal position across the upper abdomen from the pylorus (to the right of midline) to the ligament of Treitz (to the left of midline). This fixation is absolutely critical, because from the ligament of Treitz to the cecum (the next retroperitoneal portion of the GI tract located in the right lower quadrant), the bowel is on a mesentery and free to float about the peritoneal cavity. The bowel thus becomes fixed within the peritoneal cavity at the two most widely separated points available—the ligament of Treitz in the left upper quadrant and the cecum in the right lower quadrant. Because the mesenteric base is, therefore, so broad, it is impossible for the floating, intraperitoneal bowel to twist on its mesentery, thus compromising its own blood supply. However, any failure of proper rotation and fixation of the bowel can lead to the twisting of the bowel on its mesentery (i.e., volvulus) and the subsequent catastrophe of interruption of the flow of blood to the bowel.

The rotation of the bowel occurs during the 6th-10th weeks of gestation. Concurrently, there is a rapid epithelial



• **Fig. 81.1** Normal rotation of the developing gut. Eight weeks' gestation: elongation of the midgut and superior mesenteric artery, herniating into the umbilical stalk. Nine and eleven weeks' gestation: 270-degree counterclockwise rotation of duodenal-jejunal segment and 270-degree counterclockwise rotation of ileo-colic segment. Twelve weeks' gestation: final orientation of the normally rotated gut.

proliferation (along with the rectum and esophagus) that obliterates the hollow lumen and converts the duodenum to a solid, cordlike structure. Vacuoles then appear and gradual recanalization occurs. The distal duodenum does not appear to pass through a solid phase. Defects in this proliferation and recanalization process are believed to lead to the problems of duodenal atresia, web, and stenosis.

The duodenum is divided into four portions corresponding to the curvatures of the C loop. The blood supply is derived from the celiac axis through the superior pancreaticoduodenal branches of the gastroduodenal artery and the superior mesenteric artery through the inferior pancreaticoduodenal branches. Consistent with the location of the original liver bud, this transition from celiac to superior mesenteric blood supply defines the transition from foregut to midgut. A consistent landmark in the medial portion of the duodenum, near the end of the foregut, is the ampulla of Vater, which represents the confluence of common bile duct and pancreatic ducts and their entry into the duodenum.

The liver and biliary system develops within a bud along the free edge of the ventral mesentery, with stomach

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and bowel rotation bringing them to their final location in the right upper quadrant.[2] Also within this bud is the primordial ventral pancreas. Opposite this ventral pancreatic bud (including liver and biliary primordium) is the dorsal pancreatic bud. During rotation, the ventral pancreatic bud fuses to the dorsal bud and becomes one organ. Failure of this rotation leads to the problem of annular pancreas. The biliary and pancreatic drainage systems also fuse during rotation so that the common bile duct descends in the remnant-free edge of ventral mesentery, along with the portal vein and hepatic artery, then passes behind the duodenum to join with the main pancreatic duct at the ampulla of Vater. This main pancreatic duct is formed from the confluence of the original ventral pancreatic duct with the distal dorsal pancreatic duct. The proximal dorsal pancreatic duct remains as the accessory pancreatic duct. The biliary and pancreatic ductal systems are complete by the 10th-12th gestational week. With so many rotation and fusion requirements to produce the "classic" biliary-pancreatic ductal anatomy, it is no wonder that one sees the "classic" form less than 50% of the time. Blood supply to the gallbladder arises from the celiac artery.[8] The layers of the duodenum are the muscularis, the submucosa, and the mucosa. The muscularis is made up of smooth muscle cells, which are divided distinctly into two separate layers: an outer, longitudinal layer and an inner, circular layer. The submucosa is a band of dense connective tissue lying just under the mucosa. The mucosa is the innermost layer and is composed of three distinct layers: the muscularis mucosa, the lamina propria, and the epithelial cell lining. The most striking feature is the villi, 1.5 mm tall in the duodenum and decreasing in size through to the ileum. Crypts of Lieberkühn surround the base of each villus and average one-third to one-fourth the height of the villi.

Like the rest of the small bowel, the duodenal mucosa is made up mainly of enterocytes, tall, columnar epithelial cells that are responsible for absorption. The duodenum is also richly populated with enteroendocrine cells, along with goblet cells, Paneth cells, and lymphoid aggregates of Peyer patches. The enteroendocrine cells are stimulated by nutritional substrates delivered from the stomach, and they secrete mediators that regulate a variety of digestive processes. Secretin is produced by the duodenal S cells in response to luminal acid, stimulating bicarbonate secretion from the pancreas, liver, and duodenal Brunner glands and mucosal cells. Cholecystokinin, produced by duodenal I cells in response to certain fatty acids and amino acids, stimulates gallbladder contraction and pancreatic exocrine secretion.

The pancreas is a central metabolic organ with key roles in both exocrine and endocrine function.[6] It is the primary source of digestive enzymes: More than 20 different enzymes are synthesized and stored in the secretory acini. The proteolytic enzymes such as trypsin, chymotrypsin, and carboxypeptidase are secreted as inactive proenzymes. They are converted to active enzymes by enterokinase, an intestinal brush border enzyme, when they reach the duodenal lumen. These enzymes, in turn, can activate other proenzymes. Pancreatic amylase and lipase are secreted in their active form. The secretory acinar cells are under complex CNS, ENS, and hormonal regulation. The ducts that drain the acini are lined by cells that secrete water and bicarbonate. Secretin stimulates this fluid and bicarbonate secretion, which raises intestinal pH and thereby facilitates pancreatic enzyme activity.

The pancreas also has an essential role in the hormonal regulation of metabolism and glucose homeostasis. These endocrine functions are provided by the islets of Langerhans, which make up about 1%-2% of the pancreatic mass. These 1-2 million islets are more plentiful on the pancreatic tail and are also under complex CNS, ENS, and hormonal control. There are four distinct cell types within the islets: alpha cells for glucagon production, beta cells for insulin, gamma cells for somatostatin, and PP cells for pancreatic polypeptide.

Small Intestine

The small intestine is the major digestive and absorptive portion of the GI tract. The gut initially herniates out of the fetus's abdominal domain and lengthens rapidly during the 6th-12th weeks of gestation.[1] As described earlier, on reentry into the abdominal cavity, the small bowel undergoes a 270-degree twist around the superior mesenteric artery axis to bring it into its final anatomic position. This positioning is complete by the 20th week. The "small" of small intestine clearly relates only to the circumference of the structure, as its length is anything but small. The small intestine typically measures between 200 and 300 cm at birth in the full-term neonate after doubling its length between 26 and 38 weeks of gestation. After birth, the small intestine continues to grow, finally reaching its maximum length of 600-800 cm after 4 years of age.[12] During this time, and continuing through puberty, there are also increases in intestinal diameter, along with development of the plicae circulares, villi, and microvilli that enlarge the absorptive surface area of the small intestine from about 950 cm^3 at birth to 7500 cm^3 in the adult. The blood supply of the small intestine is provided solely by branches of the superior mesenteric artery running in the mesentery of the small intestine.

The circular muscles of the small intestine appear at 6 weeks of gestation and the longitudinal muscles at 8 weeks. Neuroblasts appear at 7 weeks of gestation, and the myenteric and submucosal plexuses are noted to appear between the 9th and 13th weeks. Although there is some peristalsis noted as soon as the plexuses appear, it is poorly coordinated. The appearance of myenteric muscle contractions at 32-34 weeks leads to more coordinated contractions, but intestinal transit time at this gestation time is as long as 9 hours—nearly twice as long as in the term infant. It is not until about 38 weeks' gestation that the myenteric muscle contractions are fully present and fasting motor activity is mature. Even so, limited feedings can be accomplished in

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infants as young as 25 weeks, because they appear to stimulate contractions, albeit immature.

Villi appear during weeks 8-11 and acquire their final, fingerlike shape by week 14. However, the villi remain shorter in the ileum than in the jejunum, leading to a fourfold greater absorptive area in the jejunum. Microvilli appear and the enterocytes are morphologically mature and display a well-organized brush border by 14 weeks of gestation. Endocrine cells appear at 9 weeks and continue to proliferate, with all the various gut peptide hormones and neurotransmitters present by 20 weeks' gestation. These include enteroglucagon, neurotensin, gastrin, pancreatic polypeptide, motilin, and VIP. Although all are present at birth, many of them show remarkable increases in basal levels during the first 2 weeks of life in the fed infant. Interestingly, when feedings are withheld in infants, intestinal growth and functional maturation are delayed and basal levels of the intestinal peptides remain low, suggesting some form of cause-and-effect relationship.

It is generally held that the enteric ganglion cells are derived from vagal neural crest cells. As mentioned, neural crest–derived neuroblasts first appear in the developing esophagus at 5 weeks. They then begin a migration down to the anal canal in a craniocaudal direction during the 5th-12th weeks of gestation. The neural crest cells first form the myenteric plexuses just outside the circular muscle layer. The mesenchymally derived longitudinal muscle layer then forms, sandwiching the myenteric plexus after it has been formed in the 12th week of gestation. Finally, the submucous plexus is formed by neuroblasts, which migrate from the myenteric plexus across the circular muscle layer and into the submucosa and the mucosa. This also progresses in a craniocaudal direction, but it occurs during the 12th-16th weeks of gestation.

Colon, Rectum, and Anus

The colon is a continuation of the intestine with two basic functions: (1) the absorption of water and electrolytes and (2) the storage and elimination of feces. Its absorptive function is significant in that the colon absorbs more than 80% of the water left after passage through the small intestine. The rectum and anus are critical in the complex act of controlled defecation.

The colon is divided into six areas: the cecum, the appendix, and the ascending, transverse, descending, and sigmoid colon. Like the duodenum, the colon also undergoes a 270-degree counterclockwise rotation during the 10th-12th weeks of gestation to bring it into the proper position.[3] Although this is nearly concurrent with the duodenal rotation, the two are not completely codependent. Either one, or both, can go astray, so it is possible to have a nonrotated colon with a properly rotated duodenum and vice versa. If properly rotated, the cecum lies in the right lower quadrant, the ascending colon along the right gutter, the transverse colon from the hepatic flexure to the splenic flexure, and the descending colon along the left gutter; the sigmoid colon connects the descending colon to the rectum approximately at the level of the third sacral vertebrae. The ascending colon and the descending colon are retroperitoneal structures with peritoneum covering only their anterior and lateral surfaces. The cecum is variably fixed—sometimes completely retroperitoneal (along with the appendix) and sometimes on a short mesentery. The transverse and sigmoid colon are on a mesentery. The posterior border of the greater omentum is also attached to the transverse colon.

The blood supply of the colon is supplied by both the superior and inferior mesenteric arteries. The watershed area between the distribution of the two vessels is typically located around the mid transverse colon to the splenic flexure. This also marks the boundary of the midgut and hindgut. The rectum is supplied by the inferior mesenteric artery as well as branches off the iliac arteries.

Although it is developmentally similar to the small intestine in general structure, the colon has unique elements. Most obvious is the concentration of the longitudinal muscle coat into three bands—the teniae coli. The teniae create sacculations, called *haustra*, that permit radiographic differentiation of the small from the large intestine after infancy. The mucosa of the colon is characterized by crypts of Lieberkühn, which are lined with absorptive, goblet, and endocrine cells.

The development of the anorectum requires unique attention, because problems result in a wide variety of anorectal malformations. As mentioned previously, during the 3rd week of gestation, the bilaminar germ disc transforms into a trilaminar disc of ectoderm, mesoderm, and endoderm. At either end of the embryo, the endoderm and ectoderm fuse, excluding the mesoderm from these areas and giving rise to the oropharyngeal and cloacal membranes. The former breaks down in the 4th week to give rise to the mouth, whereas the cloacal membrane does not open until the 8th week. Between weeks 4 and 6, it is widely held that the primitive gut tube at the level of the cloacal membrane gets canalized and partitioned into an anterior urogenital sinus and a posterior anorectum by the cranial-caudal growth of a mesodermally derived partition called the urorectal septum. Eventually, the urorectal septum fuses with the cloacal membrane, and the fusion site is called the *perineal body*. The newly formed anorectal canal remains closed by the posterior aspect of the cloacal membrane, which is now called the *anal membrane*. The ectoderm in this region then goes on to form the anal pit or proctodeum, so the distal third of the anal canal is eventually made up of ectoderm, the proximal two-thirds is made up of mesoderm, and the two cell types are divided by the anal membrane. The membrane breaks down during week 8, and the two cell populations fuse at what is called the *pectinate* or *dentate line*.

Aside from the previously described migration of neural crest cells to form enteric ganglion cells, the anorectum has an important neurologic milestone during the 4th week of gestation. At this time, spinal nerves from sacral levels 2, 3, and 4, which contribute to the peripheral parasympathetic

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nervous system, form. In contrast to the motility problems noted with failure of migration and thus the absence of ganglion cells, problems related to the proper development of these spinal nerves during week 4 may lead to the proprioceptive and motility problems associated with anorectal malformations.

Key Points

- Gastrointestinal development requires maturation of various digestive, absorptive, and endocrine functions.
- Sympathetic, parasympathetic, and intrinsic enteric neurons all contribute to the maturation of gastrointestinal motility.
- The fore- and midgut undergo unique rotations during 6th-10th weeks of gestation, which ensure fixation in the peritoneal cavity and prevent twisting and remittent bowel obstruction.
- The colon acquires key absorptive and motility functions. Aberrant anorectal maturation may lead to a variety of anorectal malformations.

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Gastrointestinal Reflux and Motility in the Neonate

ANNA MARIA HIBBS

Definitions

Gastroesophageal reflux (GER) is the physiologic retrograde passage of fluid from the stomach to the esophagus. Gastroesophageal reflux events occur in healthy infants multiple times per day. Gastroesophageal reflux disease (GERD) is the pathologic condition wherein such retrograde flow into the esophagus causes medical complications.[106] Regurgitation and vomiting are common and often nonpathologic complications of GER.[51] A definitive determination of GERD in infants is often elusive. Esophageal complications of GERD are often indirectly suggested because of difficulty in directly visualizing the esophagus in very small patients; for instance, infants who have arching, discomfort, or fussiness may be suspected of having esophagitis. Putative extraesophageal GERD-defining complications in infants, such as apnea or worsening of respiratory disease, are controversial, in large part, owing to lack of strong evidence in the literature.[33] In most cases, no single test can diagnose or exclude GERD, and a comprehensive approach including testing and clinical assessments over time is needed to make the diagnosis.

Physiology of Gastroesophageal Reflux

Upper Gastrointestinal Motility and Physiologic Gastroesophageal Reflux

By as early as 26 weeks' gestational age, esophageal motor function is well developed in infants.[67,68] In both term and preterm infants, swallowing triggers coordinated esophageal peristalsis and lower esophageal sphincter (LES) relaxation.[68] However, the velocity of propagation is significantly slower in preterm compared with term infants.[45] Esophageal activity unrelated to swallowing often takes the form of incomplete or asynchronous waves; this type of nonperistaltic motor activity occurs more frequently in preterm infants than in adults.[68] Infants with functional or anatomic esophageal abnormalities, such as those with repaired esophageal atresia or neuropathy affecting smooth muscle, are at risk for impaired esophageal clearance of fluid.

Gastroesophageal reflux events are part of the normal functioning of the upper gastrointestinal tract. The lower esophageal sphincter, which limits the retrograde passage of air and fluids from the stomach to the esophagus, is made up of intrinsic esophageal smooth muscle and diaphragmatic skeletal muscle.[59] Several manometry studies have documented good LES tone, even in extremely low birth weight infants.[68-70] In both preterm and term infants, just as in more mature patients, transient lower esophageal sphincter relaxations (TLESRs) unrelated to swallowing are the major mechanism allowing GER by dropping lower esophageal pressure below gastric pressure, thereby promoting the retrograde passage of fluid.[20,68,70] Transient lower esophageal sphincter relaxations are frequent in preterm infants, occurring several times per hour, although the majority of TLESR events are not associated with GER.[20] A similar frequency of TLESRs is seen in infants with and without GERD, but a higher percentage of acid GER events during TLESRs occurs in infants with GERD.[20] It has been hypothesized that increased intraabdominal pressure during a TLESR, for instance due to straining, may increase the likelihood of a GER event. Although LES relaxations also occur during normal swallowing, these are less often associated with GER events than isolated TLESR events,[20] presumably owing to the coordinated waves of esophageal muscular activity propelling fluid antegrade during a swallow. The number of GER events and the height the fluid bolus reaches in the esophagus are increased after feeding; refluxate after feeding is less acidic than fluid refluxed before feeding.[93] Other factors also promote GER in infants, particularly patients in a neonatal intensive care unit (NICU). For instance, infants ingest a much higher volume per kilogram of body weight, approximately 180 mL/kg per day, than older children and adults.[80] In the NICU population, preterm and term patients with nasogastric or orogastric feeding tubes may experience more reflux episodes because of mechanical impairment of the competence of the LES.[56,79] Infants with anatomic abnormalities of the structures that comprise the LES, such as infants with congenital diaphragmatic hernia, are at risk for experiencing a higher-than-normal frequency of GER events.

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Abstract

Gastroesophageal reflux is a frequently occurring normal physiologic process, primarily associated with relaxations of the lower esophageal sphincter. Gastroesophageal reflux disease is defined as GER that triggers complications or morbidities. Nonpharmacologic therapy, including thickened feeds, is the mainstay of therapy. Because of their underlying developmental trajectories, many infants experience an improvement in symptoms over several weeks. Pharmacologic therapy has not been shown to be safe or effective.

Keywords

gastroesophageal reflux (GER)
gastroesophageal reflux disease (GERD)
transient lower esophageal sphincter relaxation (TLESR)
fundoplication
thickened feeds
histamine-2 receptor blocker
proton pump inhibitor

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Gastric emptying also plays a strategic role in upper gastrointestinal tract function. Between 25 and 30 weeks' gestational age, gastric emptying time seems to be inversely and linearly correlated with gestational age at birth. Simultaneously decreasing the osmolality and increasing the volume of feeds may accelerate gastric emptying, although changes in osmolality or volume alone did not seem to have a significant effect.[81] Human milk also promotes gastric emptying, but fortification may increase emptying time.[14,26] Unfortunately, although breastfeeding is protective against GERD, mothers whose infants were diagnosed with reflux are more likely to wean.[14] In formula-fed infants, several small studies suggest that prebiotics and probiotics may speed gastric emptying time.[41,42] The literature on the impact of hydrolyzed formulas is mixed.[17,57,96] However, although it seems logical that slower gastric emptying would promote GER because of increased fluid and possibly pressure in the stomach, a study of the relationship between gastric emptying and GER in preterm infants found no association.[25]

Gastroesophageal reflux events are frequent in healthy preterm and term infants. Among 509 healthy asymptomatic infants age 3-365 days, the mean number of acid reflux episodes in 24 hours was 31.28, with a standard deviation of 20.68.[105] The reflux index, the percent of time the esophageal pH was less than 4, ranged from less than 1%-23%, with the median and 95th percentile being 4% and 10%, respectively. Among the neonates in this study, the 95th percentile for the reflux index was as high as 13%. In a smaller study of 21 asymptomatic preterm infants, continuous combined esophageal pH and impedance monitoring detected refluxed fluid in the esophagus by impedance for a median of 0.73% (range, 0.3%-1.22%) of the recording time, and acid exposure detected by pH monitoring for a median of 5.59% (range, 0.04%-20.69%) of the recording time. These studies make it clear that GER events occur frequently in asymptomatic infants, and a wide range of reflux measurements may be seen in healthy preterm infants without GERD.

In a study of infants in general pediatric practice, half of all parents reported at least daily regurgitation at 0-3 months of age.[61] The peak prevalence occurred at 4 months, with 67% reporting regurgitation. Thus benign regurgitation was the norm in the first few months of life. Parents reported regurgitation to be a problem when it was associated with increased crying or fussiness, perceived pain, or back arching. The prevalence of regurgitation perceived as a problem peaked at 23% at 6 months and was down to 14% by 7 months. The majority of these children did not receive treatment for GERD from their pediatrician. Infants who did and did not experience frequent regurgitation between 6 and 12 months of age were followed up a year later.[62] At this time, none of the parents described regurgitation as a current problem. Infants with frequent spitting at 6-12 months of age did not experience more infections of the ear, sinuses, or upper respiratory tract, nor did they experience more wheezing.

It is also important to remember that regurgitation and vomiting are not necessarily caused by GER or GERD. Clinical correlation is needed to determine whether other pathologic processes are present. The differential diagnosis includes gastrointestinal obstruction, motility abnormalities, infection, inborn errors of metabolism, adrenal insufficiency and other hormonal abnormalities, and neurologic abnormalities, including increased intracerebral pressure. Commonly, milk protein allergy may mimic GERD.[51]

The distinction between GER and GERD is important when communicating with families. One study showed that in infants with a label of GERD, families were more likely than those with a GER label to be interested in medications, even when they were told that those medications were likely ineffective.[84]

Gastroesophageal Reflux Disease

Symptoms and Complications

Identifying whether troublesome symptoms are in fact caused by reflux can be challenging in infants.[83,87] Symptoms frequently attributed to GERD in infants include regurgitation, Sandifer posturing, worsening of lung disease, food refusal or intolerance, apnea, bradycardia, crying or fussiness, and stridor. Regurgitation may be a symptom of GERD in infants but in itself is neither necessary nor sufficient to make a diagnosis.[87] Clustering regurgitation with other symptoms may increase the accuracy of diagnosis, as demonstrated by the I-GERQ-R infant reflux questionnaire.[49,87] However, the validity of such questionnaires has not been established in the NICU population, which includes preterm infants and sick term neonates who have multiple other potential reasons for the symptoms frequently attributed to GERD.

Although GERD and bronchopulmonary dysplasia (BPD) seem to be associated, causality has not been determined.[1,27,31,47,87] Patients with increased work of breathing may generate more negative intrathoracic pressures, thereby promoting the passage of gastric contents into the esophagus. Conversely, aspirated refluxate could injure the lungs, thereby promoting chronic lung disease. Finally, immaturity and severity of illness predispose to both conditions, and there may be no causal link in the majority of patients. In addition, part of the apparent association between BPD and GERD may be the result of an increased index of suspicion for GERD in patients with BPD, leading to increased rates of diagnosis.[31]

A similar issue exists for apnea in premature infants. Although in animal models, esophageal stimulation may trigger airway protective reflexes,[95] there is insufficient evidence in human infant patients to confirm that reflux causes apnea.[29,87] In fact, apnea may itself trigger reflux.[48,66] Finally, immature infants are simply prone to both apnea and reflux, and there may be no causal association.[94] In a cohort of infants referred for overnight esophageal and respiratory monitoring for suspicion of GERD-induced

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apnea, desaturation, or bradycardia, fewer than 3% of all cardiorespiratory events were preceded by a reflux event.[21] Conversely, 9.1% of reflux events were preceded by a cardiorespiratory event. Thus it was more common for a cardiorespiratory event to precede reflux than for reflux to precede a cardiorespiratory event. Even in this population referred for suspicion of GER-triggering cardiorespiratory events, only a small minority of cardiorespiratory events were in fact preceded by reflux. However, data from small or moderately sized research cohorts cannot rule out the possibility that reflux can trigger the majority of cardiorespiratory events in a small subset of patients. Because bedside recording of apnea events is known to be inaccurate, correlation of apnea with feeding or reflux events in a specific patient requires simultaneous respiratory and esophageal monitoring.

It is unclear what component of the refluxate triggers complications. Acidity is often implicated, but it is not clear which, if any, complications are triggered by acidity.[87,94] The other characteristics of the refluxate that have been postulated to be associated with symptoms include the height of the bolus in the esophagus, the volume of the bolus, or the pressure exerted on the esophagus. One study found an association with acid GER into the middle or proximal esophagus and cough in dysphagic preterm neonates.[91]

Diagnostic Tools

Numerous tests exist to measure acid and nonacid GER in infants. Because the definition of GERD is based on clinical complications and not physiologic measurements, most available tests for GERD cannot definitively confirm or exclude the diagnosis. Numerous GER events are not sufficiently diagnostic of GERD without evidence of clinical complications. Because the diagnosis of GERD relies on the presence of clinical complications, no physiologic test that only characterizes the frequency or characteristics of GER events in a patient can by itself confirm the diagnosis of GERD. Esophageal monitoring for 12-24 hours gathers the best data on the timing and frequency of GER events. Esophageal pH probes measure acid reflux, and esophageal multichannel intraluminal impedance (MII) measures the presence of fluid in the esophagus regardless of pH. Multichannel intraluminal impedance and pH sensors can be combined in one probe. Esophageal monitoring may be correlated with respiratory monitoring or with the timing of a clinical symptom in order to attempt to temporally correlate symptoms and GER events. However, showing that a GER event preceded a clinical event is not proof of causality.

An upper gastrointestinal radiographic series is a poor measure of the frequency or severity of GER, because it captures only a brief window in time. Capturing a GER event on an upper gastrointestinal series is not informative with regard to either the frequency of GER or the diagnosis of GERD. However, this study may be useful in ruling out anatomic abnormalities that may mimic GERD.

A nuclear medicine scintigraphy study can identify postprandial reflux and aspiration and quantify gastric emptying time. Because of a lack of age-specific norms and the limited focus on postprandial GER, it is not recommended as a routine test for infants suspected of having GERD.[51,106] However, in an infant suspected of chronically microaspirating refluxed fluid, it can document this complication and confirm the diagnosis of GERD. In addition, scintigraphy allows for the calculation of gastric emptying time, which may be useful in infants in whom delayed gastric emptying is part of the differential diagnosis.

Endoscopy with visualization and biopsy of the esophagus can document esophagitis caused by acid or conditions mimicking GERD, such as eosinophilic esophagitis. Unfortunately, many preterm and young term infants are too small for endoscopy to directly assess esophagitis, and so esophageal symptoms can only be inferred from vague symptoms such as food refusal or fussiness.

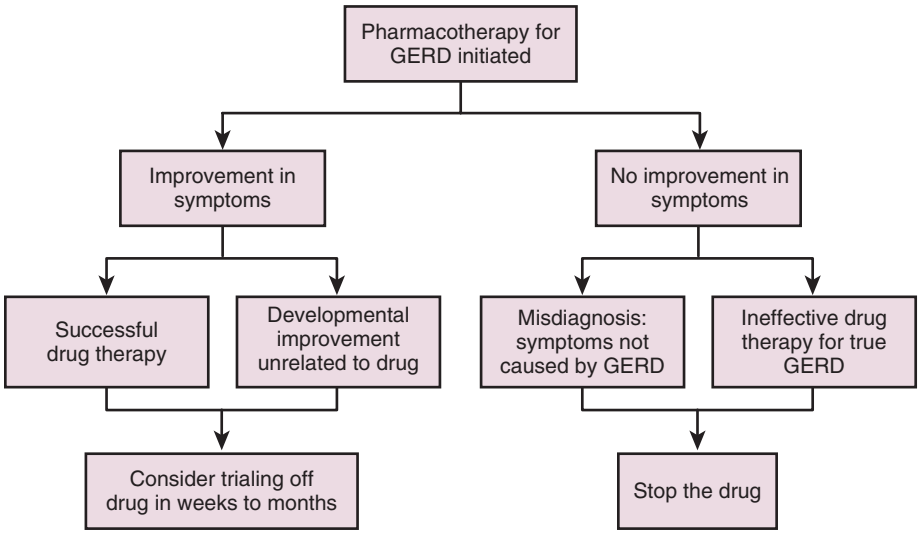
Treatment

The general categories of interventions available to treat GERD are conservative nonpharmacologic, pharmacologic, and surgical. The natural history of GERD, often with improvement within a few weeks,[73,74,108] must be remembered when interpreting the impact of an intervention. Treatment failures may result from either a failure of the medication to achieve its intended action or from the erroneous application of drugs to symptoms not caused by GERD. Apparent successes may result from either a true drug effect or from the natural resolution of symptoms with maturation (Fig. 82.1). Because the goal of therapy is to treat GERD, not physiologic GER, the gold standard for gauging therapeutic success must be improvement in symptoms or complications, not simply improvement in physiologic measures. The most effective treatment for GERD is time and maturation, and so expectant conservative management is the mainstay of therapy in most cases. With regard to pharmacologic therapy, the American Academy of Pediatrics Section on Perinatal Pediatrics Choosing Wisely campaign advised, "Avoid routine use of anti-reflux medications for treatment of symptomatic gastroesophageal reflux disease (GERD) or for treatment of apnea and desaturation in preterm infants."[37]

Conservative Nonpharmacologic Management

Commonly used conservative interventions for GERD include positioning, thickening feeds, and decreasing the volume while increasing the frequency of feeds. When milk protein allergy is thought to be mimicking or triggering GERD, changing to a more elemental formula may also be appropriate. In the run-in period for a randomized control trial of a pharmacotherapeutic intervention for GERD, the majority of infants seemed to improve over a 2-week period with such a multipronged conservative management strategy, although this effect simply could also be attributed to time and maturation.[74]

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• **Fig. 82.1** Approach after pharmacotherapy has been initiated. Gastroesophageal reflux disease (GERD) medications should be discontinued in infants who fail to improve on therapy. Due to rapid maturational changes, even apparently effective medication therapy may only be needed for a limited duration.

Although typical positioning precautions for an infant with a diagnosis of GERD include elevating the head of the bed, there is not an advantage to supine upright versus supine flat positioning.[13] Prone positioning seems to be associated with fewer GER events than supine but is generally contraindicated because of the increased risk of sudden infant death.[3,13] Lateral positioning with the right side down results in more frequent reflux events than left lateral positioning, but it is not clear whether this results in more symptoms.[71]

Thickening feeds has been shown to decrease episodes of clinical vomiting, although it does not seem to decrease physiologic measures of GER.[13,24,38] Feeds may be thickened by adding a thickening agent or using a prethickened commercially available formula. Common thickeners include rice, carob, cornstarch, and locust-bean gum. Rice and some prethickened rice-based formulas require gastric acidity to fully increase their viscosity, so their action may be impaired by drugs that block gastric acidity.[107] An insufficient number of large trials have been conducted to assess the safety of thickening agents in infants, and concerns have been raised about the potential for various thickening agents to cause diarrhea, increased cough, poor growth, and nutrient malabsorption.[38] The efficacy and safety of thickened feeds have not been well studied in preterm infants. A US Food and Drug Administration (FDA) warning cautioned against the use of one brand of commercial thickener in preterm infants because of reports of late-onset NEC.[103] In addition, concerns about the arsenic content in infant rice cereals have raised concerns about their use as thickeners.[11,46]

Drugs That Increase Gastric pH

Histamine-2 (H_2) receptor antagonists and proton pump inhibitors (PPIs) decrease gastric acidity. These drugs were developed to treat esophagitis and prevent Barrett's esophagus in adults. Increasing the pH of refluxate is thought to decrease esophageal mucosal damage and its associated discomfort. Proposed complications of reflux in NICU patients, such as food refusal, arching or fussiness, and pharyngeal or vocal cord edema, could theoretically stem from the effect of acid on the esophagus or airway. Because of either a limited capacity to produce acid or frequent buffering of gastric contents by milk feeds, many infants may experience less acidic GER(D) than older patients. Acid GER predominates preprandially, and nonacid GER predominates postprandially.[15,93] In fact, the majority of GER events in infants are nonacid.[15,93] However, at least some preterm infants are able to experience significant acid GER, as measured by an esophageal pH of less than four for more than 10% of the time.[22] However, it remains unclear if acidity is the mechanism by which reflux causes complications in infants.[87,94]

Pharmacologically increasing gastric pH raises some potential safety concerns. Gastric acidity seems to play a role in defense against infection. The use of H_2 receptor antagonists in preterm infants has been associated with an increased risk of necrotizing enterocolitis,[34] although it is not clear if this is a causal relationship. However, one small study did show that gastric acidification decreases necrotizing enterocolitis.[12] Infants treated with ranitidine have been demonstrated to have higher rates of gastric colonization with bacteria or yeast, although an increase in infection was not seen in this study.[18] Ranitidine was associated with increased late-onset sepsis in NICU patients in a cohort study; however, confounding by indication or severity of illness cannot completely be excluded as the cause of this association.[8] In older patients, an association between acid suppression and lower respiratory tract infections, including ventilator-associated pneumonia, has been proposed but remains controversial.[4,6,10,16,50,58,86,98,112]

Histamine-2 Receptor Antagonists

Examples of H_2 receptor antagonists include ranitidine, cimetidine, and famotidine. They block the H_2 receptor in acid-producing gastric parietal cells. Parietal cells continuously produce a baseline amount of HCl, even when they are not stimulated by histamine. Histamine-2 receptor antagonists suppress HCl production below physiologic

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basal secretion rates and also decrease meal-triggered acid production. In addition, this class of drugs impairs the ability of other substances that stimulate acid production, such as acetylcholine and gastrin to trigger acid production.

There are few randomized clinical trials of H_2 receptor antagonists assessing their impact on the symptoms of GERD in term or preterm infants. In one small double-blind study, infants age 1.3-10.5 months were randomized to a higher or lower dose of famotidine and then a placebo-controlled withdrawal.[75] Infants receiving both doses experienced less emesis than those receiving placebo. Infants on the higher dose also demonstrated decreased crying time and volume of emesis. However, famotidine was also noted to be associated with agitation and a head-rubbing behavior that was attributed to headache.

In another randomized trial of H_2 receptor antagonists, very low birth weight (VLBW) infants were randomized to cimetidine or placebo, with the hypothesis that cimetidine could decrease CYP-mediated oxidative injury in the lung.[19] The goal of this study was not treatment of GERD, but it is one of the few studies in which VLBW infants were randomized to an H_2 receptor antagonist early in life. The trial was stopped by the data safety monitoring committee for increased death and intraventricular hemorrhage in the treatment group. The mechanism of these apparent adverse effects is unknown.

Finally, in a small crossover trial of combined ranitidine and metoclopramide therapy in preterm infants with bradycardia attributed to GERD, infants on therapy experienced significantly more bradycardic events than those receiving placebo.[108] This is biologically plausible, because histamine receptors are present in the heart, and ranitidine has been associated with bradyarrhythmias.[2,36,40,60,72,99,110] Of course, the lack of effect found in this study could also have been the result of misidentification of bradycardia as a symptom of GERD, an association that is not well supported by the literature. Even if reflux causes cardiorespiratory events in some infants periodically, the majority of cardiorespiratory events in preterm infants are not temporally related to GER, so bradycardia is likely to have poor specificity for the identification of GERD, and treatment of GERD is unlikely to impact the majority of cardiorespiratory events.[21]

Proton Pump Inhibitors

Proton pump inhibitors irreversibly block the gastric hydrogen/potassium adenosine triphosphatase that secretes hydrogen ions into the gastric lumen. Examples of PPIs include omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazole, and rabeprazole. PPIs continue to be frequently prescribed for infants, despite a poor safety and efficacy profile.[5,9,92]

Proton pump inhibitors have not been shown to be effective in infants.[104] For instance, in a trial of outpatient infants who had failed a run-in period of nonpharmacologic management to lansoprazole or placebo, there was no difference in efficacy between the groups, with slightly more than half of the infants in each group experiencing improvement in symptoms.[73] However, there was a significant increase in serious adverse events in the lansoprazole group; among these adverse events, a nonsignificant increase in lower respiratory tract infections was seen.

The FDA released a class labeling change for PPIs based on findings that adults on high doses or prolonged courses of PPIs may experience more fractures.[101,102] The impact of acid suppression by PPIs or H_2 receptor antagonists on bone health in healthy neonates or preterm infants with osteopenia of prematurity is unknown. Acid suppression has also been associated with *Clostridium difficile* infection in some adults, with PPIs seeming to have a higher risk than H_2 receptor antagonists.[39,52] The relationship between PPI use and pathogenic or colonizing *Clostridium difficile* in infants has not been reported.

Drugs to Improve Motility

Drugs to promote gastrointestinal motility are thought to decrease GER by increasing gastric emptying or by improving esophageal motility and lower esophageal sphincter tone. The primary motility agents currently available in the United States are metoclopramide and erythromycin. Cisapride was removed from the market owing to the risk of serious cardiac arrhythmias and QT prolongation.[109] Domperidone is used in some countries but is not approved in the United States owing to concerns about arrhythmia, and studies have shown that oral domperidone can increase the QT interval in neonates.[23]

Metoclopramide

Metoclopramide is an antagonist of the dopamine D2 receptor subtype. A systematic review of metoclopramide therapy for GERD in infants found insufficient evidence for either efficacy or safety in this population.[35] Published after this, the previously described placebo-controlled crossover study of combined therapy with ranitidine and metoclopramide found an increase in bradycardia in the treatment group, although this finding is not necessarily attributable to metoclopramide.[108]

Metoclopramide acts on central dopamine receptors. Its ability to cross the blood–brain barrier also allows for neurologic side effects. Reported complications of metoclopramide in infants include irritability, drowsiness, oculogyric crisis, dystonic reaction, apnea, and emesis.[35] In 2009, the FDA issued a black-box warning about the risk of tardive dyskinesia with prolonged or high-dose metoclopramide exposure.[100] Tardive dyskinesia may persist after the drug is stopped and has no known treatment. Whether neonates or preterm infants are at greater or lesser risk of tardive dyskinesia than older patients has not been established. Metoclopramide has also been reported to cause lactation and gynecomastia in neonates.[54,78]

Erythromycin

Erythromycin is a high-affinity analog of the hormone motilin, which is normally produced by duodenal and jejunal enterochromaffin cells.[28,43,44] Stimulation of the

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motilin receptor promotes gastrointestinal migrating motor complexes. Infants with a gestational age greater than 32 weeks may be better able to respond to stimulation of the motilin receptor.[63,77] Prokinetic doses are typically lower than antimicrobial doses.

The majority of studies of erythromycin as a prokinetic in preterm infants have focused on improving feeding intolerance and not specifically on treating GERD.[63,77] In a masked randomized trial of erythromycin to promote feeding intolerance in 24 preterm infants, measuring GER as a secondary end point, erythromycin did not decrease the time to attain full enteral feeds, and there were no changes in GER as measured by esophageal pH probe.[65] Gastroesophageal reflux disease symptoms were not addressed in this study. In a review of 10 studies using erythromycin as a prokinetic to promote feeding tolerance, erythromycin seemed to promote the establishment of enteral feeding and was not associated with any adverse events, including pyloric stenosis or arrhythmia. However, rare or long-term adverse events had not been fully studied.[64]

Like cimetidine, erythromycin is an inhibitor of CYP3A.[82] It has been implicated in arrhythmias and QT prolongation when co-administered with cisapride, but also has a direct proarrhythmic effect by itself. Erythromycin blocks the rapidly activating component of the cardiac delayed rectifier potassium current, thereby prolonging repolarization in a manner similar to some antiarrhythmic drugs.[90] This action may prolong the QT interval and predispose the patient to torsades de pointes. Although cardiac adverse events have not been reported in the trials of erythromycin for feeding intolerance in preterm infants,[63] caution should be used in infants at risk for arrhythmia or in infants on other CYP3A inhibitors, such as cimetidine, methadone, and some protease inhibitors.[90]

Fundoplication

Several open and laparoscopic gastric fundoplication techniques may also be considered for infants with severe or life-threatening GERD when other attempts at management have failed and symptoms have not improved over time.[51,106] Fundoplication acts by artificially augmenting LES pressure. Very high rates of complications and recurrence of GERD symptoms have been reported.[32,53,55,76,85,88] In addition, infants with medical co-morbidities, such as neurologic, cardiac, or pulmonary disease, are also those at highest risk for morbidity and mortality associated with the procedure. A great deal of regional variability exists in the use of fundoplication to treat GERD.[89] While some centers routinely evaluate children referred for gastric tube placement for fundoplication, this practice is not supported by the literature, as concomitant fundoplication increased morbidity and does not seem to decrease the use of reflux medications or reflux-related complications.[7,30,111] In addition, in neurologically impaired children, fundoplication has not been shown to decrease reflux-related rehospitalization rates compared to gastrojejunal feeding.[97]

Summary

Because of limitations in the safety and efficacy of pharmacologic and surgical interventions for GERD, and a natural history of improvement over time, conservative expectant management is the mainstay of GERD management in infants. None of the medications commonly used to treat GERD in the NICU has been demonstrated to be safe and effective, and many have the potential to cause harm. Fundoplication also has a high rate of failure and complications and should be considered judiciously.

Key Points

- GER is a frequent normal physiologic process.
- GERD is defined as GER that triggers complications or morbidities.
- Pharmacologic therapy for GERD is common, but the literature does not support its safety or efficacy in infants.
- Conservative nonpharmacologic management is the mainstay of therapy.

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83

Disorders of Digestion in the Neonate

CATHERINE LARSON-NATH, BHASKAR GURRAM, AND GISELA CHELIMSKY

Chronic and prolonged diarrhea is a symptom complex with a variety of underlying etiologies. This chapter focuses on the approach to infants with protracted diarrhea and is a review of recent literature on infantile diarrheal illnesses.

Intractable diarrhea is a term developed many years ago by Avery to describe chronic, unexplained diarrhea in young children.[85] This phrase describes a symptom complex rather than a discrete disease entity and is not favored by many experts. *Protracted diarrhea* has been used more recently to describe infants with loose and frequent stools of sufficient severity to require nutritional support in the form of parenteral alimentation. This emphasis on adequate support of total caloric intake and nutritional rehabilitation has dramatically improved the survival of affected infants.

Diarrhea is classified as either secretory or osmotic; however, in several cases both mechanisms may be involved.[140] A strategic problem in these diarrheal disorders is the presence of fluid and electrolyte secretion into one or more segments of the small intestine, large intestine, or both. Secretory diarrhea is the result of either impaired absorption of NaCl from villous enterocytes or increased chloride secretion from crypt cells, secondary to exogenous toxins from bacteria or viruses or endogenous substances (hormones, neurotransmitters, or cytokines), or from inherent defects in the sodium or chloride channels. The secretory diarrhea usually presents as a large volume of watery stools and does not improve with fasting. Osmotic diarrhea results from nonabsorbable substances in the intestinal lumen, which increases the osmolality of the luminal contents. This results in either retention of fluid or secretion of fluid into the intestinal lumen, therefore leading to diarrhea. In contrast to secretory diarrhea, osmotic diarrhea typically improves with fasting. Osmotic diarrhea can be distinguished from secretory diarrhea by measuring the electrolyte concentration in the stool and the osmotic gap. In osmotic diarrhea, there is a significant osmotic gap (>50 mOsm/kg) between the stool osmolality and twice the concentrations of sodium and potassium in the stool (Table 83.1). However, in clinical practice, usually the diagnosis is made by a trial of fasting to determine if there is improvement in the stool output. Some diarrheal disorders may have a secretory and osmotic component, as is sometimes seen for example in celiac disease.[13] In the absence of carbohydrate malabsorption in a patient with osmotic diarrhea, it is essential to determine whether steatorrhea is present (Table 83.2). Although diarrhea alone may be responsible for an increase in fat excretion of up to 11 g per day (normally <7 g fat/day is excreted by persons consuming 100 g fat/day), when larger amounts of fat are found in the stool the patient should be evaluated for a disorder of fat absorption. Based on the description of diarrhea as osmotic or secretory or mixed osmotic and secretory components, infantile diarrheal etiologies can be distinguished, as shown in Box 83.1.

Disorders of Carbohydrate Absorption

The enterocytes in the small intestine have at their apical surface brush border various enzymes responsible for the digestion of carbohydrates.[194] These carbohydrate hydrolases convert disaccharides and oligosaccharides into simple monosaccharides that are absorbed easily through transport proteins that exist on the intestinal surface.[125] These proteins include maltase-glucoamylase,[194] sucrase-isomaltase (SI), and lactase-phlorhizin hydrolase.[124] The clinical symptoms of carbohydrate malabsorption occur either because of the deficiency of a particular enzyme (e.g., congenital sucrase-isomaltase deficiency) or because of an abnormality in a transport protein involved with the absorption of digestion product (e.g., glucose-galactose malabsorption). Obtaining a detailed feeding history may yield a correlation between the age the diarrhea started and the particular food that was introduced into the baby's diet (Table 83.3) and give clues to the etiology of the diarrhea.

Patients with carbohydrate malabsorption disorders, regardless of the cause, present with severe watery diarrhea, which results from osmotic action exerted by the malabsorbed oligosaccharide[194] (lactose or sucrose) in the intestinal lumen. The malabsorbed sugars are then fermented by colonic bacteria, producing a mixture of gases (e.g., hydrogen, methane, carbon dioxide)[194] and short-chain fatty acids.[151] In normal digestion, the short-chain fatty acids are absorbed via the colonic epithelium, providing energy and decreasing the colonic osmolality. In the presence of a large carbohydrate load, these protective mechanisms become overwhelmed, causing diarrhea.[194] The increased volume

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Abstract

Protracted diarrhea of infancy describes infants with loose or frequent stools of sufficient severity to require nutritional support in the form of parenteral nutrition. When evaluating for diarrhea, it is critical to determine if the diarrhea is secretory, osmotic, or has a component of both. Secretory diarrhea usually presents as a large volume of watery stools and does not improve with fasting. Osmotic diarrhea results from nonabsorbable substances in the intestinal lumen, which increases the osmolality of the luminal contents. This results in either retention of fluid or secretion of fluid into the intestinal lumen, therefore leading to diarrhea. In contrast to secretory diarrhea, osmotic diarrhea typically improves with fasting. Osmotic diarrhea can be distinguished from secretory diarrhea by measuring the electrolyte concentration in the stool and the osmotic gap. In osmotic diarrhea, there is a significant osmotic gap (>50 mOsm/kg) between the stool osmolality and twice the concentrations of sodium and potassium in the stool. This chapter reviews the presentation and causes of diarrhea in infants based on carbohydrate, fat, protein, and bile acid malabsorption. We have also included diarrhea due to disordered villous architecture, allergic colitis, food protein-induced enterocolitis (FPIES) and autoimmune enteropathy, and immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome.

Keywords

protracted diarrhea
osmotic diarrhea
secretory diarrhea
carbohydrate malabsorption
fat malabsorption
protein malabsorption
allergic colitis
autoimmune enteropathy

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associated with low pH will stimulate gut motility, decreasing intestinal transit time.[85] In this kind of disorder, the diarrhea resolves when oral feeds are discontinued.

Disaccharidase Deficiencies

Congenital Sucrase-Isomaltase Deficiency

Congenital sucrase-isomaltase deficiency (CSID) is the most common congenital disorder of carbohydrate malabsorption.[112] CSID is most common in native Canadians, Inuits, and Greenland Eskimo populations (3%-10%). The prevalence in North American populations is around 0.05%-0.2%.[183]

Etiology

Congenital sucrase-isomaltase deficiency leads to reduced activity of the brush border enzyme sucrase-isomaltase and an inability to metabolize specific carbohydrates like sucrose, maltose, and starch.[149] It is transmitted in an autosomal

TABLE 83.1 Differentiating Osmotic From Secretory Diarrhea

	Osmotic	Secretory
Stool volume	Small	Large
Response to fasting (72 hours)	Improves	Unchanged
Stool sodium	<70	>70
Stool osmotic gap (290-2[stool Na+stool K])	>50	<50

TABLE 83.2 Clues to Distinguish Osmotic Diarrhea From Carbohydrate Versus Fat Malabsorption

	Isolated Carbohydrate Malabsorption	Isolated Fat Malabsorption
Stool character	Loose and watery Non-foul-smelling	Bulky large stool Foul-smelling Oil droplets visible
Perianal rash/skin erosion	+	+
Signs of fat soluble vitamin deficiency	±	+
Stool pH	Acidic (usually <6)	Alkaline
Stool reducing/nonreducing substances	+	–

+, Present; –, not present; ±, may or may not be present.

TABLE 83.3 Age of Onset of Different Carbohydrate Malabsorption Syndromes

Age of Onset	Disorder
Immediate neonatal period	Glucose-galactose malabsorption Congenital lactase deficiency
Weaning age	Glucoamylase deficiency Congenital sucrase-isomaltase deficiency

• BOX 83.1 Causes of Infantile Chronic and Protracted Diarrheal Illness

Osmotic Diarrhea

- Carbohydrate Malabsorption
  - Glucose-galactose malabsorption
  - Sucrase-isomaltase deficiency
  - Congenital lactase deficiency
  - Maltase-glucoamylase deficiency
- Fat Malabsorption
  - Pancreatic insufficiency
  - Defective handling of bile acids—primary bile acid malabsorption, cholestasis
  - Defective mucosal lipid handling—intestinal lymphangiectasia, abetalipoproteinemia, chylomicron retention disease
- Protein Malabsorption
  - Primary enterokinase deficiency
  - Hartnup disease

Secretory Diarrhea

- Normal Villous Architecture
  - Chloride-losing diarrhea (Cl^--HCO_3^- exchanger defect)
  - Sodium-losing diarrhea (Na^+-H^+ exchanger defect)
  - Neurogenin-3 mutation
- Villous Atrophy
  - Microvillous inclusion disease
  - Tufting enteropathy
  - Acrodermatitis enteropathica
  - Trichohepatoenteric syndrome (phenotypic or syndromic diarrhea)
  - Congenital disorders of glycosylation defects (CDG1b)

Combined Secretory and Osmotic Diarrhea (Partial Response to Fasting With Some Decrease in Diarrhea)

- Autoimmune Enteropathy and Infantile Onset Inflammatory Bowel Disease
  - IL10/IL10R defects
  - Hyperimmunoglobulin D from mevalonate kinase deficiency presenting as severe neonatal colitis
  - IPEX/IPEX-like syndrome
- Infectious Enteropathies
- Postinfectious Enteropathies
- Allergic Enteropathy
- Idiopathic

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recessive form.[149] However, some heterozygotes can be symptomatic.[160] Several theories have been proposed for the pathogenesis of this enzyme deficiency, and there are at least seven known phenotypes.[91]

Clinical Features

Patients present with diarrhea, abdominal pain, and bloating upon ingestion of sucrose, maltose, and starch, typically noticed around the age of 3-6 months when the infant is weaned from breast milk to baby foods that contain sucrose. If the baby has been switched to a sucrose-containing formula, the diarrhea will develop earlier, around the time of the dietary change. Affected infants present with severe, chronic, or intermittent watery diarrhea; abdominal distention; cramping; metabolic acidosis; and failure to thrive.[11] Severity of symptoms is influenced by residual enzymatic activity, levels of carbohydrate intake, gut motility, and colonic fermentation. The stool pH is less than 7 as a result of fermentation of unabsorbed carbohydrates by colonic bacteria, but because sucrose is a nonreducing sugar, Clinitest or a test for stool-reducing substances is negative.[112]

Diagnosis and Treatment

A detailed history will provide the correlation of the onset of diarrhea and the dietary changes. Stools are acidotic but test negative for reducing substances. Stool osmolality reveals an elevated osmolar gap (>50 mOsm), indicating the presence of malabsorbed sugars. Sucrose hydrogen breath testing is a noninvasive test to evaluate for sucrase-isomaltase deficiency,[66] but it is not specific for a congenital deficiency and will be abnormal also if there is mucosal injury and secondary disaccharidase deficiency, for example, from bacterial overgrowth.[150] The gold standard for diagnosis is endoscopy with biopsies analyzing the actual enzyme level.[91] Treatment consists of strict lifelong avoidance of sucrose-containing fruits and beverages.[150] Affected patients can try a supplemental sacrosidase when ingesting sucrose-containing foods.[110,184] One study has documented a poor response to diet restriction and a good response to enzyme replacement therapy with supplemental sacrosidase at 8500 U at meal times.[146]

Congenital Lactase Deficiency

Congenital lactase deficiency is a very rare autosomal recessive disorder. Patients usually present very soon after birth with watery diarrhea, vomiting, poor weight gain, lactosuria, aminoaciduria, and changes in the nervous system.[79,111] Most of the cases reported are from Finland, where more than 42 cases have been described since the first documented diagnosis in 1959.[72] More recently, mutations have been reported in a Japanese infant[185] and patients from Italy and Turkey.[44,72]

Etiology

Congenital lactase deficiency is caused by the deficiency of lactase in the small intestine and has been linked to chromosome 2q21.[79] Villous architecture of the intestinal mucosa is preserved, as seen on biopsy specimens of the small intestine.[194] Congenital lactase deficiency is different from the adult-type hypolactasia, which is very common. Usually, congenital lactase deficiency is an isolated deficiency, but Nichols and coworkers have reported it in association with other disaccharidase deficiencies such as maltase-glucoamylase.[125]

Clinical Features

The symptoms appear when lactose-containing milk is introduced to the diet. Breast milk and other commercial formulas have lactose; therefore, the onset is usually within the first 10 days of life.[79] As with other disaccharidase deficiencies, the stool is acidic and the diarrhea resolves after switching to a lactose-free formula,[91] which confirms the diagnosis. Apart from diarrhea, these babies are lively and have a good appetite; they exhibit poor weight gain but no vomiting.[91,158] Occasionally, they can have hypercalcemia and nephrocalcinosis.[158] The hypercalcemia is probably secondary to the metabolic acidosis or to enhanced absorption of calcium in the ileum, facilitated by the nonabsorbed lactose. The hypercalcemia resolves after starting a lactose-free diet.[158] As a result of metabolic acidosis, the urinary excretion of citrate decreases, producing hypocitruria, which, associated with the hypercalcemia, facilitates the development of nephrocalcinosis.[134]

Diagnosis and Treatment

Congenital lactase deficiency can be diagnosed by obtaining a good dietary history and can be demonstrated by a lack of increase in blood sugar after a load of lactose.[106] The blood sugar does increase after the intake of individual monosaccharides and other disaccharides.[106] The diagnostic gold standard is quantification of the enzyme levels from duodenal biopsy specimens,[194] but this may not be possible in all cases.[106]

The treatment consists of avoiding lactose-containing formula and breast milk. When treated appropriately, patients have good catch-up growth with normal psychomotor development. Some patients may even tolerate supplementation with lactase as they age.[194]

Maltase-Glucoamylase Deficiency

Maltase-glucoamylase is a brush border hydrolase[125] that serves as an alternate pathway for starch digestion. It compensates partially for the lack of sucrase-isomaltase and vice versa.[194] Congenital maltase-glucoamylase deficiency, first described in 1994, is very rare,[124] with an estimated incidence of 1.8% among children with congenital diarrhea.[91] Maltase-glucoamylase is very similar to sucrase-isomaltase (59% homology) and has two catalytic sites that are identical to those of sucrase-isomaltase.[125] Therefore, patients may have a deficiency of both enzymes.

Clinical Features

The clinical symptoms are very similar to other disaccharidase deficiencies with diarrhea, abdominal distention, and

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bloating. In this disorder, the symptoms start with the introduction of starch into the infant's diet, usually at the time of weaning.[194]

Diagnosis and Treatment

Endoscopy with biopsies will show decreased levels of the enzyme when symptomatic treatment requires starch elimination from the diet.[194]

Transport Defects

Glucose–Galactose Malabsorption

Glucose–galactose malabsorption is a rare disorder. Infants present in the neonatal period with hypernatremia and severe watery diarrhea, which can lead to rapid dehydration and death.[194] Clinically, it cannot be differentiated from congenital lactase deficiency.[134] It was first reported in 1962 in Sweden by Lindquist and Meeuwisse[107] and is transmitted in an autosomal recessive manner.[181]

Etiology

Glucose–galactose malabsorption derives from a defect in the intestinal glucose–galactose transport protein, SGLT1,[194] located on the brush border membrane. SGLT1 transports glucose and galactose intracellularly coupled with Na^+, using an electrical gradient to transport against the concentration gradient.[134,194] The transporter has been mapped to chromosome 22q13.1, which is the site of the gene *SLC5A1*.[186] Multiple mutations have been identified in the *SLC5A1* gene, but not all mutations produce glucose–galactose malabsorption; therefore, the results of mutation analysis must be used in combination with dietary changes and intestinal biopsy when trying to establish the diagnosis.

Clinical Features

The predominant sugar of breast milk is lactose, which is hydrolyzed to glucose and galactose before being absorbed. Therefore, these infants present at the start of breastfeeding or with ingestion of glucose-containing formula. This severe watery diarrhea is often confused with urine. This diarrhea can lead to rapid dehydration and electrolyte imbalance.[181] The diarrhea is osmotic and acidotic, caused by fermentation of the nonabsorbed sugars (glucose and galactose) by the bacteria.[194] If undiagnosed, this diarrhea can rapidly progress to death. A stool test is positive for reducing substances.[134] An oral glucose tolerance test demonstrates a flat glucose tolerance curve with the presence of glucose in stools. The histology is normal on endoscopy and colonoscopy. Because SGLT1 is also expressed in renal tubular cells, patients may also have glucosuria.[134] Case reports of nephrocalcinosis and urinary calculus formation in patients with glucose–galactose malabsorption have been described in the literature.[134,178,181] Mechanisms responsible for renal stone formation, as explained earlier for congenital lactase deficiency, may also exist in glucose–galactose malabsorption. As with congenital lactase deficiency, hypercalcemia resolves after initiation of a glucose-free diet and control of diarrhea.[134,178]

Diagnosis and Treatment

The diagnosis is made by the onset of diarrhea after the introduction of glucose, the presence of glucose in stools, hypoglycemia, hypernatremic dehydration, and normal intestinal morphology. The diarrhea improves on elimination of glucose, galactose, and lactose from the diet.[194] The diagnosis can be further established by an abnormal glucose breath hydrogen test and SGLT1 sequencing, although these are not needed to confirm the diagnosis.[194] The treatment consists of avoiding the "offending" sugars by using a fructose-containing formula.[134] Parents should be counseled on looking at labels to be sure no glucose and galactose are added in foods and medications.

Fat Malabsorption

The absorption of lipids from the gastrointestinal tract occurs in five steps:

1. Pancreatic enzyme lipolysis with lipase and colipase. Infants produce limited amounts of pancreatic lipase and only reach adult levels by 2 years of age[103]; therefore, infants rely on gastric lipase for fat digestion.[65]
2. Bile salt stabilization of fatty acids and monoglycerides to form micelles, which in turn stabilize cholesterols, diglycerides, and fat-soluble vitamins.
3. Flow of micelles, fatty acids, and monoglycerides across luminal brush and transport of cholesterol across the brush border via ABC transporter protein. In the terminal ileum, the transport of bile salts is through the ASBT transport protein.
4. Formation of the chylomicron and VLDL, which takes place in the enterocyte with triglycerides, phospholipids, and cholesterol. In the terminal ileum, the bile salts are bound with ileal bile acid-binding protein.
5. Uptake of chylomicrons into the lymphatic system through pinocytosis.

When any of these steps is disrupted, it will result in fat malabsorption and, consequently, diarrhea.

Pancreatic Insufficiency

Pancreatic insufficiency results in the absence of pancreatic enzymes needed for nutrient digestion. Stool fecal elastase is highly sensitive and specific for pancreatic insufficiency.[177] For an infant older than 2 weeks, elastase greater than 200 μg/g of feces is sufficient, and less than 100 μg/g of stool is considered a marker of pancreatic insufficiency.[127] Fecal elastase may miss cases of mild pancreatic insufficiency.[195] Some of the most common causes of pancreatic insufficiency include cystic fibrosis, Shwachman-Diamond syndrome, and Johanson-Blizzard syndrome.

Cystic Fibrosis

Cystic fibrosis (CF) is one of the most common fatal genetic disorders.[32] It is also the most common cause of exocrine pancreatic insufficiency and lung disease in childhood.[60] Although in the past, the prognosis was very

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poor in childhood, currently the estimated survival is 43 years.[48]

Cystic fibrosis affects between 1 in 1900 and 1 in 3700 live births in the white population[170] and is much less common among African Americans (1 in 17,000)[170] and Asian populations (1 in 90,000).[32] Despite these racial differences, CF should be considered in the differential for any child who presents with poor weight gain and chronic lung disease.[152]

Etiology

Cystic fibrosis is transmitted in an autosomal recessive manner.[60] In whites, about 1 in 20 individuals have the recessive form of the allele.[43] In 1989, the gene responsible for CF was cloned.[87] The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene is located on chromosome 7q31.2.[28] Currently, more than 1600 mutations in the *CFTR* gene have been described and about 1300 are thought to be pathogenic.[28] The ΔF508 mutation accounts for two-thirds of mutations in patients with CF.[28]

Clinical Features

This disorder can present very early in life with meconium ileus, which is an obstruction of the ileum as a result of thick meconium plugs.[170] On abdominal x-rays, the small bowel loops may have a ground-glass appearance resulting from dilated loops of bowel with bubbles of gas and meconium without air-fluid levels.[152] The infants may also present with microcolon.[194] About half of the infants presenting with meconium ileus develop complications, including peritonitis, volvulus, atresia, and necrosis, which may show up as calcifications on abdominal x-ray.[152] The presence of meconium plug syndrome, which is a temporary obstruction of the distal colon, should also raise concerns for the possibility of CF.[152]

Another common presentation of CF is chronic diarrhea secondary to pancreatic fat malabsorption.[91] Some CF mutations (class I-III) present earlier in life, usually within the first month with pancreatic insufficiency.[196]

Infants can present less commonly with extrahepatic biliary duct obstruction as a result of thick inspissated bile.[152] Therefore CF should be included in the differential diagnosis of any neonate with prolonged conjugated hyperbilirubinemia.[76,170] If not supplemented with pancreatic enzymes, infants and children with pancreatic insufficiency have poor weight gain and worse pulmonary outcomes.[152]

Diagnosis and Treatment

Since 2010, every state in the United States plus the District of Columbia includes screening for CF as part of the newborn screen.[192] The screening program is less accurate in children with less common alleles; therefore, a normal newborn screen does not rule out the presence of CF.[26] The diagnosis is confirmed by a sweat chloride test showing a chloride greater than 60 mEq/L,[170] which is present in 99% of patients with CF.[170] However, certain conditions may give falsely positive and negative values.[32,170] When confirming the diagnosis of CF, the sweat test should be done in centers certified by the Cystic Fibrosis Foundation.[32] Genetic testing can also be performed.[172] Nevertheless, even with the most comprehensive testing, 1%-5% of the mutation will be missed.[28]

The prenatal diagnosis of CF can be done based on the carrier status of the parents by mutational analysis of fetal cells obtained by chorionic villus sampling or amniocentesis. The diagnosis should be confirmed by sweat testing after birth.[152]

Management

The management of infants and children with CF is a multidisciplinary team effort that includes a gastroenterologist, a pulmonologist, a nutritionist, and a social worker,[194] and it focuses on caloric intake, the replacement of fat-soluble vitamins, meticulous pulmonary toilet and chest physiotherapy, pancreatic enzyme replacement, and the provision of supportive care.[152] Any infant with a fecal elastase level less than 200 μg/g or with a mutation associated with pancreatic insufficiency should be treated with pancreatic enzyme supplementation.[131,163]

Shwachman-Diamond Syndrome

The Shwachman-Diamond syndrome complex includes exocrine pancreatic insufficiency, bone marrow failure, and skeletal changes. It was described by many groups, including Nezelof and Watchi (1961),[123] Bodian and colleagues in the United Kingdom (1964),[17] Burke and coworkers in Australia (1967),[21] and Shwachman in the United States (1964).[173] Although it is a rare cause of pancreatic insufficiency, it is the second most common cause of bone marrow failure.[35] It has been reported in the North American population (1 in 50,000), Europe, Asia, and Africa.[194]

Etiology

This disorder is probably transmitted in an autosomal recessive mode. A majority of patients have compound, heterozygous, loss-of-function mutations in the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene.[18] Recently, patients who are negative for the *SBDS*-gene mutations have been detected to carry a de novo missense variant in *SRP54* (encoding signal recognition particle 54 kDa).[25] The gene affected in Shwachman-Diamond syndrome has been mapped to chromosome 7.[36]

Clinical Features

Patients present with failure to thrive in infancy secondary to exocrine pancreatic insufficiency and variable degrees of bone marrow failure.[153] The most common hematologic abnormality is neutropenia with defective neutrophil chemotaxis, resulting in frequent bacterial infections.[34] The neutropenia is cyclic, ranging from low values to normal white cell counts.[35] These patients may also have anemia or thrombocytopenia.[194] The bone marrow is hypocellular and is replaced with fatty infiltration.[36]

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Diagnosis and Treatment

Diagnosis of Shwachman-Diamond syndrome requires fulfillment of two criteria. The first criterion is demonstration of a hematologic cytopenia, which includes any of the three cell lines. The neutropenia is usually cyclic; therefore, neutrophils of less than 1.5×10^9/L must be demonstrated on two separate occasions over at least a 3-month period. The second criterion is documentation of exocrine pancreatic insufficiency.[122] Other findings support the diagnosis of Shwachman-Diamond syndrome, such as persistent elevation of hemoglobin F, persistent macrocytosis, abnormal 72-hour fecal fat, reduced levels of at least two fat-soluble vitamins, evidence of pancreatic lipomatosis, bone abnormalities, behavioral problems, or the presence of other family members with Shwachman-Diamond syndrome. Genetic testing is available, but up to 10% of patients are negative for mutations in the *SBDS* gene.[37]

The management of children with Shwachman-Diamond syndrome includes pancreatic enzyme replacement and supportive care. When the cytopenia is severe, these patients may require G-CSF therapy and blood and platelet transfusion.[37] Children should be monitored by measuring CBC, levels of fat-soluble vitamins, growth, bone density, and neuropsychological functioning.[37]

Johanson-Blizzard Syndrome

Johanson-Blizzard syndrome (JBS) is a very rare autosomal recessive disorder that was first described in 1971 by Johanson and Blizzard,[72] and there are still fewer than 100 patients reported worldwide.[147]

Etiology

Johanson-Blizzard syndrome results from mutations in the *UBRI* gene on the long arm of chromosome 15.[7]

Clinical Features

Affected infants have characteristic phenotypic features with varied penetration,[38] including aplastic alae nasi (which gives the appearance of a beaklike nose with large nostrils),[8] extension of the hairline to the forehead with upswept frontal hair,[62] low-set ears, large anterior fontanelle, micrognathia, thin lips, microcephaly,[46] aplasia cutis (patchy distribution of hair with areas of alopecia), dental anomalies, poor growth, pancreatic exocrine insufficiency, and anorectal anomalies (mainly imperforate anus).[8,180] Other findings include mental retardation, deafness, genitourinary abnormalities, hypothyroidism, cardiac malformations,[8] cholestatic liver disease,[3] growth hormone deficiency,[180] and transfusion-dependent anemia.[4]

Diagnosis

Patients present with exocrine pancreatic insufficiency with poor weight gain, failure to thrive, hypoalbuminemia, edema, and anemia.[8] Sometimes, prenatal ultrasound can show a beaklike nose and dilation of the sigmoid colon as a result of an imperforate anus.[8] These infants have normal karyotype.[8]

Miscellaneous Causes of Pancreatic Insufficiency

Many other syndromes and diagnoses can be associated with pancreatic insufficiency. Donlan syndrome is similar to JBS, but with normal alae nasi and cleft palate.[62] Pearson syndrome is characterized by pancreatic insufficiency, sideroblastic anemia,[62] variable neutropenia, thrombocytopenia, and vacuolization of bone marrow precursors.[194] Jeune syndrome is a rare autosomal recessive disorder of pancreatic insufficiency and asphyxiating thoracic dystrophy.[194] Isolated deficiencies of amylase, lipase, colipase, and trypsinogen have also been described. Familial pancreatitis with mutations in the trypsinogen gene can cause chronic pancreatitis, pancreatic insufficiency, and chronic diarrhea although infants are rarely symptomatic.

Defective Handling of Bile Acids

Chronic diarrhea can also stem from alterations in bile acid metabolism and enterohepatic circulation. These disorders should be considered when the more common causes of chronic diarrhea have been ruled out. Bile acid diarrhea happens when there is disease or resection of the terminal ileum as well as congenital conditions affecting the terminal ileum, which disrupt the enterohepatic circulation.[130] The enterohepatic circulation of bile is the primary mechanism by which the body reabsorbs 98% of the bile that then is reused as bile salts.[119] When the bile is not reabsorbed, it reaches the colonic mucosa with subsequent secretion of fluid and electrolytes, leading to diarrhea, steatorrhea, and decreased blood cholesterol levels.[130]

Primary Bile Acid Malabsorption

Etiology

Primary bile acid malabsorption is linked to a missense mutation in the sodium–bile acid cotransporter gene, *SCL10A2*.[120,130] The pathophysiology is not clear but may be related to a reduced secretion of the hormone fibroblast growth factor 19, which prevents bile acid secretion through a negative feedback mechanism. When this factor is decreased, then the excessive bile acid leads to diarrheal fat malabsorption and secretion of fluids from the colonocytes secondary to bile acid stimulation.[83,137]

Clinical Features

The symptoms develop in infancy with diarrhea and failure to thrive. Patients may also have low levels of low-density lipoprotein (LDL). The diarrhea is exacerbated when dietary fats are added and often persists during fasting.

Diagnosis and Treatment

The measurement of bile acids in stool is done mainly for research.[83] Clinically, it can be done by ingesting a capsule with a gamma emitter selenium 75-homocholic acid taurine (SeHCAT), which is a selenium-labeled bile acid. The results are expressed as a percent retention, with retention of less than 10% after 7 days having a sensitivity

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of up to 100% and specificity of up to 94% for primary bile acid malabsorption.[83,137] Treatment of primary bile acid malabsorption is the use of bile acid resins such as cholestyramine, which prevents the secretory action of bile acids.[83,137]

Defective Mucosal Lipid Handling

Primary Intestinal Lymphangiectasia (Waldmann Disease)

In 1961, Waldmann and coworkers described the first 18 cases of idiopathic hypercatabolic hypoproteinemia.[193] These patients had edema associated with hypoproteinemia and low serum albumin and gammaglobulin levels. Microscopic examination of small intestine biopsies showed variable degrees of dilation of the lymph vessels in the mucosa and submucosa. The authors also proposed the term *intestinal lymphangiectasia*.[193]

Primary intestinal lymphangiectasia is a rare disorder generally diagnosed before 3 years of age but may be diagnosed in older patients with unknown prevalence.

Etiology

Largely, the etiology of isolated primary intestinal lymphangiectasia is unknown. However, primary intestinal lymphangiectasia can be a component of multisystemic genetic syndromes, including Hennekam syndrome (caused by biallelic loss-of-function variants in *CCBE1* or *FAT4*). There is also a recent report of 11 patients associated with CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE syndrome), caused by abnormal complement activation due to biallelic loss-of-function mutations in *CD55*.[133] Intestinal lymphangiectasia is responsible for lymph leakage into the bowel lumen, which leads to hypoalbuminemia, hypogammaglobulinemia, and lymphopenia. The edema that accompanies the disease is the consequence of hypoproteinemia with decreased oncotic pressure.

Clinical Findings

Primary intestinal lymphangiectasia most often presents with mild to moderate peripheral edema.[102] Patients may develop anasarca, which includes pleural effusion, pericardial effusion, and chylous ascites. Other signs and symptoms include fatigue, abdominal pain, weight loss or inability to gain weight, diarrhea, fat-soluble vitamin deficiencies caused by malabsorption, and lymphopenia. The lymphopenia is secondary to leakage of lymph into the gastrointestinal tract.[190] In some patients, limb lymphedema is associated with primary intestinal lymphangiectasia, and it is difficult to distinguish lymphedema from edema. These patients also have diarrhea.[104]

Five syndromes are associated with intestinal lymphangiectasia: von Recklinghausen, Turner (X0), Noonan, Klippel-Trenaunay, and Hennekam.[68] Primary intestinal lymphangiectasia may be suspected during pregnancy based on ultrasonography images, which can identify fetal ascites or lower limb lymphedema.[164]

Diagnosis and Treatment

The diagnosis of primary intestinal lymphangiectasia is made by the combination of elevated fecal alpha-1 antitrypsin levels and endoscopic evidence of intestinal lymphangiectasia.[189] A high-fat meal prior to endoscopy can increase the sensitivity of endoscopic evaluation.

Children are treated with a low-fat diet supplemented with medium-chain triglycerides.[81] The lack of fat in the diet prevents the engorgement of the intestinal lymphatics with chyle, therefore preventing their rupture with the subsequent loss of protein and T cells. Medium-chain triglycerides can be added to the diet, because they are absorbed directly into the portal venous circulation, avoiding lacteal engorgement and improving nutrition and caloric intake. Other treatments such as antiplasmin, octreotide, corticosteroid administration, and everoliums have been tried with inconsistent results.[102,132] Patients with primary intestinal lymphangiectasia and *CD55* mutation could benefit from eculizumab (terminal complement inhibitor).[98] Occasionally, when the lymphangiectasia is segmental and localized, intestinal surgical resection of the small bowel may be an option.[89,190]

DGAT1-Associated Congenital Diarrhea

DGAT1-associated congenital diarrhea was first described in 2012 in one family with two of three children affected by a congenital diarrhea and protein-losing enteropathy.[63]

Etiology

The *DGAT1* gene encodes acyl-CoA:diacylglycerol acyl transferase, which converts diacylglycerides to triglycerides. Several homozygous mutations in this gene have been linked to a congenital diarrhea with protein-losing eneropathy.[51,63,179]

Clinical Manifestations, Diagnosis, and Treatment

Symptoms of DGAT1-associated congenital diarrhea vary in severity and include diarrhea, malnutrition, and edema. Signs related to the associated protein-losing enteropathy include fat-soluble vitamin deficiency, hypoalbuminemia, elevated fecal alpha-1-antitrypsin, hypogammaglobulinemia, and lymphopenia.[51,63,179] Hypertriglycemia is also seen in some patients.[51] Clinical diagnosis is made based on improvement in hypoalbuminemia and lymphopenia with elimination of enteral lipid provision through administration of parenteral nutrition and intravenous lipids and elimination of other etiologies of protein-losing enteropathy. Exome sequencing can be used to confirm the diagnosis.[51,63,179]

Other Causes of Protein-Losing Enteropathy

Congenital disorders of glycosylation and Fontan surgery to correct single-ventricular hearts can cause a protein-losing enteropathy. Congenital disorders of glycosylation are caused by defects in protein N-glycosylation and are associated with mental and psychomotor retardation, sometimes

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with coagulopathy, hypoglycemia, and liver fibrosis without neurologic involvement.[77] Westphal reported protein-losing enteropathy in a patient with a congenital disorder of glycosylation who showed reduced heparan sulfate accumulation in the enterocytes.[199] Protein-losing enteropathy in these children develops secondary to a combination of genetic and environmental factors, with loss of heparan sulfate proteoglycans from the basolateral surface of the intestinal epithelial cells, suggesting a link to protein leak.[16]

Hypobetalipoproteinemia and Abetalipoproteinemia

Etiology

Abetalipoproteinemia (ABL) is a rare autosomal recessive disorder resulting from mutations in the gene encoding the large subunit of microsomal triglyceride transfer protein (MTP) located on chromosome 4. In ABL, fatty acids can be converted to triglycerides, but because of the lack of apoprotein B, they are not converted to chylomicrons and, therefore, fat accumulates in the intestinal absorptive cell. To date, more than 33 MTP mutations have been identified in patients with ABL.[203]

Hypobetalipoproteinemia is an autosomal dominant disorder characterized by decreased or absent plasma concentrations of apolipoprotein (apo)-B–containing lipoproteins and low-density lipoprotein (LDL) cholesterol.[165] In heterozygous individuals, the disorder is usually clinically silent, because the concentrations of apo-B and LDL cholesterol are 25%-50% of normal, whereas homozygous individuals have extremely low levels and are indistinguishable from patients with abetalipoproteinemia.[91]

Clinical Presentation

Abetalipoproteinemia (ABL) is characterized by fat malabsorption, acanthocytosis, and hypocholesterolemia in infancy. Later in life, many of the symptoms are secondary to the deficiency of fat-soluble vitamins such as development of atypical retinitis pigmentosa, coagulopathy, posterior column neuropathy, and myopathy. Sometimes these patients have associated adrenal insufficiency and hypogonadism.[96]

In patients with the severe form of homozygous hypobetalipoproteinemia, there is complete absence of betalipoproteins, so they present clinically in a similar fashion to the subjects with ABL.[108] In contrast, patients with heterozygous hypobetalipoproteinemia may be asymptomatic or may have subtle neurologic findings.[91]

Diagnosis and Treatment

Diagnosis of abetalipoproteinemia and homozygous hypobetalipoproteinemia is made through low triglyceride and cholesterol levels. Endoscopic evaluation may reveal a yellow appearance of the small bowel, and pathology is significant for fat-laden enterocytes.[91] The management includes a low-fat diet and supplementation with fat-soluble vitamins.[194]

Chylomicron Retention Disease

Etiology

Chylomicron retention disease, also known as Anderson disease,[194] is a rare autosomal recessive disorder of lipoprotein assembly.[12,139] The mutations are in the *SAR1B* gene encoding the Sar1b protein. As a result of these mutations in the polypeptide subunit of microsomal triglyceride transfer protein, the enterocytes are unable to secrete chylomicrons across the basolateral membrane.[12]

Clinical Manifestations

The disease is characterized by hypocholesterolemia, fat malabsorption, and failure to thrive, with onset of diarrhea shortly after birth. These children may have vomiting, abdominal distention, and less often, hepatomegaly.[139] As with hypobetalipoproteinemia and abetalipoproteinemia, they may develop neurologic manifestations such as areflexia, proprioceptive abnormalities, ataxia, myopathy, and sensory neuropathy presenting in the early second decade of life,[139] but retinitis pigmentosa and neuromuscular manifestations are less severe.[194] It is not unusual to diagnose chylomicron retention disease in neonates who present with diarrhea, but it may get delayed until adolescence and present with vitamin E deficiency.

Diagnosis and Treatment

Patients with chylomicron retention disease have normal triglycerides with decreased total cholesterol, LDL, and high-density lipoprotein (HDL). On endoscopy, the duodenal mucosa may have a white coloration.[139] Pathology shows vacuolated enterocytes that stain strongly with oil red, indicating the presence of fat within the enterocytes.[12] On electron microscopy, lipid-laden enterocytes are seen.[12] The diagnosis is confirmed with the identification of the mutation in *SAR1B*.[139]

The treatment of chylomicron retention disease is with a low-fat diet with added essential fatty acids and medium-chain triglycerides to aid in fat absorption and supplementation with high doses of the fat-soluble vitamins A, D, E, and K. In severe cases, intralipid infusion may be required.[139]

Disorders of Protein Absorption

Primary Intestinal Enteropeptidase Deficiency

Enteropeptidase, formerly known as enterokinase, is located in the proximal small intestine and belongs to the group of serine proteases.[73] This enzyme initiates the digestion of protein in the small intestine by facilitating the conversion of trypsinogen to active trypsin, which in turn activates other pancreatic zymogens.[58]

Etiology

Congenital enteropeptidase deficiency is a rare recessively inherited disorder of the pro-enteropeptidase gene.[73]

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Clinical Features

Affected infants present with symptoms and findings of a protein-losing enteropathy, including diarrhea, failure to thrive, edema, and hypoproteinemia.[11] These children also have fat malabsorption, because trypsin is required for activation of colipase and phospholipase.

Diagnosis and Treatment

Infants present with watery diarrhea with normal osmolality and absent osmolar gap. These children have significant hypoalbuminemia and hypoproteinemia. The diagnosis can be made by quantifying the enteropeptidase on small intestinal biopsies or by assaying the enzyme levels in the duodenal fluid.[58] The diagnosis can also be confirmed by switching the diet from an intact-protein-based formula to a protein-hydrolysate formula.[194] Treatment consists of pancreatic enzyme supplementation.[194]

Hartnup Disease

Hartnup disease was first described in 1956.[10] It is an autosomal recessive disorder with an incidence between 2.5 and 5.5 per 100,000 births.[166,201] In Hartnup disease, patients have increased urinary and intestinal neutral amino acid secretion. The symptoms result from deficiency of tryptophan.[161]

Etiology

The genetic abnormality responsible for the loss of the amino acids is in the neutral amino acid transporter SLC6A19 located on the brush border of renal and intestinal epithelia.[92,169]

Clinical Features

The clinical presentation can range from no symptoms[161,166] to a pellagra-like rash with cerebellar ataxia, psychiatric disturbances, and emotional lability.[95]

Diagnosis and Treatment

The diagnosis is established by the patterns of urine aminoaciduria, which includes increased alanine, asparagine, glutamine, histidine, isoleucine, leucine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine.[161] Patients with symptomatic Hartnup disease are treated with lifelong oral nicotinamide supplementation.[161]

Lysinuric Protein Intolerance

Lysinuric protein intolerance, also known as hyperdibasic aminoaciduria type 2 or familial protein intolerance,[135] is a disorder of amino acid transport characterized by subnormal plasma levels of dibasic amino acids, such as ornithine, arginine, and lysine, and their enhanced urinary excretion. This disorder is transmitted in an autosomal recessive manner and is found mainly in Finland, Italy, and Japan.[135] There is varied phenotypic presentation with signs and symptoms, including failure to thrive, lung disease, renal disease, protein intolerance, developmental delay, autoimmunity, and hemophagocytic-lymphohistiocytosis.[113] The infants usually develop symptoms around the time of weaning when they are switched from breastfeeding to high-protein foods.[135] These subjects are treated with supplementation with citrulline and a protein-restricted diet (1.5 g/kg per day).[167,194]

Disorders of Electrolyte Absorption

Congenital chloride diarrhea and congenital sodium diarrhea present in a similar fashion in the prenatal and newborn period. Both entities can present with polyhydramnios, suggesting that both conditions may start before delivery.[2] The fetus may have a distended abdomen and hypoechoic loops of bowel.[39] Newborns usually fail to pass meconium, probably secondary to severe secretory diarrhea in utero.[118] Diarrhea starts soon after birth, but because of the watery aspect, the diarrhea is often confused with urine and the diarrhea is initially missed. Because of the degree of stool output and dehydration, both entities can cause renal disease.[2,39,71] Infants can occasionally present with a picture mimicking bowel obstruction[101] or present with meconium ileus.[171] In both conditions, there is history of consanguinity,[39] and both congenital diarrheas are transmitted in an autosomal recessive manner.[69,117] Congenital chloride diarrhea is more common than congenital sodium diarrhea. Both are secretory diarrheas with severe electrolyte imbalance, although the electrolyte losses and serum electrolyte disturbances are different.

Congenital Chloride Diarrhea

Congenital chloride diarrhea is the most common cause of congenital secretory diarrhea with intact mucosal histopathology. This disorder occurs more frequently in Finland (1 in 20,000), Poland, and the Middle East.[69] Congenital chloride diarrhea is caused by mutations in the intestinal Cl^- $HCO3^-$ exchange transporter (SLC26A3), which results in sodium, chloride, and fluid depletion.[194]

Patients with congenital chloride diarrhea have a decrease in serum potassium, serum chloride, and urine chloride and high stool chloride. Evaluation should include measurement of fecal chloride concentration that is greater than 90 mmol/L.[39,70]

Because the abnormality cannot be corrected, treatment is aimed at replacing the decreased serum electrolytes. This is a lifelong treatment, and the concept is based on the presence of normal electrolyte absorption in the jejunum. Initially, patients may need intravenous replacement but then can be transitioned to oral supplementation. In the study of Elrefas and coworkers in 12 Arabic children, eight did well on long-term follow-up.[39] Other treatments have been tried, including proton pump inhibitors that decrease the chloride load to the gut[142] and oral butyrate. Butyrate stimulates intestinal water and ion absorption through

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different mechanisms, including the activation of a parallel Cl^-/butyrate. A 12-month trial in one case did not produce any side effects, and stools were more formed, allowing the child to perform normal activities.[24]

Congenital Sodium Diarrhea

Congenital sodium diarrhea is a very rare secretory diarrhea that presents soon after birth. Congenital sodium diarrhea is related to a defect in the sodium-hydrogen exchanger in the proximal intestine[19,86] that is responsible for the absorption of Na^+ in exchange for H^+. Mutations in the *SPINT2* gene, *SLC9A2* gene, and *GUCY2C* gene are associated with syndromic congenital sodium diarrhea.[42,78] There may be an increased risk of inflammatory bowel disease in patients with mutations in either the *SLC9A2* or *GUCY2C* gene.[78]

This disorder has been diagnosed in premature infants.[2] The diarrhea is very high in sodium (>100-150 mmol/L), and the pH is greater than 7. Urine sodium concentrations are low-normal.[117]

As with congenital chloride diarrhea, biopsies of the small intestine are usually normal.[45,198] However, Muller and colleagues did report cryptic hyperplasia with jejunal villous atrophy on light microscopy in three patients, which on transmission electron microscopy had vacuolation of the surface epithelium.[117] The evaluation of an infant with severe watery diarrhea should include fecal electrolytes, stool osmolality, and pH. Stool osmolality of less than 50 mOsm, high fecal sodium losses, and alkaline stool pH are characteristic of congenital sodium diarrhea. Serum hyponatremia, metabolic acidosis, and hypokalemia are noted, which is in contrast to patients with congenital chloride diarrhea (Table 83.4). However, because of the rarity of the condition, it is not often entertained in the differential diagnosis, and affected infants may be diagnosed very late in the course of the disorder. Treatment is aimed at aggressive fluid and electrolyte replacement, either orally or intravenously.

TABLE 83.4 Characteristics of Congenital Chloride Diarrhea and Congenital Sodium Diarrhea

	Congenital Chloride Diarrhea	Congenital Sodium Diarrhea
Serum pH	Metabolic alkalosis	Metabolic acidosis
Serum chloride	Low	Normal to high
Serum potassium	Low	High
Serum sodium	Low	Low or normal
Stool bicarbonate	Low	High
Stool pH	Acidic	Alkaline
Stool sodium	—	High
Stool chloride	High	—

—, Not established.

Disordered Villous Architecture

Microvillus Inclusion Disease

Microvillus inclusion disease (MVI), also known as *microvillus atrophy*, is a secretory diarrhea that presents in two different forms: (1) congenital, which is rare and has a poor prognosis, and (2) late-onset, which usually starts at 6-12 weeks of life.[27,138,141] These infants have a prenatal history of polyhydramnios, although this is not as prevalent as in congenital chloride diarrhea.[141,156] In the congenital form, a secretory diarrhea starts soon after birth, and when untreated, progresses soon to dehydration and death.[138] In a study of 23 infants conducted by Phillips and coworkers,[141] 15 were girls, with 16 white, 6 Arabic, and 1 Asian. The gender predominance is not clear in this disorder, with a slight male predominance in a study done in the Navajo population.[143] In Phillips' study, more than half of the infants were born preterm, and 75% died before 9 months of age.

The diagnosis is made by histology. The histologic findings are present in the small intestine and also to a lesser degree in the colon. Under hematoxylin and eosin (H&E) staining, the mucosa shows some degree of villous atrophy without significant crypt hyperplasia. The diagnosis is made mainly by periodic acid-Schiff (PAS) staining, which shows accumulation of the PAS-positive granules in the apical side of the enterocytes. Also, the brush border looks atypical with an intracytoplasmic band along the apical border. Immunostaining with techniques directed against CD10 can also show the abnormal linear band on the brush border. In congenital microvillous inclusion disease, abnormal PAS staining is present in upper crypt cells, whereas in the late-onset form, abnormal PAS staining is present in the lower part of the crypt. Electron microscopy is also helpful in the diagnosis of this disease, showing decreased or absent microvilli in the apical membranes as well as an increased number of vacuoles.[156]

Treatment consists of nutritional support with parenteral nutrition, frequently for life. In the late-onset form, some children may start tolerating some enteral feeds and could have decreased need for parenteral nutrition. In the congenital form, there is no improvement in the intestinal structure over time. Many children die before the age of 3 years from central line infections and complications from liver failure.[156] Intestinal transplantation alone or with liver transplant is also an option. Ruemmele and coworkers[157] described 12 patients with early-onset microvillous inclusion disease who were evaluated for transplant. Seven underwent transplantation; four had combined intestinal and liver transplantation. At 3 years' follow-up, 100% survived in the group that underwent intestinal transplant alone and 75% in the other group. All were weaned from parenteral nutrition.[157]

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This disorder may be caused by mutations in myosin 5B (MYO5B). The microvillus inclusions are a consequence of the MYO5B loss in the neonatal period.[74] MVID patients are also at risk of developing a progressive familial intrahepatic cholestasis (PFIC)-like liver disease manifesting as cholestasis with normal gamma-gluatmyl transferase (GGT), which may hamper outcomes of intestinal transplant.[50,52] A second mutation in STX3 has also been identified.[200] Both of these genes are involved in apical membrane trafficking.[191] It has an autosomal recessive inheritance.

Tufting Enteropathy

Tufting enteropathy is also called intestinal epithelial dysplasia. It is a congenital secretory diarrhea that presents very early in life and is very rare but perhaps more common than microvillous inclusion disease. It is more common in countries where consanguinity is common, suggesting an autosomal recessive inheritance.

Usually, there is no history of polyhydramnios, and infants pass large volumes of very liquid stool in the range of 100-200 mL/kg. This congenital diarrhea can be associated with choanal atresia, esophageal atresia, and imperforate anus.[14,53] This disorder can be associated with other malformations, such as dysmorphic facial features and abnormal hair.[14]

The diagnosis is made by biopsy of the intestine. Tufting enteropathy affects not only the small intestine but also the colon. All subjects have some degree of villous atrophy. The epithelium shows crowding and disorganization, which look like tufts. These tufts are localized close to the tips of the villi, but crowding also occurs at the crypt level. Sometimes biopsies can be near normal and make the diagnosis more difficult. Therefore, in these cases, it is important to repeat the endoscopy with biopsy at a later time.[53] Sivagnanam and coworkers identified an epithelial cell adhesion molecule (EpCAM) as the gene for congenital tufting enteropathy in a family with two children affected with tufting enteropathy.[176] These mutations have been reported in other cases as well.[29,93,159] This mutation produces abnormalities in the epithelial tight junction proteins, leading to decreased transport of ions in the intestine and increased intestinal permeability.[94] These infants require parenteral nutrition for life. The diarrhea continues to a lesser degree even when nothing is given enterally. Some infants have a milder form of the disease that allows them to tolerate some enteral feeds.[23] Some of these infants have undergone bowel transplantation.[100,136] Recently, siblings of ages 17 and 19 were diagnosed with tufting enteropathy after many years of diarrhea requiring parenteral nutrition supplementation. The diagnosis was done by whole exome sequencing, showing mutations in the EpCAM gene.[64]

Acrodermatitis Enteropathica

Acrodermatitis enteropathica (see Chapter 94) is a rare autosomal recessive disorder resulting from the inability to absorb zinc from the diet. This disorder usually starts with diarrhea after the infants are weaned from breast milk, suggesting perhaps that breast milk may have some factors that improve the absorption of zinc. The diarrhea has been reported to start between 15 days and 9 months of age. These infants also develop a perioral rash that can be very severe,[6,88] such as in perioral or perianal areas. These infants may also develop alopecia, irritability, apathy, and sometimes growth failure.

The serum zinc level is usually low, but there is no good correlation between the zinc level and the clinical picture.[88] This disorder is caused by a genetic defect in chromosome 8q24.3 in the intestinal zinc-specific transporter gene *SLC39A4*.[99] Treatment is supplementation with zinc gluconate or zinc sulfate with significant improvement in the rash within 3 weeks.[88]

Trichohepatoenteric Syndrome (Phenotypic or Syndromic Diarrhea)

Trichohepatoenteric syndrome (THE-S), previously referred to as syndromic diarrhea or phenotypic diarrhea, presents in most infants with chronic secretory diarrhea, polyhydramnios, premature birth, and intrauterine growth restriction. Most of these infants develop diarrhea between 2 weeks and 7 months of age, although a report shows a 12-year-old with the genetic mutation and all the phenotypic characteristics without diarrhea.[148] Affected infants frequently have a history of consanguinity in their ancestors. Many of the subjects have shown two types of mutations with the same phenotype. These mutations were found in TTC37 and in SKIV2L.[41,67]

Most patients also have dysmorphic features (wide forehead, broad nasal root, and hypertelorism) and immune disorders, and some develop early onset of severe liver cirrhosis. Other features include hypopigmentation or café-au-lait spots, hair changes with trichorrhexis nodosa, and cardiac anomalies such as ventricular septal defect, tetralogy of Fallot, aortic insufficiency, and pulmonic stenosis. Some children are developmentally delayed. There is a case series of six patients with THE-S presenting with pancolitis and variable degree of enteritis with some responding to immunosuppressive therapy.[22]

Blood work shows low immunoglobulins and thrombocytosis, sometimes with large platelets. On intestinal biopsies, majority show villous atrophy with a variable degree of mononuclear infiltration.[54,67] Immunologic defects commonly seen in this population include hypogammaglobulinemia, defect in antibody production after vaccinations, and low lymphocyte counts.[40] Management includes long-term use of parenteral nutrition. Periodically, enteral feeds with either a semi-elemental or an elemental formula should be tried, because some infants will progressively tolerate enteral feeds and be able to wean from parenteral nutrition. Mortality is very high with up to 40% by 15 years of age.

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Autoimmune Enteropathy

Autoimmune enteropathy (AIE) is a clinic–pathologic diagnosis that is characterized by severe intractable inflammatory diarrhea with intestinal biopsies showing villous atrophy, increased epithelial apoptosis, and mononuclear cell infiltration with or without the presence of anti-enterocyte antibodies.[55] Patients with autoimmune enteropathy commonly present before 6 months of age but can manifest at any age. These patients typically need prolonged immunosuppressive therapy. With recent technologic advances in genetic diagnostics, some patients presenting with AIE were identified to have specific diagnoses such as IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, and X-linked), IL-10 and IL-10R defects, and APCED (autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia).[15,49]

Children with AIE can have intestinal and extraintestinal manifestations.[115] These infants have refractory diarrhea, with malabsorption, and anorexia, with severe weight loss, that requires treatment with total parenteral nutrition. The extraintestinal manifestations may include endocrine, renal, pulmonary, hepatic, hematologic, and musculoskeletal system involvement. The diagnostic criteria for AIE include chronic diarrhea for greater than 6 weeks with malabsorption, partial or complete blunting of the small bowel villi, deep crypt lymphocytosis, increased crypt apoptotic bodies, minimal intraepithelial lymphocytosis, and no other causes that may explain the villous atrophy. The diagnosis could also be supported by detecting anti-enterocyte (AE) or anti-goblet (AG) cell antibodies.

Management includes total parenteral nutrition. In addition, medical therapy is commonly used, usually with corticosteroids (budesonide and prednisone). However, some patients are refractory to corticosteroids and may require immunosuppressive therapy with azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, infliximab, and rituximab.[49]

IPEX Syndrome

This is a rare syndrome inherited in an X-linked recessive pattern with expression only in males.[30] Patients usually present with a watery diarrhea, eczematous dermatitis, and endocrinopathy. It is caused by germ-line mutations in the *FOXP3* gene, which is a transcriptional regulator for the development of CD4 regulatory T (Treg) cells.[1] These children have decreased and/or dysfunctional regulatory T cells, which then lead to loss of peripheral immune tolerance.

Male infants present usually at less than 3 months of life with severe watery diarrhea that may have mucus and blood, malabsorption, and failure to thrive, and they eventually develop cachexia. Severe cases require total parenteral nutrition (TPN).[155] Some children can present at older ages, but most do not survive past the third decade of life. The most common endocrinopathy is type 1 diabetes mellitus with onset in the first months of life. Hypothyroidism is also common. The skin manifestation is usually eczematous dermatitis, but some develop erythroderma, psoriasiform dermatitis, and pemphigus nodularis.[126] Some of the affected children have other autoimmune disorders, including autoimmune thrombocytopenia, autoimmune neutropenia, Coombs-positive anemia, and tubular nephropathy.

Evaluation shows normal B cells, $CD8^+$ T cells, and NK cells. These children have increased IgE and sometimes eosinophilia. The other immunoglobulins are usually normal, but if the protein-losing enteropathy is severe, they may be decreased. Small intestine biopsy shows villous atrophy with a mononuclear cell infiltrate (activated T cells) in the lamina propria. Colon biopsy shows mucosal lymphoplasmacytic infiltration.[155]

The diagnosis is suspected primarily by the presenting clinical features and then by flow cytometry, showing decreased FOXP3- and CD25-expressing regulatory T cells. The definitive diagnosis is done by sequence analysis of the *FOXP3* gene.[30] It should be recognized that up to 25% of patients with IPEX syndrome could have normal FOXP3 expression despite having mutations in *FOXP3* gene.[168]

Treatment requires aggressive immunosuppression either with steroids alone or in combination with azathioprine, cyclosporin A, or tacrolimus, sirolimus, or bone marrow transplantation.[155]

Infectious Enteropathy

Intestinal infections should always be considered as a potential etiology of chronic diarrhea in infants.[59,61] Stool studies for bacterial cultures and viral antigen detection should be a part of the work-up for infantile diarrhea (see Chapters 48 and 50).

In developing countries, entero-adherent *Escherichia coli* and *Cryptosporidium parvum* can produce severe chronic diarrhea. In developed countries, viral infections such as rotavirus and norovirus are more common causes of chronic infectious diarrhea. After certain infections, infants and children can develop a postenteritis syndrome. In these cases, small intestinal mucosal damage persists after the acute gastroenteritis. Some of these children have a secondary disaccharidase deficiency or may develop food sensitization.[140]

Small bowel bacterial overgrowth is produced by an increased number of bacteria in the duodenal fluid or the presence of anaerobic bacteria. It induces chronic diarrhea through villous damage with loss of absorptive surface and/or fermentation of ingested nutrients producing an osmotic overload. Many times, the diagnosis is made by empiric treatment with antibiotics and evaluation of the response.

Allergic Colitis or Eosinophilic Proctocolitis

Allergic colitis or eosinophilic proctocolitis usually develops in the first few months of life.[116] Cow milk protein and soy proteins are the most common offending antigens.[20,129] Breastfeeding is not protective for this disorder, and up to

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50% of cases of allergic colitis occur in breastfed infants who become sensitized to dietary cow milk in the mother's milk. This disorder is a non-IgE, cell-mediated, delayed-onset hypersensitivity reaction limited to the GI tract.[116]

These infants present with vomiting, diarrhea, abdominal pain, rectal bleeding, and sometimes anemia. They often have irritability and straining with stools. Rarely, infants may present with failure to thrive. The mean age of diagnosis is 60 days, but infants as young as 2 days could present with allergic colitis,[97] suggesting in utero sensitization. Furthermore, 30%-40% of infants with cow milk protein intolerance are intolerant of soy protein.[129]

The diagnosis is made based on the clinical history and is confirmed by a response to elimination of cow milk protein and soy protein. These infants may have eosinophilia and sometimes increased serum IgE.

Although colonoscopy is not routinely done anymore, when performed, it may show mucosal erythema and in severe cases, ulceration. Biopsies demonstrate intense eosinophilic infiltration of the lamina propria and muscularis mucosa, without features of chronicity.[202]

The treatment consists of changing the infant's formula to a protein hydrolysate[188](close to 95% response rate) or an amino acid–based formula (almost 100% response rate) when bottle-fed. There is some evidence for benefit of supplementing extensively hydrolyzed formulae with probiotics, especially *Lactobacillus* GG.[9] In breastfed infants, elimination of milk- and soy-containing products in the mother's diet may be beneficial; however, care should be taken to ensure that the maternal diet remains balanced and includes calcium and vitamin D intake from other sources. In breast fed babies who do not improve with soy and milk elimination of the maternal diet, atopy patch test could be helpful in determining which foods should be avoided.[109] The improvement is drastic after elimination of the offending protein.[31] The prognosis is excellent, and the majority of patients are able to reintroduce milk protein by 1-3 years of age.[116]

Food Protein-Induced Enterocolitis Syndrome

Food protein-induced enterocolitis syndrome (FPIES) is an uncommon pediatric non-immunoglobulin E (IgE)-mediated disorder triggered by the ingestion of certain food proteins. The incidence is between 0.0% and 0.34% of newborns.[84] The pathophysiologic features are still poorly understood, although they are probably produced by stimulation of the T cells in the gastrointestinal tract by some food protein.[57,116,187] The diagnosis is clinical. Children present about 2 hours after ingestion of a food protein with profuse vomiting and/or diarrhea, often with pallor, lethargy, cyanosis, metabolic acidosis, and neutrophilia.[121,144,174,175] They usually recover within a few hours, although up to 20% of children may present in hypovolemic shock, requiring fluid resuscitation.[47,128]

Often, these infants are thought to have sepsis, a metabolic disorder, or a surgical abdominal emergency.[5,80,116] The mean age at initial presentation is around 5 months. Children frequently experience multiple episodes before a correct diagnosis is made. Most of the children react to only one food product, but some may react to two. The most common problem foods are cow milk, soy, and rice, although other food products such as vegetables and fruits, legumes, meats, and seafood are also reported.[84] These infants usually present with vomiting followed by lethargy, pallor, diarrhea, and hypothermia (<36°C).

Diagnosis is suspected based on the clinical presentation and three of the five criteria described below, and it has to be confirmed by an oral food challenge (OFC) performed by an allergist.[105] Although an OFC is the most conclusive diagnostic method, it has been associated with risk of systemic reactions; therefore, the risks and benefits of the challenge need to be evaluated. Because of the potential severity of the response, an allergist should handle reintroduction of foods when clinically indicated. The five criteria include: (1) vomiting and/or diarrhea, (2) blood in the stool, (3) leukocytes in the stool, (4) eosinophils in the stool, and (5) a change in the blood polymorphonuclear neutrophil count.[145]

Treatment is elimination of the offending food or the use of a hypoallergenic infant formula (protein hydrolysate and elemental formulae). Most individuals tolerate reintroduction of foods by 2-3 years of age.[114] In a study of Korean infants with cow milk FPIES, 64% tolerated cow milk at 10 months and 92% tolerated soy at 10 months.[75] Sometimes patients with FPIES develop an IgE-mediated allergy to the same food products.[84]

Other Causes of Infantile Diarrhea

Motility Disorders and Small Intestinal Bacterial Overgrowth

Severe and extensive motility disorders such as total or subtotal intestinal aganglionosis (long-segment Hirschsprung disease) or chronic intestinal pseudo-obstruction syndrome[140] may also cause permanent intestinal failure. Small intestine bacterial overgrowth is a common problem in motility disorders and contributes to diarrhea and malabsorption. Children undergoing bowel surgery in the neonatal period and those having more than one procedure are at greater risk of developing small intestine bacterial overgrowth postoperatively. Patients with bacterial overgrowth could have carbohydrate, fat, and protein malabsorption leading to diarrhea. They frequently have vitamin B_{12} deficiency. Empiric response to a trial of metronidazole may be diagnostic and therapeutic.

Neurogenin-3 Mutation in Malabsorptive Diarrhea

This is a newly described entity with just a few case reports. Patients present during the first several weeks of life with

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vomiting, diarrhea, and dehydration, and develop hyperchloremic metabolic acidosis. The diarrhea stops when there is no enteral intake except water. Even when water is mixed with amino acids or medium-chain triglycerides, the diarrhea relapses. Small bowel biopsies are grossly normal, with normal villi and no increase in inflammatory cells. Special staining for chromogranin A of the small and large intestine shows very decreased to absent entero-endocrine cells. These infants show homozygous missense mutation in the neurogenin-3 gene (*NEUROG3*).[197] In Wang's report of three cases, the children developed diabetes at around age 8 years. Diabetes can also present at birth. The association with diabetes is related to the need of the transcription factor neurogenin-3 in the early specification of the endocrine portion of the pancreas, as well as in the developmental pathway of gut epithelial stem cells destined to become endocrine cells.[82] Neurogenin-3 is differentially required for endocrine cell fate specification in the intestinal and gastric epithelium.[56,154]

There is no treatment for the diarrhea except parenteral nutrition. In the three cases reported by Wang and coworkers, one underwent transplantation but died of sepsis.

Mevalonate Kinase Deficiency Manifesting as Severe Colitis in Neonates

Mevalonate kinase deficiency (MVD) presents in most patients in the first 12 months of life and in some in the neonatal period with attacks of severe diarrhea, often bloody, with fever, vomiting, abdominal pain, stomatitis, and in some with arthralgia and myalgia. These patients could have up to 10 attacks per year that last for variable duration. Some may continue to manifest symptoms in between attacks. Up to 75% of patients could have elevated IgD levels. The best screening test currently available is urinary mevalonic acid levels with a sensitivity of 93% in a large cohort.[182] Treatment is mainly immunosuppressive therapy with corticosteroids and biologic agents directed against IL-1 and TNF.

Intestinal Failure

Intestinal failure is a condition in which there is insufficient functional bowel to allow for adequate nutrient and fluid absorption to sustain adequate growth in children, necessitating parenteral nutrition. There can be medical and surgical causes for intestinal failure. Surgical causes include patients with necrotizing enterocolitis, intestinal atresias, and midgut volvulus, among others. Many of these conditions do not intrinsically cause intestinal failure, but their natural histories often lead to surgical resection of bowel, resulting in short bowel syndrome and its complications. Medical causes of intestinal failure include infants with dysmotility disorders[33] or patients with severe intractable diarrheas described above. Children with surgical causes of intestinal failure have greater potential for bowel adaptation than children with medical causes of intestinal failure.[33] Patients with intestinal failure need intestinal rehabilitation, which is done by improving nutrition as well as using pharmacologic and surgical methodologies to improve enteral nutrition. Commonly used surgical modalities include the STEP (serial transverse enteroplasty) and Bianchi procedures. A systematic review did not find superiority of one procedure over another.[90] Intestinal transplantation is indicated in patients in whom long-term parenteral nutrition cannot be performed safely. Common reasons for intestinal transplantation include short bowel syndrome, congenital mucosal diseases, and motility disorders.[162] In children with intestinal failure, transplantation must be discussed early and should evolve from being a rescue procedure to becoming a true therapeutic option.[162]

Key Points

- There are many causes of diarrhea presenting in newborns or early infancy.
- Be aware of these conditions in the presence of polyhydramnios, failure to pass meconium, and profound diarrhea.
- Examination of serum electrolytes, complete blood count, immunoglobulin levels, and the contents of the stool are essential to determine the diagnosis.
- Biopsies may be necessary to distinguish the etiology of the many disorders, and genomic analysis has also resolved the underlying causes.
- Supportive care includes enteral and parenteral nutrition, elimination of offending agents, and the use of special formulae.
- Bowel and liver transplantation may be necessary for certain rare but complex conditions.

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84

Selected Gastrointestinal Anomalies in the Neonate

MICHAEL DINGELDEIN

Thoracic Anomalies

Esophageal Atresia and Tracheoesophageal Fistula

Combined anomalies of the esophagus and trachea are regular occurrences in most tertiary neonatal units caring for high-risk infants. The spectrum of recognized deformities comprises a variety of combinations involving esophageal atresia (EA) and tracheoesophageal fistula (TEF). These malformations are well-recognized entities, yet they continue to stimulate a great deal of interest for a variety of reasons, and almost all are lethal unless surgically corrected. Many have concurrent pulmonary complications, and most are associated with other congenital anomalies that require careful coordination of interdisciplinary care. There are few conditions, if any, that require a greater degree of cooperation between neonatologist and surgeon.

The reported incidence of EA/TEF is roughly 1-2 per 3500 live births.[105] The incidence of EA/TEF is higher in white populations than in nonwhite. There is also a slight preponderance of males and a disproportionate rate of twinning among affected infants. Although the majority of cases are sporadic, there are numerous well-recognized genetic associations. Approximately 7% of affected infants have a chromosomal abnormality such as trisomy 13, 18, or 21. Additionally, EA/TEF has been reported in infants with the Pierre-Robin, DiGeorge, Fanconi, and polysplenia syndromes.

Although usually sporadic, most cases of EA/TEF are not isolated. Most affected infants, up to 70% in some series, have at least one other anomaly.[37] The likelihood of coexisting anomalies is considered to be greatest with pure EA and least with pure TEF. The most widely recognized relationship between EA/TEF and other congenital anomalies is within the constellation of defects referred to as the VACTERL association—abnormalities involving *v*ertebral, *a*norectal, *c*ardiac, *t*racheal, *e*sophageal, *r*enal/genitourinary, and *l*imb structures. There is a lesser association with CHARGE *s*yndrome (*c*oloboma, *h*eart defects, *a*tresia choanae, *r*etarded development, *g*enital hypoplasia, *e*ar defects/deafness). Gastrointestinal anomalies (other than anorectal defects) associated with EA/TEF include duodenal atresia, annular pancreas, jejunoileal atresia, and intestinal malrotation. Neurologic defects, especially hydrocephalus, may be associated with EA/TEF, as may diaphragmatic hernia and abdominal wall defects. In order of approximate frequency, the affected organ systems most commonly associated with EA/TEF are cardiovascular (35%-45%), gastrointestinal (25%), genitourinary (25%), skeletal (15%), and neurologic (10%).

The anatomy of EA/TEF includes five well-recognized variants. A number of anatomic classifications have been devised but have been largely discarded in favor of simple descriptive nomenclature. The most common variant is the combination of a proximal esophageal atresia and a distal tracheoesophageal fistula. The proximal atresia/distal fistula variant occurs in about 85% of affected patients. It manifests classically as a dilated, blind-ending proximal pouch that extends to the lower neck or upper mediastinum, and a distal esophageal segment that originates from the posterior membranous wall of the trachea, carina, or main stem bronchus and connects to the stomach in a normal fashion. The next two most common variants are isolated EA and isolated TEF, both of which occur in approximately 5%-10% of patients. An isolated TEF is often referred to as an H-type fistula; the fistula itself is usually angled downward, with the esophageal end inferior to the tracheal end. The rarest variants include the proximal fistula/distal atresia, and the double fistula, both occurring in no more than 1% or 2% of patients.

No single unified model of pathogenesis has been developed to explain a variety of anomalies seen with esophageal atresia. Normal development of the esophagus and trachea includes the formation of a primordial lung bud as a diverticulum of the ventral foregut during the 4th week of gestation. The appearance of this diverticulum is associated with a pair of lateral infoldings of the foregut—the laryngotracheal folds—which begin at the caudal end of the lung bud and fuse to form the tracheoesophageal septum.

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Abstract

This chapter discusses the commonly seen congenital anomalies of the GI tract and their management.

Keywords

tracheoesophageal fistula
esophageal atresia
duodenal atresia
intestinal atresia
GI duplication cysts
Hirschsprung disease

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This process of lateral invagination and fusion was historically believed to proceed cranially, displacing the orifice of the lung bud in a cephalad direction and separating the developing trachea from the esophagus as the tracheal bifurcation moved caudally in a relative sense. Therefore, in the traditional model for the cause of tracheoesophageal malformations, the esophagus and trachea shared a common foregut precursor over a significant distance, becoming separated by the cephalad movement of the tracheoesophageal septum. Perturbations of this process would account for the observed variety of abnormal connections between these two adjacent structures. This theory of cephalad migration of a tracheoesophageal septum is now controversial. Evidence suggests that the position of the laryngeal orifice remains constant relative to the developing notochord and that the tracheal bifurcation descends simply as a result of linear tracheal growth without any cephalad movement of a tracheoesophageal septum.[36,73]

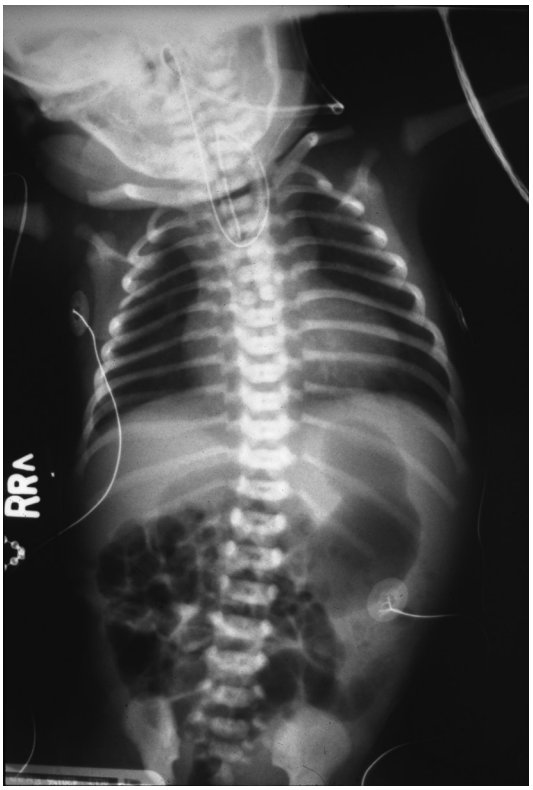
Given this alternative scheme of tracheoesophageal development, a different etiologic theory is required to explain tracheoesophageal anomalies. One such theory has arisen from observations in the Adriamycin-treated rat model of VACTERL deformities. In this model, pregnant rats are exposed to Adriamycin during early gestation and give birth to offspring that express VACTERL phenotypes, including EA/TEF. Investigations have demonstrated that the distal "esophageal" segment in EA/TEF arises from a respiratory precursor, descends from the carina along with the two main stem bronchi, and elongates caudally to merge with the stomach. A respiratory origin for this third structure is supported by the finding of pseudostratified respiratory epithelium and respiratory-specific thyroid transcription factor-1 (TTF-1) in distal fistulas from Adriamycin-treated rat model sources, and of TTF-1 expression in distal fistula specimens from human sources.[16,17,95] This structure does not branch as the developing bronchi do, because of abnormal epithelial-mesenchymal interactions caused by deficiencies of mesenchymal fibroblast growth factor and epithelial FGF receptors.[18] In support of this hypothesis, findings document a brief stage in the Adriamycin-treated rat model during which the stomach is anatomically disconnected from the rest of the developing foregut.[94]

If current proposals of a respiratory-derived distal fistula are accurate, the proximal atresia must, therefore, have a separate etiology. One proposed explanation is an abnormal concentration gradient of the early embryonic morphogen known as *sonic hedgehog* (Shh), which is elaborated by the developing notochord and is believed to participate in early foregut differentiation. Notochord abnormalities have been documented in the Adriamycin-treated rat model and in specimens of human distal fistulas that had been shown to be specifically deficient in Shh.[27,96] A unifying theory that links these newer models and provides a comprehensive explanation for tracheoesophageal maldevelopment is still lacking.

The clinical presentation of infants with EA/TEF depends on the specific anatomic variant encountered. Many cases of EA/TEF are not diagnosed prenatally, but current prenatal imaging techniques may raise a suspicion of EA/TEF in a significant number of infants. The combination of maternal polyhydramnios and a small or absent stomach has both sensitivity and a positive predictive value for EA/TEF of approximately 40%-60% in most series.[43,92] The finding of a dilated upper pouch in the neck by high-resolution ultrasonography or magnetic resonance imaging can increase the diagnostic accuracy in this selected group of patients to nearly 100%.[54,88]

In most affected infants, the diagnosis is made in the immediate postnatal period. The infant cannot swallow secretions and appears to drool excessively. As the upper pouch fills, antegrade aspiration may occur, leading to significant coughing, respiratory distress, and cyanosis. In patients with a distal fistula, the stomach may dilate with air, leading to the reflux of gastric secretions back into the lungs, resulting in significant and progressive respiratory distress caused by reactive bronchoconstriction and chemical pneumonitis.

Attempted passage of a gastric tube is usually diagnostic. The tube fails to pass distally and extrudes back through the mouth. A simple chest radiograph usually establishes the diagnosis by demonstrating the radiopaque catheter curled in the upper pouch (Fig. 84.1). If the diagnosis is still in question, the upper pouch should be cautiously evaluated with water-soluble contrast by an experienced imager, because aspiration can cause parenchymal lung injury. Air itself makes an excellent contrast agent, and the catheter can



• **Fig. 84.1** Typical chest radiograph of a patient with a tracheoesophageal fistula, with proximal atresia and a distal fistula.

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• **Fig. 84.2** Chest radiograph of patient with pure esophageal atresia.

be pulled back under fluoroscopic guidance until the tip is positioned in the proximal esophagus, and then 5-10 mL of air is injected slowly. A radiolucent dilated pouch is then easily documented. If there is no luminal gas below the diaphragm, the anomaly can be further defined as a pure or distal atresia (Fig. 84.2). The clinical presentation of an H-type TEF is typically much more subtle and delayed. It usually includes a history of coughing during feedings and occasionally the development of pneumonia owing to aspiration through the fistula. An H-type TEF may be very difficult to confirm radiographically. Contrast must be injected through a tube positioned in the thoracic esophagus, with the patient prone and in the Trendelenburg position, allowing the contrast to flow back up the angled fistula. Often, an H-type fistula is documented only on rigid bronchoscopy during evaluation for respiratory distress.

Once the diagnosis is established, efforts are made to prevent aspiration-induced lung injury, to provide respiratory support if necessary, and to define associated anomalies while preparing the patient for surgical correction. Gastric acid blockade should be instituted while the infant is maintained in a slightly head-up position to reduce reflux of gastric secretions into the airway. A small-caliber sump tube is kept in the upper pouch and suctioned intermittently. The use of preoperative broad-spectrum antibiotics during the first several days should be considered. Spontaneous ventilation is preferred to minimize the introduction of air into the stomach, as gastric decompression is possible only by percutaneous needle aspiration. This is particularly important in the presence of distal intestinal obstruction. The use of continuous positive airway pressure is discouraged. If parenchymal lung disease mandates the use of positive-pressure ventilation, mean airway pressures are minimized to avoid shunting of tidal volume through the fistula. This may be difficult in patients with lung disease and poor compliance. Under these circumstances, the use of high-frequency oscillatory ventilation (HFOV) may allow adequate gas exchange to occur at lower peak airway pressures, preventing the loss of ventilation through the fistula. The failure or unavailability of HFOV in a patient requiring aggressive ventilatory support may be an indication for urgent surgical intervention to ligate the fistula, ligate the gastroesophageal junction, or occlude the fistula with a balloon catheter.

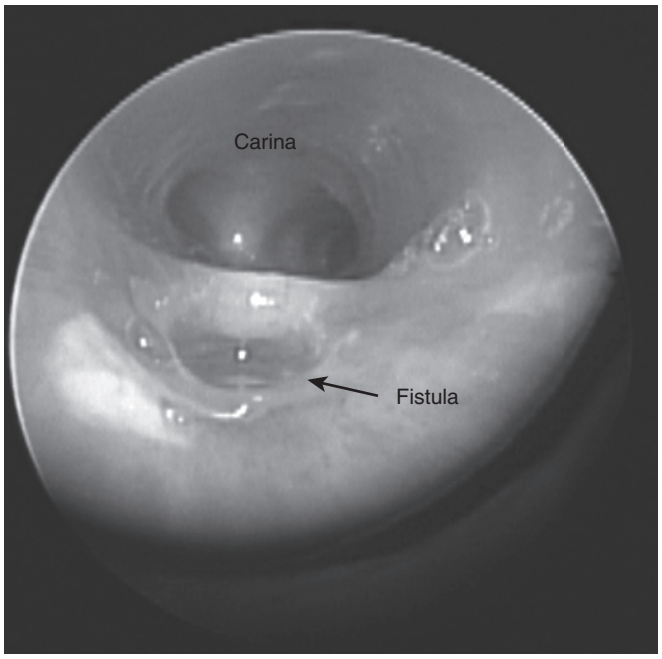
A thorough evaluation for other VACTERL-associated defects is mandatory. A preoperative radiograph provides much information regarding cardiopulmonary status, diaphragmatic integrity, and the presence of vertebral abnormalities. The only other studies necessary before surgical management of the EA/TEF are an echocardiogram in all patients and a renal ultrasound. Echocardiography not only identifies significant cardiac anomalies that may influence anesthetic management but also establishes the presence of aortic arch anomalies that may alter the surgical approach.

Patients with respiratory compromise and EA/TEF can present a particular challenge to the care team. Endotracheal intubation and the conversion to positive pressure ventilation can often lead to worsening respiratory status, because frequently the path of least resistance is through the fistula and into the GI tract. This leads to inadequate pulmonary ventilation. At the same time, the stomach becomes grossly distended, increasing intrathoracic pressure and further decreasing bronchial airflow. These children may require emergent bedside gastric decompression or fistula ligation to stabilize the pulmonary status. Any decision to place EA/TEF patients on positive pressure ventilation must be discussed among all team members.

The nature and timing of surgical intervention depend on the specific anatomic variant being treated. Surgical strategies include immediate primary repair, delayed primary repair, staged repair, and esophageal replacement. Immediate primary repair is appropriate for the majority of infants with EA/TEF. Rigid bronchoscopy immediately before surgical repair is often a useful adjunct to confirm the diagnosis before thoracotomy and to obtain useful information; the location of the fistula can be determined, the presence of a second upper pouch fistula can be detected, and the structural status of the trachea can be assessed (Fig. 84.3).

An open repair is approached through a right extrapleural thoracotomy, or through the left side if preoperative echocardiography documents a right-sided aortic arch. An extrapleural approach is preferred to avoid a pleural empyema if an anastomotic leak subsequently develops, but this is more of a historic and not evidence-based decision. The division of the fistula is the key step of the procedure.

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• **Fig. 84.3** Bronchoscopic view of tracheoesophageal fistula.

Fistula division allows stabilization of the pulmonary mechanics. The fistula is divided and the tracheal side closed transversely to prevent narrowing of the trachea. A primary anastomosis between the proximal esophageal pouch and the distal esophageal segment is then performed.[51]

Thorascopic repair of EA/TEF, although technically challenging, has become a standard mode of repair especially in full-term infants with relatively normal respiration. Thorascopic technique typically uses two 3-mm ports and one 5-mm port. Advocates of thorascopic repair have been able to demonstrate improved cosmoses, improved pain control, improved postoperative respiration, chest wall maldevelopment, and scoliosis, all known complications of neonatal thoracotomy. Leak and stricture rates are similar to open repair.[9]

Compared with open repair (OR), a longer operative time has been associated with a thoracoscopic approach (TR), although the TR procedure could possibly reduce the length of hospital stay, time to extubation, and first oral feeding time. Meanwhile, the occurrence rates for leaks, strictures, and pulmonary complications; the fundoplication rate of GERD; and blood loss were similar between the OR and TR groups.[114,115]

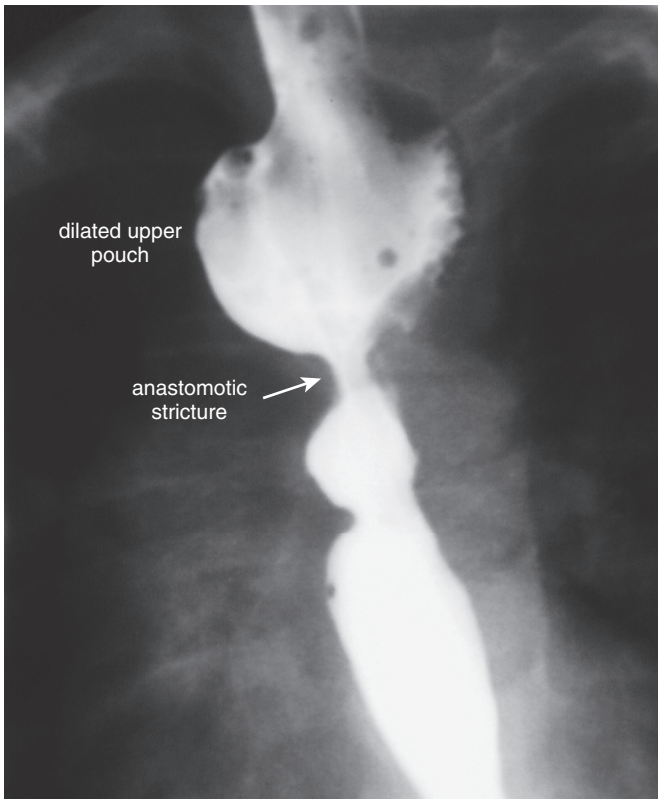
In most patients, a gap of some degree exists between the proximal and distal esophagus, requiring mobilization of both ends and still resulting in some degree of tension at the anastomosis. Anastomotic ischemia caused by overaggressive mobilization or excessive tension leads to fibrosis and stricture formation. The blood supply to the cervical esophagus originates proximally and extends distally through the submucosal plexus, allowing extensive mobilization of the upper pouch without causing ischemia at the distal tip. The blood supply to the normal thoracic esophagus derives from the intercostal vessels and is, therefore, more segmental. Whether or not this limits the ability to mobilize the distal fistula without causing ischemia is debated. If careful mobilization does not sufficiently reduce tension at the anastomosis, two options are available. One option is to lengthen the upper pouch by performing a circular or spiral myotomy. A second option is to employ a technique first described by Foker that obtains length by placing the two ends under tension for a prolonged period—up to 3 weeks in some patients—prior to primary anastamosis.[67] Although met with great resistance when first described,[24] it is now an accepted option and considered the first choice for repair of long-gap atresia by many surgeons.

The postoperative care of patients with primary esophageal repairs must be meticulous and conservative. Removal of the endotracheal tube should occur only after respiratory mechanics have been optimized, as failure of extubation may lead to aggressive bag-mask ventilation and reintubation—events that place the tracheal and esophageal repair at risk for disruption. The head of the bed is elevated and gastric acidity neutralized to minimize reflux injury to the healing anastomosis. After 5-7 days, a contrast esophagram is carefully performed with a water-soluble agent followed by barium. If no leak is demonstrated, oral feedings are initiated and the chest tube is removed. Small, asymptomatic leaks that are adequately controlled by the existing extrapleural chest tube may be managed nonoperatively and repeat studies performed until healing is documented. Large leaks and intrapleural leaks often mandate exploration for repair or diversion.

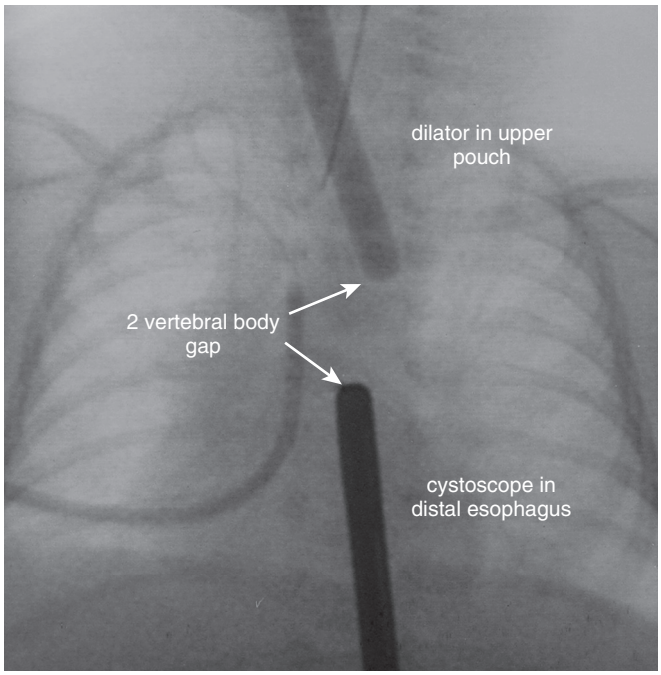
In many clinical situations, the described primary approach is neither feasible nor appropriate. In the premature infant with very low birth weight, or in any infant with a significant cardiac defect, respiratory compromise, or sepsis, primary anastomosis should be postponed until the patient is a better surgical candidate. If the anticipated surgical delay is brief, careful upper pouch suctioning and parenteral nutrition may be used until the delayed primary repair can be carried out. If a lengthy or indeterminate delay is expected, a staged approach may be required. This strategy provides temporizing measures that allow later esophageal repair to be undertaken electively. Typically, a gastrostomy tube is placed for decompression and feeding, and the fistula is divided via an extrapleural approach to protect the lungs from further injury. Later, a transpleural approach may be taken to restore esophageal continuity.

The list of postoperative complications that occur in this complex group of patients is long and varied. Beyond the immediate postsurgical period, when anastomotic leak is the most feared problem, anastomotic strictures represent the most common complications of surgical treatment, occurring in up to 40% of patients in some series.[45] Strictures result from fibrosis during healing, which in turn results from ischemia, excessive tension, leakage, or acid-peptic injury. An anastomotic stricture should be suspected whenever dysphagia or respiratory symptoms occur in a patient who had previously tolerated oral feedings. A contrast esophagram reliably demonstrates the stricture and

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• **Fig. 84.4** Barium esophagram demonstrating anastomotic stricture and upper pouch dilation.



• **Fig. 84.5** Measuring gap length in pure esophageal atresia.

often demonstrates distention of the upper pouch with posterior compression of the trachea—the so-called upper pouch syndrome (Fig. 84.4). Strictures are best treated by tangential dilation under fluoroscopic guidance and control of acid reflux. Near-occlusive strictures require placement of an indwelling transanastomotic guide line that can be used to pull sequential dilators safely through the stricture on a frequent basis. If pharmacologic suppression of gastric acid secretion fails to prevent recurrent strictures, an antireflux procedure may be required. Finally, a stricture refractory to aggressive management may require segmental resection.

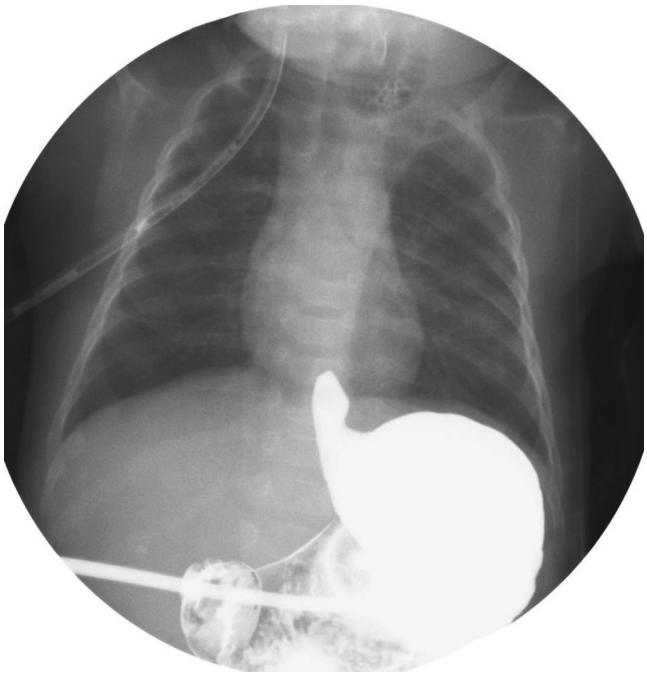
Recurrent fistulas occur in 5%-10% of cases and usually present with respiratory distress during feeding or with recurrent aspiration pneumonia.[22] Diagnosis is made with a dilute barium esophagram in the prone position. Most recurrent fistulas result from small, contained anastomotic leaks that cause chronic inflammatory changes and gradually erode back through the tracheal repair. Surgical options range from primary closure to segmental esophageal resection, and they must include interposition of healthy, well-vascularized soft tissue such as a pleural or strap muscle rotation flap. Some repairs can be approached from a cervical incision, which limits the complications associated with secondary leaks.

Functional disturbances of the esophagus are nearly universal after repair of EA/TEF. Occasionally, dysphagia is associated with severe esophageal dysmotility in the absence of a stricture. Solid-phase esophagography demonstrates that solid foods have great difficulty traversing the anastomosis and lower esophagus because of a lack of peristaltic force. In these situations, dietary modification and adjustment of feeding behavior may be all that can be offered. Gastroesophageal reflux (GER) disease is present to some degree in most of these patients and may be clinically significant in up to 50% of patients with tracheoesophageal malformations.[107] Some advocate lifelong follow-up care.[59] Deficient autonomic and enteric innervation, intrinsic developmental abnormalities of the lower esophageal muscle, shortening of the intra-abdominal esophagus, and distortion of the angle of His may all contribute to lower esophageal sphincter dysfunction in varying degrees. Lower esophageal sphincter incompetence is exacerbated by esophageal dysmotility, reducing clearance of gastric acid from the esophagus. Some degree of tracheomalacia is also expected in all patients with EA/TEF. Most patients exhibit the typical raspy cough caused by vibration of the weak and flattened tracheal wall, and they outgrow these minor symptoms with age.

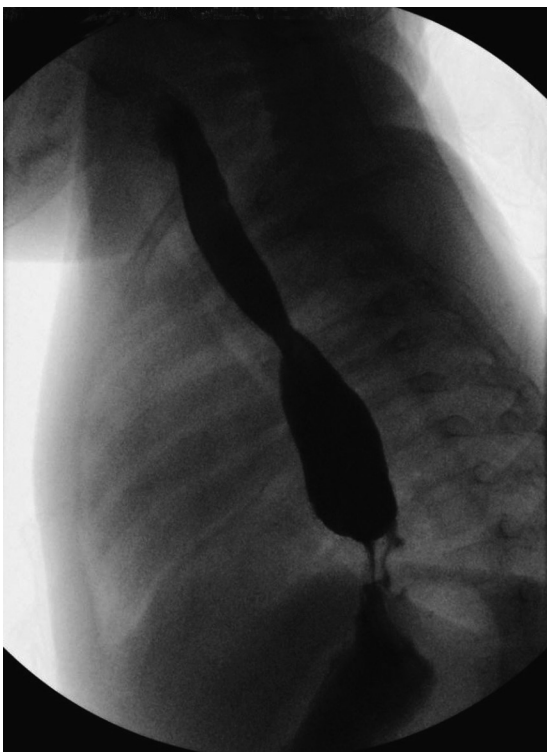
In patients with isolated EA, a long gap is anticipated, and primary repair, immediate or delayed, is not feasible. Historically, long-gap EA had been an absolute indication for esophageal substitution without attempts at staged primary repair. Over the past two decades, however, the proportion of patients with pure atresia who eventually undergo successful esophageal repair has increased dramatically, obviating esophageal substitution in a large number of children.[10,24] There is no universal agreement regarding the maximal gap that will permit esophageal repair.[76,97] However, a fluoroscopically measured gap of greater than four vertebral bodies with the segments in neutral position, or greater than two vertebral bodies (Fig. 84.5) with the segments stretched toward each other, portends a low

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likelihood of successful primary anastomosis. Elongating the upper and lower pouches over a 1- to 3-week period, followed by primary anastomosis, has been very successful at keeping the native esophagus and avoiding esophageal replacement.[24] Fig. 84.6 and Fig. 84.7 show preoperative and postoperative contrast images of a patient with a long-gap atresia of nearly seven vertebral bodies treated by elongation and primary repair. Reflux requiring fundoplication is common in these patients, as are dilations to relieve strictures. However, when compared with the multiple, significant complications associated with esophageal replacement using either small or large bowel, the Foker procedure requires strong consideration in all patients with long-gap esophageal atresia.[67,100] Esophageal replacement is reserved for those cases of long-gap atresia unsuitable for immediate or delayed primary repair, and when attempted primary repair has failed irretrievably because of leakage or stricture.



• **Fig. 84.6** Long-gap esophageal atresia. Note proximal air-filled upper pouch and small distal esophagus. Gap is approximately seven vertebral bodies in length.



• **Fig. 84.7** Same patient as in Fig. 84.6 after Foker repair and Nissen fundoplication. Patient is able to eat all foods without difficulty.

Long-term outcomes for all variants of EA/TEF have improved steadily over the last three to four decades.[11,36] Waterston and colleagues were the first to stratify patients on the basis of risk factors shown to affect prognosis and to recommend treatment strategy based on this stratification.[113] In this analysis, prognosis was dependent on birth weight, associated anomalies, and the presence of pneumonia. Many stratification schemes subsequently evolved, and Spitz and associates refined this prognostic model to include only birth weight and the presence of significant congenital heart disease (Table 84.1).[98] In the current era, most infants born with tracheoesophageal anomalies ultimately experience a positive outcome owing equally to refinements in surgical technique and to neonatal support over the past several decades.

Esophageal Duplications

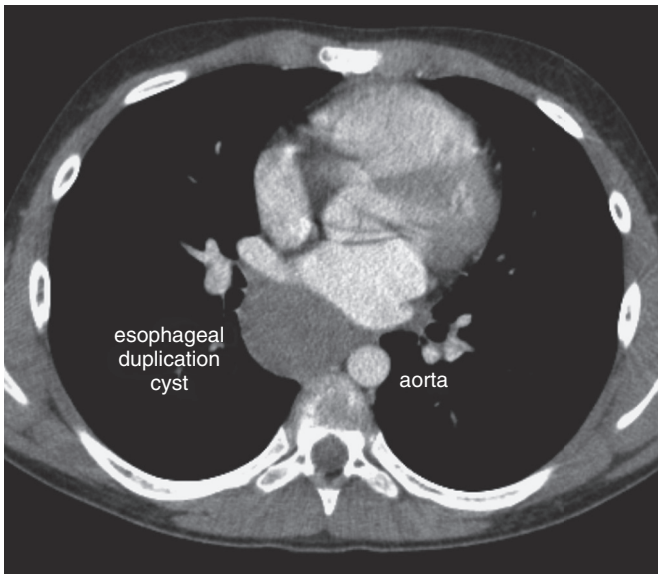
Esophageal duplication cysts are uncommon causes of esophageal obstruction during infancy. These structures result either from abnormalities in the vacuolization process that re-establishes the esophageal lumen after obliterative epithelial proliferation during early embryonic development, or from the "budding" and separation of a portion of the developing foregut. These structures are usually cystic, but they may be tubular and may be located within the muscular wall of the esophagus or exist separately in the posterior mediastinum. They contain an epithelial lining derived from any foregut structure: squamous, columnar, or pseudostratified ciliated respiratory epithelium. They may also contain gastric epithelium and pancreatic or adrenal rests.

TABLE 84.1 Determinants of Survival in Cases of Tracheoesophageal Malformation

Group	Characteristics	Survival
I	Birth weight >1500 g without CHD	97%
II	Birth weight <1500 g or CHD	59%
III	Birth weight <1500 g and CHD	22%

CHD, Congenital heart disease (major).

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• **Fig. 84.8** Esophageal duplication cyst demonstrated by computed tomography.

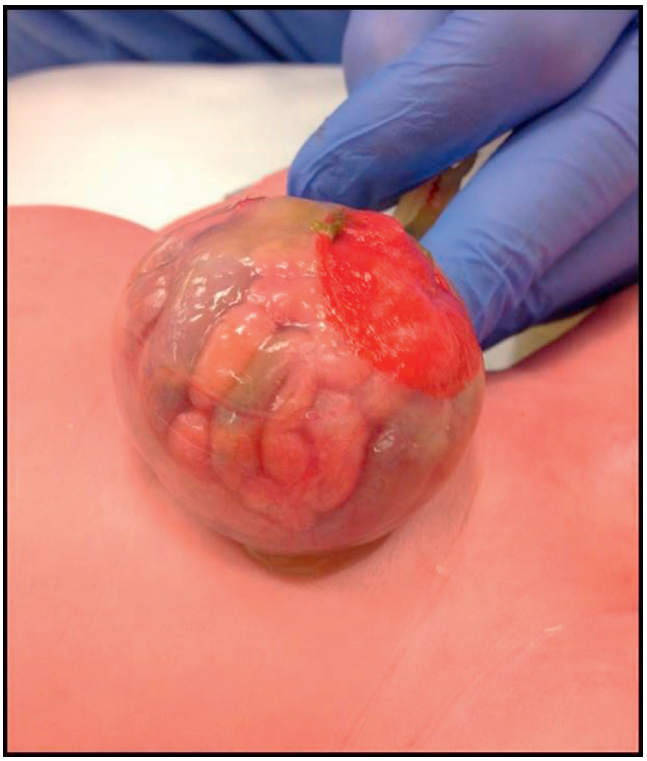
Infants with esophageal duplication cysts are usually asymptomatic, and the diagnosis is made when chest radiography unexpectedly demonstrates a mediastinal mass. Some infants, however, experience feeding difficulties or respiratory compromise if the cystic structure compresses the adjacent esophagus or trachea. Cysts containing gastric mucosa may present with complications of acid-induced injury: upper gastrointestinal hemorrhage, ulceration, perforation, or erosion into the bronchial tree.

Although the diagnosis may be suggested by a plain chest radiograph or by contrast esophagram, computed tomography is definitive and helpful in planning the operative approach (Fig. 84.8). Magnetic resonance imaging provides additional information about the status of the spinal cord, which may be abnormal; this information should be obtained in all patients with a vertebral abnormality or a cystic structure in close proximity to the spine. Esophagoscopy is unnecessary and potentially harmful.

Surgical treatment involves resection of the cyst and repair of any esophageal defect. This may require a thoracotomy, but many lesions lend themselves to thoracoscopic resection. Cysts complicated by infection with abscess formation or by internal hemorrhage may expand rapidly and may require urgent drainage before resection. Duplications that are deemed unresectable because of their extensive nature, which may include extension into the abdomen, should be treated by stripping the mucosa from the duplication and leaving the muscular remnant to heal to the existing esophageal wall. Excellent results can be expected in most patients.

Congenital Diaphragmatic Hernia

See Chapter 66.



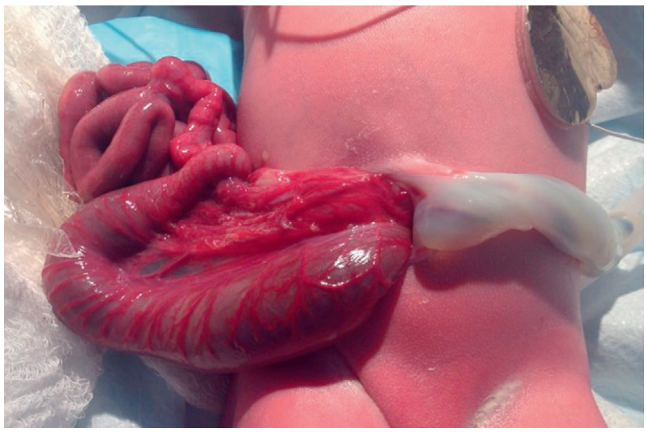
• **Fig. 84.9** Small omphalocele with open Meckel diverticulum.

Abdominal Wall Defects

The most common abdominal wall defects seen in neonates are omphalocele and gastroschisis, occurring in approximately 4 per 10,000 live births. These conditions result from different developmental miscues and manifest as distinct clinical entities. In the case of omphalocele, a central abdominal wall defect of variable size is covered by a domelike mesenchymal membrane composed of amnion. The umbilical cord connects to the central portion of this membrane (Fig. 84.9). The underlying abdominal organs are protected from exposure to amniotic fluid. In gastroschisis, the defect is usually smaller and located to the right of the umbilical attachment. There is no protective membranous covering. The abdominal contents, therefore, are eviscerated and suspended in amniotic fluid during gestation (Fig. 84.10).

Omphalocele results from a failure in the folding mechanism that converts the flat trilaminar germ disc into a complex "tubular" structure starting at about 5 weeks' gestation. The lateral body folds and craniocaudal folds converge at the umbilical ring, which contracts, closing the ventral abdominal wall. In patients with omphalocele, this ring fails to contract and leaves a round defect of variable size and a corresponding sac composed of amnion. The liver and small intestine usually occupy a portion of the sac, along with a variable amount of other abdominal contents. The underlying failure of umbilical ring closure may be related to aberrant development and migration of abdominal wall muscular components, or to failure of the developing midgut to

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• **Fig. 84.10** Typical gastroschisis defect with mild "peel."



• **Fig. 84.11** Pentalogy of Cantrell.

return to the abdominal cavity after a period of herniation into the umbilical stalk. Rarely, the defect is cephalad to the umbilicus, producing a complex deformity referred to as the pentalogy of Cantrell: sternal, diaphragmatic, and pericardial defects; upper abdominal omphalocele; and ectopia cordis (Fig. 84.11). When centered below the umbilicus, bladder or cloacal exstrophy may occur. The cause of gastroschisis is equally unclear, but it may involve a rupture of the umbilical stalk during the period of midgut herniation. Gastroschisis is usually described as an abdominal wall defect, to the right of a normally inserted umbilical cord, without membranous covering of the extruded organs. Etiologically it has been suggested that gastroschisis represents a failure in the normal attachment between umbilical cord and umbilical ring.[83] Competing theories involving thromboembolic infarction of the developing abdominal wall or a failure of mesenchymal migration are less convincing.



• **Fig. 84.12** Giant omphalocele with predominant liver component.

The factors influencing morbidity and survival in these two distinct conditions are very different. Omphalocele, with a stable incidence of about 2-2.5 per 10,000 live births, is associated with other structural or genetic defects in 50%-75% of affected infants.[15] These associated anomalies, which may involve the cardiovascular, gastrointestinal, genitourinary, or central nervous systems, account for most of the morbidity in these patients. Because the abdominal contents are protected throughout gestation, little morbidity accrues from injury to the intestinal tract. The discrepancy between the volume of eviscerated abdominal organs and the size of the abdominal cavity—the "loss of domain"—accounts for the other major source of morbidity in these patients. In a giant omphalocele (Fig. 84.12), eventual closure of the abdominal wall by any means may be challenging, leading to a variety of problems related to structural integrity of the torso, chronic ventral hernias, and posture and gait development. Additionally, infants with giant omphaloceles may have a high incidence of pulmonary hypoplasia, resulting in respiratory compromise and pulmonary hypertension.[4]

The syndromes most often associated with omphalocele include the VACTERL association, Beckwith-Wiedemann syndrome (macrosomia, macroglossia, visceromegaly, hemihypertrophy, hypoglycemia, renal pathology), EEC syndrome (ectodermal dysplasia, ectrodactyly, cleft palate), and OEIS complex (omphalocele, exstrophy, imperforate anus, spinal defects). An oft-reported association of omphalocele with cryptorchidism is unsubstantiated. Chromosomal abnormalities, including trisomies 13, 18, and 21, occur in 25%-50% of affected patients. The presence of a small sac, the absence of liver in the sac, and the presence of other malformations strongly predict an abnormal karyotype.[20,26]

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Gastroschisis, in contrast, is sporadic in the vast majority of cases. The incidence of gastroschisis is approximately 1.5 per 10,000 live births and increasing. Risk factors for gastroschisis include young maternal age, lower socioeconomic status, and exposure to external agents, such as vasoconstricting decongestants, nonsteroidal anti-inflammatory agents, cocaine, and possibly pesticides/herbicides.[29,106] The 5%-20% incidence of associated defects is lower than for omphalocele, and it represents mostly intestinal atresias directly associated with ischemic or mechanical injury to the eviscerated bowel during gestation. Abnormalities not directly related to the abdominal wall defect are uncommon.

Morbidity in infants with gastroschisis, as opposed to those with omphalocele, is almost entirely related to intestinal dysfunction caused by in utero injury to the eviscerated bowel. The spectrum of injury displayed by the eviscerated bowel in gastroschisis ranges from mild to catastrophic. Morphologically, the bowel appears edematous, matted, and foreshortened. Often, the mass appears to be contained within an inflammatory rind—the "peel" of gastroschisis (Fig. 84.13). Histologically, the intestine is characterized by villous atrophy and blunting, submucosal fibrosis, muscular hypertrophy and hyperplasia, and serosal inflammation.[52,99] The cause of injury is unclear, but it is probably related to a combination of two separate insults. Exposure to amniotic fluid appears to be a major contributing factor, as amniotic fluid exchange can prevent peel formation.[2] The second cause of injury may be the partial closure of the defect around the base of the eviscerated intestinal mass. This causes progressive constriction around the intestinal mesentery, resulting in the obstruction of luminal, lymphatic, and venous outflow. Intra-abdominal bowel distension is associated with increased postnatal complications, including delay to full feeds and increased duration of hospital stay in infants with prenatally diagnosed gastroschisis; however, this association seems to be limited to those with multiple loops of dilated intra-abdominal bowel.[42]

The functional consequences of these structural changes include impaired absorption, reduced brush border enzyme synthesis, and a prolonged motility disorder related to rigidity of the bowel wall and possible derangements in the production of enteric neurotransmitters such as nitric oxide.[5] These changes concur with the clinical observation that infants with a dense peel suffer prolonged gastrointestinal dysfunction that requires precise nutritional management. This nutritional failure and the complications arising from prolonged enteral and parenteral nutritional therapy constitute a significant proportion of the adverse clinical outcomes in these patients.

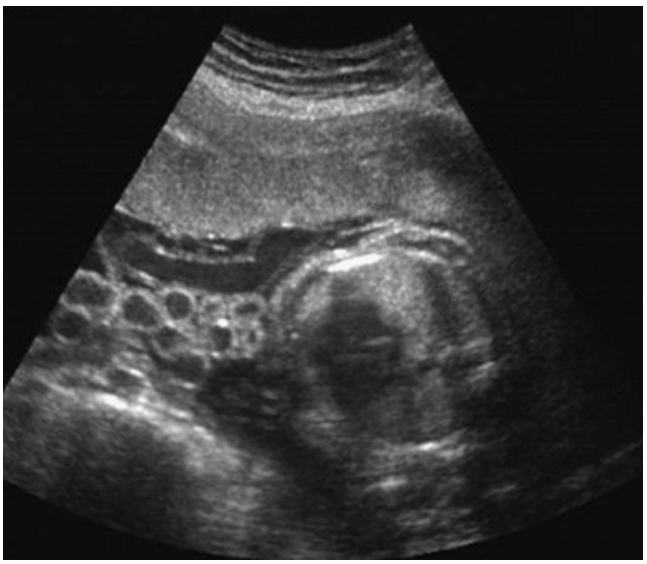
The prenatal diagnosis of abdominal wall defects by fetal ultrasonography is well established (Fig. 84.14). Any uncertainty in distinguishing omphalocele from gastroschisis may be eliminated by measuring amniotic fluid α-fetoprotein levels, which should be elevated in gastroschisis only. A prenatal diagnosis of omphalocele should prompt a thorough sonographic survey of the entire fetus to evaluate for associated anomalies. Chromosomal analysis may also be helpful in determining postnatal management and prognosis.

The obstetric decisions related to timing and route of delivery continue to engender considerable debate. In the case of omphalocele, if the membrane is intact, the pregnancy should be carried to term if possible, because early delivery has no theoretical benefit for the fetus. Cesarean delivery has historically been recommended to prevent rupture of the omphalocele membrane (Fig. 84.15), which would necessitate emergent surgical intervention without the benefit of preoperative evaluation and stabilization. Studies, however, have suggested that the route of delivery has no effect on morbidity or prognosis in abdominal wall defects in general.[3,40,87] Recommendations regarding the route of delivery for a fetus with a giant omphalocele or associated anomalies should be individualized.

Early delivery after lung maturation has been enthusiastically endorsed by some, but definitive evidence that this strategy confers any statistically verifiable benefit is lacking. A more selective approach in which early delivery

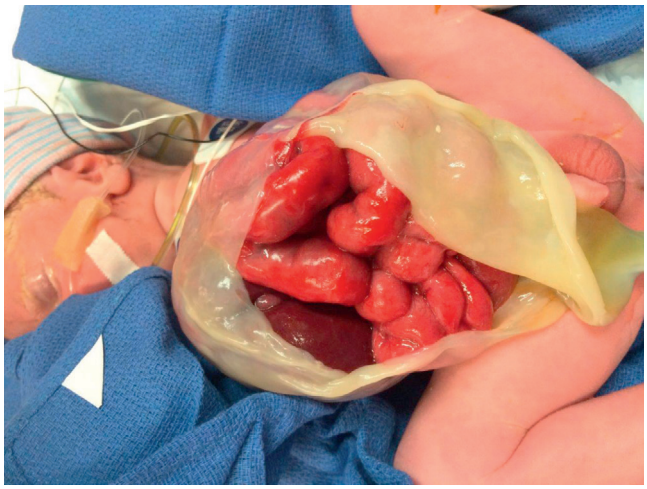


• **Fig. 84.13** Gastroschisis with thick peel.



• **Fig. 84.14** Ultrasound of fetus with gastroschisis.

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• **Fig. 84.15** Ruptured omphalocele.

is undertaken when sonographic surveillance suggests progressive bowel injury, as defined by bowel dilation and wall thickening, has yielded numerous conflicting reports.[41,64] Until the efficacy of selective early delivery for gastroschisis has been studied in a prospective, randomized fashion, support for this strategy will remain anecdotal.[31] Regardless of the timing of delivery, almost all infants with gastroschisis may be delivered vaginally without increased injury to the bowel.

The surgical goal of establishing complete fascial and skin closure without causing further injury to the underlying bowel is common to patients with both omphalocele and those with gastroschisis. The surgical strategies applied to these two conditions are, however, quite different. In patients with gastroschisis, urgent closure or coverage of the defect is of the highest priority to limit intestinal injury and reduce morbidity. The eviscerated intestine should be completely covered in the delivery room to prevent water and heat loss through evaporation, conduction, and convection. Temporary coverage can be provided by wrapping the torso with transparent plastic film or by placing the baby in a transparent surgical "bowel bag" and cinching the drawstring closed gently under the axillae. This arrangement effectively limits heat and water loss, and it allows the intestine to be visualized at all times so that inadvertent volvulus and ischemia can be detected and reversed. A lateral decubitus position is often better tolerated than supine. A gastric decompression tube is placed immediately to prevent intestinal dilation. Great care must be taken to keep the bowel directly above the belly and not draped to one side or the other while waiting for surgical repair. This keeps the vessels supplying the exposed bowel—the superior mesenteric artery and vein—from kinking and further compromising the bowel.

Many infants with gastroschisis are born prematurely, and aggressive respiratory care, including supplemental oxygen, endotracheal intubation, and intratracheal surfactant, may be necessary. Intravenous access is established for fluid resuscitation and administration of broad-spectrum



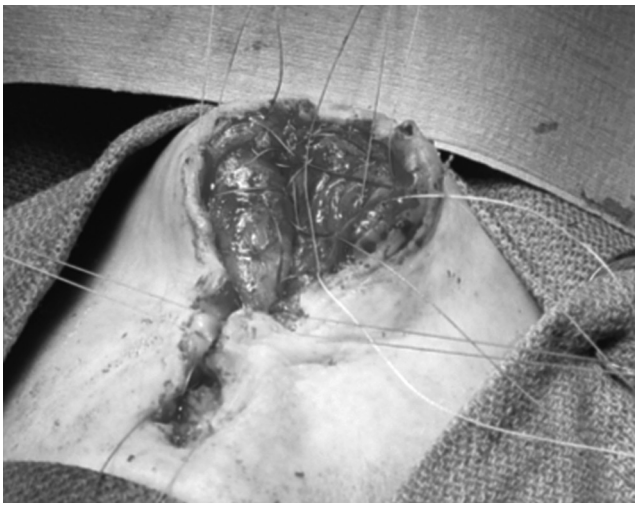
• **Fig. 84.16** Gastroschisis in silo bag for delayed primary closure of abdominal wall defects.

antibiotics. As soon as the baby is physiologically stable, surgical management is advisable. Unnecessary delay only compounds the problems of further bowel swelling and possible ischemia.

Gastroschisis can be managed by either primary or staged closure, depending on the size discrepancy and the infant's physiologic status. Although 60% to 70% of gastroschisis cases can be closed primarily, the decision to do so is individualized in each circumstance. As the intestine is returned to the abdominal cavity and the abdominal fascia approximated, increased abdominal pressure may prevent safe, complete closure. In infants with preexisting pulmonary compromise, the restriction of diaphragmatic excursion may decrease extrinsic compliance and cause ventilatory pressures to rise to unacceptable levels. Increased abdominal pressures may also impair mesenteric, hepatic, and renal perfusion. Trials of a "plastic closure" for gastroschisis have reported good success.[85] In this technique, the bowel is returned to the abdomen in the NICU, and the umbilicus is placed over the defect with a dressing. The defect closes on its own without the need for sutures. A number of these patients have a resulting umbilical hernia, most of which close spontaneously with time.

When respiratory problems or abdominal pressures prevent safe primary closure, placement of a temporary prosthetic "silo" allows for more gradual reduction of the eviscerated intestine into the abdominal cavity and delayed primary closure at a later time (Fig. 84.16). Previous retrospective studies had documented improved survival with primary closure, prompting an era marked by an aggressive approach to immediate closure. Appreciation of the fact that this survival advantage simply represented a selection bias, along with recognition of the deleterious effects of high

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• **Fig. 84.17** Final reduction and closure of abdominal wall defect after silo reduction.

intra-abdominal pressures, has led to a more liberal use of temporary silo coverage. Current commercially available presized silos are now available that can be placed in the NICU, obviating the need for a trip to the operating room. Some have suggested that prolonged silo placement leads to increased wound infection rates and fascial dehiscence, but these are small retrospective studies.

When a silo has been constructed, the intestinal contents are squeezed back into the abdominal cavity in daily increments. Abdominal wall cellulitis related to the open wound and presence of the prosthetic material limits the use of a silo to a period of approximately 1 week. When reduction of the silo contents is complete, the patient is returned to the operating room for final closure (Fig. 84.17). Broad-spectrum antibiotics are given until the silo is removed. Placement of a silo does not preclude postoperative extubation, and spontaneous ventilation during staged closure is preferable to positive-pressure ventilation. Infants should be maintained on a ventilator to allow for neuromuscular paralysis in only the most severe cases of abdominovisceral disproportion requiring aggressive closure. When postoperative mechanical ventilation is required, increased levels of positive end-expiratory pressure may be necessary to maintain functional residual capacity and optimize compliance.

During staged closure, parenteral nutrition is administered through a peripherally inserted central venous catheter, or one placed at the time of silo placement. Complete bowel rest and gastric decompression are maintained during reduction of the silo. After abdominal wall closure, whether primary or delayed, enteral feedings should be initiated only after clinical resolution of the ileus is apparent—cessation of bilious gastric aspirates, presence of bowel sounds, and passage of meconium. Advancement of enteral feedings should be conservative, as infants with gastroschisis, especially those with a dense peel requiring silo closure, are extremely sensitive to changes in nutritional substrate load. Delayed enteral feedings and prolonged parenteral infusions are a principal source of morbidity in this group. Development of cholestatic jaundice is common, and hepatic dysfunction and fibrosis may occur in a small number of refractory patients. Early administration of partial enteral mini-feedings, meticulous avoidance of infection, and reduction of copper and manganese have all been advocated to reduce the incidence of cholestatic liver disease.[61]

The coexistence of intestinal atresias with gastroschisis deserves special mention. Intestinal atresias occur in 5%-25% of patients with gastroschisis, and they are one of several independent variables that have a negative impact on prognosis in gastroschisis. In a patient who fails to exhibit intestinal patency within 1 month of abdominal wall closure, a water-soluble lower gastrointestinal contrast study should be obtained to exclude the presence of an unrecognized atresia. Introduction of exclusive human milk feedings after gastric repair has been shown to decrease the time to achieve full enteral feeds and time to discharge.[48]

The mortality of infants with complex gastroschisis (gastroschisis with atresia, necrosis, perforation, or volvulus) present in 17% of cases with gastroschisis was more than double that of simple gastroschisis. Significantly different outcome was found for the following parameters: Infants with complex gastroschisis are started on enteral feedings later, and they take longer to full enteral feedings with a subsequent longer duration of parenteral nutrition. Their risk of sepsis, short bowel syndrome, and necrotizing enterocolitis is higher. They stay longer in hospital and are more likely to be sent home with enteral tube feedings and parenteral nutrition.[6]

The surgical options for abdominal wall closure for omphalocele are similar to those for gastroschisis. The main difference relates to the preoperative management of these patients. A careful assessment of physiologic status and a thorough search for syndromic and chromosomal anomalies are imperative to guide anesthetic management and to identify prognostic factors. The presence of a protective membrane allows a careful and unhurried preoperative evaluation.

As defined previously, the factors affecting prognosis for gastroschisis and omphalocele are quite distinct. Prematurity, degree of peel formation, and associated atresias account for most of the morbidity in gastroschisis, which has an overall survival rate of 90%-95%.[34,69] Most of the deaths attributed to gastroschisis are related to perioperative complications, such as sepsis, necrotizing enterocolitis, and abdominal visceral ischemia, or to late hepatic failure caused by parenteral nutrition-related cholestatic disease. Surprisingly, midgut volvulus related to obligatory intestinal malrotation in these patients is virtually nonexistent, possibly because of the development of peritoneal adhesions that limit mobility of the intestine. The reported survival rate for infants with omphalocele ranges from 30%-80%.[68,116] When mortality caused by associated malformations is excluded, the survival rates approach those for gastroschisis. Long-term tolerance of enteral feedings, as well as physical

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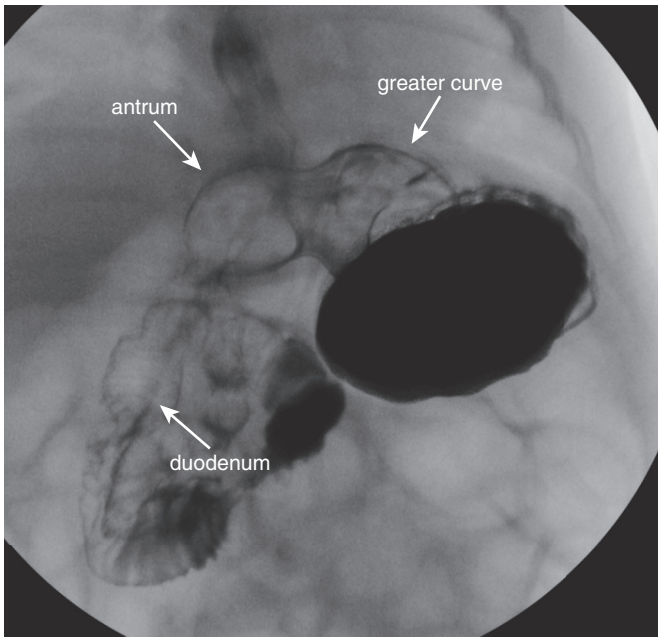
growth and development, are usually normal after 1 or 2 years, even in severe cases. With thoughtful management and attention to the prevention of parenteral nutrition–related hepatic complications, most infants born with abdominal wall defects should survive with an acceptable quality of life.

Gastric Volvulus

Congenital deficiencies of mesenteric fixation of the stomach to the surrounding structures predispose to gastric volvulus and can take two distinct forms. Absence or laxity of the gastrohepatic and gastrosplenic ligaments allows the stomach to rotate around its longitudinal axis, producing an organoaxial volvulus. Similar abnormalities of the gastrophrenic ligament and duodenal attachments allow rotation around the stomach's transverse axis, referred to as a *mesentericoaxial volvulus*. Organoaxial volvulus is the more common of the two types in infants and children. A strong association has been found between gastric volvulus and malrotation, asplenia, and congenital abnormalities of the diaphragm.[60] Gastric volvulus may also be associated with conditions that result in gastric distention, such as aerophagia and hypertrophic pyloric stenosis. Because these entities all result in absence or stretching of stabilizing attachments, a causative role is assumed.

Although gastric volvulus can occur as either an acute or a chronic problem, the acute form is more common in children. The classic presentation of sudden epigastric pain, retching without emesis, and inability to advance a nasogastric tube into the stomach is rarely encountered in the actual clinical setting. Children may experience emesis, which can be bilious or nonbilious, and may not have abdominal distention. Intermittent gastric volvulus may be considered in the workup of infants presenting with apparent life-threatening events.[72] Any combination of symptoms suggesting a partial or complete proximal mechanical obstruction may be present. Profound physiologic decompensation, hemodynamic instability, or unrelenting metabolic acidosis suggests strangulation, ischemic necrosis, and possibly perforation.

Radiologic assessment can reveal several characteristic findings. On plain abdominal radiographs, massive gastric dilation can usually be seen, often with a distinct incisura pointing toward the right upper quadrant. The spleen and small intestine may be displaced inferiorly. If a contrast study has been attempted, the contrast column may be confined to the esophagus, with a long, gradual tapering at the bottom. Occasionally, a paraesophageal hiatal hernia is detected. Classic findings on barium upper gastrointestinal study include transverse lie of the stomach and inversion of the greater curvature and pylorus (Fig. 84.18). Operative treatment of acute gastric volvulus includes gastric decompression by nasogastric suction or needle aspiration and reduction of the volvulus. Coexisting anomalies, such as malrotation and diaphragmatic defects, should be corrected, and recurrence is rare.



• **Fig. 84.18** Upper gastrointestinal contrast study demonstrating gastric volvulus with rotation of the greater curve and antrum of the stomach above the duodenal bulb.

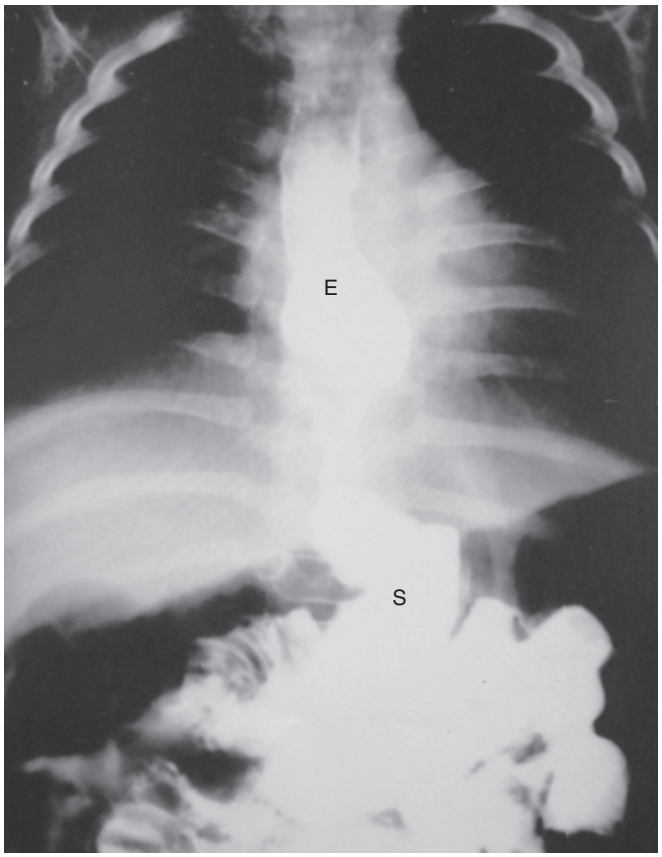
Microgastria

Congenital microgastria is a rare anomaly (only 43 cases have been reported) in which the stomach is characterized by very small volume, a tubular shape, and abnormal fixation. Gastric volume does not undergo complete compensatory growth and remains relatively small as the child ages.[8] Associated abnormalities include megaesophagus, GER, intrinsic duodenal obstruction, malrotation, biliary anomalies, situs inversus, asplenia, and skeletal defects.[86]

Microgastria presents with vomiting and failure to thrive in the infant, often associated with persistent diarrhea. Vomiting may be caused by gastric insufficiency, GER, or duodenal obstruction. Diarrhea is presumed to be due to rapid gastric transit and dumping. The diagnosis is established by contrast upper gastrointestinal tract study, which reveals a small stomach with a transverse lie and frequently a large, patulous esophagus (Fig. 84.19). Particular attention should be given to the anatomy of the duodenum and the ligament of Treitz.

The initial management of microgastria includes continuous drip enteral feeding and supplemental parenteral nutrition. When continuous feedings can be maintained for several weeks, the stomach may undergo some enlargement, allowing for a gradual transition to bolus and ad libitum feedings. Antireflux precautions, including small, frequent meals, may be required indefinitely. Although case reports of successful management by gastrojejunostomy exist, the favored surgical approach involves gastric augmentation with a Roux-en-Y jejunal reservoir.[110]

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• **Fig. 84.19** Upper gastrointestinal contrast study of patient with microgastria (*S*) and megaesophagus (*E*).

Gastric Perforation

The causes of gastric perforation in neonates can be categorized as traumatic, ischemic, or spontaneous. In addition, the use of postnatal steroids for bronchopulmonary dysplasia (possibly in combination with cyclooxygenase inhibitors for ductal closure) has been implicated. Traumatic perforations are generally caused by puncture of the stomach during placement of a gastric tube, or by gastric distention from bag-mask ventilation or positive-pressure ventilation in an infant with a tracheoesophageal fistula. Usually these appear as short lacerations or discrete puncture wounds. Ischemic perforations occur in the setting of severe physiologic stress, such as extreme prematurity, perinatal asphyxia, or necrotizing enterocolitis. The pathophysiology of these lesions is presumed to be associated with a reduction in submucosal blood flow resulting in impaired mucosal defense and/or focal infarction of the gastric wall. It is possible that some of these lesions represent perforated stress ulcers. Rarely, a healthy neonate presents with a spontaneous gastric perforation of unknown cause. The most common location is high on the greater curvature near the gastroesophageal junction.

The most constant diagnostic feature of gastric perforation in the neonate is massive pneumoperitoneum, unless the perforation is posterior and contained within the lesser sac. Surgical management is individualized to either simple debridement and closure or closure around a temporary gastrostomy tube. Extensive gastric resections have not been necessary. Outcomes depend on the cause of the perforation and any associated disease, such as respiratory failure and complex congenital malformations.

Lactobezoars

Lactobezoars are compact aggregations of undigested milk constituents that develop within the gastric lumen in infants. Little is known about their underlying cause, although a single etiology is unlikely. Historically, they were believed to result from commercial formulas of high caloric density, particularly those rich in casein protein, which precipitated in the stomachs of premature neonates. Lactobezoars, however, have been reported in term neonates and older infants on diets of human milk and homogenized cow milk.[89,108]

The majority of infants with lactobezoars present with abdominal distention, nonbilious emesis, and diarrhea. A palpable mass may be detectable on physical examination. Plain radiographs often display a frothy appearance in the gastric lumen. An upper gastrointestinal tract contrast series is diagnostic. Ultrasonography, which can detect a hyperechoic intraluminal gastric mass, may also be used to establish the diagnosis.[65] Treatment is nonsurgical in the great majority of patients who do not present with perforation. Simple withholding of enteral feedings and administration of parenteral nutrition usually results in spontaneous resolution of the bezoar; gastric lavage may hasten this process.[21] After follow-up imaging studies document resolution, enteral feedings can be reinstituted using the same formula. Recurrence has not been reported.

Pyloric Atresia

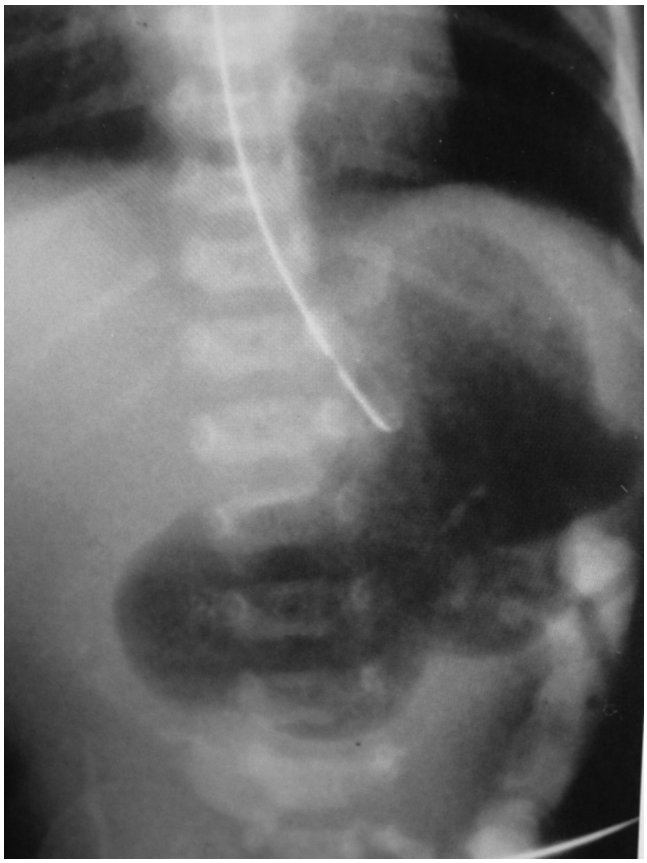
Congenital partial or complete gastric outlet obstructions are rare causes of feeding intolerance in infants. The obstruction may involve either the antrum or the pylorus and may take the form of a segmental defect (gap), which is sometimes bridged by a fibrous cord, or a membrane (web), which can have one or more apertures through which gastric contents pass. Histologically, such membranes consist of mucosa and submucosa without a muscularis. Prepyloric membranes become redundant after exposure to antegrade propulsive pressures, creating a "windsock" web that can prolapse through the pyloric channel. Pyloric webs account for two-thirds of these obstructions, pyloric atresia accounts for about a quarter, and most of the remainder are antral webs and atresias. Another rare cause for the obstruction is the presence of ectopic pancreatic tissue within the submucosa of the pyloric channel that bulges into the lumen and causes a partial obstruction.

The etiology of antral and pyloric atresia is not understood. An in utero vascular accident, such as results in jejunoileal atresias, is unlikely because of the stomach's redundant blood supply. As the stomach (unlike the duodenum) does

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not undergo a solid embryonic phase, failure of recanalization cannot account for these anomalies. Instead, some form of foregut segmentation mechanism is proposed but unproved. A genetic cause has been identified for some cases of pyloric atresia that occur in association with epidermolysis bullosa lethalis (Herlitz and Carmi syndromes), which is inherited in an autosomal recessive manner. A hemidesmosome defect has been identified in the gastric mucosal epithelium in this syndrome, and genetic studies have documented a variety of mutations in the genes coding for cell-surface beta 4 integrins.[66] This condition is marked by extreme mucocutaneous fragility and is usually lethal in the first year of life.

Complete membranes or atresias appear in the first few days of life as acute gastric outlet obstruction with nonbilious vomiting. There is often a history of maternal polyhydramnios. Gastric distention leading to respiratory compromise can occur, and frank gastric perforation has been reported as early as 12 hours of life. Incomplete gastric outlet obstruction caused by perforated membranes or heterotopic pancreatic tissue can present early in the neonatal period or later in childhood. Radiologic evaluation reveals a large gastric air bubble, with little or no gas in the distal intestine (Fig. 84.20). Because neonatal gastric hypotonia can reproduce these radiographic findings, upper gastrointestinal tract contrast studies are mandatory. These studies either show nonfilling of the duodenum or delineate the membrane when viewed laterally. Ectopic pancreatic tissue can cause an eccentric protrusion into the pyloric channel.



• **Fig. 84.20** Plain radiograph of gastric bubble in patient with pyloric atresia.

Preoperative resuscitation and gastric decompression are necessary in infants with complete gastric outlet obstruction. A chloride-responsive contraction alkalosis is often seen and requires specific measures to restore fluid volume and correct chloride and potassium deficits. Prolonged vomiting in the neonate can also lead to profound hypoglycemia, which must be anticipated and corrected. In general, webs can be excised and closed transversely to avoid stenosis. Complete atresias with anatomic disconnection can usually be corrected by primary anastomosis, such as gastroduodenostomy. Gastrojejunostomy is poorly tolerated in the neonate and should be avoided whenever possible. Recognition of windsock deformities and distal atresias by passage of a balloon catheter proximally and distally can be helpful in defining the exact anatomy and in detecting additional distal obstructions. Ectopic pancreatic tissue in the pylorus requires excision of the mass and reconstruction of the pylorus.

Hypertrophic Pyloric Stenosis

Hypertrophic pyloric stenosis (HPS) is an acquired condition in which the circumferential muscle layer of the pyloric sphincter becomes thickened, resulting in narrowing and elongation of the pyloric channel. This produces a high-grade gastric outlet obstruction with compensatory dilation, hypertrophy, and hyperperistalsis of the stomach. The incidence of HPS ranges between 0.1% and 1% in the general population and appears to be rising. A longitudinal study using ultrasound in 1400 randomly selected term neonates documented that all nine infants (0.65%) in whom HPS later developed had normal pyloric dimensions at birth.[84] There is a significant male predominance of about 4:1, although the long-held belief that HPS primarily afflicts first-born males is unproven. The incidence in whites exceeds that in blacks by several-fold; the incidence in Asian infants is low. The transmission of HPS appears to involve multifactorial threshold inheritance or the effects of multiple interacting loci. Transmission from mothers is more common than from fathers: HPS develops in 19% of boys and 7% of girls whose mothers had HPS as infants, and in 5% of boys and 2.5% of girls whose fathers were previously affected.[63]

The pathophysiology underlying pyloric dysfunction in HPS is undetermined. Observations of decreased ganglion cell density and elevated levels of prostaglandins E_2 and F_2 have not been causally linked to the development of HPS. Gastric outlet obstruction owing to pylorospasm has been reported in neonates receiving prostaglandin infusions, but pyloric dysfunction in these infants does not lead to muscular hypertrophy.[62]

Perhaps a more promising hypothesis for the pathophysiology of HPS is a primary abnormality of the enteric nervous system (ENS). Axonal degeneration in both the myenteric plexus and the intramuscular nerves has been

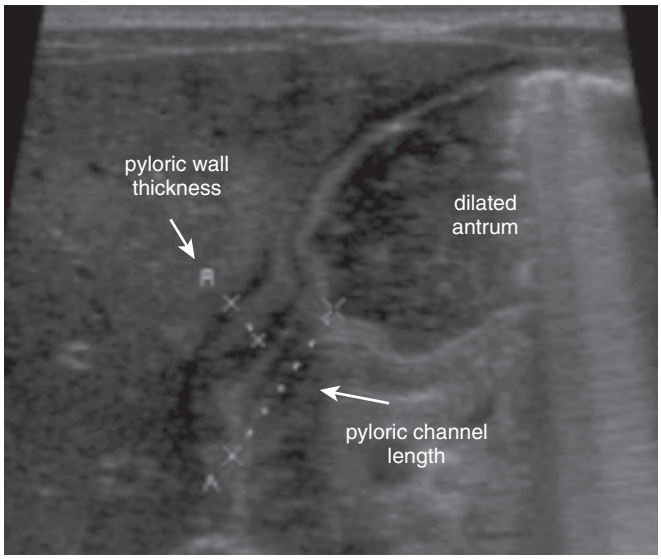
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observed in patients with HPS. Studies have documented decreased and disordered innervation of the circumferential muscle layer in specimens of pyloric muscle taken at the time of pyloromyotomy.[47,53] Furthermore, the muscle layer in HPS appears to be nearly devoid of neurotrophins—peptides that govern differentiation and survival of ENS neurons.[33] Circumstantial evidence exists to suggest that such neural immaturity is transient, consistent with the observation that HPS does not recur after reconstitution of the pyloric sphincter after pyloromyotomy.[46] Immunohistochemical staining for neuropeptides has revealed a marked reduction in a variety of neuropeptides, such as gastrin-releasing peptide, vasoactive intestinal peptide, somatostatin, and substance P, in patients with HPS.[1] Nitric oxide synthase, which can be identified in significant concentrations in the circular and longitudinal pyloric muscle layers and the myenteric plexus in normal controls, has been shown to be selectively absent in the circular muscle layer in patients with HPS.[109] This has also been documented for nitric oxide synthase mRNA.[49] A deficiency of nitric oxide, a ubiquitous paracrine and neurocrine mediator of smooth muscle relaxation, might be a final common pathway in the dysregulation of pyloric function in HPS.

The typical patient is a term male infant between 3 and 6 weeks of age who has progressive, nonbilious, projectile vomiting. Many infants with HPS are significantly dehydrated at the time of presentation, and chemistry analyses may reflect a hypochloremic, hypokalemic, contraction metabolic alkalosis with paradoxical aciduria. Significant hypoglycemia can also be present and may precipitate seizures. Unconjugated hyperbilirubinemia is common and correlates with a decrease in hepatic glucuronyl transferase activity. This jaundice is transient and resolves as soon as the gastric outlet obstruction is corrected, making it attractive to speculate that the hepatic defect is secondary to abnormal enteroendocrine feedback between the stomach and the hepatocyte.

The hallmark of the diagnosis is the finding of a small, mobile, ovoid mass in the epigastrium. The process of detecting this mass, the "olive," on examination may be quite difficult. A positive examination is very accurate, with a selectivity value of more than 97%.[28] If the pylorus is unequivocally felt, the diagnosis is established, and no further diagnostic maneuvers are necessary.

If the pylorus is not detected and the clinical presentation is sufficiently suggestive to warrant further evaluation, radiologic evaluation can be definitive. Real-time ultrasonography has supplanted barium upper gastrointestinal tract study as the procedure of choice. The hypertrophied pylorus appears to have a characteristic appearance on B-mode ultrasound, and measurement of pyloric dimensions accurately establishes the diagnosis of HPS. Parameters measured include overall diameter, single wall thickness, and pyloric channel length, with the latter two being the most commonly used (Fig. 84.21). Measurements found to have greater than 90% positive predictive value include overall diameter of 17 mm or more, muscular wall thickness of 4 mm or greater, and



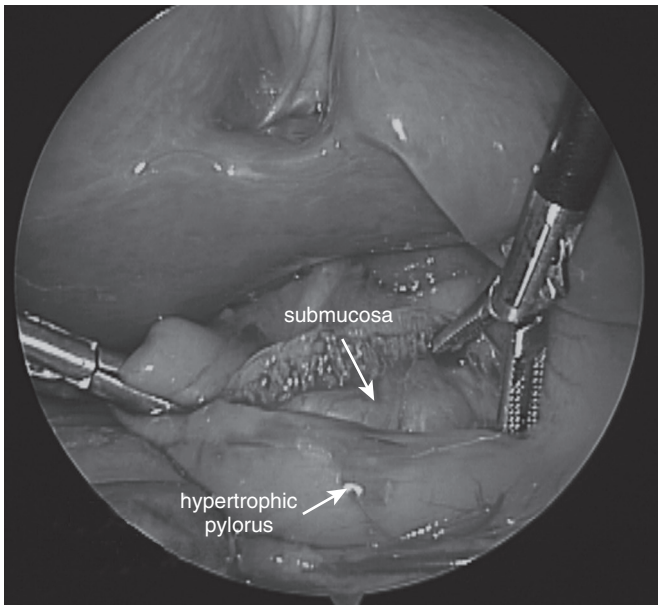
• **Fig. 84.21** Abdominal ultrasound of patient with hypertrophic pyloric stenosis.

channel length of 17 mm or greater. In infants 30 days of age or younger, it has been suggested that diagnostic criteria for wall thickness be reduced to 3 mm. Real-time lack of movement of gastric contents across the pylorus is also an important observation when assessing for hypertrophic pyloric stenosis. When parameters are equivocal, an upper gastrointestinal tract study can be diagnostic by demonstrating an elongated and narrowed pyloric channel, with the characteristic shoulders of the hypertrophied pylorus bulging into the gastric lumen. Although an accurate diagnosis based on physical examination should be possible in most cases, and should be attempted in all, it is evident that an increasing reliance on ultrasonography will continue to erode the skills of examiners. A review comparing diagnostic accuracy between two eras in a single pediatric institution found that the sensitivity of physical examination declined by half during a period of increasing reliance on ultrasound.[57]

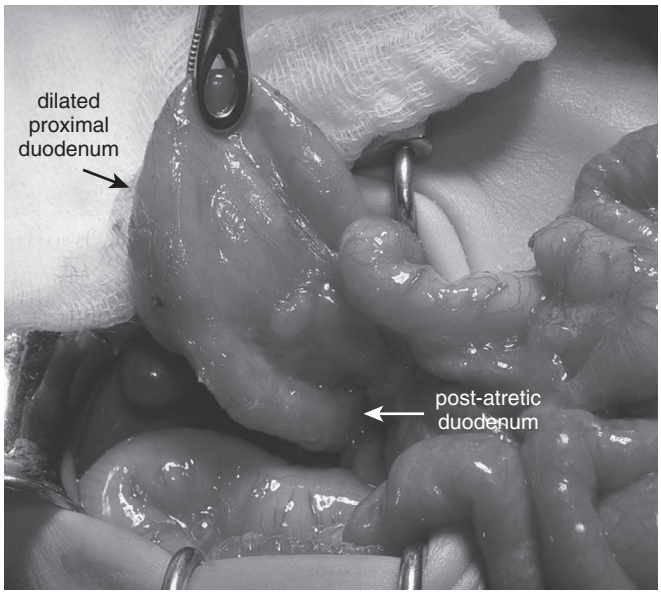
Preoperative preparation is critical once the diagnosis is made. Hypertrophic pyloric stenosis is not a surgical emergency, so careful correction of fluid and electrolyte losses should be accomplished before operative intervention. The infant who presents early in the course of the disease with no clinical dehydration, normal serum electrolytes and glucose, and a normal urine output can be operated on at the earliest convenience. Many patients, however, present with dehydration, hypoglycemia, or a contraction alkalosis of sufficient severity to require preoperative resuscitation for 24-48 hours. Once volume status and urine output have improved, serum chloride, potassium, and bicarbonate have normalized, and paradoxical aciduria has resolved, surgery can be conducted safely.

The treatment of HPS is pyloromyotomy, which is never emergent. Historically, the operation is performed through a transverse right upper quadrant incision. Laparoscopic repair has become common and is standard at most US

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• **Fig. 84.22** Laparoscopic pyloromyotomy.



• **Fig. 84.23** Type I duodenal atresia with continuity of muscular wall.

medical centers (Fig. 84.22).[25] It is common for occasional emesis to occur after pyloromyotomy; this should not delay the progression of the feeding schedule in most cases. In general, most infants so managed can be discharged within 24-48 hours of surgery. Persistent postoperative vomiting beyond 48 hours is uncommon. In this circumstance, the possibilities of an incomplete myotomy or unrecognized perforation should be considered.

Most children treated for HPS can expect excellent short- and long-term outcomes. With appropriate resuscitation, expert anesthesia, and a standard surgical approach, mortality has been virtually eliminated. Wound infection and dehiscence, which were significant problems in previous eras, are relatively uncommon today. Postoperative ultrasound studies have documented a return to normal muscle thickness within 4 weeks, associated with healing of the pyloric muscle and return of function. A study addressing gastric emptying and abdominal symptoms after pyloromyotomy found no differences between treatment and control groups several decades after surgery.[56]

Duodenal Atresia and Stenosis

Congenital duodenal obstruction may be complete or partial, intrinsic or extrinsic. Intrinsic atresias or stenoses have an incidence of about 1 in 7000 live births and account for about half of all small intestinal atresias. Extrinsic obstruction has many causes, including malrotation with Ladd bands, preduodenal portal vein, gastroduodenal duplications, cysts or pseudocysts of the pancreas and biliary tree, and annular pancreas. Annular pancreas is commonly associated with an intrinsic cause of duodenal obstruction.

Intrinsic duodenal obstructions and annular pancreas result from events that occur during early development of the foregut. Duodenal atresia and stenosis are believed to result from a failure of recanalization of the embryonic duodenum, which becomes solid as a result of early epithelial proliferation. Annular pancreas occurs when the ventral pancreatic bud fails to rotate behind the duodenum, leaving a nondistensible ring of pancreatic tissue fully encircling the second portion of the duodenum.[102] Annular pancreas frequently coexists with intrinsic duodenal anomalies and anomalies of the pancreaticobiliary ductal system, suggesting closely linked mechanisms of pancreatic, duodenal, and biliary development during this stage.

Atresias of the duodenum have several basic morphologies. Type I atresias constitute luminal webs or membranes, some of which contain a central defect or fenestration of variable size and result in a marked size discrepancy with mural continuity (Fig. 84.23). Type II atresias have dilated proximal and diminutive distal segments connected by a fibrous cord. Type III atresias are characterized by a complete discontinuity between the segments. The relationship between the point of obstruction and the ampulla of Vater is important. Most series document a predominance of postampullary obstructions, although some have described a preampullary predominance. Obstructions caused by type I membranes are frequently associated with anomalies of the common bile duct in which the common bile duct may terminate within the membrane itself.

Congenital duodenal obstructions are often associated with other congenital anomalies, which account for most of the morbidity and mortality in these patients. Various reports put the incidence of associated conditions between 50% and 80%. Congenital heart disease and trisomy 21 are the most common associated conditions, each occurring in about 30% of cases.[32] Not infrequently, all three conditions coexist in the same patient.[23] Among patients with trisomy 21 who underwent prenatal ultrasonography, about 4% were found to have prenatal evidence of duodenal atresia.[71]

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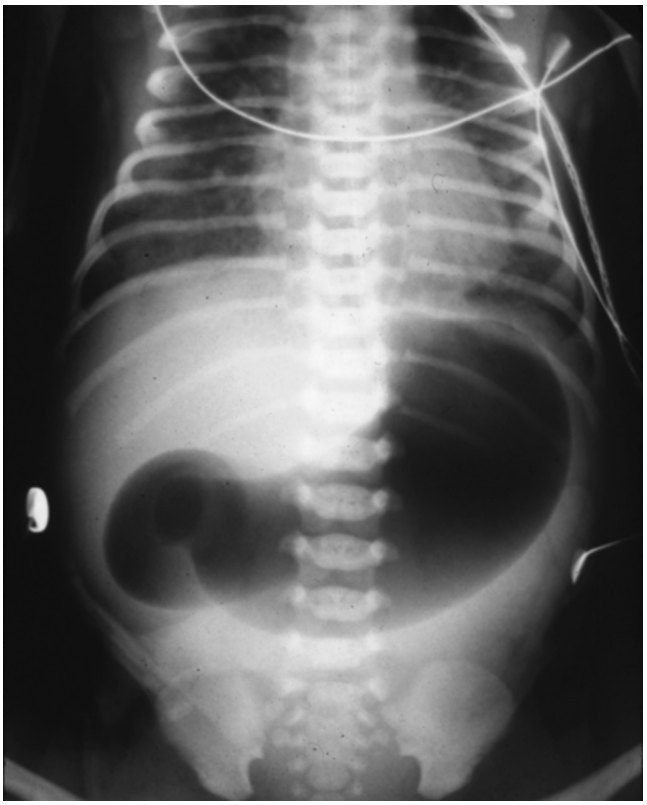
Other associated anomalies include intestinal malrotation (20%), esophageal atresia, imperforate anus (10%-20%), thoracoabdominal heterotaxia, and gallbladder agenesis. The outcome for patients with duodenal atresia depends more on the severity of these associated anomalies and the ease with which they can be corrected than on the surgical management of the obstruction itself.

Many patients with duodenal atresia have the diagnosis suggested by prenatal ultrasonography. A maternal history of polyhydramnios is common in congenital duodenal obstruction, approaching 75% in one series.[93] Prenatal sonographic evaluation of the fetus at 22-23 weeks of gestation can reliably detect two dilated, fluid-filled structures consistent with a double bubble. The unavailability of a sonographic diagnosis until relatively late in gestation frequently results in an ethical dilemma for prospective parents, who may consider elective termination based on the association of duodenal atresia with trisomy 21.

The clinical presentation of the infant with congenital duodenal obstruction depends on the presence or absence of a membranous aperture, its size, and the location of the obstruction relative to the ampulla. The classic presentation of a complete postampullary obstruction includes bilious vomiting within 24 hours of birth in an otherwise stable infant with a nondistended abdomen. Plain radiographs of the abdomen typically show the classic double-bubble sign—two distinct gas collections or air-fluid levels in the upper abdomen resulting from the markedly dilated stomach and proximal duodenal bulb (Fig. 84.24). Air makes an excellent contrast agent and may obviate a barium or water-soluble contrast study in routine cases. The distal intestinal tract may be gasless or may contain a small amount of intraluminal air owing to a membranous aperture or perforation or an anomalous bile duct with openings on both sides of the obstructing diaphragm.[75]

The importance of differentiating intrinsic duodenal obstruction from intestinal malrotation with a midgut volvulus in the infant who presents with bilious vomiting cannot be overstated. A clue may be derived from the appearance of the duodenum on the plain radiograph. In the classic double-bubble sign, the duodenum appears distended and round because of chronic intrauterine obstruction. When a distended stomach is associated with a normal-caliber duodenum, the diagnosis of malrotation with duodenal obstruction secondary to Ladd bands or volvulus must be entertained. In an unstable patient, echocardiography and contrast studies may be required to distinguish hemodynamic compromise caused by volvulus from that caused by cardiac disease. Even when the diagnosis of duodenal atresia is established in the stable patient, cardiac anatomy and function should be evaluated before surgical correction.

Preoperative preparation includes nasogastric decompression, fluid and electrolyte replacement, and a thorough evaluation for associated anomalies. If malrotation is ruled out, surgical correction of duodenal atresia can be temporarily postponed and more urgent conditions evaluated and treated. Prophylactic perioperative antibiotics are begun preoperatively.



• **Fig. 84.24** Plain abdominal radiograph in patient with duodenal atresia.

The surgical management of an intrinsic duodenal web is usually limited to excision of a portion of the web and an enteroplasty to widen the duodenal lumen at that point. *As the membrane occasionally contains the terminal common bile duct, great caution must be taken in excising or incising the membrane to avoid biliary injury and stricture formation.* The most widely accepted surgical management of both true atresia and annular pancreas involves constructing an anastomosis between the dilated proximal duodenum and the diminutive distal duodenum. Open and laparoscopic repair are acceptable. Laparoscopic repair can be technically challenging because of the high rate of other congenital anomalies seen in duodenal atresia patients.

A feeding gastrostomy should not be necessary for postoperative management of an uncomplicated duodenal repair. Gastroduodenal function usually returns within 5-7 days, at which time enteral feeding can be initiated with small boluses and the volume progressively advanced as tolerated. One of the most problematic issues following repair of duodenal atresia is delayed transit, usually associated with a persistently dilated and dyskinetic proximal duodenum. A significant number of infants with corrected duodenal atresia also experience GER, which may be exacerbated by an impairment in gastric emptying. Survival rates of 95% are reported in those who are deemed satisfactory surgical candidates. As mentioned earlier, morbidity and mortality are usually related to associated anomalies.

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Gastrointestinal Duplications

The stomach and duodenum are the least common regions of the gastrointestinal tract in which duplications occur. For most congenital lesions of the stomach and duodenum included in this category, the term *duplication* may be a misnomer. The actual embryologic cause of these lesions is unknown, but the designation of *enterogenous cyst* or *congenital diverticulum* may be more accurate. Nevertheless, it is important to recognize that gastric and duodenal duplications are occasionally associated with other gastrointestinal duplications or with vertebral anomalies. Communications with or attachments to an abnormal vertebral column suggest they may be caused by aberrant splitting of the primitive notochord during early embryonic development.

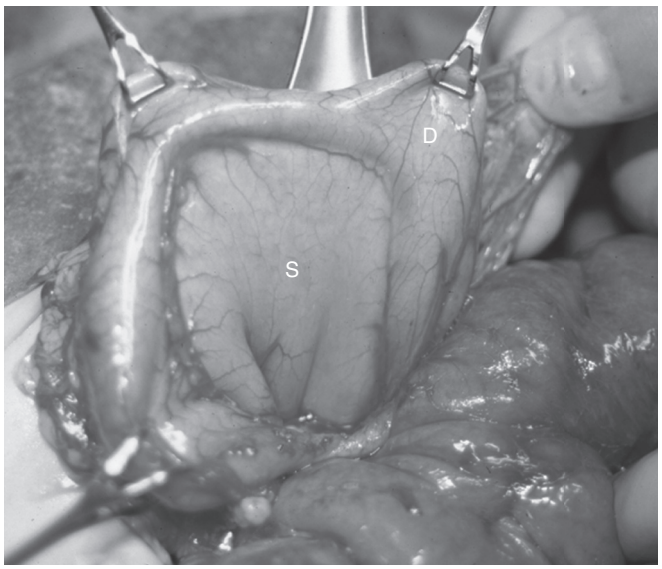
Classically, four pathologic criteria are considered necessary to establish the diagnosis of gastric duplication: (1) contiguity with the stomach, (2) an outer smooth muscle layer, (3) a shared blood supply with the stomach, and (4) a gastric epithelial lining (which may also contain pancreatic tissue). Most gastric duplications are cystic, do not communicate with the gastric lumen, and are located along the greater curvature of the stomach. When a luminal communication is present, it may result from peptic ulceration of the common wall between the two structures. Tubular duplications are less common, frequently communicate with the gastric lumen, and are also most commonly found on the greater curvature (Fig. 84.25). Extragastric cystic structures lined by gastric epithelium and exhibiting a muscular wall, however, are usually referred to as gastric duplications regardless of their proximity to the stomach.

In the neonatal period, duplications often present with symptoms and signs of proximal gastrointestinal obstruction. Vomiting is common and can be bilious or nonbilious, depending on the location of the extrinsic compression relative to the ampulla of Vater. Case reports of gastric duplications, both adjacent to the stomach and in the retroperitoneum, have described connections to the pancreatic ductal system and have resulted in chronic pancreatitis and pseudocyst formation. Connections to the biliary system and to extrapulmonary sequestrations have also been reported. Duodenal duplications most commonly occur in the first or second portion, usually on the posterior surface, and may be lined with gastric mucosa. These may also cause pancreatitis by compression of the pancreatic duct within the duodenal wall. Gastroduodenal hemorrhage or perforation secondary to peptic ulceration is the usual emergency indication for surgery. Gastrointestinal hemorrhage secondary to ulcer penetration from a noncommunicating duplication cyst into an adherent loop of intestine or colon has been reported.

Gastroduodenal duplications are being detected by antenatal ultrasound with increasing frequency and should be considered along with choledochal cysts and omental cysts in the differential diagnosis of a fetal right upper quadrant cystic mass. Postnatally, an upper gastrointestinal tract contrast study may demonstrate an extrinsic compression of the stomach or duodenum, but ultrasound and computed tomography can definitively reveal the mass itself. Technetium-99m scans may identify duplications distant from the stomach if they contain ectopic gastric mucosa but are not specific for duplications per se.

Resection of the entire duplication, either by enucleation or by limited gastric resection, is the treatment of choice. Successful laparoscopic resection has been reported and may be advisable for smaller, uncomplicated lesions. Extensive duplications, however, require removal of the entire mucosal cyst lining to avoid potential malignant degeneration.

Duplications of the small or large intestine are more common than those of the stomach and duodenum. They are usually cystic but may be tubular and extend for a variable distance (Fig. 84.26). Cystic duplications may cause obstruction or volvulus, and they may present with a palpable mass. Either type may present with hemorrhage. Simple cystic duplications of the small or large intestine are most easily managed by resection and primary anastomosis.



• **Fig. 84.25** Gastric duplication of greater curvature. D, Duplication; S, stomach.



• **Fig. 84.26** Long tubular duplication on mesenteric side of small intestine.

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Long tubular duplications may be managed by mucosal stripping to prevent future peptic complications and remove potentially dysplastic epithelium. Long colonic duplications may result in anal duplication. If the second anus is within the muscular sphincter, division of the septum to establish a common lumen may be sufficient. Cystic rectal duplications must be distinguished from sacrococcygeal teratomas and meningoceles before trans-sacral or posterior sagittal resection is undertaken.

Malrotation and Midgut Volvulus

Malrotation of the intestine is a widely varied group of anomalies. As described in the development chapter, the bowel undergoes two independent 270-degree counterclockwise rotations during the 6th-12th weeks of gestation. One involves the duodenojejunal junction around the axis of the superior mesenteric artery, and the other involves the ileocolic junction around the same axis. Although this is difficult to grasp spatially, the concept is simple. When the bowel rotates appropriately during development, it fixes itself in the abdomen in such a way that it absolutely cannot twist and obstruct itself or, as occurs in volvulus, compromise its own blood supply (Fig. 84.27). This is remarkable, considering the length of bowel involved. However, if the bowel does not rotate and fix itself in the abdomen properly, the stage is set for later obstruction or volvulus. Yet malrotation, more comprehensively described as an anomaly of intestinal fixation and rotation, is not a problem in itself. It is estimated that nearly 1 in 100 people have some form of improper rotation or fixation, yet 1% of the population do not have the related clinical symptoms. Rather, 1 in 6000 live births leads to a clinical discovery.[14,112]

Because so many variations of malrotation can exist, there are many possible clinical presentations. Any case of unexplained abdominal pain or emesis should have malrotation somewhere in the differential diagnosis. However, the main symptom complexes can be grouped together as those related to acute volvulus, to duodenal obstruction, to evidence of intermittent or chronic abdominal pain, or as an incidental finding in an otherwise asymptomatic patient. More than half of patients present in the first month of life, with half of the rest in the first year. However, 25% can still present at any other time in life.[101] Bilious emesis in any child younger than 1 year of age should be assumed to be caused by malrotation until proved otherwise.

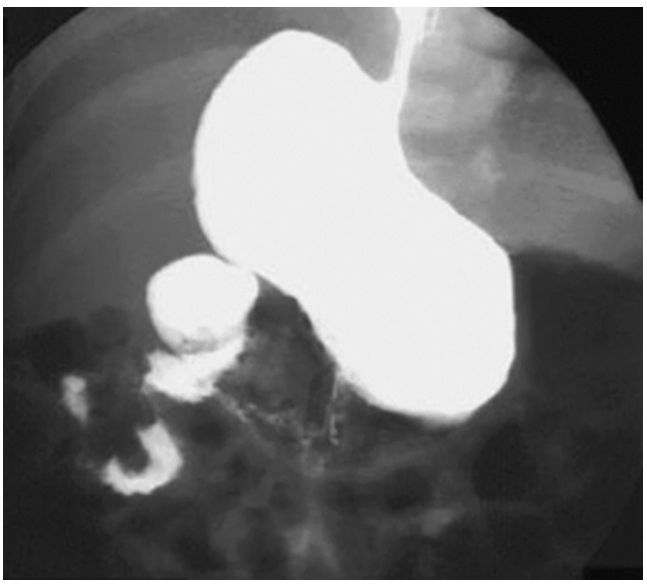
The preoperative evaluation of the malrotation or midgut volvulus is the radiologic determination of the position of the ligament of Treitz, and secondarily, its distance and relation to the ileocecal junction.[111] The initial film is typically a plain radiograph. Although alone it is not sufficient for a diagnosis, obvious obstruction of the stomach with little or no distal air in an acutely ill newborn or infant can be enough to warrant taking the child immediately to the operating room. Midgut volvulus is one of the few pediatric emergencies in which operating takes precedence over resuscitation. More typically, plain radiographs are nonspecific and further urgent evaluation is warranted.

The upper gastrointestinal series is the gold standard for making the diagnosis of malrotation. The procedure must be performed in the radiology suite by a trained radiologist using fluoroscopy. In cases of volvulus, the site of obstruction is in the second or third portion of the duodenum and has the appearance of a bird's beak. If the duodenum is partially obstructed, a spiral or corkscrew configuration may be seen (Fig. 84.28). In diagnosing malrotation alone, the position of the duodenojejunal junction must be documented. Normally, it is to the left of midline, rising to approximately the level of the pylorus and fixed well posteriorly. In a patient with malrotation, it is anterior, low, and often midline or to the right of midline (Fig. 84.29). The diagnosis requires judgment and, therefore, an experienced and confident radiologist.

Barium enema was historically the procedure of choice, but it has several limitations. Most importantly, the cecum can be in the proper position in the patient with duodenojejunal malrotation, and the latter can, therefore, be missed. As the risk for midgut volvulus is related to duodenojejunal

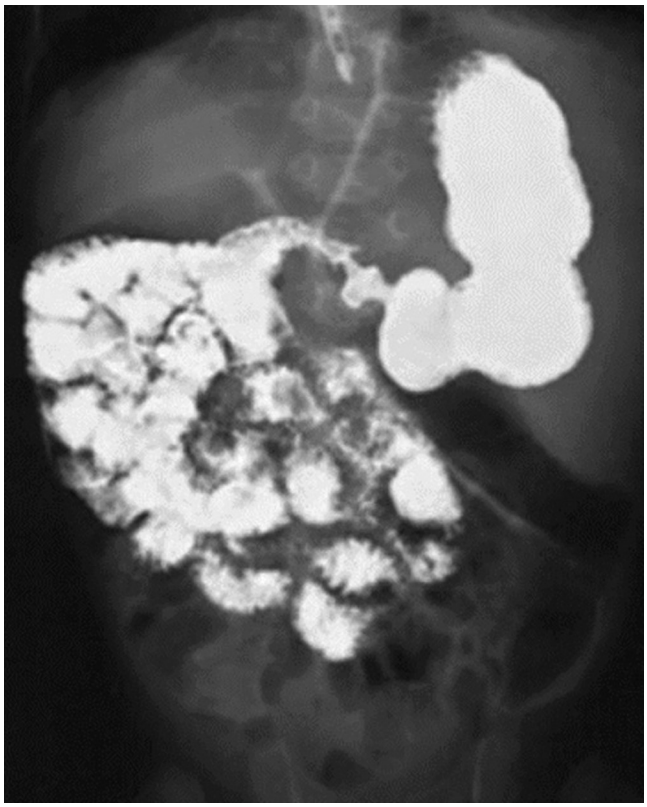


• **Fig. 84.27** Malrotation with midgut volvulus.



• **Fig. 84.28** Upper gastrointestinal contrast study in patient with malrotation and midgut volvulus.

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• **Fig. 84.29** Upper gastrointestinal contrast study in patient with malrotation without volvulus. Note location of duodenojejunal junction and small intestine to right of midline.

malrotation and not jejunoileal, the barium enema cannot be depended on. A contrast enema can, however, help determine the potential width of the mesenteric base, and therefore the risk of volvulus, in a child when the location of the duodenojejunal junction on upper gastrointestinal investigation is unclear.

Ultrasonography can be used to determine the orientation of the superior mesenteric vessels and thus may be helpful in the diagnosis of malrotation. Normally, the superior mesenteric vein lies to the right of the superior mesenteric artery. If the superior mesenteric vein lies either anterior or to the left of the superior mesenteric artery, malrotation may be present. However, this is inconsistent and does not lead to a definitive diagnosis. Currently, ultrasound should not be considered the definitive imaging of choice.

An acutely ill child with the presumed diagnosis of volvulus requires urgent operative intervention even at the expense of full resuscitation. Imaging is not required and not appropriate. As the operation gets under way, intravenous fluids continue, bladder and stomach catheters can be placed, blood is drawn for type and crossmatch, and broad-spectrum antibiotics are administered. *Time is critical*. In patients with malrotation without volvulus or obstruction, urgency is somewhat less. As long as all caregivers are vigilant for the development of volvulus, early operation (within a day or two of diagnosis) would appear to be justified. Older individuals with intermittent symptoms can be treated more electively.

The surgical treatment of these emergent patients involves seven aspects: evisceration of the bowel, detorsion of a volvulus, division of Ladd bands, widening the mesenteric base, relieving duodenal obstruction, incidental appendectomy, and nonrotational return of the bowel to the abdomen. Ladd bands extend from the ascending colon (on the medial aspect of the duodenum in patients with malrotation) across the duodenum and attach to the posterior aspect of the right upper quadrant. They presumably represent the attempt of the ascending colon to become retroperitoneal, as it is in the normally rotated individual. They must be completely divided. Techniques to widen the mesenteric base and relieve duodenal obstruction are then used. Incidental appendectomy and nonrotational return of the bowel to the abdomen may seem unusual. It would seem logical to try to rotate the bowel properly or to try to fix it in place. However, this does not work in practice. Experience has shown that returning the bowel with the small bowel on the right and the large bowel on the left (total nonrotation) is effective. Thus once a patient has malrotation, they have abnormal intestinal rotation for the rest of their lives. It is a chronic condition and families must be educated to that point.

Laparoscopic Ladd's procedure is effective for nonurgent malrotation patients. It is not appropriate for critical midgut volvulus patients. While laparoscopic Ladd's procedure has become common at many medical centers, long-term prospective randomized trails comparing it to traditional Ladd's procedure are lacking.

Recurrent volvulus is relatively infrequent (less than 10%) but must always be considered. Gastrointestinal motility disturbances are not uncommon after operative correction of malrotation. Other complications can occur as a result of compromised bowel from ischemia caused by volvulus, such as reperfusion injury with hemodynamic instability and delayed stricture formation. Adhesive bowel obstruction is possible in any patient after abdominal exploration. Finally, midgut volvulus accounts for nearly 20% of the cases of short gut syndrome in the pediatric population.

Meconium Syndromes

Meconium syndromes are associated with intestinal obstruction resulting from thick, inspissated meconium. These syndromes are broadly characterized by several patterns of clinical presentation, including meconium ileus, meconium plug syndrome, meconium peritonitis, and meconium ileus equivalent. In meconium ileus, which is almost always associated with cystic fibrosis, the inspissated meconium typically obstructs the small bowel, usually at the level of the distal jejunum or the proximal ileum. Meconium plug syndrome is observed more frequently in preterm infants and involves obstruction at the level of the colon. It is thought to occur as a result of poor intestinal motility, but it can be associated with cystic fibrosis in a minority of infants. Meconium peritonitis results from bowel perforation, usually intrauterine, which is secondary to

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meconium-related obstruction. Meconium ileus equivalent is a condition associated with stool-related bowel obstruction in older children with cystic fibrosis.

Meconium Ileus

Meconium ileus occurs in approximately 10%-20% of newborns with cystic fibrosis. Cystic fibrosis is caused by mutations in the gene that codes for a protein called *cystic fibrosis transmembrane conductance regulator* (CFTR), which regulates chloride transport across epithelia.[19,82] Luminal epithelial cells of patients with cystic fibrosis either lack or have defective CFTR and are relatively impermeable to chloride and excessively reabsorb sodium. This leads to dehydration and hyperviscosity of secretions with secondary obstruction of the lumina that these cells line, including the mucus-secreting glands of the bowel wall and the ductal cells of the exocrine pancreas.

The hyperviscosity of mucosal cell secretion leads to the formation of thick, tarlike meconium, which becomes increasingly inspissated farther along the small bowel lumen, eventually resulting distally in the formation of small, dense meconium pellets and a microcolon. Resultant small bowel obstruction is usually present at birth and can even be diagnosed antenatally on ultrasonic examination of the maternal abdomen. Postnatal clinical signs of bowel obstruction usually evolve within 24-48 hours, including increased abdominal distention associated with failure to defecate and eventual bilious vomiting. Bowel loops, which have a pliant, doughlike quality, can often be palpated on abdominal examination. Abdominal radiographs may have a granular, soap-bubble appearance as a result of air bubbles in the meconium. This clinical picture is classically used to characterize *simple meconium ileus.* However, luminal bowel obstruction of this sort can progress to volvulus, necrosis, and perforation, and these clinical situations constitute *complicated meconium ileus*. If bowel necrosis and perforation have occurred in utero, a pseudocyst may form and present as a palpable mass on abdominal examination at birth. Volvulus can also present as a palpable abdominal mass. In addition to the classic features of intestinal obstruction (i.e., multiple distended bowel loops), abdominal radiography may reveal a large mass containing calcified material (pseudocyst) or calcifications distributed throughout the peritoneal cavity (meconium peritonitis) in association with this process. Ascites, free air, or a granular, soap-bubble appearance caused by air bubbles in the meconium may also be present. The absence of any or all of these radiographic findings does not necessarily rule out meconium ileus. However, a contrast enema almost always demonstrates a microcolon, usually associated with small, "rabbit-pellet" meconium concretions seen proximally. The differential diagnosis includes meconium plug syndrome, small bowel and proximal colonic atresia, total colonic Hirschsprung disease, and congenital hypothyroidism.

Management options to treat meconium ileus depend on the type of presentation. General management principles always include prompt rehydration with adequate fluid and electrolyte support, gastric decompression with a dual-lumen sump nasogastric tube, and appropriate antibiotic coverage.

Simple meconium ileus can be treated either nonoperatively or operatively. Nonoperative intervention requires that other causes of distal bowel obstruction be ruled out and that complicated meconium ileus (volvulus, necrosis, perforation, pseudocyst, or peritonitis) does not exist. A hyperosmolar solution (typically Gastrografin®) is administered as an enema and allowed to reflux into the ileum. The hypertonic solution (1900 mOsm/L) establishes a concentration gradient across the bowel wall that draws fluid into the lumen and promotes passage of the meconium. It is extremely important that the infant receive adequate intravenous fluid therapy before and during this procedure to compensate for the rapid fluid shift out of the plasma compartment as a result of the intestinal osmotic load. This procedure should be performed by an appropriately trained and experienced pediatric radiologist, with a pediatric surgeon available. Although the technique is successful a little over 50% of the time, there is also an 11% perforation rate.[80] Furthermore, necrotizing enterocolitis can result from the exposure of the bowel to the hyperosmolar solution. Surgical treatment involves evacuation of the meconium from the intestine. This can be accomplished by creating an enterotomy and irrigating the bowel with 2%-4% N-acetyl-L-cysteine, which helps to partially dissolve the inspissated meconium, making it easier to flush through the lumen. In addition, the bowel can be partially diverted using a variety of techniques (Bishop-Koop, Santulli-Blanc, or Mikulicz procedures), which allow for evacuation of the meconium over a longer term with gradual resumption of distal bowel utilization.

Complicated meconium ileus requires an exploratory laparotomy. Volvulus can be relieved by untwisting the bowel. Bowel resection is usually required to treat atresia, necrotic, and perforated bowel, and in some instances, remarkably dilated bowel. Partial or complete temporary intestinal diversion is usually required along with the irrigation techniques previously mentioned. Initial postoperative care involves adequate fluid and electrolyte support, continued nasogastric sump tube decompression of the stomach, and appropriate antibiotic therapy. Careful ostomy irrigation by the pediatric surgeon can be continued postoperatively to facilitate further meconium evacuation if needed. Bowel function usually returns within 3-5 days, at which time oral nutritional support can be initiated, first with elemental formulations if the inflammation encountered at exploration was extensive or if surgery was complicated by intra-abdominal infection. Pancreatic enzyme supplementation should also be considered. If bowel function does not return within this period, parenteral nutritional support should be initiated. Early postoperative recovery is usually good. Proper ostomy care is essential, and surgical closure is usually carried out 4-6 weeks after the initial surgery. Because long-term mortality in patients with cystic fibrosis is most frequently associated with respiratory complications,

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aggressive pulmonary toilet during the initial postoperative period is mandatory.

Meconium Peritonitis

Intestinal obstruction from a variety of causes, including, but not limited to, meconium ileus, volvulus, atresia, peritoneal bands, and internal hernia, can result in bowel necrosis and perforation during the fetal period. Meconium escaping into the peritoneal cavity combined with intestinal necrosis can cause an inflammatory reaction, leading to calcification and extensive scarring (fibroadhesive peritonitis), which seals the perforation; cystic meconium peritonitis (if a seal does not form and meconium continues to leak into the peritoneal cavity); or meconium pseudocyst (when loops of bowel and necrotic tissue are encased in scar tissue and surround the extramural meconium). Meconium ascites present as a large amount of liquid meconium, presumably resulting from a recent perforation just before birth, which fills the peritoneal cavity.

Asymptomatic patients with radiographic evidence of intraperitoneal calcification can be managed conservatively; however, babies with meconium peritonitis who present with bowel obstruction usually require surgical intervention. Surgical management is based on the findings at laparotomy and may include resection of necrotic bowel or temporary intestinal diversion or both. Every attempt should be made to preserve as much bowel length as possible to decrease the risk of developing short gut syndrome. The principles of postoperative care are similar to those for meconium ileus.

Meconium Plug Syndrome

Meconium plug syndrome is believed to relate to colonic hypomotility. It is more frequently observed in preterm infants and in infants of diabetic mothers and is termed *neonatal small left colon syndrome*. Several factors known to affect bowel motility have been implicated. These include hypermagnesemia and hypoglycemia. A hypermagnesemia-associated decrease in the release of acetylcholine can result in myoneural depression. This mechanism has been used to explain meconium plug syndrome observed in preterm neonates whose mothers received magnesium to treat eclampsia. Furthermore, immature development of the myenteric plexus of preterm infants may impair intestinal motility, accounting for the increased observation of meconium plug syndrome in this patient population. Hypoglycemia, frequently observed in infants of diabetic mothers, is thought to induce increased glucagon secretion and may be associated with intestinal hypomotility.

This disorder is seen in preterm infants who present with abdominal distention associated with minimal passage of meconium. Multiple dilated bowel loops are present on abdominal radiography. Although a digital rectal examination can sometimes result in the passage of the obstructing meconium, a water-soluble contrast enema is valuable both for diagnostic purposes (usually demonstrating a microcolon distal to the obstruction) and for therapy (to induce passage of the obstructing meconium plug). Surgical therapy is infrequently required to relieve the blockage. Because of the association of meconium plug syndrome with cystic fibrosis and Hirschsprung disease, patients with this disorder may need to be evaluated for cystic fibrosis and undergo a rectal biopsy.

Jejunoileal Atresia and Stenosis

The potential pathogenesis of small bowel atresia is varied and includes events during the second and third trimester of intrauterine life, such as intussusception, internal herniation of bowel, volvulus, bowel perforation, vascular constriction in association with gastroschisis (and, less frequently, omphalocele), mesenteric thrombosis, and possibly excessive resorption of the intestinal attachment of the omphalomesenteric remnant. The suggestion of in utero vascular compromise as an etiologic factor was first demonstrated in beagle puppies by Christian Barnard and colleagues, who observed that the late-gestational ligation of mesenteric vessels resulted in a classic V-shaped mesenteric defect in association with a noncontiguous gap atresia (most likely caused by resorption of the ischemic bowel supplied by the ligated vessels).[55]

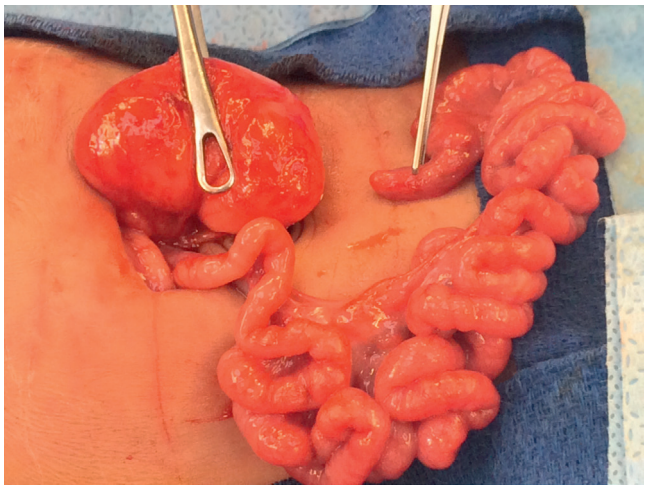
These observations have subsequently been confirmed in a number of different animal models. The notion that the etiologic events occur after the 12th week of embryonic life is supported by the frequent clinical finding of bile pigments and lanugo hairs in the postatretic bowel segment, because secretion of bile into the bowel lumen and fetal swallowing of amniotic fluid begin during the 11th-12th weeks of gestation. Another potential etiologic factor is linked to the concept of epithelial plugging. From the 5th-8th weeks of gestation, the intestine undergoes a period of epithelial growth so rapid that it can completely obliterate the intestinal lumen (solid-cord stage). After the 8th week, the intestinal lumen is re-established through a process termed *revacuolization*. Lack of complete revacuolization has been postulated to account for the development of intestinal stenoses and webs (membranous atresias).

The classification of jejunoileal atresia is as follows. Operative management of intestinal atresia and stenosis is based on pathologic findings.

Type I: Mucosal (membranous) web
Type II: Blind ends connected by a fibrous cord
Type IIIa: Blind ends separated by a V-shaped mesenteric defect
Type IIIb: Apple-peel or Christmas-tree deformity (blind ends; distal small bowel segment forms corkscrew around ileocecal artery terminus) (Fig. 84.30)
Type IV: Multiple atresias (string of sausages)

The anatomic distribution is approximately 50% in the jejunum (proximal 30%, distal 20%) and 50% in the ileum

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• **Fig. 84.30** Type IIIb intestinal atresia.



• **Fig. 84.31** Operative photograph of a type II ileal atresia.

(proximal 15%, distal 35%). Approximately 90% of all small bowel atresias are single. Type IV atresias more often involve the proximal jejunum.

The initial diagnosis is often entertained when pregnant mothers present with polyhydramnios, resulting from the inability of the fetus to absorb amniotic fluid via the obstructed bowel. Prenatal ultrasonography shows distended loops of fetal bowel consistent with obstruction. Newborn infants typically present with the abdominal distention and bilious vomiting often associated with failure to pass meconium. A more proximal (higher) location of the obstruction is characterized by an earlier onset of bilious vomiting and less abdominal distention in comparison with a more distal (lower) obstruction. On plain abdominal radiography, distended air-filled bowel loops are usually observed. The lower the obstruction, the greater the number of distended loops and air-fluid levels. Often, a markedly distended loop (relative to other bowel loops) is visualized, which may help to identify the location of the blind end of the obstructed bowel. A contrast enema typically reveals a microcolon, which results from the fact that little or no gastrointestinal contents have passed distal to the obstruction.

The differential diagnosis includes malrotation (with or without volvulus), meconium syndromes, duodenal or colonic atresia, internal hernia, intestinal duplication, and total colonic Hirschsprung disease. The particular distinguishing features of these conditions are discussed elsewhere in this chapter; however, jejunoileal atresia may coexist with malrotation (10%-18%), meconium peritonitis (12%), meconium ileus (10%), and, less frequently, with other comorbid obstructive conditions. Intestinal ileus secondary to sepsis can also present with abdominal distention and bilious vomiting. When the level and pattern of obstruction suggest the possibility of malrotation, a limited upper gastrointestinal contrast study should be performed to demonstrate a normally positioned ligament of Treitz (located to the left of the vertebral column at the level of the pylorus).

Initial treatment should include prompt adequate intravenous hydration and orogastric decompression of the stomach with a sump tube placed at intermittent suction with frequent regular irrigation of the tube to ensure patency. The operative management of the child should not be undertaken until the fluid and electrolyte status is within normal range. Bilious drainage from the stomach should be replaced and good urine output maintained.

Operative intervention is based on the type of atresia, the presence of associated surgical co-morbidities, and the condition of the bowel at the time of surgical exploration. Abdominal exploration is usually carried out through a transverse incision above the level of the umbilicus. In considering the most appropriate operation, a general strategy is to preserve as much viable bowel as possible. Although dilation of the bowel proximal to the obstructing blind end is always present, a marked and relatively abrupt increase in the caliber of dilation is often found at the terminus itself, creating a large, bulbous pouch (Fig. 84.31). Because peristalsis of massively dilated bowel is thought to be ineffective, a primary anastomosis between such a pouch and the small-caliber, unused distal bowel should not be attempted. Instead, the pouch should be surgically tapered (or resected, if the involved segment is appropriately limited to avoid creating short gut syndrome) to allow for better postoperative peristalsis.

Before creation of the anastomosis, the distal lumen of the bowel is gently irrigated (inflated) to ensure that no further atretic segments or webs are present. Multiple atresias can be managed either by multiple resections and anastomoses or by intramural stenting.[12] This latter method may help to preserve intestinal length. Particular care is required in handling the distal bowel involved in the fragile apple-peel deformity, as the entire length of the segment is based on a delicate, easily injured ileocecal artery terminus. If the bowel is compromised by inflammation or ischemia, a primary anastomosis is postponed and the bowel is diverted.

Postoperative care involves adequate nutritional support, often administered parenterally until adequate bowel function is present. In a large series spanning 10 years, 80% of patients weaned off parenteral nutrition; 20% required

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prolonged home TPN. All patients survived.[70] The most serious postoperative complications usually involve anastomotic leakage and sepsis. Over the longer term, anastomotic stricture can be problematic.

Hirschsprung Disease

Congenital intestinal aganglionosis (Hirschsprung disease) is the result of arrested fetal development of the myenteric nervous system (see Chapter 81). Hirschsprung disease is the most common cause of intestinal obstruction in the neonate. It occurs in about 1 in 5000 live births with a male-to-female ratio of 3.4:1. Total-colon Hirschsprung disease, noted in up to 8% of cases, favors females at a ratio of 1.6:1. More than 75% of the time, the transition zone from normal to involved colon is located in the rectosigmoid region. Down syndrome is the most commonly associated anomaly, occurring in 8%-16% of patients. Approximately 5% of patients with Down syndrome have Hirschsprung disease. Family history is important because the risk of a sibling having Hirschsprung disease is 1%-5% for short-segment disease and 9%-33% with long-segment disease. Familial Hirschsprung disease occurs in 4%-8% of patients.[39,79,81,103] Hirschsprung disease or tumors of neural crest origin (neuroblastoma, ganglioneuroblastoma, and ganglioneuroma) occur in association with congenital central hypoventilation syndrome in approximately 20% and 6% of cases, respectively.[7] Advances in the genetics of Hirschsprung disease have increased understanding of the molecular pathology of neural crest cell migration.

Approximately 80%-90% of patients present in the neonatal period with complete intestinal obstruction characterized by abdominal distention, emesis, and failure to pass meconium. Approximately 95% of normal, full-term infants pass meconium in the first 24 hours, whereas an equal number of patients with Hirschsprung disease do not. Physical examination shows a distended, soft abdomen, but rectal examination can produce an explosive stool. A contrast examination can be diagnostic in 80% of newborns. Findings may include a rectum with a smaller diameter than the sigmoid colon, a transition zone, normal caliber in the majority of the colon, and failure to completely evacuate on a 24-hour delayed film. Contrast enemas in all age groups are performed on unprepared bowel if the diagnosis of Hirschsprung disease is being considered. The definitive diagnosis of Hirschsprung disease, however, rests on demonstration of aganglionosis and hypertrophy of the nerve trunks on biopsy. In newborns, adequate biopsy specimens can often be obtained by the suction technique in the nursery.

Hirschsprung-associated enterocolitis occurs in 10% of patients overall and is more common beyond the neonatal period. This can be fatal and can happen even after treatment for Hirschsprung disease has been completed. All practitioners should be aware of this complication and treat for it whenever it is suspected. Enterocolitis is associated with abdominal distention, fever, emesis, and spontaneous diarrhea or an explosive diarrheal stool with gas during and after rectal examination. Enterocolitis is treated with decompression of the rectum with a large catheter and with warm saline irrigations using 20 mL/kg three or four times per day, volume resuscitation, and administration of broad-spectrum antibiotics.

The initial goal of treatment is decompression. Traditionally, this was performed with a leveling ostomy. Leveling here refers to the intraoperative determination of where on the bowel the ganglion cells make an appearance. This is done by taking seromuscular biopsies and having the pathologist review the frozen sections. The ostomy is then placed proximal to this to ensure its adequate function. Primary pull-through procedures are being performed with much greater frequency and would now be considered the standard of care. Here, instead of the traditional three stages (ostomy, definitive repair, ostomy takedown), the operation is done in one stage and without a protective stoma. Occasionally, a primary repair with a protective ostomy is performed—a two-stage operation in that ostomy takedown is still required.

The three traditional open abdominal surgical methods used to treat Hirschsprung disease are (1) Swenson, (2) Soave, and (3) Duhamel. No statistically significant difference has been shown among the outcomes of any of these procedures if they are performed properly. Over the last decade, experience with laparoscopic/transanal approaches has increased. Systematic reviews show that more children achieved continence with the laparoscopic/transanal approach.[30] Another meta-analysis concentrated on short-term outcomes and showed shorter intraoperative time and hospital stay, less incontinence, and less constipation.[13] The laparoscopic/transanal approach is considered the preferred approach at many specialty children's hospitals at this time.

Regardless of the procedure performed, these patients must be followed for years postoperatively. Postoperative care and long-term issues are similar to those for patients with anorectal malformations. Mandatory dilations are not necessary in Hirschsprung disease, because a neorectum is not created. However, strictures are not uncommon, and these patients need to be diligently followed during the first year. If any narrowing is noted, a full dilation program is started. Because there appears to be no detriment to dilations, some surgeons start a dilator program in all patients, including home dilation by the parents. There is debate over the necessity of this.[104] Also, enterocolitis is not typically seen in patients with anorectal malformations but can absolutely occur after repair in a patient with Hirschsprung disease. All patients with Hirschsprung disease, at any time in their lives, should have enterocolitis included in their differential diagnosis whenever they have abdominal pain, distention, or diarrhea. Also, unique to patients with Hirschsprung disease is the possibility of a retained aganglionic segment contributing to ongoing, postoperative constipation. This occurs when poorly vascularized, poorly ganglionated, or frankly aganglionic bowel is brought down in the pull-through. Repeat biopsy is necessary. Anal sphincter achalasia can also occur, and injection with botulinum toxin can help make this diagnosis. If suspected, an anal myomectomy can

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provide a permanent solution. All the potential complications, however, must be balanced by the long-term results, which indicate that approximately 90% of these patients ultimately achieve normal or near-normal bowel function.

Anorectal Anomalies

Anorectal malformations, or imperforate anus, are a class of congenital malformations that covers a wide spectrum of defects.[38,74,77] They can be quite minor in appearance—for example, a mildly anteriorly displaced anus—or quite severe. Overall, most patients do reasonably well, with more than 75% attaining a good degree of bowel control when they have adequate treatment.[77] The most severe forms of pelvic malformations, such as cloacal exstrophy, are not discussed here; this discussion is limited to malformations of the anus and rectum alone.

Imperforate anus occurs in 1 of every 4000-5000 newborns. The estimated risk for a couple having a second child with an anorectal malformation is approximately 1%. The frequency of this defect is slightly higher in male than in female patients.

Traditionally, the terms high, intermediate, and low were used to describe various degrees of imperforate anus. However, terminology should relate to the location of the rectal fistula for both prognostic and therapeutic implications.

More than 80% of male patients with imperforate anus have a fistulous connection between the rectum and the urinary tract. This can go from the rectum to the bladder (rectovesical), to the prostatic urethra (rectoprostatic), and to the bulbar urethra (rectobulbar). When the rectal fistula opens onto the perineal skin, it is called a *perineal fistula*. An unusual form of imperforate anus occurs when the rectum ends blindly in the pelvis. More than 50% of these patients have Down syndrome and almost all patients with Down syndrome and imperforate anus have this variant.

In female patients, there are three main types of malformations: perineal fistulas, vestibular fistulas, and complex malformations called *cloacae*. In the perineal fistula, the rectum opens on the perineal skin anterior to the anal dimple. A vestibular fistula opens in the posterior aspect of the introitus but outside the hymen. A cloaca is a malformation in which the rectum, vagina, and urethra all open into a common channel of variable length, which then opens onto the perineum. A rectovaginal fistula is extremely uncommon; these are usually rectovestibular fistulas.

Anorectal malformations may be associated with malformations of the sacrum and spine. One missing vertebra does not appear to have prognostic significance; however, two or more missing sacral vertebrae is a poor prognostic sign in terms of bowel continence and, sometimes, urinary control. Hemivertebrae in the thoracic and lumbar spine are also associated with imperforate anus.

Tethered cord is a defect frequently associated with imperforate anus, seen in up to 25% of cases. The actual repercussions of tethered cord are more difficult to determine. It usually coincides with very high anal defects, a very abnormal sacrum, or spina bifida. Cause and effect is unclear, as is the benefit of surgical treatment of the tethered cord, but the current standard of care is to look for tethered cord in all patients with imperforate anus and surgically treat if discovered.

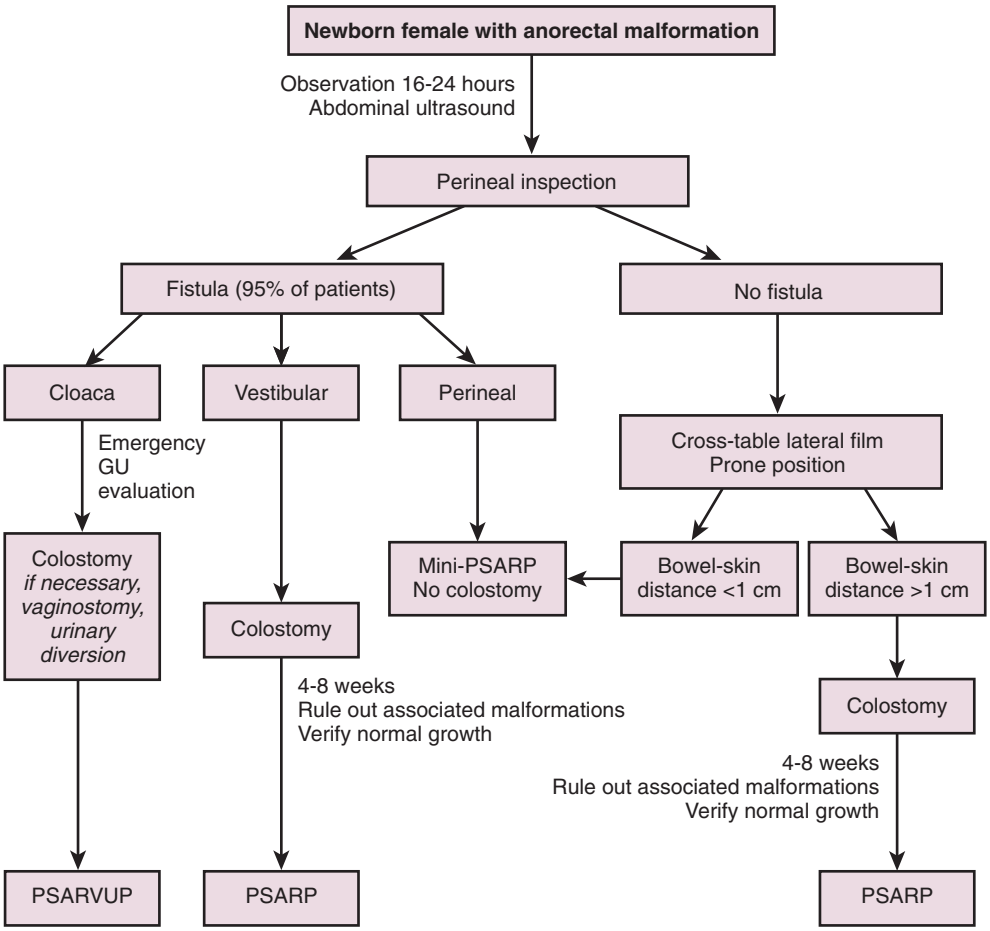
The frequency of associated genitourinary defects varies from 20%-50%. The width of the range is most likely related to how diligently the defects are sought. The higher the malformation, the more frequent are the associated urologic abnormalities. Patients with a persistent cloaca or rectovesical fistula have a 90% chance of an associated genitourinary abnormality. Conversely, children with perineal fistulas have less than a 10% chance of an associated urologic defect. Hydronephrosis, urosepsis, and metabolic acidosis from poor renal function are the main sources of mortality and morbidity in newborns with anorectal malformation. In fact, a thorough urologic evaluation should take precedence over the colostomy itself in patients with high lesions. In patients with lower lesions such as perineal fistulas, the urologic evaluation can be performed on an elective basis. This evaluation must include an ultrasonographic study of the kidneys and the entire abdomen to rule out the presence of hydronephrosis or any other obstructive process.

Approximately 5% of patients with imperforate anus have associated esophageal atresia, and up to 10% have significant cardiac malformations such as tetralogy of Fallot, ventricular septal defect, or patent ductus arteriosus.

The initial diagnosis of imperforate anus is almost always made during the first newborn physical examination. Occasionally, a mild perineal fistula is missed. Two important questions need to be answered within the first 24 hours. The first is whether a colostomy will be needed, deferring definitive repair until later in life, or whether to proceed with definitive repair. The second is to determine whether associated defects, such as urologic abnormalities, require more urgent treatment. It should be stressed that imperforate anus is not a surgical emergency and rarely needs to be operated on within the first 24 hours of life. This time should be used to complete the workup and discuss options with the family. On the other hand, some associated abnormalities can carry morbidity and mortality risks in the first 24 hours, and these must be addressed. Intravenous fluids, antibiotic coverage, an abdominal ultrasound, a radiograph of the spine, anteroposterior and lateral radiographs of the sacrum, a cardiac evaluation, and a nasogastric tube are indicated.

The decision to perform a colostomy or to proceed with the definitive repair can be answered within the first 24 hours by physical examination alone in more than 80% of male patients and 95% of female patients (Fig. 84.32 and Fig. 84.33). In the male, the presence of a well-developed midline groove between the buttocks, a prominent anal dimple, and meconium exiting through a small orifice located anterior to the sphincter in the midline of the perineum are evidence of a perineal fistula. Occasionally, there is a prominent skin bridge that an instrument can be passed beneath (known as a "bucket handle") or a midline

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• **Fig. 84.32** Algorithm for neonatal management of anorectal malformation in female patients. GU, Genitourinary; PSARP, posterior sagittal anorectoplasty; PSARVUP, posterior sagittal anorectal vaginourethroplasty.

raphe "black ribbon" of subepithelial meconium. These malformations can be repaired via a perineal approach during the newborn period without a colostomy. However, flat buttocks with no evidence of a perineal opening and the presence of meconium in the urine are indications of a rectourethral fistula. A small gauze pad over the tip of the penis can be helpful in spotting meconium in the urine. Most surgeons place a colostomy in these patients.

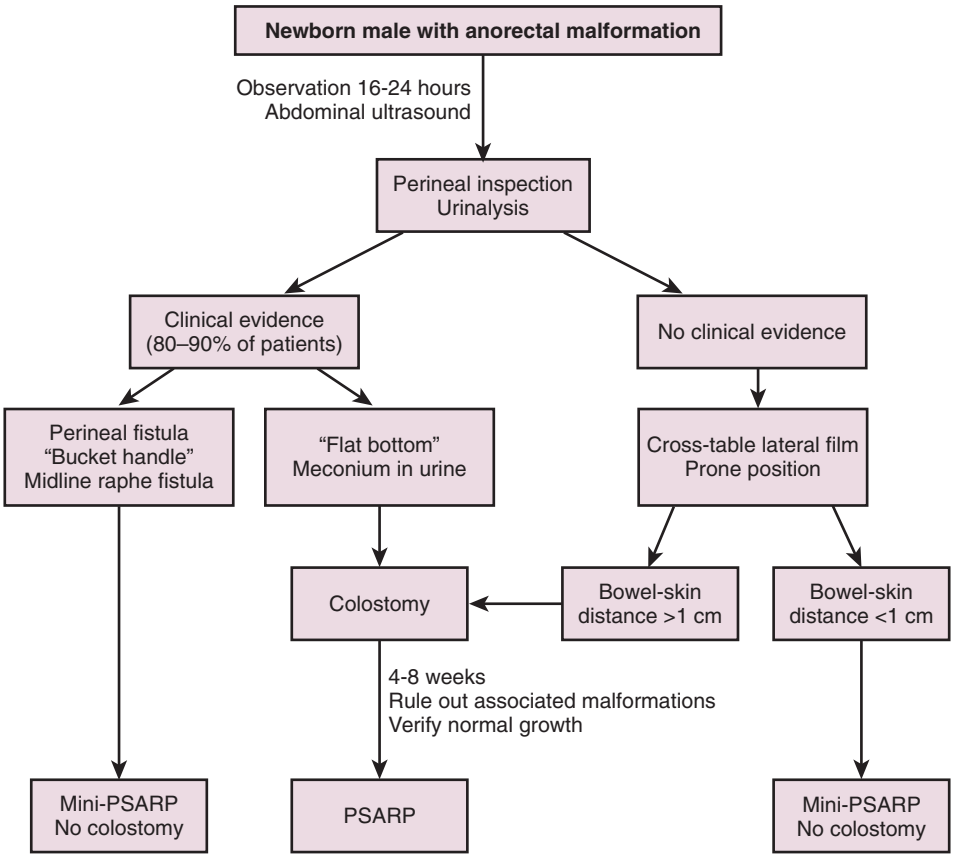
It can take up to 24 hours for enough pressure to build up in the colon to push meconium out of a perineal fistula. So, unless meconium is definitely seen in the urine, waiting is appropriate. If the diagnosis is still in doubt after 24 hours, a cross-table lateral radiograph of the abdomen and pelvis with the infant in the prone position is indicated. By identifying the anal dimple with a lead marker, the distance between the end of the dilated bowel and the skin can be estimated. If this distance is less than 1 cm, a primary repair can be attempted. It is important to wait 24 hours before obtaining this radiograph, because pressure within the colon is necessary for its prognostic value. Fewer than 20% of male patients need this radiograph.

In the female patient, physical examination alone can lead to the proper initial surgical treatment in more than 95% of cases. If a single perineal opening is observed where the urethra is normally located, the diagnosis of cloaca is established and a colostomy is indicated. A normal urethra and an opening within the vestibule of the female genitalia but outside of the hymen confirms the diagnosis of rectovestibular fistula. Initial treatment of this defect is the most variable. Pediatric surgeons experienced in its repair often either temporarily dilate the fistula and perform a definitive repair in a few weeks or proceed directly to definitive repair. The most conservative option is to place a colostomy and perform the repair at a later date. This is by far the most common defect seen in girls.

A fistula tract located anterior to the center of the sphincter but posterior to the vestibule of the genitalia establishes the diagnosis of perineal fistula. These babies undergo primary anoplasty without a protective colostomy. In the absence of any fistulous tract in the female patient, imperforate anus without fistula is the diagnosis, particularly in patients with Down syndrome. The cross-table film is needed for fewer than 5% of female patients.

The surgical care of patients with anorectal malformations often involves a complex interplay between clinical judgment and technical expertise. Surgical strategies include the creation of a temporizing or palliative colostomy and various types of corrective repairs.

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• **Fig. 84.33** Algorithm for neonatal management of anorectal malformation in male patients. GU, Genitourinary; PSARP, posterior sagittal anorectoplasty.

The main purpose of a colostomy is to provide immediate relief of bowel obstruction related to imperforate anus. It also allows the medical and surgical team time to plan the definitive repair, and it permits other medical and surgical issues, some of which may be more pressing, to be properly addressed. A colostomy is nearly always a temporary measure, as patients with imperforate anus very rarely require permanent diversion.

It is extremely important that the surgeon know the exact location of the fistula before undertaking the definitive repair. A distal colostogram must be obtained for all male patients who undergo a colostomy and all female patients with a cloaca. This study accurately shows the location of the fistula between the rectum and the genitourinary tract, the length of available colon from the colostomy to the fistula site, the distance from the rectum to the anal dimple, its relationship with the sacrum, the characteristics of the urethra in the male patient, the characteristics of the vagina in a female patient, and the presence or absence of vesicoureteral reflux.

The goal of the definitive repair is to place a neoanus in the appropriate location, allowing control by the patient. For the vast majority of patients with imperforate anus, surgery can be approached via the posterior sagittal route by a posterior sagittal anorectoplasty. Male patients with a bladder neck fistula and female patients with a long common channel (greater than 2.5 cm) require combined abdominal and posterior sagittal approaches. Laparoscopic/transanal approaches are also possible.[35]

After colostomy, broad-spectrum antibiotics are continued for 3 days. A stoma appliance is fitted, and the mucous fistula is typically left exposed. Once the colostomy is productive, feedings are begun.

Two to three weeks after surgery, dilations are begun using Hagar dilators. That this procedure is critical for success must be impressed on the patient's caregivers. Dilations continue for 6-12 months postoperatively. If this process is interrupted, there is a high likelihood that a stricture will develop. If a colostomy is present, it can be closed once the desired anal size is reached, typically a 14 Hegar dilator in a 6-month-old child. The importance of dilation cannot be overstated.

After colostomy closure or primary definitive repair, the usual multiple bowel movements frequently produce severe perianal excoriations. These may take time to heal, and caregivers should be forewarned. Every attempt to prevent prolonged contact of stool and skin should be made. Barrier products are frequently used, but it is most helpful to avoid using a diaper on the patient as much as possible.

These patients need lifelong follow-up. Constipation is the most common sequela in patients with anorectal malformations, and it can be most severe in the benign group of malformations. The more complex malformations have a poorer prognosis in terms of bowel control but

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less chance for constipation. Constipation must be treated aggressively, and prolonged use of laxatives in this population is indicated.

Twenty-five percent of patients with anorectal malformations suffer from some level of fecal incontinence and require some form of bowel management.[74,77,78] Urinary incontinence is not common in boys; 99% enjoy control. In females with cloacae, 50%-60% have control, 20% require a continent diversion, and the rest remain dry with intermittent catheterization.

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Key Points

- In infants with esophageal atresia/tracheoesophageal fistula, look for associated anomalies, VATER, and VACTRL syndromes.
- Omphalocele and gastroschisis are distinct entities. The former is associated with other structural or genetic defects in more than 50% of cases; in contrast, the latter is typically sporadic and only accompanied by gastrointestinal morbidity.
- In the face of projectile emesis, ultrasonography has high sensitivity for diagnosing hypertrophic pyloric stenosis.
- A "double bubble" on either pre- or postnatal imaging is almost diagnostic of duodenal obstruction and other structural anomalies and/or trisomy 21 should be excluded.
- Bilious emesis requires the urgent exclusion of malrotation with midgut volvulus by imaging the position of the duodenojejunal junction.
- Hirschsprung disease is the most common cause of neonatal intestinal obstruction, definitively diagnosed by rectal biopsy, often at bedside.

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85

Neonatal Necrotizing Enterocolitis

OLEKSANDR KUDIN AND JOSEF NEU

Summary

Necrotizing enterocolitis (NEC) is a devastating disease of the gastrointestinal tract that affects mostly premature infants. It is the most significant contributor of gastrointestinal morbidity and mortality in preterm infants. NEC was first described over 60 years ago but despite significant research efforts, its pathogenesis remains poorly understood. A general lack of reliable and specific early clinical or laboratory signs affects the ability to promptly and accurately diagnose this disease and initiate treatment. The absence of a clear definition for NEC impedes the ability to study its epidemiology, pathogenesis, and preventive and treatment modalities. Decades have passed without any significant and meaningful additions to treatment options. Currently, a heterogeneous group of pathologic processes is lumped into one diagnosis termed "NEC." Those entities are similar in that they can lead to the same outcome—intestinal necrosis. The inciting factors and initial changes in these entities, however, are different. This chapter will describe some of these pathologic processes while focusing on a "classic" form of NEC.

Definition of NEC

A clear definition of any given disease provides a common foundation to study its epidemiology, pathogenesis, outcomes, and effectiveness of treatments. The lack of a clear definition for NEC has complicated efforts directed at studying this disease. A primary cause for the inability to clearly define NEC is the fact that it is not simply one disease entity, but rather a spectrum of conditions.[29,63] These conditions have a similar outcome—necrosis of the intestine. However, the pathophysiology of these conditions is very different. The chain of events that leads to intestinal necrosis in a term infant with intestinal ischemia caused by a congenital heart lesion is very different when compared to a 6-week-old infant who was born at 24 weeks of gestation. Grouping multiple conditions under one umbrella of NEC affects the reliability of statistical data collected for this disease and stalls efforts to develop effective preventive and treatment strategies (Table 85.1).

Another important issue is developing strict, well-defined diagnostic criteria of the disease. Criteria should be specific, sensitive, and accurate and allow clinicians to differentiate between subsets of NEC and other entities such as spontaneous intestinal perforation (SIP).[63]

This chapter will focus on the "classic" form of NEC. This form of NEC peaks in preterm infants at a similar corrected gestational age and is most often accompanied by clinical deterioration and clear signs of intestinal inflammation, including abdominal distension, periumbilical erythema, bloody stools, elevation of nonspecific inflammatory markers, and distinctive radiologic changes such as pneumatosis intestinalis and portal venous gas.

Epidemiology

Incidence of NEC inversely correlates with gestational age at birth with a higher incidence in babies born at lower gestational ages. About 90% of NEC cases occurred in preterm infants. There is also a correlation between gestational age at birth and length of interval between birth and onset of disease: the earlier an infant is born, the more time will pass between birth and onset of NEC. This results in the highest NEC incidence between 28 and 33 weeks of corrected gestational age.[28,96] In infants whose gestational age ranges from 22-28 weeks, the incidence of NEC in the United States declined from 13% in 2008 to 9% in 2012.[87] However, the Canadian Neonatal Network reported an average NEC prevalence of 5.9% and in the Japanese Neonatal Research Network it was 1.6%.[36] Infants born at a gestational age of up to 32 weeks were included in this review, which could in part explain lower NEC rates reported in Canada and Japan.[36]

About 10% of cases of NEC occur in term infants, but when compared with premature infants, these cases have a strong association with such risk factors as congenital heart disease, gastroschisis, and/or hypoxic-ischemic events. In addition to gestational age, other risk factors for the development of NEC are being investigated. Race seems to affect the risk for development of NEC, with African-American infants being at higher risk compared to Caucasian.[79] Genetic predisposition is evolving as a risk factor for NEC as well.[77,78]

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Abstract

Necrotizing enterocolitis (NEC) is a devastating disease of the gastrointestinal tract that affects mostly premature infants. It is the most significant contributor of gastrointestinal morbidity and mortality in preterm infants. NEC was first described over 60 years ago, but despite significant research efforts, its pathogenesis remains poorly understood. A general lack of reliable and specific early clinical or laboratory signs affects the ability to promptly and accurately diagnose this disease and initiate treatment. The absence of a clear definition for NEC impedes the ability to study its epidemiology, pathogenesis, and preventive and treatment modalities. Decades have passed without any significant and meaningful additions to treatment options. Currently, a heterogeneous group of pathologic processes is lumped into one diagnosis termed "NEC." Those entities are similar in that they can lead to the same outcome—intestinal necrosis. The inciting factors and initial changes in these entities however are different. This chapter will describe some of these pathologic processes while focusing on a "classic" form of NEC.

Keywords

necrotizing enterocolitis
neonate
intestine
inflammation
infection
dysbiosis

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TABLE 85.1 Clinical Scenarios That Are Often Misdiagnosed as Necrotizing Enterocolitis (NEC)

Spontaneous intestinal perforation
Food protein–induced enterocolitis syndrome (FPIES)
Bowel ischemia due to congenital heart disease
Congenital bowel anomalies (Meckel diverticulum, Hirschsprung disease, etc.)
Misinterpretation of stool gas as pneumatosis intestinalis

Adapted from: Neu J. Necrotizing enterocolitis: the mystery goes on. *Neonatology*. 2014;106(4):289-95.

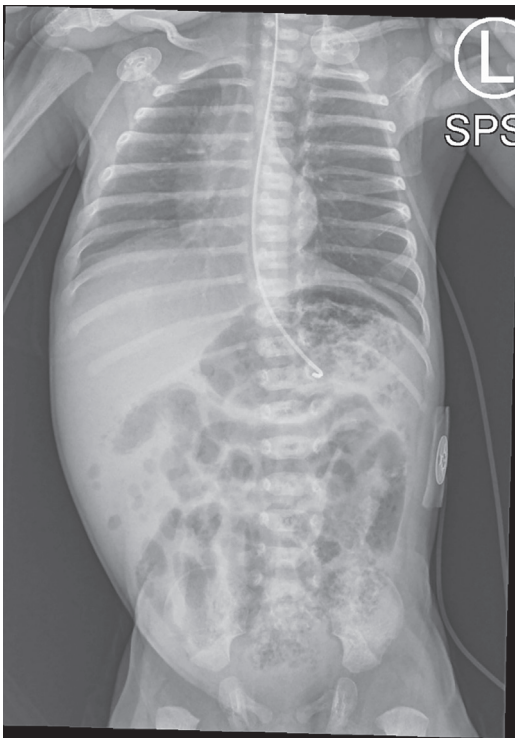
Clinical Features

Presentation

Early clinical signs of NEC are usually vague and nonspecific and may include slight changes in vital signs (tachy- or bradycardia), new onset or increased apneic episodes, feeding intolerance or increased gastric residuals, and emesis. As the disease progresses, deterioration becomes obvious on physical examination. The signs of disease progression are also nonspecific: hypotonia, respiratory distress, and cardiovascular instability. The abdominal exam reveals distention, tenderness, discoloration of the abdominal wall, and lack of bowel sounds. Laboratory changes are notable for neutropenia, thrombocytopenia, and metabolic acidosis. Blood may be noticed in gastric contents and or stool.

Diagnosis

Diagnosis is made using a combination of clinical, laboratory, and radiologic findings with the latter being more important for determining severity of the disease process. NEC was systematically described and staging criteria proposed by Bell et al. in 1978 with modifications of staging made by Kliegman et al. in 1987. Modified Bell's criteria are widely used for data collection and in research. However, there are limitations to this classification. Stage I consists of a combination of highly nonspecific findings. It significantly distorts the incidence of NEC. Pneumatosis intestinalis, a hallmark of Stage II disease, may be hard to find on radiographs. Additionally, presence of heterogeneously appearing intestinal stool content may be misinterpreted as pneumatosis intestinalis (Fig. 85.1). A hallmark of stage III is perforated viscus with free intraperitoneal air, which could be due to spontaneous intestinal perforation or NEC. True diagnosis remains unknown when a primary peritoneal drain is placed and no direct bowel visualization and histologic evaluation is performed. This classification also falls short when NEC progresses without exhibiting pneumatosis intestinalis or portal venous gas. Even with free intraperitoneal air, if only a drain is placed without direct observation by the surgeon, the definitive diagnosis of NEC cannot be made.



• **Fig. 85.1** Radiograph showing heterogeneous stool that may easily be confused with pneumatosis intestinalis.

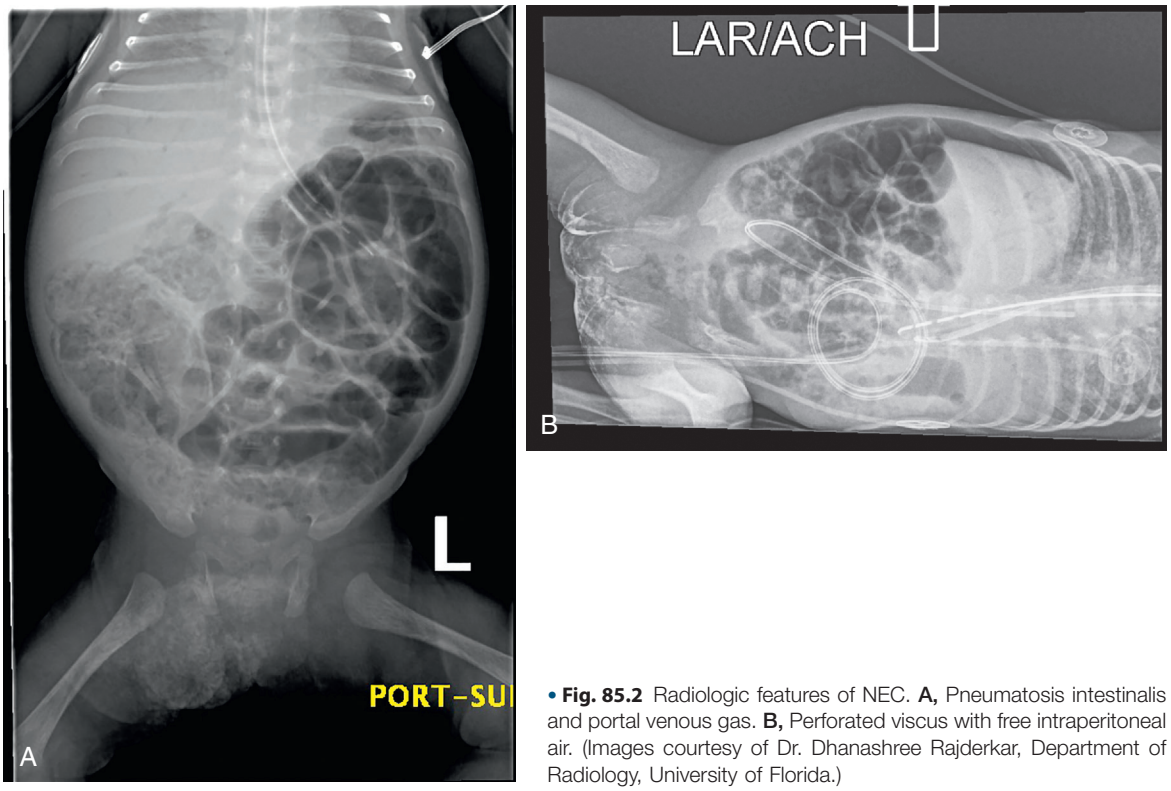
It is important to note that available modes of diagnostics for NEC are able to recognize only changes that occur in the late stages of the disease when the intestinal epithelial barrier has already been compromised and the signs of systemic response and deterioration are obvious.

Decreasing platelet counts, elevated I/T ratio, and elevated or decreased neutrophil counts have been used as laboratory signs of NEC with none of them being specific for this disease. Multiple inflammatory and immunologic markers have been studied as potential predictive biomarkers of NEC. Among them are C-reactive protein (CRP), procalcitonin, an array of cytokines and chemokines, platelet activating factor (PAF), and inter alpha inhibitory protein (IaIp) to name a few. So far, none of them has shown significant ability to do so.[26] Markers of intestinal inflammation and injury such as fatty acid binding protein (FABP), fecal calprotectin (FC), and claudins are being investigated as well. Their usefulness as early screening markers for NEC is questionable.[26] The absence of a clear definition of NEC and limited understanding of its initial pathophysiologic changes impede the ability to develop reliable biomarkers of early disease.

Radiologic signs used to diagnose NEC include pneumatosis intestinalis and portal venous gas (Fig. 85.2), free intraperitoneal air, distended and fixed loops of bowel, and a gasless abdomen. However, studies have shown significant variability in interpretation of abdominal radiographs of infants with suspected NEC.[22,51]

Abdominal ultrasound (US) may be emerging as an important imaging modality in evaluating infants with suspected NEC. Its advantages over x-ray are real-time imaging

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• **Fig. 85.2** Radiologic features of NEC. **A,** Pneumatosis intestinalis and portal venous gas. **B,** Perforated viscus with free intraperitoneal air. (Images courtesy of Dr. Dhanashree Rajderkar, Department of Radiology, University of Florida.)

(ability to assess for presence of peristalsis), detection of even minimal ascites, accurate detection of intestinal wall thickness, and perfusion.[8,23]

The above factors lead to uncertainty in diagnosing early stages of the disease and unnecessary exposure of significant numbers of ELBW infants to interruptions of enteral feedings, courses of broad-spectrum antibiotics, and prolonged need for central access. These interventions are associated with an increased incidence of late onset sepsis, prolongation of parenteral nutrition, and hospitalization.

Treatment

Medical Management

Because of incomplete understanding of the etiology of NEC, treatment modalities have focused mostly on supportive measures such as stopping enteral feedings, decompressing the GI tract, broad spectrum antibiotics, and correction of metabolic (acidosis) and hematologic (thrombocytopenia, anemia) derangements. Careful attention must be paid to maintenance of normal cardiovascular and respiratory functions. This may include utilization of mechanical ventilation, vasopressors, and fluid resuscitation.

Choice of antibiotics usually depends on practice in each individual unit, but in general consists of two broad-spectrum agents that cover intestinal microorganisms. Anaerobic coverage may be added as well. The effect of addition of anaerobic coverage to the antimicrobial regiment was evaluated in a large propensity matched study.[10] Overall, the infants in the anaerobic coverage group developed more strictures (OR 1.73; 95% CI, 1.11-2.72 [p = 0.02]). In infants with surgical NEC, death was significantly less common (OR 0.70; 95% CI, 0.52-0.95 [p = 0.02]).[10] Antimicrobial therapy may be tailored to a specific microorganism in case of a positive blood culture. The length of the antibiotic course usually ranges from 7-10 days. The decision to stop or prolong antimicrobial therapy is usually guided by clinical status and nonspecific laboratory markers of inflammation such as C-reactive protein (CRP). There is, however, little evidence-based data to help clinicians determine the appropriate duration of antimicrobial therapy. It is also unclear how beneficial antibiotics are in NEC cases with negative blood cultures.

Serial abdominal x-rays are used to monitor progression of radiologic findings and are useful in determining the need for surgical intervention.

Surgical Management

Surgical intervention is required in about 30%-40% of NEC cases.[86,94] Two types of surgical approaches used in NEC are exploratory laparotomy and peritoneal drain placement. Historically, exploratory laparotomy (ExLap) with resection of nonviable intestine was a procedure of choice since the 1970s. Primary peritoneal drain (PPD) placement, however, started being utilized initially as a temporary measure in infants who were deemed to be too sick to tolerate exploratory laparotomy. PPD placement became more accepted as a definitive therapy after reports supporting this approach were published in the late 1990s and early 2000s. Two RCTs aiming to find a superior

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surgical approach were published about 10 years ago.[59,72] Both studies showed no differences in survival, length of hospital stay, and need for parenteral nutrition in ExLap vs. PPD groups. A randomized trial of laparotomy vs. drainage for infants with necrotizing enterocolitis (NCT01029353) that assesses outcomes at two years of age was completed in 2018. Results from this trial, the largest study of patients with NEC, will yield insights into the optimal surgical NEC management.

Outcomes

A diagnosis of NEC has significant negative impact on neonatal survival and on other outcomes. Mortality depends on the gestational age, birth weight, extent of bowel involvement, and the need for surgical intervention. The overall mortality due to NEC ranges from 20%-30%.[35,64] In infants who underwent surgery, the mortality rate is higher (35%) compared to infants who required only medical treatment (21%).[35] Mortality in medically treated neonates decreases with increase in birth weight. Such correlation was weaker in infants with NEC who required surgical intervention. The mortality in that group plateaued around 30%.[35] Survivors of NEC have an increase in adverse neurologic outcomes, specifically elevated rates of IVH and PVL, and perform worse on neurodevelopmental assessment.[82,90] Gastrointestinal complications include development of bowel stricture, short bowel syndrome, and intestinal failure. However, it is noted that patients with intestinal failure due to NEC have higher potential for rehabilitation compared with other causes (volvulus, intestinal atresia, and gastroschisis).[85] NEC is also a significant contributor to health care costs. The annual economic burden of the disease is estimated to be between 500 million and 1 billion US dollars.[64] Longer hospitalization, increase in amount of required procedures, and other resources contribute to the cost of initial hospitalization. Cost of care for infants with NEC is significantly higher compared to infants of the same gestational age but without this disease.[39] Care for infants who had NEC remains more expensive after discharge as well. According to data from Texas Medicaid, cost of care for infants with medically treated NEC became similar to children who did not have NEC after 1 year of age.[25] Medical expenses in children who underwent surgical intervention for NEC continued to be higher for an additional 1-2 years.[25]

Outpatient follow-up of infants who had NEC is important because of significant long-term consequences of this disease. Standardized multidisciplinary approaches with special attention to nutrition and rehabilitation should be utilized.

Pathophysiology of Necrotizing Enterocolitis

A "classic" form of necrotizing enterocolitis is associated with prematurity. It occurs at 2-6 weeks of age with highest incidence of the disease at 28-32 weeks of corrected gestational age.[27] Although there are many factors that predispose preterm infants to NEC, prematurity along with formula feeding and intestinal dysbiosis are considered the major contributing factors for NEC development.[31,43] A concerted effort is directed at elucidating the factors associated with prematurity that predispose this already vulnerable population to NEC. Those factors are categorized and described below.

Altered Host Defense

The ability of premature infants to respond to and control infection is significantly different from full-term newborns. This complicated and interconnected system is comprised of:

- Physical barriers that prevent intrusion of infectious agents (skin, mucous membranes, epithelium of the intestine with the mucous layer, and biomedical factors)
- Innate and adaptive immune systems (including cellular and humoral components)

Both human and animal studies indicate that the above-mentioned barriers are deficient in premature infants when compared to term infants and adults.[12,17] This deficiency can be quantitative, qualitative, or both for different elements of the host defense. Ability of gastric parietal cells to secrete acid is diminished as well in premature infants. Coordination of contractile activity in the developing gut corresponds with gestational age. The mature pattern of peristalsis is not developed until around 36 weeks of gestational age.

There is lack of data on gestational development of tight junctional barrier, but this barrier is thought to be deficient in premature infants.[15] The defense mechanisms of intestinal epithelial layer itself are underdeveloped in preterm infants. This includes decreased numbers of Paneth cells.[53] Paneth cells produce a number of peptides (lysozyme, defensins, secretory phospholipase A2) that play important roles in protecting intestinal epithelium from bacterial invasion and shaping the microbiome. The ability of Goblet cells to secrete mucin is also increasing throughout gestation and achieves maturity at term.[14] The mucous layer protects intestinal epithelium from interacting with pathogenic microorganisms while creating an environment for growth of commensal microorganisms.[88]

Of particular interest is an excessive pro-inflammatory phenotype of macrophages observed in patients with NEC when compared to healthy term infants. Studies explain this phenomenon by upregulation of Smad7 in macrophages of patients with NEC, which in turn inhibits TGF-β.[56,61] The latter factor downregulates pro-inflammatory response of macrophages. Intraepithelial lymphocytes (IEL) can be viewed as an important way of communication between intestinal content and the adaptive immune system. The predominant type of IELs in the intestine of preterm infants is γδ cells.[93] They play an important role in mucosal defense and are significantly decreased in intestinal samples obtained from infants with NEC.[93]

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Another disbalance in the cellular component of the immune system of infants with NEC is a shift in T-cell differentiation with an increase in $CD4^+$ TH17 lymphocytes and a decrease in counter-inflammatory Treg cells.[20] IL17, a product of $CD4^+$ TH17 lymphocytes, leads to increased apoptosis of enterocytes and negatively affects both intestinal epithelial tight junctions and proliferation of enterocytes.[20,34] The $CD4^+$ TH17/Treg disbalance was also shown to result in apoptosis of $LGR5^+$ intestinal stem cells in the mouse model.[65] The B-cell arm of the adaptive immune system serves as antigen-presenting cells and produces immunoglobulins. IgA is of particular significance as animal studies have shown that sIgA shapes intestinal microbiota and by this token regulates the maturation of intestinal epithelial cells (ILC) and development of intestinal barrier function.[54,74] Short- and long-term benefits of exposure to maternal sIgA were shown as well.[74] sIgA in human breast milk is considered to be one of the components that contributes to the protective effect of this mode of nutrition, especially in preterm infants. A review of studies that evaluated the potential benefit of Igs in preterm infants did not show a reduction in NEC incidence.[68] It is important to point out that only studies of intravenous Igs were reviewed.

Intestinal epithelium to some extent can be viewed as a teeter-totter, with the microbiome on one side and the hyper-activated immune system on the other. Pathogen-associated molecular patterns (PAMPs) of intestinal microbiota are binding and activate a series of pattern recognition receptors (PRRs). The roles of human toll-like receptors (TLRs) and intracellular nucleotide-binding oligomerization domains (NODs) in the pathogenesis of NEC have been under much scrutiny in last 10-15 years.

TLR-4 receptors and their activation is one of the cornerstones in NEC pathogenesis.[20] These receptors participate in normal gut development in humans and mice.[62] This explains a higher level of expression of these receptors in the developing gut.[62] In premature infants, TLR-4 expression remains elevated after birth.[66] The TLR-4 receptors located on IECs are activated by lipopolysaccharide (LPS), which is abundant in cell walls of gram-negative bacteria that colonize the gut.[4] This activation leads to a number of negative effects: increased apoptosis, impaired regeneration of IECs, and proinflammatory cytokine response.[47] Endoplasmic reticulum (ER) stress was also shown to be a result of TLR-4 activation in animal studies.[3] All of the above features are important elements of NEC. New data is emerging about other members of the TLR family.

NOD receptors are a family of intracellular receptors that are present in monocytes, Paneth cells, and IECs.[81] Peptidoglycan from the bacterial wall of Gram-positive and Gram-negative bacteria serves as a ligand for NOD receptors. NOD2 receptors mediate production of defensins by Paneth cells.[89] NOD2 activation was shown to inhibit TLR-4 in IECs and decrease apoptosis while improving mucosal intestinal injury repair.[73] NOD2 provides a way of communication between intestinal commensal bacteria and the innate immune system. One population-based study from Germany showed that VLBW infants with two or more NOD2 variant alleles were at higher risk of developing surgical NEC.[33]

Refer to Table 85.2 for the role of cytokines and chemokines in the pathogenesis of NEC. Vascular endothelial growth factor (VEGF) and development of intestinal microvasculature also appear to be involved in the pathogenesis of NEC. One study demonstrated that the level of VEGF is decreased in intestinal tissue obtained from infants with NEC.[75] An animal study also demonstrated the importance of VEGF and its receptor signaling for

TABLE 85.2 Selected Signaling Agents and Their Role in the Pathogenesis of Necrotizing Enterocolitis (NEC)

Signaling Agents	Role
Platelet activating factor (PAF)	Pro-inflammatory mediator. In animal models, causes ischemic necrosis in small intestine. Degrading enzyme PAF-acetylhydrolase (PAF-AH) remains low for weeks after birth. Breast milk contains PAF-AH.
Tumor necrosis factor (TNF)	Inflammatory cytokine that activates NF-κB pathway. Elevated in intestinal tissue of patients with NEC.
IL-1	Pro-inflammatory cytokine. Initiates production of other mediators of inflammation, leads to tissue damage.
IL-6	Acute phase immune mediator.
IL-8	Belongs to chemokine family. Helps with neutrophil recruitment to the site of inflammation.
IL-10	Important dampener of immune response in intestine. Thought to be an important protective factor in NEC.
IL-17A	Participates in chemokine induction and neutrophil activation. Leads to loss of intestinal intracellular tight junction, reduces enterocyte proliferation, increases enterocyte apoptosis.
TGF-β	Promotes Treg function but also activates Th17 cells. Downregulates inflammatory cytokine production. Reduced in preterm infants and in infants with NEC.

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maintenance of integrity of intestinal microvasculature in the postnatal period.[95] Interestingly, the peak incidence of NEC occurs at the same corrected gestational age as retinopathy of prematurity. This coincidence is intriguing and whether this relates to the VEGF system requires additional research.

Dysbiosis

Until recently, sterility of the fetus in utero was a well-accepted notion. However, now we know that microorganisms colonize the fetal gut before birth.[60] Culture and non-culture-based studies revealed the presence of microorganisms in the amniotic fluid, placenta, and meconium. Known factors that affect gut colonization in infants are preterm birth, mode of delivery, and breastmilk vs. formula feeding. Resemblance between fetal and neonatal bacterial colonization on one side and bacterial flora of the maternal oral cavity and placenta on the other side strongly points to hematogenous transfer of bacteria during gestation.[1,49] The microbiome of a developing gut can modify health outcomes of both term and preterm infants for years to come. More studies are needed to elucidate the mechanisms of this influence. The study of gut colonization in preterm infants showed that shifts in predominant bacterial classes are well orchestrated and abrupt: from bacilli to Gammaproteobacteria and then to Clostridia.[46] The proportion of anaerobes approached that of older children by 33-36 weeks of postconceptual age (PCA). Factors like gestational age at sample collection, mode of delivery, and treatment with antibiotics affected the pace of colonization but not the actual sequence of bacterial classes.[46]

Studies comparing stool microbiome of preterm infants who developed NEC with matched controls found an increase in Gammaproteobacteria and decrease in Clostridia and Negativicutes in those infants who developed NEC.[92] Recent systematic review and meta-analysis of sequencing data from 14 studies showed that preterm infants that developed NEC had increased relative abundance of Gammaproteobacteria and decreased relative abundance of Firmicutes and Bacteroidetes.[69] Increased relative abundance of Gammaproteobacteria prior to development of NEC emerged as a key element of a dysbiotic shift observed in this pathology. This provides an abundance of LPS—a ligand of the TLR-4 receptor. TLR-4 activation, as discussed earlier, is a very important step in pathogenesis of NEC.

Enteral Feedings

The vast majority of NEC cases occur in infants who have received partial or full enteral nutrition. The disease usually develops days to weeks after initiation of enteral feedings. This form of alimentation, therefore, was regarded as an important risk factor for "classic" form of NEC for decades. Delaying initiation and slow advancement of enteral feedings were used to avoid this dreaded disease. Results from animal and adult human studies provide compelling evidence that these practices have a negative impact on the GI tract. This includes mucosal atrophy, bacterial translocation, sepsis, and dysregulation in the secretion of trophic hormones. Recent neonatal studies suggest that longer NPO status in preterm infants is associated with an increased risk for NEC and an increase in intestinal inflammation.[42,44] In 2014, a Cochrane review dedicated to this question found no evidence that delaying initiation of enteral feeds beyond 4 days of life affects the risk of NEC development.[58] This review included 1106 infants from 9 randomized controlled trials (RCTs). Once enteral nutrition is initiated, the controversy shifts toward determining the optimal rate of volume advancement. Another Cochrane database review was published in 2017 and included data from 10 RCTs with a total of 3753 infants. Slow advancement was defined as daily increment of 15-20 mL/kg of enteral feeding volume and faster advancement as a daily increment of 30-40 mL/kg. No difference in the risk of NEC, and all-cause mortality was found between the groups.[67]

Role of Breast Milk

Breast milk provided by the mother of an infant, mother's own milk (MOM), is considered the gold standard of nutrition for an infant of any gestational age. Breast milk contains multiple bioactive components that collectively confer protective benefits to the growing premature infant. These benefits include augmentation of the infant's immune system, anti-inflammatory effects, strengthening of the mucosal barrier, and enriching of beneficial bacterial flora of the gut. Breast milk components include epidermal growth factor (EGF), heparin-binding EGF-like growth factor, platelet activating factor acetyl hydrolase (PAF-AH), secretory IgA (sIgA), lactoferrin, human milk oligosaccharides (HMO), nitrates, glutamine, IL-10, etc. It is important to know that freezing/thawing and pasteurization of breast milk affects the content of these components and will likely decrease its protective effect.

In many cases, however, mothers of preterm infants do not produce sufficient amounts of breast milk, especially in the immediate postnatal period, and formula supplementation is required. Human donor breast milk (HDM) emerged as an alternative for nutrition of preterm infants when MOM is unavailable. A 2014 Cochrane database review that included nine trials (1070 infants) concluded that formula-fed infants had higher risk for NEC development—risk ratio of 2.77 when compared with infants who received HDM.[71] Meinzen-Derr et al. (2009) showed that human milk has a dose-dependent protective effect against NEC. In their study, likelihood of NEC or death after 2 weeks decreased by a factor of 0.83 for each 10% increase in proportion of human milk in the total intake. Another study showed that administration of exclusive breast milk for less than 7 days in the first month of life increased risk of NEC fourfold in VLBW infants.[40]

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Fortification of human milk products (MOM and HDM) is necessary to meet nutritional needs of the preterm infant. Studies suggest that feeding only human milk and human milk-based fortifier provides better protection against NEC when compared to feeding bovine products.[2] The occurrence of NEC reportedly decreased from 17% to 5% and surgical NEC from 12% to 1%, but the studies used in this analysis were not powered to detect NEC occurrence as a primary outcome.[2] A recent multicenter retrospective cohort study found that exclusive human milk diet (MOM and/or HDM + human milk–based fortifier) significantly reduced the incidence of NEC, late-onset sepsis, retinopathy of prematurity, bronchopulmonary dysplasia, and mortality when compared with bovine-based diet.[32]

Role of Blood Transfusions

Premature infants are at higher risk of needing packed red blood cell (pRBC) transfusions, with some studies estimating that about 90% of infants with birth weight below 1500 g receive at least one.[11] This highly prevalent intervention has long been under scrutiny for its potential role in NEC pathogenesis. Distinguishing whether transfusions predispose preterm infants to NEC or whether NEC is related to a pretransfusion deteriorating status remains difficult. Transfusion guidelines are not uniform and changes in the clinical status of the infant frequently trigger laboratory evaluations with subsequent pRBC transfusions. This subset of NEC is called transfusion-associated NEC (TANEC).

Studies that found associations between pRBC transfusion and development of NEC prompted the development of the term transfusion-associated gut injury (TRAGI).[13,48] This association was reinforced by a systematic review of 12 retrospective studies, although only part of those studies were included in calculation of odds ratios.[55] Only 5 out of 12 included studies reported unadjusted estimates of infants' exposure to transfusion in the previous 48 hours, and NEC and only 4 studies reported adjusted estimates of such exposure.[55] Several mechanisms were proposed to explain the role of transfusions in the development of NEC: (1) reperfusion injury due to transfusion; (2) immunologic reactions and injury of intestinal mucosa triggered by cytokines, fragmented RBCs, and free hemoglobin; and (3) transient mesenteric ischemia after blood transfusion. A prospective observational study found significant elevation of proinflammatory cytokines (IL-1β, IL-8, IFN-γ, IL-17, MCP-1, IP-10, and ICAM-1) at different time points following blood transfusion in preterm infants less than 32 weeks of gestation.[18]

Alternatively, evidence has also accumulated about the lack of association between pRBC transfusions and NEC.[83,91] Moreover, some studies found that blood transfusions are associated with a lower risk for NEC.[7,84] In a recent prospective multicenter study, secondary analysis revealed that severe anemia (Hb <8 g/dL), but not blood transfusion, was associated with development of NEC.[70] In one meta-analysis, authors found that data from RCTs conflict with the results of observational studies. The RCTs show that blood transfusions are associated with lower risk for NEC, and the observational studies show that transfusions are associated with NEC.[41] A large ongoing randomized controlled trial, Transfusion of Prematures, should provide additional information about this controversial topic (ClinicalTrials.gov identifier: NCT01702805).

Administration of enteral feedings during blood transfusion is another daunting issue. A small case-control study found that implementation of a policy for withholding of enteral feedings during pRBC transfusion was associated with reduction of NEC incidence.[21] Another small study looked at trends of mesenteric tissue oxygenation during and after pRBC transfusions relative to feeding status.[50] This study found that infants who received enteral alimentation during pRBC transfusions had negative trends in postprandial mesenteric tissue oxygenation for up to 15 hours after the transfusion compared to infants who were not fed. There was no difference in mesenteric oxygenation during the transfusion between the groups. The authors suggested a relative postprandial ischemia after transfusion in infants who were fed. It is important to note that in this study the majority of infants who were fed during transfusion were getting formula feedings (6 out of 8) and the majority of infants whose feeds were held during transfusion were receiving breast milk feedings (7 out of 9).[50] This difference could have had significant impact on the difference in the NEC incidence by itself. A systematic review recently evaluated the evidence for withholding enteral feedings during pRBC transfusions.[38] This review showed that the practice of withholding enteral feedings during pRBC transfusions significantly reduced the incidence of transfusion-associated NEC with RR of 0.47; 95% CI: 0.28-0.80 ($P = 0.005$). No RCTs were included in this review since they were not found. Conclusions were drawn by comparing rates of transfusion-associated NEC before and after implementation of the practice to withhold feedings in the peri-transfusion period.[38] Authors stated that the quality of the generated evidence was moderate.[38] In summary, controlled and adequately powered studies are needed to generate better evidence to determine the association between withholding enteral feedings during pRBC transfusions and NEC.

Preventive Strategies

Developing preventive strategies to decrease the incidence of NEC is very important in view of the limited ability to diagnose early stages of the disease and to treat it. Below is a discussion of several of the most important aspects of NEC prevention. Readers should keep in mind that:

- Only evidence-based measures should be employed.
- A combination of measures, rather than any separate intervention, has the highest potential for decreasing incidence of NEC in the NICU setting.

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Standardized evidence-based feeding protocols have been shown not only to decrease the incidence of NEC but also to improve other important outcomes like shortening the time to achieve full enteral feeds and decreasing the incidence of late onset sepsis and mortality.[52,80] The advantages of maternal breast milk and donor breast milk over formula products have been discussed earlier. This evidence should be incorporated into feeding guidelines for VLBW and ELBW infants.

Understanding of the role dysbiosis plays in the development of NEC leads to development of new strategies that aim to avoid alteration of the developing intestinal microbiome.

Antibiotics are among the most commonly used medications in the NICU. The vast majority of VLBW and ELBW infants receive broad-spectrum antibiotics in the NICU. These medications alter the intestinal microbiome in neonates.[9,30] Prolonged use of broad-spectrum antibiotics in culture-negative infants is associated with worse outcomes, including increased risk of NEC, late onset sepsis, and higher mortality.[45] One study found an almost threefold increase in risk of NEC when infants were exposed to antibiotics for more than 10 days.[5] Antibiotic stewardship is, therefore, a necessary part of the medical culture in the NICU.

Antireflux medications (both H2 blockers and proton pump inhibitors) have also been overused in the NICU. These medications are mostly prescribed not to treat the symptoms of gastroesophageal reflux (GER) per se but with a hope to decrease the amount of apneas and episodes of bradycardia and desaturation in preterm infants. A large study showed that only about 3% of these events follow an episode of GER.[19] Therefore, the prescription of antireflux medications is clinically unsubstantiated in the vast majority of infants. Additionally, it is shown that prescription of antireflux medications leads to undesired effects: alteration of microbiome, bacterial overgrowth, impaired bactericidal properties of gastric secretions, delayed gastric emptying, and impaired chemotactic response.[76] Indeed, a large systematic review has shown a strong association between the use of antireflux medications and NEC in preterm infants.[57] Routine use of these medications, therefore, should be avoided in premature infants.

Perhaps the most controversial topic in NEC prevention is use of probiotics. This seems to be a logical step given the importance of dysbiosis in the pathogenesis of NEC. Probiotics are live bacteria that confer health benefits on the host when administered in adequate amounts. Multiple studies and meta-analyses were performed to study whether probiotics reduce NEC in preterm infants. Results of the latest Cochrane review showed a statistically significant reduction in the incidence of NEC and mortality in infants who received enteral probiotics.[6] The trials included in the above-mentioned review, however, were highly variable in their inclusion criteria; baseline risk of NEC in control groups; and most importantly, timing, dose, formulation of probiotics, and feeding regimen.[6] This variability necessitates the caution with which the results may be interpreted.

The largest randomized adequately powered, double-blinded, placebo-controlled trial that showed a statistically significant reduction of NEC in VLBW infants was published in 2013.[37] This trial was conducted in 10 centers across Australia and New Zealand and used a combination of three bacteria in the intervention group: Bifidobacterium infantis, Streptococcus thermophilus, and Bifidobacterium lactis. There were no differences in primary outcomes between the groups (late-onset sepsis and all-cause mortality). NEC incidence was a secondary outcome. The incidence of NEC was reduced from 4.4% in the control group to 2% in the intervention group (RR 0.46 with 95% CI 0.23-0.93. $P = 0.03$). Babies with birth weights of less than 1000 grams did not show a benefit, a finding also seen in previous studies. The results of that trial were marred by the fact that in 2014 the manufacturer recalled the product used in the intervention group (ABC Dophilus; Solgar, Inc). The reason for the recall was a report by CDC that showed contamination of the product by a fungus Rhizopus oryzae, which caused a lethal infection in a premature infant.[24] This incident brings a safety concern for using live bacteria in preparations that are not considered pharmaceutical-grade quality in preterm infants whose immune systems are compromised.

Results of a large study that evaluated the effect of the probiotic bacterium Bifidibacterium breve BBG-001 on NEC and sepsis were published in 2016.[16] This study was randomized, double-blinded, and adequately powered to detect differences in primary outcomes: NEC (Bell stage 2 or 3), late-onset culture-positive sepsis, and death before discharge. There was no statistically significant reduction of NEC in the intervention group. No differences in other primary outcomes were observed between the groups either. This study also revealed that about half of the infants in the control group were colonized with the bacterium used for intervention by the end of the trial, raising a concern about potential cross-contamination of infants in the control groups of probiotic studies.[16]

In conclusion, although probiotics remain a promising preventative strategy for NEC, we should not recommend them for routine use in NICUs at this time. Strong evidence supporting the use of specific probiotics that are pharmaceutical grade for NEC prevention is lacking, especially in ELBW infants who are at the highest risk for developing this devastating disease. The following issues need to be addressed:

1. Probiotic formulations need to be manufactured under strict pharmaceutical regulations by country-specific agencies to ensure safety and quality of these agents.
2. Each probiotic strain or a combination of strains needs to be assessed separately by an adequately powered, randomized, blinded, and placebo-controlled trial before any recommendation for their widespread use can be made.

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Key Points

- Different medical entities are currently grouped in one diagnosis of NEC.
- Development of a clear definition for NEC is needed for advancement of research as well as diagnostic, prevention, and treatment efforts.
- GI tract immaturity, intestinal inflammation, and dysbiosis are important pathophysiologic components of "classic" NEC.
- No reliable markers of early stages of this disease are available at this time and diagnosis is often delayed.
- Treatment options for NEC that are utilized at this time are only supportive.
- Standard feeding protocols using breast milk have been shown to decrease incidence of NEC.

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86

Disorders of Carbohydrate Metabolism in the Neonate

MEENA GARG AND SHERIN U. DEVASKAR

The fetus depends entirely on the mother for its nutritional needs, of which glucose is the principal energy substrate that fuels fetal growth and metabolism. At birth, when the maternal supply is discontinued, the neonate must adjust to an independent existence. This transition to the extrauterine environment is often perturbed by alterations in the mother's metabolism or by intrinsic fetal and placental problems that result in changes in the neonate's glucose homeostasis. An understanding of the normal physiologic adaptation of the maternal–fetal nutritional relationship during pregnancy and of fetal glucose homeostasis and glucose metabolism during the transition to extrauterine life serves as a framework for evaluating disordered glucose metabolism in the neonate.

Placental Transport of Nutrients: Maternal–Fetal Relationship

The fetus is entirely dependent on the mother for nutrients supplied by the placenta. Yet the fetus is hormonally independent of the mother (Fig. 86.1), since no maternal peptide hormones are transported to the fetus in any significant amounts. The fetal endocrine and paracrine responses are mediated by the transport of nutrients such as glucose and amino acids.

Glucose

Glucose is the primary substrate for fetal energy metabolism for which the fetus depends entirely on maternal glucose because of minimal fetal gluconeogenesis.[26,63] Glucose is transported to the fetus along a downward concentration gradient via facilitated transport mediated by glucose transporters (GLUTs) encoded by the SCL2A genes.[64] A higher concentration of GLUT 1 is present on the maternal side of the syncytiotrophoblastic (SC) membrane compared to the fetal side of the SC basal membrane, suggesting a rate limiting step in glucose transport. In normal pregnancies, the plasma glucose concentration of the fetus is about 70%-80% of that of the mother. Because the range of glucose concentrations observed in human pregnancy does not saturate maternal–fetal glucose transfer, even when complicated by diabetes, fetal glucose uptake becomes excessive as the maternal glucose concentration increases. When fetal glucose uptake exceeds the requirements of energy production and growth, the excess glucose is stored as glycogen and triglycerides. Glucose transfer by placenta is also affected by the placental surface area, glucose metabolism, and blood flow.

Fatty Acids

A significant amount of fatty acids are transported to the fetus, as they are a critical source of energy and are an essential component of cell membranes, tissue development (white adipose tissue), and organogenesis (brain).[63] The transfer of nonesterified fatty acids (NEFA) from the mother to the fetus occurs by simple diffusion. A progressive shortening of chain length from C16-C8 is associated with an increased transfer rate. Protein binding appears to slow the rate of transfer. A number of fatty acid transport proteins (FATP 1-4, and 6) that are present in SC membranes in placenta are involved in the cellular uptake of long-chain fatty acids.[64] In addition, a significant amount of nonessential fatty acids appears to be synthesized de novo by the fetus in utero. Maternal adipose tissue and dietary intake are the primary sources of transplacental long chain polyunsaturated fatty acids (LCPUFA) to the fetus.[43]

Amino Acids

Amino acids are transported to the fetus against a concentration gradient by a carrier-mediated transport process. Amino acids may be transported through the placenta either unchanged or after placental metabolism and processing; for example, leucine can be transferred intact or as its keto analogue α-ketoisocaproic acid. The syncytiotrophoblast is usually considered the main transport epithelium of the term placenta (see Fig. 86.1). Amino acids are transported by means of energy-dependent processes through selective amino acid transport systems.

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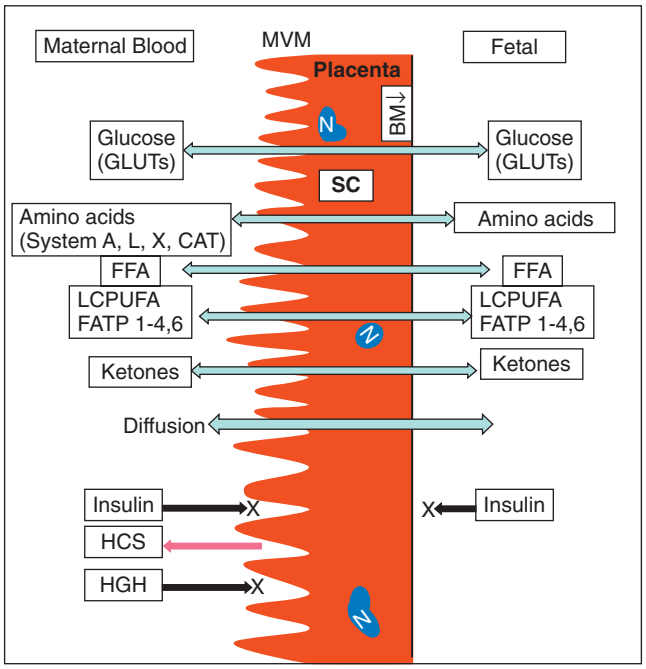
Abstract

Glucose, a six-carbon sugar, is the most important source of energy for all cells and is a universal currency for energy (ATP) production. It is also an essential source of energy for brain metabolism. The fasting blood glucose concentration in the adult is regulated within a rather narrow range (70-100 mg/dL), representing a balance between utilization of glucose to fuel cellular metabolic processes and availability of glucose to sustain the fetus via maternal–placental transport, transitioning in the newborn by glycogenolysis and gluconeogenesis while nutritional intake is established. After separation from the placenta, disturbances in the glucose homeostasis resulting in hypoglycemia are common occurrences in the preterm and term newborn infants. Yet uncertainty regarding the definition of hypoglycemia and long-term untoward effects of transient or recurrent hypoglycemia remain. The pancreatic beta cell maintains steady state blood glucose by a complex feedback mechanism involving the glucose sensing K_{ATP} channels toward regulating insulin secretion. Mutations in K_{ATP} channel genes can result in hyperinsulinemia due to loss of K_{ATP} function and continuous opening of Ca+ channels facilitating insulin release or neonatal diabetes due to gain of K_{ATP} channel function and closure of Ca+ channels that deters insulin release. Adequate storage of glucose and function of skeletal muscle, cardiac muscle, and white adipose tissue requires hormonal regulation by insulin and glucagon. Hepatic glycogen storage is essential for successful glycogenolysis, a process necessary for maintaining glucose homeostasis during the fasting state encountered between milk intake in the newborn. In this chapter we discuss various congenital and acquired conditions in the neonate that perturb glucose homeostasis.

Keywords

hypoglycemia
hyperglycemia
gestational diabetes
infant of diabetic mother
congenital hyperinsulinism
Glut1 deficiency syndrome
neonatal diabetes mellitus

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• **Fig. 86.1** Maternal–fetal substrate hormone relationship. FFA, Free fatty acids; HCS, human chorionic somatomammotropin; HGH, human growth hormone. BM, Fetal facing basal plasma membrane; FATP, fatty acid transport protein; GLUTs, glucose transporters; LCPUFA, long-chain polyunsaturated fatty acids; MVM, microvillous membrane; N, nucleus; SC, syncytiotrophoblast.

Other Fetal Substrates

β-Hydroxybutyrate and possibly acetoacetate, the major ketone bodies, are transported along a concentration gradient.[22,34] The concentration of β-hydroxybutyrate in fetal blood is significantly less than that in maternal plasma (≈50%); however, a linear correlation between the maternal and fetal concentrations has been reported.

Glycerol

There is a linear correlation between maternal and fetal glycerol levels, with the fetal level in most instances being somewhat lower than the simultaneously determined maternal plasma level.[63]

Lactate

Data on the maternal–fetal lactate relationship in human studies are conflicting. Experimental data in sheep demonstrated placental production and fetal use of lactate, but data in human studies showed higher levels of lactate in fetal than in maternal blood. In the few studies in which umbilical artery and vein samples were obtained simultaneously, the data could be interpreted as net fetal production and placental clearance of lactate.

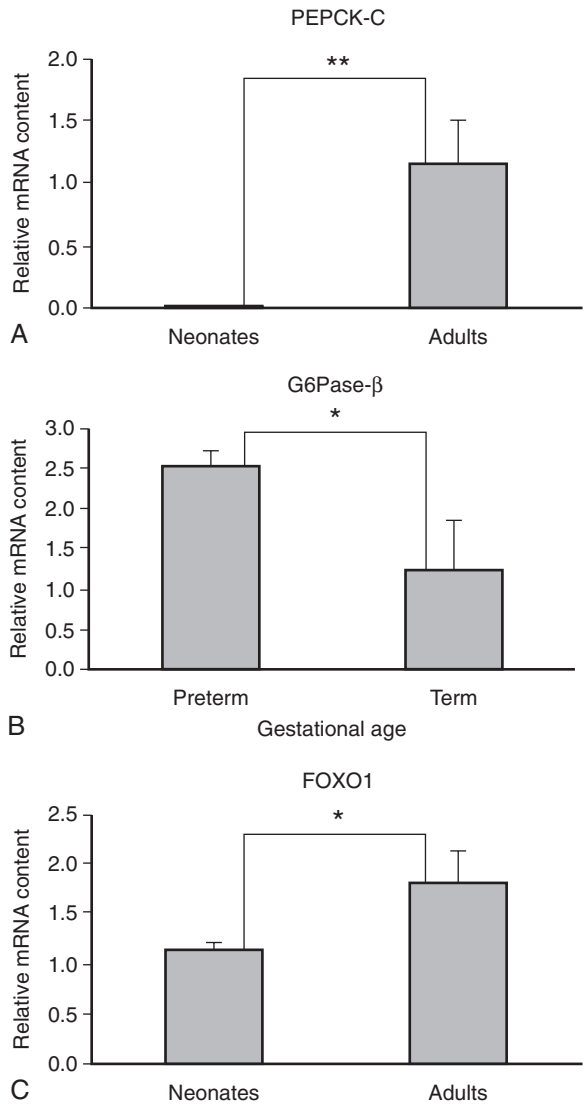
Fetal Hormones Mediating Growth

Insulin-like growth factors (IGF I and II) are highly expressed in all fetal tissues. IGF I in fetus is nutrient sensitive and corresponds with fetal growth independent of growth hormone. Immunoreactive insulin has been demonstrated in both plasma and pancreatic tissue as early as 8 weeks of gestation; the source appears to be the fetal pancreas, because the placenta is impermeable to insulin. At 13-18 weeks of gestation, the fetal insulin response to sustained maternal hyperglycemia is negligible. However, at term, the fetus is capable of a significant response to prolonged hyperglycemia, although to a lesser degree than adults. When the fetus receives appropriate glucose from the mother, the requirement for an insulin response is minimal. With repeated episodes of hyperglycemia, as in maternal diabetes, a greater insulin response is seen, indicating that B-cell sensitivity is being induced or enhanced. That insulin may modify the growth rate in utero has been shown by the positive correlation between the fetal plasma insulin concentration and fetal weight. Human growth hormone (GH) has been measured as early as 9 weeks of gestation and increases rapidly between the 11th and 16th weeks. Because the transplacental transfer of GH is negligible, the fetal pituitary appears to be its source in the fetus. At term, fetal plasma GH levels are higher than those of maternal plasma. Unlike those of adults, fetal GH levels are not suppressed during hyperglycemia and actually show a paradoxic rise. Several studies have demonstrated the role of insulin as the growth-promoting hormone of the fetus and that the fetus can sustain normal growth in the absence of GH.

Fetal Glucose Metabolism

Under normal circumstances (i.e., in an uncomplicated, normal pregnancy), the fetus is entirely dependent on the mother for a continuous supply of glucose for both energy metabolism and the synthesis of other metabolic substrates.[63] The fetal liver contains the full complement of enzymes required for the synthesis and breakdown of glycogen. Hepatic glycogen content is low early in gestation; a slow, continuous increase occurs between 15 and 20 weeks; and a rapid accumulation of glycogen in the liver is observed late. The fetus also has all the strategic hepatic enzymes involved in gluconeogenesis, although their levels are lower than those in adults.[38] The only exception is cytosolic phosphoenolpyruvate carboxykinase (PEPCK), which, at least in the rat, is not expressed in utero and appears immediately after birth (Fig. 86.2).[23] Data in humans in vivo are not available; however, in nonhuman primates, mitochondrial PEPCK and PEPCK-C gene expression increase with advancing gestational age, while glucose-6-phosphatase-alpha (G6Pase-a) and its target gene FOXO1 expression are higher at preterm compared to term gestation.[38] In the mammalian species studied, the gluconeogenic capacity is not expressed in utero under unperturbed circumstances, and the contribution of gluconeogenesis from lactate, pyruvate, or alanine to glucose is quantitatively negligible.[15,25] Studies in humans and animals have consistently demonstrated that the fetus does not produce glucose and that maternal glucose is the only source of fetal glucose.

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• **Fig. 86.2** Postnatal changes in gene expression of key gluconeogenic molecules in preterm baboons at 125 days, term 185 d and adult PEPCK-C **(A)**, G6Pase-b **(B)**, and FOXO1 **(C)**. (From McGill-Vargas LL, Johnson-Pais T, Johnson MC, Blanco CL. Developmental regulation of key gluconeogenic molecules in nonhuman primates. *Physiol Rep*. 2014;2(12):e12243.) Data are means ± SE. * P<0.05; ** P<0.001.

Fluctuations in maternal blood glucose are rapidly reflected in parallel changes in fetal glucose concentration. These variations occur even in response to acute hypoglycemia induced by insulin infusion in the mother during sheep pregnancy. However, if maternal hypoglycemia is prolonged, the fetus begins glucose production.[5] Whether such a response can occur in human pregnancy has not been examined and cannot be pursued without violating ethical standards. Glucose is the primary fuel for the fetus, accounting for about 80% of fetal energy consumption. The remaining 20% of fetal energy needs is provided by lactate, amino acids, and other means.

Glucose Metabolism After Birth

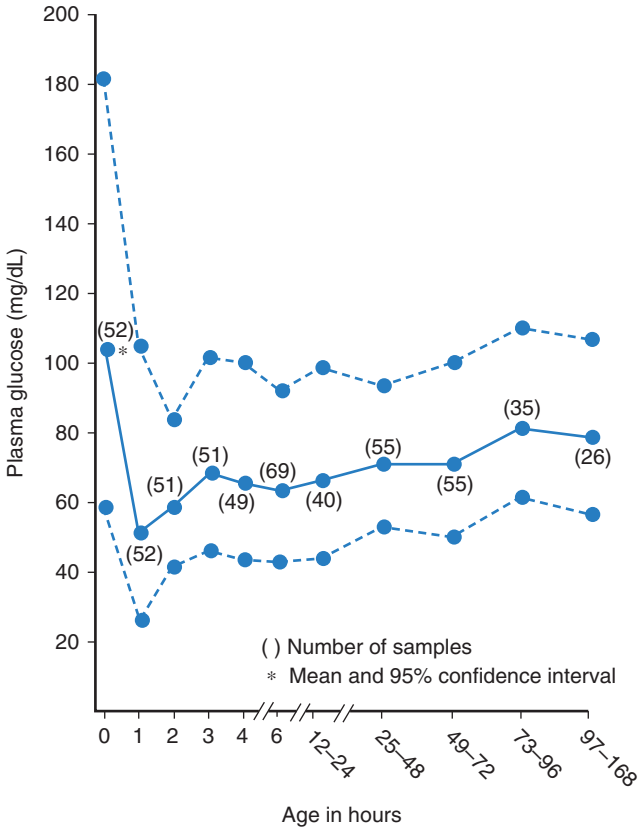
At birth, after separation from the umbilical circulation, the supply of glucose and other nutrients abruptly ceases, and the newborn infant has to mobilize its depots to meet energy requirements. This initial drop in glucose concentration may be an essential step in activating physiologic processes necessary for postnatal survival, such as promoting glucose production by gluconeogenesis, stimulation of appetite, adaptation to fast/feed cycles, and enhancement of oxidative fat metabolism. Acute surge in the levels of circulating epinephrine, norepinephrine, and glucagon and a fall in the levels of insulin coincides with clamping of the umbilical cord. These hormones concomitantly mobilize hepatic glycogen and stimulate gluconeogenesis, resulting in a steady rate of glucose production and maintenance of the plasma glucose concentration.

The plasma glucose concentration in umbilical vein blood is about 80% of the prevailing maternal blood glucose concentration. After birth, the plasma glucose concentration falls in all infants, reaching its lowest value between 30 and 90 minutes after birth. Thereafter, in full-term healthy neonates, the plasma glucose concentration rises and is maintained at a steady level of 40-80 mg/dL. Full-term newborn infants can tolerate fasting without a significant change in the blood glucose concentration. Fasting up to 9 hours after a meal did not cause a decrease in the plasma glucose concentration. After 4-6 hours post feeding state, steady state plasma glucose concentration is maintained with interactions between insulin and counter regulatory hormones (glucagon, cortisol, GH, epinephrine, and norepinephrine). Prolonged fasting state triggers increased utilization of FFA and ketone bodies with decrease in hepatic glycogenesis and increase in gluconeogenesis in response to increase in circulating glucagon and decrease in insulin concentrations.[25]

In full-term infants, the plasma glucose levels obtained at random intervals during the first week after birth have ranged from 40-100 mg/dL, with a mean of 80 mg/dL (Fig. 86.3).[25,34,64] These levels are higher than those previously reported in fasting infants and reflect changes in feeding practices and the random nature of measurements. The plasma glucose concentration in healthy, asymptomatic, breastfed babies has been reported to be lower with an average of 65 mg/dL (range 27-95 mg/dL) than that in formula-fed infants (mean 72 mg/dL, range 45-112 mg/dL) during the first 24 hours of life, but reveal higher blood ketone body concentration.[25] The plasma glucose values in infants who are small for gestational age (SGA) and in premature infants are somewhat lower.[28,32] Hypoglycemia in the neonatal period cannot be described by a single value. Most investigators consider a plasma glucose level lower than 45 mg/dL in the first 24 hours of life, and preprandial glucose less than 50 mg/dL up to 48 hours of age and less than 60 mg/dL after 48 hours of age[2] as meeting the criteria of hypoglycemia. Additionally, there are differences between arterial and venous sample values, venous being 10% lower and when comparing whole blood versus plasma, whole blood being 15% lower.

During hypoglycemia, endogenous hepatic glucose production (EHGP) is derived from gluconeogenesis and

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• **Fig. 86.3** Plasma glucose levels in healthy term neonates delivered vaginally with birth weight between 2.5 and 4 kg. (From Srinivasan G, et al. Plasma glucose values in normal neonates: a new look. *J Pediatr.* 1986;109:114.)

glycogenolysis. The rates of endogenous glucose production in both full-term and preterm infants are significantly higher than in adults.[19] In preterm infants, gluconeogenesis is attributed to account for 72% of EHGP.[52,53] On average, the neonate produces glucose at rates between 4 and 6 mg/kg per minute. The higher rates of glucose production in the neonate reflect the higher ratio of brain to body weight, the brain being the major glucose-utilizing organ. In the first few days after birth, the rate of glucose production during fasting in full-term infants has been reported to decrease slightly. As the infant grows, the rate of glucose production expressed per unit of body weight decreases, so by adolescence, it approaches the rate seen in adults.

EHGP depends on (1) adequate glycogen stores, (2) sufficient supplies of endogenous gluconeogenic precursors, (3) normally functioning hepatic gluconeogenic and glycogenolytic systems, and (4) a normal endocrine system for modulating these processes. At birth, the neonate has glycogen stores that are greater than those in the adult. However, because of twofold greater basal glucose use, the stores begin to decline within 2-3 hours after birth. Muscle and cardiac carbohydrate levels fall more slowly. During asphyxia, the energy requirements are met by anaerobic glycolysis, an inefficient mechanism that results in a limited amount of energy and a decrease in glycogen stores. In premature infants, both total carbohydrate and fat content are reduced, and depletion of liver carbohydrates occurs. Endogenous *gluconeogenic* substrate availability is probably not a limiting factor, because the concentration of plasma amino acids is high at birth as a consequence of active placental transport. Similarly, other *gluconeogenic* precursors, such as lactate, pyruvate, and glycerol, are also increased. Nevertheless, active gluconeogenesis has been demonstrated in the human newborn soon after birth.[15] Finally, EHGP is normally regulated; that is, it decreases in response to glucose as well as insulin infusion in both full-term and preterm healthy neonates.[29] However, in extremely immature infants and in sick or stressed neonates, exogenous glucose infusion may not completely suppress endogenous glucose production.

The fall in blood glucose that normally occurs after birth is accompanied by an increased level of GH, a relatively low concentration of immunoreactive insulin, and an increase in plasma glucagon. The neonate shows an attenuated but significant insulin response to a variety of stimuli. After the oral administration of glucose, the insulin response in the normal neonate is similar to that in adults with chemical diabetes, that is, a lag in insulin response and a delayed peak. The premature infant has a minimal and variable insulin response, but the values are markedly increased by the intravenous administration of glucose plus amino acids. The physiologic role of increased GH levels has not been defined; GH values are high during the first 48-72 hours and gradually decline but are still elevated at 8 weeks of age. In addition, the newborn shows a paradoxic rise in GH after glucose infusion. Plasma glucagon values at birth are similar to or slightly higher than maternal levels. Glucagon and GH are not suppressed during hyperglycemia. In healthy newborns, intravenous and oral alanine feedings raise plasma glucagon and glucose levels.

Adaptation to prolonged starvation in adult humans is facilitated by the ability of the brain to derive much of its energy from the oxidation of ketone bodies, which decreases the need for gluconeogenesis and spares muscle protein. The enzymes involved in ketone body utilization pathways are present in the brain tissue of human fetuses and newborns. That ketone bodies can be used by the brain of infants and children has been shown by measurements of arteriovenous differences across the brain.

The transition from an intrauterine environment to independent extrauterine life is also characterized by intense lipid mobilization, as shown by a rapid increase in plasma glycerol and FFAs. In addition, there is a shift in the sources of energy for oxidative metabolism, as evidenced by a decline in the respiratory quotient. An increased contribution of fat to oxidative metabolism is reflected in a drop in the respiratory quotient from near 1.0 at birth to a level between 0.8 and 0.85 within a few hours after birth. Evidence of significant lipolysis in the neonate has been obtained by using isotopic tracers to measure glycerol kinetics.[44] These studies showed that lipolysis in the neonate occurs at rates almost threefold greater than those in adults and that the major metabolic fate of glycerol released as a result of lipolysis

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is conversion to glucose. Free fatty acids are used by the heart and muscle in the absence of readily available glucose, producing ketone bodies that readily cross the blood–brain barrier to be used as fuel sources for the brain. Therefore, the hypoglycemic neonate may remain asymptomatic because of the ability in utilizing alternate nutrients (ketones and lactate). However, neonatal hypoglycemia caused by hyperinsulinism leads to reduced concentrations of free fatty acids and ketone bodies, depriving the brain of an alternative energy source of ketones for fueling cerebral metabolism. This results in neuroglycopenic symptoms with severe neurologic injury and dysfunction.[41]

Measurement of Glucose

Factors frequently overlooked in the interpretation of glucose concentration are the type of sample and the method of analysis. Whole blood includes red blood cells which, therefore, display a glucose concentration lower than that of plasma. Plasma glucose values are higher than those of whole blood by about 14%; the difference may be greater at very low glucose values (<30 mg/dL). Whole-blood glucose content also varies in accordance with the hematocrit. Neonatal red blood cells contain high concentrations of glycolytic intermediates; therefore, whole blood must be deproteinized before analysis. Capillary blood samples should be collected from a warm heel and kept on ice, because the rate of in vitro glycolysis is increased in red blood cells at room temperature; whole-blood glucose values may drop 15-20 mg/dL per hour if the sample is allowed to stand at room temperature. The most frequently used method for glucose determination in the laboratory is an automatic analysis technique with glucose oxidase or a commercial glucose oxidase immobilized electrode. Plasma or serum glucose concentrations are determined, and the results are very accurate.

In most newborn nurseries, the rapid point-of-care assessment of whole-blood glucose concentrations is accomplished by a glucose oxidase and peroxidase chromogen test strip method, either alone or with a reflectance colorimeter. However, all test strip methods show significant variations in glucose concentrations compared with laboratory methods, particularly in the low glucose range (<45 mg/dL).[12] Devices and operator techniques vary, with confounding influences of incubation time and the hematocrit values. There should not be sole reliance on test strip devices, and tests resulting in borderline values (<40-45 mg/dL) should be repeated by using standard laboratory methods.

Continuous glucose monitoring using a subcutaneously placed microdialysis sensor has been validated in adults and children with diabetes. The feasibility, safety, and usefulness of these techniques have been examined in babies with low birth weight.[12,39] However, similar to point-of-care devices, these methods cannot measure glucose levels less than 45 mg/dL with confidence. Thus far, continuous glucose monitoring has been used mostly for research studies, and its use in clinical setting is still limited.

Hypoglycemia

Perturbations in glucose metabolism after birth caused by failure to adapt to the extrauterine environment, as a result of either alterations in maternal metabolism or intrinsic metabolic problems in the neonate, often result in hypoglycemia. Despite many years of research, uncertainty remains regarding the concentration of glucose responsible for long-term untoward effects of transient or recurrent hypoglycemia.[1,2] The controversy arises partly because of the spontaneous decrease followed by recovery of the blood glucose concentration after birth and partly because many neonates have very low blood glucose concentrations without any clinical signs or symptoms (i.e., asymptomatic hypoglycemia).

Neuroglycopenia is known to cause seizures and permanent brain damage.[45] The critical glucose concentration at which there is an inadequate supply of glucose for the brain has been suggested to be less than 47 mg/dL because of altered somatosensory-evoked potentials and lower scores noted for mental and motor development. However, a subsequent study of 2-year-old and 15-year-old children, who were born at less than 32 weeks' gestation age with a blood glucose less than 47 mg/dL over at least 3 days when less than 10 days of postnatal age, found them to have no developmental or physical disability when compared to matched controls without hypoglycemia.[56]

Another recent study from University of Arkansas for Medical Sciences on 1400 10-year-old fourth graders with transient hypoglycemia (glucose <45 mg/dL) reported an association with decreased literacy and mathematics proficiency at fourth-grade achievement testing when compared to age and size-matched controls.[33]

McKinlay et al. reported no association between adverse neurodevelopmental outcome at 2 years and neonatal hypoglycemia (blood glucose <47 mg/dL) in 404 infants with birth weight less than 2500 g or greater than 4500 g and less than 37 weeks of gestational age.[39] The glucose was monitored continuously in this cohort, and abnormal neurodevelopmental outcomes showed a U-shaped relationship with adverse cognitive outcomes associated with time spent outside the range of 54-72 mg/dL in the first 48 hours of life.[39] In summary, inadequate blood supply to the brain or neuroglycopenia probably occurs at a range of glucose values. The harmful effect of blood glucose may be at a low, as well as unstable, high blood glucose values.

Clinical signs of hypoglycemia in the neonate are not specific to alterations in glucose concentration but rather reflect an immaturity of counter-regulatory hormonal stress response responsible for classical symptoms of hypoglycemia in older children and adults. Therefore, the presence or absence of such clinical signs cannot be used reliably to define neonatal hypoglycemia. The statistical definition of hypoglycemia is based on surveys of large numbers of infants. Abnormality is defined as a blood glucose concentration that falls outside a prescribed limit, for example, outside two standard deviations from the norm. AAP guidelines

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also recommend screening in the first 24 hours of life of all asymptomatic at-risk infants for neonatal hypoglycemia (preterm infants 34-36 6/7 weeks and term infants who were born to mothers with diabetes, small for gestational age, or large for gestational age).[2] The AAP algorithm indicates lowest acceptable transitional glucose values of 25 mg/dL. Intervention is recommended between 25 and 40 mg/dL during the first 4 hours of life or during transition after birth in healthy neonates.[2] These levels approximate epidemiologic data at the 5th-10th percentile for glucose. From 4-24 hours after birth, the lowest level requiring action is 35 mg/dL (range is 35–45 mg/dL). Early feeding initiation is critical for establishing breastfeeding as well as in maintaining plasma glucose levels. This practice is different from the 1960s when newborns were generally fasted between 8 and 24 hours after birth.

A recent recommendation has emerged from the Pediatric Endocrine Society.[55] For high-risk neonates without a suspected congenital hypoglycemia disorder, they suggest the goal of treatment be to maintain a plasma glucose concentration greater than 50 mg/dL for those aged less than 48 hours and greater than 60 mg/dL for those aged greater than 48 hours. Higher treatment targets should be considered for those with a suspected genetic hypoglycemia disorder and for symptomatic neonates, because the risks of undertreatment outweigh those of overtreatment in these patients.

The definition of hypoglycemia for preterm infants should not be any different from that for full-term infants. Finally, hypoglycemia in the neonate should be described as transient or persistent, and in either or both of these cases, as symptomatic or asymptomatic. Such a description has implications for both clinical management and long-term consequences.

Transient hypoglycemia implies low glucose values that last only a short time if not corrected and that are confined to the newborn period. In contrast, persistent and recurrent hypoglycemia implies a form that requires prolonged management (glucose infusions for several days at high rates of infusion) and perhaps pharmacologic intervention. Several of these hypoglycemia syndromes may continue throughout infancy and childhood.

The clinical manifestations of hypoglycemia are nonspecific and similar to those of many disorders in newborn infants (Box 86.1). The clinical signs and symptoms of hypoglycemia should improve with correction of the low glucose concentration. In addition, careful attention should be given to ensure that other associated disorders (e.g., sepsis, asphyxia) are not missed.

Because of its implications for both long-term prognosis and clinical management, it is worthwhile to consider two types of neonatal hypoglycemia: those cases limited to the newborn period (transient hypoglycemia) and those cases continuing over an extended period of time or occurring more than once (persistent or recurrent hypoglycemia) (Box 86.2). Transient hypoglycemia is often a consequence of changes in the metabolic environment in utero or ex utero, whereas persistent or recurrent hypoglycemia arises from intrinsic metabolic problems in the infant. Either type of hypoglycemia may manifest asymptomatically or symptomatically.

• BOX 86.1 Clinical Symptoms and Signs of Hypoglycemia*

- Abnormal crying
- Irritability
- Apnea, cyanotic spells
- Jitteriness, tremors
- Feeding difficulty
- Lethargy or stupor
- Grunting, tachypnea
- Seizures
- Hypothermia
- Sweating
- Hypotonia, limpness
- Tachycardia

*Clinical signs should be alleviated with concomitant correction of plasma glucose levels.

Transient Hypoglycemia Caused by Changes in Maternal Metabolism

Intrapartum Glucose Administration

As discussed, the fetus is entirely dependent on the mother for the supply of glucose, and fetal glucose concentration closely mimics that of the mother.[63] An increase in maternal glucose concentration as a result of exogenous glucose infusion causes an increase in fetal glucose concentration, which in turn causes an increase in fetal insulin levels. Studies in animals have shown that fetal hyperinsulinism, caused by either direct infusion of insulin to the fetus or fetal hyperglycemia, results in an increased metabolic rate in the fetus, fetal hypoxemia, and metabolic acidosis. The acute administration of glucose during the intrapartum period—for example, to prevent hypotension during the conduction of anesthesia—has been shown to result in increased glucose, insulin, and lactate levels in the cord blood obtained at delivery. Fetal hyperinsulinism leads to hyperinsulinemia and hypoglycemia in the neonate. Similar observations have been reported in a diabetic pregnancy. Therefore, caution should be exercised in the administration of glucose to the mother during labor and delivery (see Chapter 27). Blood glucose concentrations in the mother should not be allowed to exceed those observed in the normal physiologic range.

Maternal Pharmacologic Treatment

Poor glycemic control during pregnancy has increased risk of diabetic embryopathy and congenital malformations. Insulin is the most common maternal therapy for gestational hyperglycemia; oral antihyperglycemic drugs are the other option. Among these agents, metformin alone or with insulin is used most commonly toward achieving timely glucose control and is associated with a decrease

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• BOX 86.2 Causes of Neonatal Hypoglycemia

Transient Hypoglycemia

- Associated with changes in maternal metabolism
- Intrapartum administration of glucose
- Drug treatment
- Terbutaline, ritodrine, propranolol
- Oral hypoglycemic agents
- Diabetes in pregnancy: infant of diabetic mother
- Associated with neonatal problems
- Idiopathic condition or failure to adapt
- Intrauterine growth restriction
- Birth asphyxia
- Infection
- Hypothermia
- Hyperviscosity
- Erythroblastosis fetalis
- Other
- Iatrogenic causes
- Congenital cardiac malformations

Persistent or Recurrent Hypoglycemia

- Hyperinsulinism
- Congenital hyperinsulinism
- Beckwith-Wiedemann syndrome
- Endocrine disorders
- Pituitary insufficiency
- Cortisol deficiency
- Congenital glucagon deficiency
- Epinephrine deficiency
- Inborn errors of metabolism
- Carbohydrate metabolism
- Galactosemia
- Hepatic glycogen storage diseases
- Fructose intolerance
- Amino acid metabolism
- Maple syrup urine disease
- Propionic acidemia
- Methylmalonic acidemia
- Hereditary tyrosinemia
- 3-hydroxy, 3-methyl glutaric acidemia
- Ethylmalonic-adipic aciduria
- Glutaric acidemia type II
- Fatty acid metabolism
- Defects in carnitine metabolism
- Acyl-coenzyme dehydrogenase defects
- Neurohypoglycemia (hypoglycorrhachia) caused by defective glucose transport

in macrosomia, respiratory distress, and need for NICU admissions.[35] Glyburide is another oral antidiabetic drug with good efficacy, but it crosses the placenta and has a higher incidence of large-for-gestational-age (LGA) infants and neonatal hypoglycemia. Older antidiabetic drugs such as tolbutamide and chlorpropamide cross the placenta and produce pancreatic beta-cell hyperplasia and increased insulin release. Tolbutamide has a markedly prolonged half-life in the neonate and has been found in higher concentrations in the newborn after delivery than those found in maternal blood.

Benzothiadiazide diuretics may cause neonatal hypoglycemia by stimulation of fetal beta cells or secondary to an elevation in maternal glucose levels. Salicylates may cause hypoglycemia by uncoupling mitochondrial oxidative phosphorylation.

Oral beta-sympathomimetic tocolytic drugs such as terbutaline and ritodrine have caused sustained hypoglycemia and elevated cord blood insulin levels in infants delivered within 2 days after termination of tocolytic therapy (see Chapter 18). These agents may cause neonatal hypoglycemia through maternal hyperglycemia and fetal hyperglycemia and hyperinsulinemia.

Beta-adrenergic blocking agents such as propranolol cross the mammalian placenta, and their effects on the fetus are easily demonstrated. These drugs are used during pregnancy for the treatment of hypertension, hyperthyroidism, cardiac arrhythmia, and other conditions. They may interfere with the effects of the normal surge in catecholamine levels at birth. In animal studies, propranolol has been shown to impair fetal growth and may cause neonatal hypoglycemia and impair the thermogenic response to cold exposure.

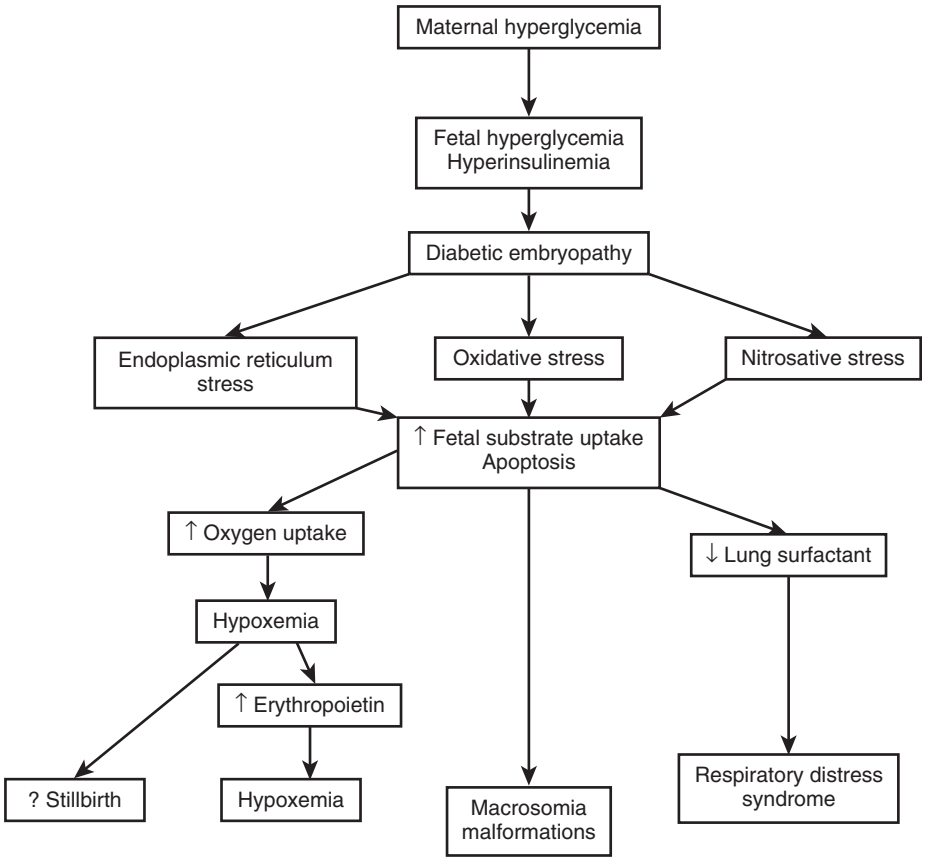
• BOX 86.3 Morbidity in Infants of Diabetic Mothers

- Congenital anomalies
- Heart failure and septal hypertrophy of heart
- Surfactant deficiency respiratory distress syndrome, transient tachypnea of the newborn, persistent pulmonary hypertension
- Hyperbilirubinemia
- Hypoglycemia, hypocalcemia, hypomagnesemia
- Macrosomia, nerve injury related to birth trauma
- Renal vein thrombosis
- Small left colon
- Unexplained intrauterine demise
- Polycythemia
- Visceromegaly
- Predisposition to later-life obesity, insulin resistance, and diabetes

Diabetes in Pregnancy: The Infant of a Diabetic Mother

Despite advances in perinatal care, gestational and pregestational diabetes in the mother continues to result in neonatal morbidities involving major organ systems (Box 86.3). Many maternal and fetal–placental factors are implicated in the development of insulin resistance and gestational diabetes (GDM). The recent worldwide increase in obesity and diabetes at younger ages raises the concern for fetal programming. Small changes in the fetal metabolic environment can result in epigenetic modifications and gene expression lasting a lifetime and modifying the phenotype. The pathogenesis of the spectrum of fetal and neonatal morbidities in the IDM has now been described by a number of careful studies in human and animal models. Intermittent hyperglycemia in the mother results in hyperglycemia that causes hyperinsulinemia in the fetus because of hypertrophy

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• **Fig. 86.4** Flow diagram of pathogenic events that result in fetal and neonatal morbidity in infants of diabetic mothers. (Modified from Schwartz R, et al. Infant of the diabetic mother. *J Pediatr Endocrinol.* 1992;5:197.)

of fetal pancreatic islets and beta cells and increased secretion of insulin. Because of the lack of significant transfer of insulin from the mother to the fetus in humans, the circulating insulin in the fetal compartment is mostly of fetal origin. Increased intracellular glucose concentration, by upregulated glucose transporters, enhances mitochondrial oxidative phosphorylation. The resulting increase in reactive oxygen species production plays an important role in diabetic embryopathy. Research studies and animal experiments show that aberrations in intracellular conditions result in oxidative stress, nitrosative stress, endoplasmic reticulum stress, and hexosamine stress.[20] These changes induce apoptosis and alterations in genetics and epigenetic systems, resulting in dysmorphogenesis.[20] Chronically higher fetal metabolic rate and oxygen consumption lead to relative hypoxemia, which in turn results in upregulation of proangiogenic factors, such as leptin, vascular endothelial growth factor (VEGF), or fibroblast growth factor 2 (FGF2), and matrix metalloproteinases (MMPs) as MMP14 and MMP15.[58] Fetal hypoxia caused by increased glycation of hemoglobin and reduced 2,3 DPG concentration, in addition to hyperglycemia and hyperinsulinemia, leads to increased erythropoietin and increased red blood cell mass resulting in polycythemia. In addition, hyperinsulinemia has been shown to suppress the production of surfactant in the lung and thus predisposes the infant to respiratory distress syndrome after birth (see Chapter 64). An excessive accumulation of glycogen in the liver, adipose tissue, and other tissues has also been observed in IDMs. The sequence of these metabolic events is outlined in Fig. 86.4.

Although the excessive transport of glucose from the mother to the fetus has been thought to be primarily responsible for fetal metabolic and physiologic perturbations in the IDM, nonglucose metabolites (fatty acids, amino acids, and micronutrients) play an important role as well. The increased concentration of these nutrients in the fetal circulation stimulates fetal insulin secretion, which in turn stimulates excessive fetal growth.

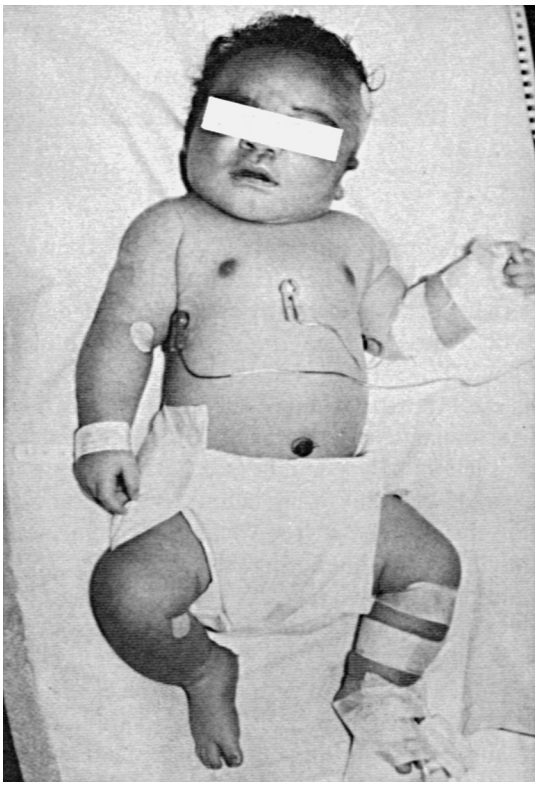
After birth, the newborn IDM whose mother's disease has not received rigorous antepartum management appears to be unable to produce sufficient circulating glucose and alternative fuels. Even infants of mothers with rigorous management (i.e., those who have maintained normoglycemia throughout gestation) develop significantly lower blood glucose concentrations than those of normal infants. In addition, they do not mobilize fatty acids from adipose tissue; as a result, their circulating levels of FFAs remain low, although a normal increase in plasma glycerol has been observed. Such a metabolic picture suggests persistent insulin action and the lack of a counter-regulatory hormonal response. The latter is confirmed by the lack of an increase in circulating glucagon and catecholamine levels in IDMs during hypoglycemia. The combination of hyperinsulinism and insufficient counter-regulation results in decreased hepatic glucose production, increased peripheral glucose uptake, and impaired lipolysis. When measured by

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TABLE 86.1 Neonatal Outcome in Infants of Rigorously Managed Diabetic Mothers

Parameter	Infants of Diabetic Mother (*N* = 78)	Controls (*N* = 78)	P
Birth weight (g)	3454 ± 817	3271 ± 621	—
Gestational age (wk)	37.9 ± 0.95	39.3 ± 1.7	.0001
K score*	0.77 ± 0.95	0.18 ± 0.91	.0001
Macrosomia (>4 kg)	19 (24%)	8 (10%)	.03
Large for gestational age	32 (41%)	12 (15%)	.0002
Hypoglycemia	11 (14%)	1 (1%)	0.0025
Hyperbilirubinemia	36 (46%)	18 (23%)	.002
Respiratory distress syndrome	9 (12%)	1 (1%)	.008
Admission to neonatal intensive care unit	21 (27%)	9 (12%)	.01

*The K score is a method of adjusting the birth weight in grams for the infant's gestational age. A K score of 1 represents the 90th percentile for weight; scores of 0 and –1 represent the 50th and 10th percentiles, respectively. Data from Aucott SW, et al. Rigorous management of insulin-dependent diabetes mellitus during pregnancy. *Acta Diabetol.* 1994;31:126.



• **Fig. 86.5** Infant of mother with gestational diabetes; the baby was born at 40 weeks of gestation with a birth weight of 4.6 kg. The infant developed hypoglycemia and was treated with intravenous glucose.

the isotope tracer dilution method, IDMs produce glucose at significantly lower rates than normal infants. In addition, their basal metabolic rates, or rates of oxygen consumption, have been reported to be lower than those of normal infants.

Several of these metabolic and morphologic abnormalities can be reversed with fastidious management of diabetes in the mother. Data from several studies showed that with rigorous management throughout pregnancy, IDMs do not become hypoglycemic and maintain normal rates of glucose production and basal metabolism.

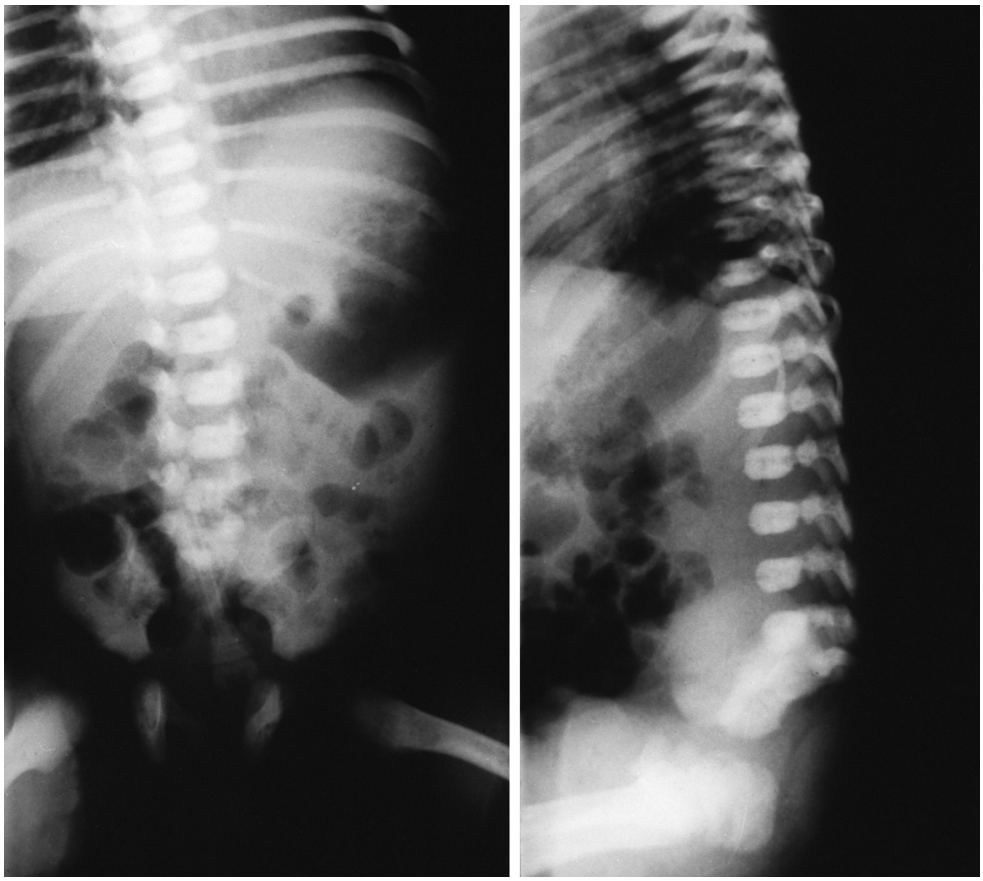
Clinical Manifestations

It should be recognized that the clinical manifestations described here relate to diabetic mothers whose metabolism has not been well controlled. Data from a study in which maternal diabetes was rigorously managed by either an insulin infusion pump or split-dose insulin therapy are shown in Table 86.1. Despite rigorous management and reduced maternal hyperglycemia, significant morbidity may persist.

Macrosomia. At birth, these infants are obese, plethoric, and large for gestational age (LGA) and show evidence of excessive fat as well as visceromegaly in the form of a large liver, spleen, and heart (Fig. 86.5). Because the growth of the brain and possibly the kidney is not dependent on insulin, these two organs are normal in size. Careful management of maternal metabolism tends to reduce the incidence of macrosomia but does not prevent it entirely.

Congenital Anomalies. The incidence of congenital malformations is increased twofold to threefold in infants of insulin-dependent diabetic mothers compared with the normal population. The frequency of congenital anomalies is not increased in infants of gestationally diabetic mothers or in those of diabetic fathers. Chronic hyperglycemia in the diabetic embryo, causing accumulation of advanced glycosylation end-products (AGE) and glycated protein and oxidative stress, has been suggested to induce malformations.[20] A number of congenital anomalies, including facial, skeletal, and neural tube defects, were induced in the diabetic environment created in a RAGE (receptor for AGE) knock-out mouse model.[20] Dysmorphology of the cardiovascular system and genitourinary system has been reported. Caudal agenesis or dysplasia syndrome (Fig. 86.6) is seen with markedly increased frequency, especially in IDMs. This syndrome consists of agenesis or hypoplasia of the femora in conjunction with agenesis of the lower vertebrae and sacrum. Data from animal models show a complex process of genetic and epigenetic processes enhancing apoptosis and resulting in diabetic embryopathy with multiple structural defects. The frequency of congenital anomalies is significantly increased in mothers with poor metabolic control, as evidenced by increased hemoglobin A_{1c} levels early in

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• **Fig. 86.6** Anteroposterior (*left*) and lateral (*right*) radiographs of sacral agenesis in an infant of a diabetic mother.

gestation, and a significant decrease in congenital malformations has been reported with rigorous metabolic regulation in the periconceptional period (see Chapter 18).

Hypoglycemia. The pathogenesis of hypoglycemia has been described already. Immediately after birth, there is a significant decrease in plasma glucose concentration, reaching a nadir between 30 and 90 minutes and followed by a spontaneous recovery in most infants. However, in some infants, the plasma glucose level remains persistently low (i.e., <45 mg/dL), necessitating intervention. Most of these infants are asymptomatic. Irrespective of symptoms, the current recommendation is to correct the hypoglycemia with an appropriate glucose infusion. It should be underscored that hypoglycemia in the newborn does not necessarily reflect the magnitude of antepartum metabolic control of the mother and may simply be the consequence of hyperglycemia during labor and delivery.

Hypocalcemia and Hypomagnesemia. See Chapter 87.

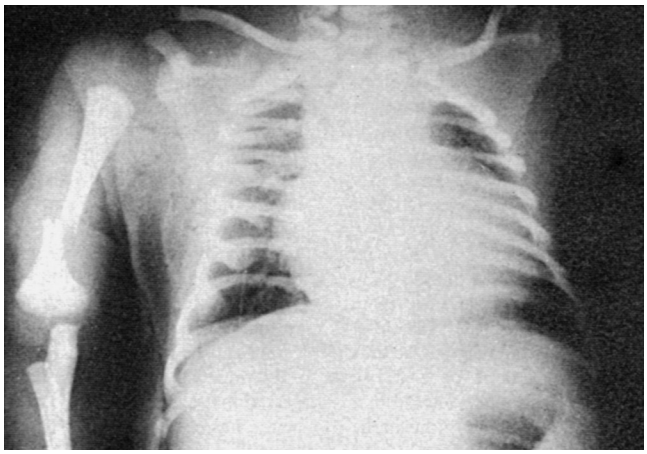
Alterations in calcium and magnesium homeostasis occur in about 50% of infants born to insulin-dependent diabetic mothers. Unlike hypoglycemia, hypocalcemia becomes apparent between 48 and 72 hours after birth. Plasma calcium concentrations of lower than 7 mg/dL are frequently observed. Hypocalcemia has been related to the severity and duration of maternal diabetes. In addition, it may be potentiated by prematurity and asphyxia. The mechanisms of hypocalcemia are probable failure of the IDM to mount an appropriate parathyroid hormone (PTH) response, persistently high levels of calcitonin, and possible alterations in vitamin D metabolism. Hypomagnesemia (≈1.5 mg/dL) has also been frequently observed. It is usually transient, and its pathophysiologic significance remains uncertain.

Both hypocalcemia and hypomagnesemia may be manifested with jitteriness and may require supplemental calcium therapy. However, in most infants, they are transient events that improve spontaneously.

The management strategies for other clinical problems, such as polycythemia (see Chapters 79 and 80), hyperbilirubinemia (see Chapter 91), and renal vein thrombosis (see Chapter 93), that occur with slightly higher frequency in IDMs are similar to those in otherwise normal infants.

Septal Hypertrophy of the Heart. Septal hypertrophy and cardiomegaly are specific phenotypic consequences of diabetes in pregnancy and may be manifested with heart failure in the neonate (Fig. 86.7). In addition, data in asymptomatic infants of gestationally diabetic mothers have shown alterations in diastolic function and decreased passive compliance of the ventricular myocardium. By serially evaluating cardiac growth in utero in the fetuses of diabetic mothers, it has been shown that despite good

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• **Fig. 86.7** Chest radiograph of a vaginally delivered, full-term infant (4.7 kg) of a diabetic mother. The infant had cardiomegaly, hepatomegaly, congested lung fields, and fractures of the right humerus and left clavicle.

metabolic control, cardiac hypertrophy developed in late gestation (34-40 weeks). Although IDMs with septal hypertrophy may present with obstructive left heart failure, they may also be asymptomatic. Follow-up data show that cardiomyopathy in an IDM is a transient disease and usually disappears spontaneously within 6 months after birth. Otherwise minor functional changes, such as impaired diastolic filling, have been reported in infants of gestational diabetic mothers and are usually not clinically significant.

Management of the Diabetic Mother

See Chapter 18.

Strict metabolic control, improved fetal surveillance, early delivery, and neonatal intensive care have led to improved survival among IDMs. Preconceptional and early postconceptional metabolic control may decrease the incidence of congenital malformations. Improving maternal compliance, preventing ketoacidosis, and recognizing and treating pregnancy-induced hypertension and pyelonephritis are particularly important. Attempts should be made to maintain maternal fasting plasma glucose values at less than 80 mg/dL and 2-hour postprandial plasma glucose values at less than 120 mg/dL.

With appropriate ambulatory support, hospitalization is not required in most mothers. Indications for hospitalization include pregnancy-induced hypertension, acute or chronic polyhydramnios, infections, and poor metabolic control. Early screening for congenital malformations includes a determination of the maternal serum alpha-fetoprotein level for open neural tube defects and a level II ultrasound at 18-20 weeks of gestation (see Chapters 10 and 11). Follow-up ultrasonography is useful in the evaluation of amniotic fluid volume, fetal growth, and placental grading. Tests of fetal well-being begin in the second trimester (28-32 weeks of gestation). These tests usually include daily fetal movement counts and biweekly biophysical testing (nonstress testing, biophysical profile, or both) or nonstress testing combined with an amniotic fluid index (see Chapter 12).

With appropriate care and fetal surveillance, most patients are now monitored expectantly for the spontaneous onset of labor at term. Vaginal delivery is preferred, but obstetric factors may justify cesarean delivery. Caution should be exercised in the delivery of a macrosomic fetus at risk for traumatic complications. During labor, glucose and insulin therapy should be adjusted to maintain normoglycemia in the mother.

Delivery should take place in a hospital, where the newborn can be carefully monitored. Glucose values are checked during the first 3 hours after birth (typically between 30 and 60 minutes), sporadically before feedings, and any time symptoms are suspected. Feedings may be started as soon as the infant is stable, usually within 2-4 hours after birth, and continued at 3- to 4-hour intervals.

Even though physiologic and clinical data clearly demonstrate a marked reduction in fetal and neonatal morbidity and mortality in pregnancy with diabetes, studies from the United Kingdom failed to show that such a goal was achieved in clinical practice. Continuous rigorous surveillance of diabetes throughout the pregnancy and fastidious management of altered metabolism are required.

Prognosis

Improvements in antepartum care, fetal monitoring, rigorous control of maternal metabolism, and maternal education have all resulted in reduced perinatal mortality and morbidity. In addition, control of maternal metabolism during the periconceptional period has resulted in a decreased incidence of congenital malformations in IDMs. However, certain morbidities such as premature birth, cesarean section deliveries, hypoglycemia, macrosomia, and polycythemia, persist.[13] Additionally, as with birth weight less than 10th percentile body weight by gestational age, increased birth weight in IDM also increases the risk of type 2 diabetes mellitus and obesity phenotypes later in life because of fetal programming. Placental studies in preexisting diabetic pregnancies show higher birth weight/placental weight ratios compared to normal pregnancies, which may correlate with an increased risk for cardiovascular diseases in adult life.[24]

Even though macrosomic IDMs tend to revert to normal body composition during early childhood, they tend to be obese with increased adipose tissue mass during adolescence, followed by the development of later-life obesity and insulin resistance, as well as development of type 2 diabetes.[9,29] While these observations indicate that fetal hyperinsulinism and hyperglycemia, as well as hyperlipidemia, contribute toward an increase in the adult metabolic syndrome, the influence of genetics, environmental programming, and maternal weight cannot be entirely separated. The incidence of overweight and obesity in later childhood at ages 5–7 years varies depending on race and ethnicity.[60]

The evaluation of neurodevelopmental outcome of IDMs is confounded by the contribution of perinatal events such

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as perinatal asphyxia and metabolic acidosis in addition to chronic metabolic insults and iron deficiency.[29] Increased red blood cell production can contribute to redistribution of iron from the developing neurons in the brain to the liver and bone marrow, producing neuronal iron deficiency, which has been correlated with limitations in cognitive development.[29] Electrophysiologic studies demonstrate a long-lasting impact on memory, indicating effect of prenatal iron deficiency on neural development.[29]

Several investigators have examined the impact of alterations in maternal metabolism, specifically changes in blood glucose and ketones, on neurodevelopment in the newborn period and early childhood in gestational diabetes as well as insulin-dependent diabetes. Intellectual delay at ages 3 and 5 years in infants born to women with acetonuria (a marker of poor metabolic control) has been observed.

Transient Hypoglycemia Associated With Neonatal Problems

Idiopathic Condition or Failure to Adapt

For apparently unknown reasons, a number of infants develop hypoglycemia, and the cases have been designated as idiopathic hypoglycemia or failure to adapt to the extrauterine environment. As maternal obstetric care continues to improve and more contributory factors are identified, the number of cases of idiopathic hypoglycemia continues to decrease. A careful maternal history should be obtained whenever an infant develops hypoglycemia for reasons that are not easily evident. Contributory factors may include maternal obesity and mild glucose intolerance in the mother.

Maternal Obesity

Many infants born to obese mothers without evidence of impaired glucose tolerance develop low blood glucose concentrations in the immediate newborn period. With the increasing incidence of obesity in the general population, the number of such babies continues to increase. Maternal obesity is associated with overweight offspring displaying abdominal obesity even in the absence of gestational hyperglycemia.[46] The exact mechanism of impaired glucose homeostasis in these infants is not clear yet but may pertain to maternal insulin resistance redirecting glucose from maternal tissues to the fetus.

Intrauterine Growth Restriction and Infants Who Are Small for Gestational Age

See Chapter 15.

Hypoglycemia has been frequently reported in infants who are SGA (<10th percentile in weight for gestational age) because of decrease in glycogen stores, adipose tissue, gluconeogenesis, decreased ability to oxidize free fatty acids, and increased sensitivity to insulin. Twenty-six percent of SGA infants were hypoglycemic (glucose <45 mg/dL) at greater than 2 hours of age in one study.[40] The incidence of hypoglycemia (blood glucose <45 mg/dL) in infants born SGA is 6%-26%, being higher in premature infants. Hypoglycemia, which may be either symptomatic or asymptomatic, is usually seen within the first 24 hours after birth. The incidence of hypoglycemia is variable, reflecting different causes of intrauterine growth restriction, such as maternal nutrition, uteroplacental insufficiency, fetal infection, or maternal metabolic perturbations. In addition, because polycythemia and fetal and neonatal hypoxemia are frequently seen in infants who are SGA, polycythemia and hypoxemia by themselves could contribute to the incidence of hypoglycemia.

The relation between neonatal hypoglycemia and so-called symmetric and asymmetric growth restriction has not been specifically addressed. In general, the consensus among investigators is that hypoglycemia is more common among infants with asymmetric growth restriction, because that group represents true intrauterine nutrient deprivation.

The pathogenesis of hypoglycemia has been the subject of numerous investigations and speculation in both humans and animal models. The IUGR fetus increases glucose uptake by increasing the transplacental glucose gradient as an adaptation to reduced placental size.[64] Clinical observations in infants who were SGA showed an early recruitment of fat for oxidative metabolism, as evidenced by a lower respiratory quotient and a higher rate of lipolysis, compared with infants who were appropriate sizes for gestational age. This finding led to the speculation of decreased glycogen stores and their early depletion in infants who are SGA. Early depletion of glycogen stores was also postulated based on the higher brain-to-body ratio of infants who are SGA and the dependence of the brain on glucose for oxidative metabolism. A decreased rate of gluconeogenesis has been proposed as a contributor to hypoglycemia in infants who are SGA based on high levels of gluconeogenic substrates and a lower glucose response to the administration of alanine, a strategic gluconeogenic amino acid. Infants who are SGA have been observed to mount a significant glucagon response to hypoglycemia. However, the response to exogenous glucagon administration has been variable, particularly in relation to plasma amino acids. Hypoglycemic infants who are SGA do not decrease plasma amino acids in response to an intravenous infusion of glucagon. The growth hormone response to hypoglycemia and glucose infusion is reported to be normal.

Studies of the IUGR placenta demonstrate a decrease in transplacental amino acid transfer (e.g., leucine and lysine) as well as an increase in FABP1-4, thereby increasing fat accumulation in response to a hypoxic IUGR fetus.[64]

When an infant born with a low birth weight exhibits a slow postnatal growth rate between 0 and 2 years of age, and an exponential growth rate thereafter, an increased propensity toward developing diabetes mellitus and cardiovascular disease as an adult in both men and women is seen.[6,18]

The management of these IUGR infants involves treatment of the associated clinical problems—hypoxia, hyperviscosity, careful monitoring for hypoglycemia, and the early establishment of adequate nutrition. The treatment of hypoglycemia is similar to the one outlined later.

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Hepatic Glucose-6-Phosphatase and Prematurity

Glucose-6-phosphatase is a membrane-bound enzyme associated with the endoplasmic reticulum in the liver and the kidney—the two important glucogenic organs. It catalyzes the breakdown of glucose-6-phosphate into free glucose, the terminal step in both glycogenolysis and gluconeogenesis. Fetal glucose-6-phosphatase–alpha is decreased but increased in term gestation.[38] In a series of studies, a suggestion has been presented that the low activity of glucose-6-phosphatase, partly influenced by hormonal, nutrient, and other factors, including stress, may contribute to hypoglycemia in premature infants. However, the direct cause-and-effect relationship is difficult to discern from their studies. A severe deficiency of glucose-6-phosphatase certainly can lead to profound hypoglycemia, as in glycogen storage disease type I.

Neonatal Encephalopathy

The mechanism of low glucose after perinatal asphyxia remains unknown. Affected infants often require high rates of glucose infusion to maintain a normal glucose concentration, suggesting either an increased insulin concentration or increased sensitivity to insulin. Because asphyxia also results in an increase in plasma glucagon, interleukin-6, hydrocortisone, and other counter-regulatory hormones, with associated changes in insulin receptor binding, it can also induce an insulin-resistant state. Both hypoglycemia and hyperglycemia are associated with worse outcomes at 18 months of age in infants with neonatal encephalopathy.[10] Therefore, from a clinical perspective it is important to carefully monitor the plasma glucose concentration in infants with neonatal encephalopathy and adjust the parenteral glucose infusions accordingly.

Infection

See Chapters 48-50.

Hypoglycemia in association with overwhelming sepsis has been reported in newborn infants. Hyperglycemia is more common than hypoglycemia. The mechanism of hypoglycemia with sepsis is not well defined. Depleted glycogen stores, impaired gluconeogenesis, and increased peripheral glucose use may all be contributing factors. The usual response to sepsis in most animal models has been an increase in the rates of glucose production and gluconeogenesis as a result of counter-regulatory hormonal responses. A decrease in these processes is seen only during an agonal stage; therefore, hypoglycemia with sepsis should be considered an indicator of a fulminate infection.

Hypothermia

See Chapter 35.

The occurrence of hypothermia secondary to hypoglycemia has been well documented and is a useful clinical sign. Studies in which 2-deoxy-D-glucose was used in adults suggest that hypoglycemia, directly or secondarily, may affect a central thermoregulatory center in the hypothalamus that is sensitive to glucose. Hypoglycemia may also be secondary to hypothermia. The normal core temperature in the neonate is between 36.5° and 37.5°C (97.7°F-99.5°F). If the body temperature falls, heat production increases several times above that of the basal level, resulting in a more rapid depletion of energy stores. Hypoglycemia is also seen in neonates who had rectal temperatures lower than 32°C (89.6°F) after prolonged exposure to cold.

Hematologic Disorders

Glucose concentration is negatively correlated with plasma hematocrit. Association between erythroblastosis fetalis due to Rh incompatibility and neonatal hypoglycemia has also been observed for a long time. There are no correlations between the severity of anemia and hypoxemia and levels of plasma insulin and C peptide. Erythroblastosis at birth is associated with an increased number of nucleated red blood cells in the peripheral blood of newborns, again an indicator of fetal hypoxia. The prenatal management of Rh immunization has markedly reduced the severity of erythroblastosis fetalis and anemia in the fetus and the newborn infant. Nevertheless, the plasma glucose concentration should be carefully monitored in these infants after birth.

Iatrogenic Causes

Reactive hypoglycemia may occur after abrupt cessation of hypertonic glucose infusions, including those used for parenteral nutrition. Marked variability of blood glucose values may also occur as a result of changing rates of glucose infusion.

Refractory hypoglycemia has been associated with an umbilical artery catheter positioned near the origin of the vessels supplying the pancreas (T11 to L1). Direct glucose infusion into the vessels of the pancreas can lead to hyperinsulinemia and hypoglycemia. Hypoglycemia was also reported with a normally positioned catheter at T8-T9; it responded to catheter repositioning.

Congenital Cardiac Malformations

The mean blood glucose concentration in neonates and older children with congenital cyanotic heart disease or congestive heart failure may be lower than that in healthy controls. Glucose disappearance rates and fasting insulin and growth hormone values are normal, but glucose values after glucagon administration are lower than those in healthy children. Although the mechanism is unknown, chronic hypoxia, leading to decreased glycogen stores, may be a contributing factor. Hypoglycemia may also lead to cardiomegaly and congestive heart failure in the absence of congenital malformations. Therefore, the presence of either hypoglycemia or congestive heart failure should be considered when one or the other appears.

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Persistent or Recurrent Hypoglycemia

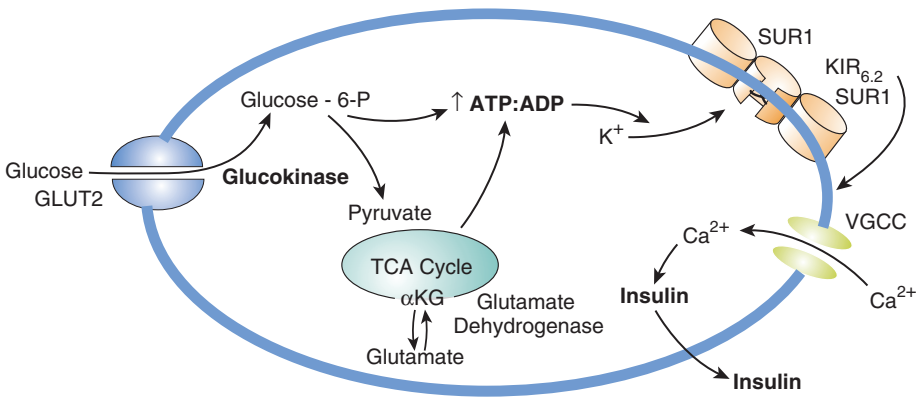
Hyperinsulinism

Congenital Hyperinsulinism (CHI)

Congenital hyperinsulinism (CHI) is unregulated insulin secretion by the pancreatic β-cells, resulting from mutations of genes regulating insulin secretion. It is characterized by profound hypoglycemia in the newborn with hyperinsulinemia that inhibits glycogenolysis and prevents availability of alternate energy sources such as ketone bodies and lactate, causing brain and long-term neurodevelopmental impairments in some cases. It is the most common cause of persistent hypoglycemia in the newborn. The incidence is estimated at 1/50,000 live births, but it may be as high as 1/2500 live births with a higher incidence of consanguinity (Saudi Arabian and Ashkenazi Jewish populations).[7,23,41] Thus far, mutations in nine different genes (*ABCC8, KCNJ11*, *GLUD1*, *CGK*, *HADH*, *SLC16A1*, *HNF4A*, *HNF1A*, and *UCP2*) have been identified in patients with congenital forms of hyperinsulinism (CHI).[41] The most severe forms of CHI are caused by mutations in *ABCC8* and *KCJN11*, which encode the two components of pancreatic β-cell ATP-sensitive potassium channel (K_{ATP}). The sulfonylurea receptor is (SUR1) encoded by the *ABCC8* gene and the inward rectifying potassium channel ($Kir_{6.2}$) encoded by the *KCNJ11* gene.[7,41]

As shown in Fig. 86.8, insulin secretion by the beta cells requires an increase in the intracellular adenosine triphosphate (ATP) concentration as a result of glycolysis and the oxidation of glucose. After entry into the beta cell, which is facilitated by a specific glucose transporter protein (GLUT2), glucose is phosphorylated to form glucose-6-phosphate. The latter enters the glycolytic pathway to form pyruvate and is oxidized in the tricarboxylic acid (TCA) cycle. Glutamate is another substrate entering the TCA cycle to form alpha-ketoglutarate, a reaction catalyzed by glutamate dehydrogenase. The ultimate increase in ATP concentration and the consequent increase in the ATP to adenosine diphosphate (ADP) ratio affects the ATP-sensitive potassium (K^+) channel (K_{ATP}), resulting in depolarization of the beta-cell membrane. This process in turn results in activation of voltage-gated calcium channels and entry of Ca^{2+} into the cell. An increase in intracellular Ca^{2+} concentration results in the release of insulin into the circulation. When closed, the K_{ATP} channel depolarizes the plasma membrane, leading to insulin secretion.

The mutations in *ABCC8* or *KCNJ11* gene abolish the K_{ATP} channel function, so these neonates are unresponsive to the K_{ATP} channel agonist (diazoxide), requiring alternative therapies. Histologically, there are three major subgroups: (1) diffuse, (2) focal, and (3) atypical. The diffuse CHI is most commonly caused by recessive and dominant mutations in *ABCC8* and *KCNJ*.[7,41] The diffuse form of disease involves all β cells in the pancreas with a variable involvement and preservation of the islet pattern. The β cells are highly active with abundant cytoplasm and abnormal nuclei. Focal CHI is sporadic and associated with inheritance of a paternal mutation in *ABCC8* or *KCNJ11* and somatic loss of the maternal 11p allele (11p15.1-11p15.5).[41] The maternal allele loss unmasks the paternally inherited K_{ATP} channel mutation in addition to an imbalance of the imprinted genes in this region. This imprinting effect and paternal isodisomy are at the same locus. The lesion is usually restricted to a small area (<10 mm in diameter) and contains large endocrine cells with large cytoplasm and dispersed abnormally shaped nuclei. The focal lesion is multilobular and can have satellites that necessitate intraoperative margin analysis to



• **Fig. 86.8** Mechanism of glucose-induced insulin secretion by the beta cell of the pancreas. Glucose entry into the beta cell is facilitated by a specific glucose transporter protein (GLUT2). Intracellular metabolism of glucose through glycolysis and in the tricarboxylic acid (TCA) cycle increases the intracellular concentration of adenosine triphosphate (ATP). The increase in the ratio of ATP to adenosine diphosphate (ADP) affects the ATP-sensitive potassium (K^+) channel, causing an efflux of K^+ and depolarization of the beta-cell membrane that in turn activate the voltage-gated calcium (Ca^{2+}) channel (VGCC) and entry of Ca^{2+} into the cell. The increase in free intracellular Ca^{2+} initiates release of insulin. As discussed in the text, mutations of glucokinase, glutamate dehydrogenase, SUR1, and $KIR_{6.2}$ have thus far been associated with hyperinsulinemic hypoglycemia. αKG, α-ketoglutarate; glucose-6-P, glucose-6-phosphate; KIR, inward-rectifying potassium channel; SUR, sulfonylurea receptor.

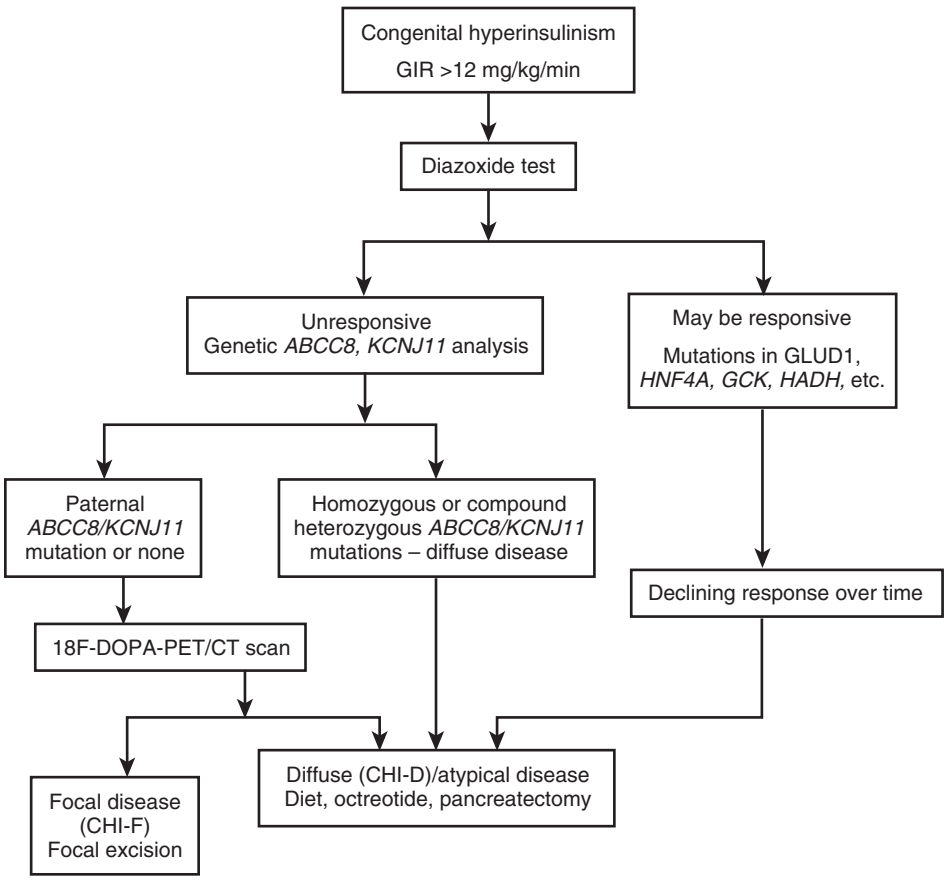
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ensure complete excision to avoid recurrence. The atypical disease shows diffuse histologic abnormalities with the coexistence of some normal and some abnormal islets. In this case, there is no clear genetic inheritance pattern established.[41]

Clinically, most infants present during the first 24-48 hours after birth with severe symptoms such as seizures, hypotonia, apnea, and cyanosis. The diagnosis is suspected when hypoglycemia appears soon after birth, requiring high rates of glucose infusion (12-13 mg/kg per min). Some neonates with CHI may be macrosomic because of hyperinsulinemia in fetal life, particularly those who carry mutations of the *HNF4* gene. Other CHI infants are normosomic, lacking positive physical findings. Sometimes facial dysmorphism may be reported later in infancy and childhood. Some patients have hypertrophic cardiomyopathy and hepatomegaly, probably reflecting fetal hyperinsulinemia. Maternal history is noncontributory, but a carefully taken history may reveal previous neonatal deaths or unexplained seizures or intellectual disability in other siblings. The diagnosis has been made at birth in asymptomatic infants and prenatally based on familial history. These infants typically have inappropriately high plasma insulin and C-peptide levels during hypoglycemia. Measurements of C peptide may be useful because of its nonpulsatile production with twice the half-life of insulin. Plasma glucose increases by glycogenolysis in response to exogenous glucagon administration, indicating absence of glycogen storage disease. Ketone body and free fatty acid content is low in both plasma and urine.

It is important to note that the mutation of glutamate dehydrogenase presents with hyperammonemia along with hyperinsulinemic hypoglycemia.[7,41] Other genetic disorders (e.g., short-chain 3-hydroxyacyl-coenzyme A dehydrogenase) have also been reported to present with hyperinsulinemic hypoglycemia. Testing of urine organic acids (high 3-OH-glutarate) and plasma acylcarnitine (high C4-OH-carnitine) is required to identify a short-chain-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency.[41]

Rapid diagnosis and prompt management of hypoglycemia is essential to prevent brain damage and improve the neurodevelopmental outcome. Clinical and biologic data can be used to differentiate the focal from the diffuse form of disease. K_{ATP} channel agonist, diazoxide, is the first line of therapy, and it acts by opening K_{ATP} channels and preventing glucose-mediated insulin release. Fig. 86.9 outlines the steps in management. Diazoxide is not effective when *ABCC8* or *KCNJ11* gene defects are present. Therefore, diazoxide-unresponsive patients should undergo rapid genetic mutation testing. Patients with genetically confirmed *ABCC8/KCNJ11* diffuse disease do not require further imaging. These patients will require near total pancreatectomy carrying an increased risk of developing diabetes mellitus and pancreatic exocrine insufficiency subsequently. Patients with paternally inherited mutation in



• **Fig. 86.9** A flow diagram of suggested management pathway of neonatal hypoglycemia caused by congenital hyperinsulinism (CHI). GIR, Glucose infusion rate.

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ABCC8 or *KCNJ11* require [^{18}F]-DOPA positron emission tomography imaging.[61] Approximately 50% of diazoxide-unresponsive infants have focal disease and can experience a complete cure after surgical excision of the lesion.

Zinc protamine glucagon, as intramuscular injections or orally administered starch, has also been used postoperatively. However, in most instances, preoperative medical therapy consisting of various combinations of glucose infusion, diazoxide, glucagon, and octreotide fails to control hypoglycemia.[41] Continuous octreotide infusion with the addition of glucagon to correct octreotide-induced hypoglucagonemia has been used for temporary preoperative medical control. In a recent study, the use of sirolimus (rapamycin mTOR inhibitor) in four patients with diffuse hyperinsulinemic hypoglycemia that is unresponsive to diazoxide was successful in weaning intravenous infusions of dextrose and glucagon.[49] While this therapy may offer a potential alternative to subtotal pancreatectomy, long-term use and side effects from sirolimus are not well studied at this time.[49]

Conservative (nonsurgical) management has been successful in some asymptomatic hypoglycemic infants who were diagnosed at birth. Infants with the CHI spectrum have a high incidence of neurologic damage, which is probably a reflection of the severity of symptomatic hypoglycemia and the delay in diagnosis. It is imperative that neonatologists approach these neonates as a metabolic emergency and ensure against delaying diagnosis. Because *SUR1* genes are also expressed in neuronal cells, it has been suggested that the neurologic deficit in these infants may be related to a *SUR1* mutation in the brain. Long-term follow-up data in infants with total pancreatectomy demonstrate variable responses—some develop no pancreatic insufficiency, whereas others develop frank diabetes as well as exocrine pancreatic insufficiency.

Neurologic impairment associated with abnormal brain MRI was observed in 47% of CHI patients in a recent international study.[31] Neurologic impairment correlated with a delay of five or more days in initiating treatment. However there was no association with early vs. late disease onset, KATP-channel mutations, disease severity, or focal vs. diffuse disease.[31]

Beckwith-Wiedemann Syndrome

The characteristic features of Beckwith-Wiedemann syndrome (BWS) include macrosomia, macroglossia, omphalocele, hyperplastic visceromegaly, and hypoglycemia, often also called *congenital overgrowth syndrome*. Since the original description by Beckwith and Wiedemann, a number of other clinical findings of this syndrome have been described (Box 86.4).[62] BWS is a clinical spectrum, and the frequency of these clinical manifestations is variable. Macroglossia, a uniform enlargement of the tongue, is present in more than 80% of cases. Other craniofacial characteristics include midface hypoplasia, a prominent occiput, and nevus flammeus. Characteristic ear creases or pits are present in about 75% of individuals. Anterior abdominal wall defects, which are present in about 80% of cases, include omphalocele, umbilical hernia, and diastasis recti abdominis. Cardiac defects are reported in about 25% of cases; however, no specific cardiac abnormality is prominent.

• BOX 86.4 Major Findings in Beckwith-Wiedemann Syndrome

Clinical Findings

- Advanced bone age
- Ear anomalies
  - Pits and/or creases
- Facial nevus flammeus
- Hemihypertrophy
- Macroglossia
- Maxillary underdevelopment
- Muscular hypertrophy
- Neonatal hypoglycemia
- Neonatal polycythemia
- Prenatal and postnatal gigantism
- Prominent occiput
- Abdominal wall defects
  - Diastasis recti abdominis
  - Omphalocele
  - Umbilical hernia
- Cardiac defects
- Clitoromegaly
- Cryptorchidism
- Tumors (Wilms tumor)
- Visceromegaly: kidney, liver, spleen

Pathologic Findings

- Adrenal cortical cytomegaly and cysts
- Hypertrophy and hyperplasia of islets of Langerhans
- Medullary dysplasia and medullary sponge kidneys
- Nephromegaly with prominent lobulation
- Persistent nephrogenesis

Most (>75%) of BWS infants are above the 90th percentile in length and weight for gestational age and tend to remain at the 90th percentile during early infancy and childhood. No differences between male and female infants have been reported. Growth begins to slow down by about age 8 years, and adult height and life expectancy are usually normal.

Hypoglycemia is present in at least half the cases[62] and may be manifested soon after birth. Endocrine evaluation of the few reported cases has not been consistent. However, based on the clinical features of hypoglycemia with low free fatty acids and ketones and autopsy findings of islet cell hyperplasia, it is believed that hypoglycemia is caused by hyperinsulinism in this syndrome. Plasma growth hormone levels have been reported to be normal, and somatomedin levels were reported to be increased in one infant. These infants may require glucose infusion at high rates in the immediate neonatal period. Spontaneous regression of hypoglycemia is suggested in most infants. Hypocalcemia has also been reported in some instances.

About 10% of children with BWS are also predisposed to certain malignancies (adrenal carcinoma, nephroblastoma)

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and appear to have an increased risk for malignancies associated with hemihypertrophy.

Genetic studies in patients with Beckwith-Wiedemann syndrome have identified three major subgroups of patients: familial, sporadic, and chromosomally abnormal. Molecular and cytogenetic testing in BWS patients display genetic and epigenetic aberrations in two domains of chromosome 11p15.5 (BWS critical region—imprinting center 1 [IC1] and imprinting center 2 [IC2]. These include loss of methylation on the maternal chromosome at IC2 in 50% of affected individuals, paternal uniparental disomy for chromosome 11p15 in 20%, and gain of methylation on the maternal chromosome at IC1 in 5%. Additionally, sequence analysis of CDKN1C (regulated by IC2) identifies a heterozygous maternally inherited pathogenic variant in approximately 40% of familial cases and 5%-10% of cases with no family history of BWS.[51,62]

Endocrine Disorders

Pituitary Insufficiency

Neonatal hypoglycemia associated with anterior pituitary hypofunction may represent a series of separate syndromes, with defects ranging from no structural abnormalities in the brain to septo-optic dysplasia, craniofacial defects, and anencephaly. Although this disorder is considered rare, the true incidence is unknown, because it usually goes unrecognized as a result of the absence of characteristic physical findings in the newborn.

Clinical and Laboratory Manifestations. Symptoms of hypoglycemia may begin during the first hours of postnatal life and are marked by their severity. They include sudden and profound limpness, convulsions, apnea, cardiovascular collapse, and cardiac arrest. The infants are of normal length and weight and born at or after term. Males predominate at a ratio of 2:1. The physical examination may be unrevealing; however, some male infants have a microphallus, poorly developed scrotum, small and undescended testes, or some combination of these features. Facial abnormalities consisting of a cleft lip and palate, a poorly developed nasal septum, hypotelorism or hypertelorism, abnormalities of antidiuretic hormone secretion, or widely spaced nipples have been described. Although the infants are of normal size at birth, growth restriction and delayed bone age may be found in children as young as 6-8 weeks of age.

Serum growth hormone (GH) values are not measurable or in the normal adult range, in contrast to the elevated values usually found in normal newborns. The paradoxic increase in GH during glucose infusion in normal newborns does not occur when hypoglycemia is associated with pituitary deficiency. The cortisol concentration may be low at the time of symptomatic hypoglycemia. Hypothyroidism is common. A deficiency in hypothalamic hormones has been shown by a rise in thyroid-stimulating hormone (TSH), or thyrotropin, after stimulation with thyrotropin-releasing hormone (TRH) and by increased prolactin levels with a poor luteinizing hormone (LH) response after stimulation with releasing hormone. The adrenals respond to adrenocorticotropic hormone (ACTH) stimulation, but a deficiency in ACTH may be demonstrated by the use of metyrapone.

Pathology. At postmortem examination, the pituitary gland may be hypoplastic or aplastic, the thyroid and adrenal glands small, and the cellular architecture of the adrenals disorganized, with atrophy or absence of the fetal cortex. Multiple congenital anomalies of the central nervous system (CNS), including holoprosencephaly and arrhinencephalia, may be found. Radiographic studies have demonstrated the absence of the septum pellucidum and massa intermedia. Hypoplasia or aplasia of the adenohypophysis without cerebral or facial anomalies may also occur. There may be different expressions of the same syndrome, depending on the extent of pituitary hypoplasia or other CNS anomalies, or both.

Pathogenesis. The underlying pathogenic mechanisms remain unclear, although aplasia of the anterior pituitary was found in siblings of three patients and in two patients with familial histories of consanguinity. This finding is consistent with a possible autosomal recessive inheritance. Whether the disorder is caused by failure of the pituitary to form or by degeneration of the pituitary is unknown. It is also possible that abnormalities of the hypothalamus with a deficiency in hypophysiotropic-releasing hormones are responsible for the multiple endocrinopathies observed in these infants. The pathophysiologic relationships among pituitary hypoplasia, CNS anomalies, and other pituitary hypofunctions are unknown. The exact mechanism of hypoglycemia in these disorders remains undefined.

Treatment. Therapy consists of replacement with synthetic GH. Cortisol is replaced cautiously, with maintenance doses of hydrocortisone for proven hypoadrenalism. Thyroxine (T_4) replacement is started when hypothyroidism is documented.

Cortisol Deficiency

Familial isolated glucocorticoid deficiency has been described in a family of five siblings; in two of the infants, glucocorticoid production was normal initially and deficient at a later age. This finding suggests that in some families there may be a degenerative process in the adrenal gland.

Maternal steroid therapy resulting in neonatal subclinical adrenal insufficiency was reported in an infant with cushingoid facies, transient hypoglycemia, and a poor response to intravenous corticotropin at 20 hours. However, maternal steroid therapy, such as that for chronic asthma, only rarely has been related to neonatal adrenal insufficiency and hypoglycemia.

Adrenocorticotropic hormone (ACTH) unresponsiveness is a hereditary disorder in which the adrenal glands fail to produce adequate cortisol but aldosterone secretion is normal and ACTH levels are increased. There are feeding problems, a failure to thrive, and regurgitation in the neonatal period; hypoglycemia, convulsions, and shock or even death may occur in infancy or early childhood.

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The syndrome is characterized by hyperpigmentation; normal serum electrolyte concentrations; and an unusually severe, untoward response to illness or stress. There is often a history of affected siblings, and an autosomal recessive mode of inheritance has been suggested. The pathogenesis of this syndrome is poorly understood. The differentiation of the zones of the adrenal cortex in utero requires ACTH except for the zona glomerulosa, which is primarily under renin-angiotensin control. The histologic examination of the adrenal glands of patients with ACTH unresponsiveness has revealed an intact zona glomerulosa and atrophy of the zona fasciculata and zona reticularis. An abnormality at the site (or sites) of ACTH action or cortisol biosynthesis has been postulated.

Adrenal hemorrhage is discussed in Chapter 29.

Congenital adrenal hyperplasia (see Chapter 89) may be diagnosed in the neonatal period because of the presence of hypoglycemia. The diagnosis is difficult in male infants when there are no positive physical findings. Family history may reveal previously unexplained neonatal deaths.

Congenital Glucagon Deficiency

Two male infants have been reported with glucagon deficiency; the disorder became evident on the second to third day of postnatal life, with repeated convulsive movements, hypotonia, weak crying, and poor sucking. In both infants, the diagnosis was based on a low basal glucagon concentration and a strong hyperglycemic response to glucagon. In one of the infants, the response to glucagon was lacking, and in the other, there was a lack of response to hypoglycemia and alanine infusion. The parents of this second infant were closely related and had partly deficient glucagon secretion; two siblings of this infant died before 5 months of age with probable hypoglycemia. Therefore an autosomal recessive inherited disorder is suggested.

Epinephrine Deficiency

This disorder is extremely rare. In infants who are SGA, it has been described secondary to adrenal hemorrhage. The diagnosis may be suspected in an infant who has been acutely ill (i.e., hypotensive) during the perinatal period and can be confirmed by measuring plasma or urine catecholamine levels. Some of these infants may develop adrenal calcification, which may be identified on follow-up.

Inborn Errors of Carbohydrate Metabolism

Galactosemia

See Chapter 90.

Hepatic Glycogen Storage Disease

See Chapter 90.

Fructose Intolerance

See Chapter 90. Fructose is the main sweetening agent in nature, occurring mostly in fruits, vegetables, and honey, and is often added as a sweetener to foods and beverages in the form of disaccharide sucrose. In humans, the liver is the main site of fructose metabolism, with significantly less important sites being the kidney, gut, and other tissues. Absorption of fructose in the gut does not appear to require an active transport system but relies on a facilitative transport system. Fructose is rapidly metabolized, disappearing from the circulation almost twice as fast as glucose. Fructose is metabolized by specific enzymes that convert it into intermediates of the glycolytic–gluconeogenic pathway. The strategic enzymes associated with disorders of fructose metabolism have been identified. Fructose is first phosphorylated to fructose-1-phosphate by fructokinase. Fructose-1-phosphate is split into dihydroxyacetone phosphate and glyceraldehyde by the action of aldolase. Glyceraldehyde is converted to glyceraldehyde-3-phosphate by the action of triokinase. Dihydroxyacetone phosphate and glyceraldehyde-3-phosphate are the intermediates in the glycolytic–gluconeogenic pathway. Additionally, fructose-1,6-bisphosphatase is a key gluconeogenic enzyme that catalyzes the conversion of fructose-1,6-biphosphate into fructose-6-phosphate.

It has been suggested that intravenous fructose be used for the treatment of hypoglycemia in both adults and newborn infants because of the lack of hyperglycemia associated with its administration and, therefore, the lack of reactive hypoglycemia. However, caution should be exercised because the metabolism of fructose in the liver causes increased lactate formation, high-energy phosphate depletion, increased uric acid formation, and inhibition of protein synthesis. The use of fructose in the treatment of hypoglycemia in the neonate, or for that matter in an adult, is not recommended.

Essential fructosemia is a rare and harmless disorder characterized by the appearance of fructose in the urine. This disorder is the consequence of a deficiency of fructokinase, which results in an inability to metabolize fructose.

Hereditary fructose intolerance, or aldolase-B deficiency, results in an inability to split fructose-1-phosphate into triose phosphates. The enzymatic activity contributing to the formation of fructose-1,6-biphosphate from triose phosphates is also reduced.

Affected babies can breastfeed without any ill effects, and symptoms do not appear until fructose or sucrose is introduced in the diet (e.g., cow milk formulas with added sucrose) or at weaning, when fruits and vegetables are introduced. Clinical manifestations after the ingestion of meals containing fructose include hypoglycemia; lethargy; nausea; vomiting; pallor; sweating; and evidence of liver dysfunction, such as jaundice, hepatomegaly, a bleeding tendency, and proximal renal tubular dysfunction. The symptoms are reported to be worse in younger infants than older children. Genetically, it is a heterogeneous disorder with wide variation in manifestations. Treatment consists of the complete elimination of all sources of fructose from the diet, including foods and medications.

Fructose-1,6-bisphosphatase deficiency should actually be called a defect in gluconeogenesis rather than a disorder of fructose metabolism, because these infants can

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tolerate fructose in their diets. Fructose-1,6-bisphosphatase is the key regulatory enzyme in the gluconeogenic pathway involved in the formation of fructose-6-phosphate, the immediate precursor of glucose-6-phosphate, and finally glucose. A deficiency of this enzyme results in an inability to make glucose from all gluconeogenic precursors (i.e., pyruvate, amino acids, glycerol) and, therefore, results in hypoglycemia when gluconeogenesis is the major source of glucose, such as that occurring during fasting. These infants can present in the neonatal period with hypoglycemia and severe metabolic acidosis. The clinical manifestations are related to hypoglycemia and acidosis and include lethargy, tachycardia, apnea, hypotonia, and tachypnea. Laboratory findings include hypoglycemia during fasting (i.e., when glycogen stores are low), high plasma lactate, alanine, and ketones with metabolic acidosis. The defect is inherited as an autosomal recessive disorder and is seen more often in girls than boys.

Treatment is aimed at the maintenance of plasma glucose through frequent feedings and avoidance of prolonged periods of fasting. A therapeutic regimen consisting of the continuous nighttime administration of glucose by the nasogastric route, as in glycogen storage disease, should be successful.

Hereditary fructose intolerance may manifest in the neonatal period if the susceptible infant is fed a sucrose-containing formula or given table sugar, fruits, or fruit juices. Symptoms include vomiting, failure to thrive, excessive sweating, and unconsciousness or convulsions. Hypoglycemia is frequently seen, as are fructosemia and fructosuria, after the ingestion of fructose.

Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

Glucose is transported from the blood to the brain and cerebrospinal fluid by a carrier-facilitated diffusion transport protein Glut1 encoded by gene *SLC2A1*. Deficiency in Glut1 results in encephalopathy and intractable seizures. Glut1 also facilitates glucose transport into red blood cells, which allows RBC Glut1 to act as a surrogate marker for genetic abnormalities seen underlying brain glucose transport. Impaired transport of glucose to brain was originally described in 1991 by DeVivo and colleagues in two children with seizures unresponsive to antiepileptic drugs, delayed development with acquired microcephaly, and developmental delay.[45] In both infants, the seizures appeared at about 2 months of age. Repeated laboratory studies showed low glucose and lactate in the cerebrospinal fluid in the presence of normal blood glucose levels. A detailed evaluation revealed no other abnormalities such as meningitis or intracranial hemorrhage as a possible cause. The glucose levels in the cerebrospinal fluid ranged between 18 and 35 mg/dL when the blood glucose concentration ranged between 86 and 120 mg/dL.

The neurologic features of Glut1 deficiency syndrome (glut1DS) without low serum glucose (<60 mg/dL) are described as: (1) seizures (infantile or absence seizures), (2) movement disorders (spasticity, ataxia, dystonia, chorea), and (3) cognitive and behavioral disturbances (cognitive impairment, delayed adaptive behavior, variable attention). The syndrome may present with variations of combinations of milder to more severe forms.[45]

Diagnostic testing includes a fasting lumbar puncture documenting hypoglycorrhachia and genetic sequencing for the *GLUT1* gene at chromosome 1p34.2 (*SLC2A1* gene). EEG obtained in the fasting state shows mild to moderate slowing. Fluorodeoxyglucose positron emission (FDG-PET) imaging in Glut1DS demonstrates hypometabolism in thalamus and neocortical regions.[45]

Treatment with multiple antiseizure medications is unsatisfactory. Because the brain can use ketones for oxidative metabolism, and the transport of ketones across the blood-brain barrier is not mediated by GLUT1 proteins, a ketogenic diet is the essential treatment for controlling seizures as well as other clinical features of Glut1DS.[45] A fat-to-carbohydrate ratio of up to 4 : 1 is used to achieve a goal of blood beta-hydroxybutyrate concentration of 4-5 mM for seizure control. This is often challenging for families, particularly with older children in whom compliance is difficult.

Management of Neonatal Hypoglycemia

The clinical management of neonatal hypoglycemia should include: (1) anticipation of the group at high risk, (2) correction of hypoglycemia, and (3) investigation and treatment of the cause of hypoglycemia. Often, it is not possible to identify the cause of hypoglycemia, and the treatment remains limited to correction of the low blood glucose concentrations.

Because hypoglycemia is asymptomatic in a large number of neonates, it has become an accepted practice to monitor blood glucose in newborn infants who are at risk for hypoglycemia.[2] This monitoring practice includes: (1) preterm infants—34-36 6/7 weeks; (2) term infants who were born to mothers with diabetes, small for gestational age, intrauterine growth restricted infants, or large for gestational age; and (3) acutely ill infants in the intensive care unit with septicemia, asphyxia, respiratory distress, prematurity, and other illnesses. In the last category, the symptoms of hypoglycemia are overshadowed by those of the acute clinical problems. In addition, blood glucose should be routinely monitored in small preterm infants who are receiving total parenteral nutrition even if they appear clinically well and stable. Glucose monitoring in healthy infants born at term gestation is not recommended.

In asymptomatic infants at risk for hypoglycemia, blood glucose should be determined during the first 4 hours after birth until feeding is established; thereafter, blood glucose should be monitored before feeding. The blood glucose levels in all neonates decline, reaching a nadir between 30 and 60 minutes after birth, and then rise to reach a stable plateau between 90 and 180 minutes after birth with lowest

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acceptable transitional glucose values of 25 mg/dL (range 25-40), requiring early feeding. Early feeding initiation is critical to establish breastfeeding as well as maintaining plasma glucose levels. Therefore, a blood glucose measurement obtained during these time periods necessitates a follow-up measurement to document whether the blood glucose level is decreasing or returning to normal, stable levels. These levels approximate epidemiologic data at the 5th-10th percentiles for glucose. From 4-24 hours after birth, the lowest level requiring action is 45 mg/dL (range 35-45 mg/dL) All bedside measurements of blood glucose concentration obtained by enzyme-strip methods should be considered only as screening results and confirmed by appropriate laboratory measurements. The enzyme-strip methods are not particularly accurate in the low blood glucose range, which is commonly observed in the newborn nursery or in the neonatal intensive care unit.

The treatment strategies for hypoglycemia depend on whether it is transient or persistent and asymptomatic or symptomatic. All infants with symptomatic hypoglycemia, regardless of cause or age, should be treated with parenteral glucose infusion.

Oral Dextrose Gel

Oral dextrose gel containing 40 g of dextrose per 100 mL aqueous solution (40%) administered at doses of 200-400 mg per kg is recommended for early transitional hypoglycemia unresponsive to early feeding.[30,47] This is a change from previous recommendations. The estimated rise in blood glucose concentration following dextrose gel was 0.4 mmol/L (95% CI 0.14-0.94; one trial, 75 infants).[59] It can be applied directly to mucosal surfaces of the mouth, including buccal and lingual surfaces with rapid access to the circulation.[27] A Cochrane review of infants treated with dextrose gel found that they were less likely to be separated from their mothers for treatment of hypoglycemia (RR 0.54, 95% CI 0.31-0.93) and improved the rate of exclusive breastfeeding after discharge without altering the rate of developmental impairment at 2 years of age.[59] Buccal gel has been shown to be highly cost effective.[23a]

The greatest variance in the management of hypoglycemia is seen in the asymptomatic infant diagnosed soon after birth (i.e., during the first 2 hours). This type of hypoglycemia is often transient and recovers spontaneously. However, in clinical practice, it is often treated with early feedings. Early breastfeeding is recommended for all neonates, as it improves infant and maternal health outcomes all over the world. Controlled studies examining the benefits or impact of this early feeding on recovery from hypoglycemia have not been performed. It has been suggested that as many as 10% of healthy infants who are the appropriate size for gestational age develop transient asymptomatic hypoglycemia, which in most cases is managed by the initiation of early, normal feeding.

Persistent hypoglycemia is ascribed to the group of infants who continue to require high rates of intravenous glucose administration over several days to maintain normal glucose concentrations. Such persistent hypoglycemia is often related to hyperinsulinemia and may require pharmacologic interventions, as discussed later.

Intravenous Glucose Infusions

Parenteral glucose is administered at a rate of 6-8 mg/kg per minute, corresponding to 3.6-4.8 mL/kg per hour of a 10% dextrose solution. This infusion rate is based on the rate of endogenous glucose production in healthy newborn infants. The aim of therapy is to maintain the plasma glucose concentration at a level higher than 45 mg/dL. Plasma glucose levels are monitored frequently (every 1-2 hours) until they are stable and then less frequently (every 4-6 hours). If the glucose concentrations do not increase to normal levels, the rate of infusion should be increased by 1-2 mg/kg per minute every 3-4 hours while monitoring the glucose response. Infants with severe hypoglycemia and those who require high rates of glucose infusion may benefit from having a securely placed intravenous line such as a central line or an umbilical vein catheter placed above the liver. Caution should be exercised in administering glucose through the umbilical artery catheter; if the catheter is placed near the celiac axis, the administered glucose may preferentially perfuse the pancreas and thus inadvertently cause an increased insulin response and hypoglycemia.

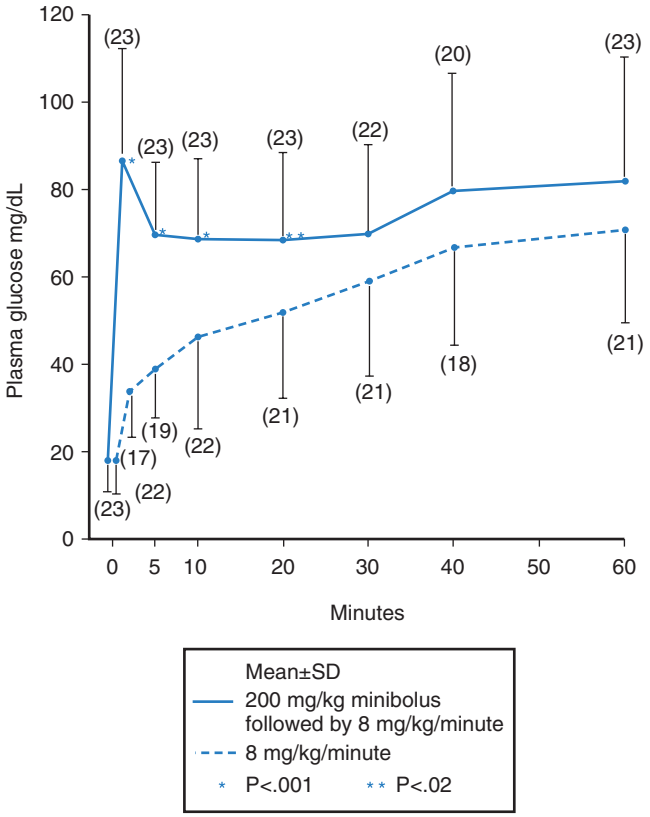
In symptomatic infants and when there is a need to rapidly increase the plasma glucose level, a minibolus of 200 mg/kg (2 mL/kg of 10% dextrose in water) may be given over 1 minute (Fig. 86.10).[3] However, any glucose bolus must be administered through a secure intravenous line so that a constant-rate infusion of glucose may follow. In fact, in most instances, an attempt should be made to first start the intravenous infusion and then give the intravenous bolus infusion for the immediate correction of low plasma glucose.

Feedings may be initiated when the blood glucose level has been stable for several hours. Some investigators suggest that the feeding should be given only as a constant-rate nasogastric drip to avoid hormonal excursion. Although such a concept is theoretically logical, there are no observed data to support it. Nevertheless, infants with persistent hypoglycemia, those who are symptomatic, and those who require high rates of glucose infusion are best managed exclusively by parenteral glucose infusion and without oral feeding until their plasma glucose concentrations have stabilized.

The infant can be weaned from the parenteral glucose infusion after the plasma glucose concentration has been stable at about 50-70 mg/dL. Glucose infusions can be decreased every 3-4 hours as long as the blood glucose concentration remains stable. The concentration of glucose in the blood should be monitored with each change in the rate of intravenous glucose infusion. Such a regimen leads to the successful discontinuation of glucose infusion in almost all infants.

If the infant continues to require high rates of intravenous glucose infusion, a diagnosis of hyperinsulinism should

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• **Fig. 86.10** A comparison of the results of two treatment regimens for hypoglycemic neonates. A group of 23 hypoglycemic infants was treated with 200 mg/kg of glucose given in a minibolus, followed by a constant glucose infusion of 8 mg/kg per minute; a separate group of 22 hypoglycemic neonates received only the constant glucose infusion (8 mg/kg per minute). (From Lilien LD, et al. Treatment of neonatal hypoglycemia with minibolus and intravenous glucose infusion. *J Pediatr.* 1980;97:25.)

be considered and pharmacologic intervention planned. The following pharmacologic agents are used for the treatment of hypoglycemia.

Glucagon

Except for the rare patient with a deficiency of this peptide, glucagon is seldom used to increase the plasma glucose concentration at an acute rate. It has been used most often for the diagnosis of hepatic glycogen storage disease, a condition in which no increase or a minimum increase in plasma glucose concentration is seen in response to glucagon. This single-chain peptide is secreted primarily by the alpha cells of the pancreas. Glucagon increases the blood glucose concentration by increasing both glycogenolysis and gluconeogenesis. An acute administration of glucagon, for example, 150-300 µg/kg given intravenously or intramuscularly, results in an increase in blood glucose by more than 50% in most normal infants. However, the effect is transient, and the administration of glucagon should be followed by intravenous glucose infusion to maintain blood glucose levels. Long-acting glucagon preparations (zinc protamine glucagon) have been used for glucagon deficiency states or in combination with somatostatin for the treatment of certain cases of CHI.

Epinephrine

Although the use of epinephrine to increase blood glucose concentration was recommended in the past, it is rarely used because of its other systemic effects. Its absolute indication would be in the rare infant with epinephrine deficiency. Epinephrine acts by increasing hepatic glucose output through glycogenolysis and decreasing peripheral glucose uptake, mostly in muscle. In addition, epinephrine suppresses insulin secretion and increases lipolysis so that the blood levels of FFAs and glycerol can increase after epinephrine administration.

Diazoxide and Chlorothiazide

Diazoxide is the first-line drug for managing hyperinsulinemic hypoglycemia and is used to evaluate the need for genetic testing and/or advanced imaging. It acts by opening the K_{ATP} channels via binding to the intact SUR1 component, thereby preventing glucose-stimulated insulin secretion (see Fig. 86.8). Diazoxide is a benzothiadiazine derivative that is structurally closely related to the thiazide diuretics, yet it has none of the diuretic effects of thiazides. Diazoxide has been shown to cause decreased insulin secretion, both in vivo and in vitro, and catecholamine release. The combined effect of decreased insulin secretion and increased epinephrine release results in an increase in hepatic glucose production and a decrease in the peripheral use of glucose. In addition, increased lipolysis results in an increase in plasma levels of FFAs and glycerol. The drug is eliminated for the most part by glomerular filtration, and hepatic transformation is quantitatively less important than renal excretion. Ninety percent of circulating diazoxide is bound to albumin. The estimated half-life in adults is 20-30 hours. Serum levels have not been related to the hypotensive effects of the drug. The usual effective dose for the management of hyperinsulinemic hypoglycemia in the newborn is 5-20 mg/kg per day, administered orally in an 8- to 12-hour dose. Significant side effects include hypotension, sodium and water retention leading to expansion of plasma volume and edema, hypertrichosis lanuginosa, thrombocytopenia, anorexia, diarrhea and vomiting, and sometimes extrapyramidal symptoms. However, these side effects are relatively uncommon except for hypertrichosis lanuginosa and fluid retention. Therefore, treatment with diazoxide is combined with chlorothiazide at a dose the same as diazoxide.

Somatostatin Analogue: Octreotide

In the neonate, octreotide is the second-line drug for hyperinsulinemic hypoglycemia, with variable success as an emergency measure. Somatostatin, a tetradecapeptide (a peptide containing 14 amino acids), was originally isolated from the rat hypothalamus and shown to inhibit the release of growth hormone. Subsequent work has shown the presence of a number of somatostatin-related peptides distributed widely in the body, including the hypothalamus, nervous

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tissue, gut, and endocrine and exocrine glands (including the pancreas). When administered exogenously, somatostatin inhibits the secretion of glucagon, insulin, growth hormone, and thyrotropin. In addition, it has a number of physiologic effects on the gut, in particular the inhibition of exocrine secretion, changes in gut motility, and reduction of splanchnic blood flow. It has been used extensively in physiologic studies to examine the role of insulin and glucagon in the regulation of glucose metabolism. Infused into a normal human, it suppresses the secretion of both insulin and glucagon, causing a fall in plasma glucose owing to the suppression of glucagon secretion, followed by a transient increase. The ability of somatostatin to suppress hormone secretion has been used in the short-term treatment of a variety of hyperfunctioning endocrine tumors, such as insulinomas, glucagonomas, gastrinomas, and growth hormone-secreting adenomas. In the neonate, somatostatin has been used to treat hyperinsulinemic hypoglycemia as an emergency measure, with variable success, and to evaluate the usefulness of pancreatectomy.

Clinical use of somatostatin has been hampered by its short half-life of less than 3 minutes and a short duration of action. Therefore, attempts have been made to synthesize long-acting analogues. Octreotide, the first somatostatin analogue introduced for clinical use, is significantly more potent in its hormone-suppressive effect. It is given at 6-8 hourly intervals by subcutaneous injections. The starting dose is 5-10 μg/kg per day, and the dose can be increased up to 15-40 μg/kg per day. Tachyphylaxis leads to a rapid decrease in the response to octreotide 24-48 hours after treatment initiation. Hence, response can be assessed only 2 days after the initiation of a new dose.

Growth Hormone

Treatment with growth hormone should be used only when its deficiency or hypopituitarism has been confirmed.

Glucocorticoids

In the past, steroids were widely used in hypoglycemic infants. With the advent of diazoxide and octreotide, together with recognition of the side-effect profile of steroids, such therapy is used less frequently.

Pancreatectomy

The focal form of congenital hyperinsulinism confirmed by genetics (paternal *ABCC8/KCNJ11* mutation or none) and [^{18}F]-DOPA-PET/CT scan requires limited pancreatectomy.[4] However, diffuse form of congenital hyperinsulinism confirmed by genetic mutation analysis requires near total pancreatectomy (85%-90%) or total removal of the pancreas. Most of these infants develop insulin-dependent diabetes during puberty.

Prognosis of Neonatal Hypoglycemia

The long-term impact of hypoglycemia in the newborn has remained a subject of controversy and debate. Neonatal hypoglycemia can cause seizures, permanent neuronal injury, and death. Other neurologic problems include developmental delay, learning and behavior problems, hyperactivity and attention difficulties, autistic features, microcephaly, and cortical blindness.[56]

The brain is an obligatory consumer of glucose, which is transported to the brain, consuming 80% of total glucose produced. Glucose is transported across the blood–brain barrier into neurons and glia (astrocytes) by two major glucose transporter isoforms, GLUT1 found mainly in the blood–brain barrier and astrocytes and GLUT3 in neurons. In addition to glucose, ketones and lactate are transported across the blood–brain barrier and into astrocytes by the monocarboxylate transporter (MCT) isoforms 1 and into neurons by MCT2.[8] It has been speculated that the availability and use of alternative energy sources (i.e., ketones and lactate) may explain the apparent tolerance of lower plasma glucose concentrations by the neonate. Although the fetal and neonatal brain has been shown to have the ability to use ketones as alternative fuels, clinical data regarding the quantitative contribution of ketones to neonatal brain metabolism have not been secured. Another built-in protective mechanism is that cerebral glucose use is low at birth (18 mmol/minute per 100 g), increasing to 60 mmol/minute per 100 g only at 50 weeks' postconceptional age. Cerebral glucose metabolism, as measured by 18F-fluorodeoxyglucose positron emission tomography shows increasing uptake with advancing gestational age.[50] The neonatal brain, and especially the cerebral white matter, has relatively low oxygen consumption. Hypoglycemia is associated with gray and white matter injuries of the brain.

Until recently, brain injury patterns identified on early MRI scans and their relationship to the nature of the hypoglycemic insult and neurodevelopmental outcomes have been poorly defined. Burns studied 35 term infants with early brain MRI scans after symptomatic neonatal hypoglycemia (median glucose level: 1 mmol/L) without evidence of neonatal encephalopathy.[16] They reported that white matter abnormalities occurred in 94% of infants with hypoglycemia, being severe in 43%, with a predominantly posterior pattern in 29% of cases. Cortical abnormalities occurred in 51% of infants; 30% had white matter hemorrhage, 40% basal ganglia/thalamic lesions, and 11% an abnormal posterior limb of the internal capsule. Twenty-three infants (65%) demonstrated impairments at 18 months that were related to the severity of white matter injury and involvement of the posterior limb of the internal capsule. MRI studies in patients with severe hypoglycemia show a predominant involvement of occipital and parietal areas; however, there may be widespread involvement of cortex, or combined with white matter, or basal ganglia and thalamus.[37]

Transient asymptomatic hypoglycemia in an otherwise healthy neonate has been associated with a good prognosis. Brand and co-workers described neurodevelopmental outcome in 75 full-term, LGA infants with transient

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hypoglycemia on the first day of life to be similar to healthy control children at the age of 4 years.

For the past 20 years, it has been thought that recurrent low blood glucose levels <2.5 mmol/L (45 mg/dL), even in the absence of any suggestive clinical signs, can harm a preterm infant's long-term development. Lucas and colleagues examined the neurodevelopmental outcome of 661 preterm infants weighing less than 1850 g at birth in a multicenter, randomized controlled trial of feeding. Moderate hypoglycemia (a plasma glucose concentration <46.8 mg/dL) occurred in 433 infants and was found in 104 infants on 3-30 separate days.[36] The number of days with moderate hypoglycemia was strongly related to reduced mental and motor developmental scores at a corrected age of 18 months, even after statistical adjustments for a wide range of factors known to influence development. Additionally, the number of days during which moderate hypoglycemia occurred was strongly related to reduced mental and motor development at 18 months corrected age.[36] However, the associated clinical problems of hypoxemia, birth trauma, respiratory distress, prematurity, and other conditions make it difficult to assess the independent long-term effects of hypoglycemia in the human neonate. The problem has been confounded by incomplete follow-up, the lack of adequate control groups, and the lack of a uniform definition of hypoglycemia.

In contrast to these observations, a prospective cohort study by Tin et al. evaluated premature infants born at <32 weeks' gestational age with hypoglycemia in the first 10 days of life. In this study, 47 premature hypoglycemic infants evaluated at 2 years, and 38 of these children evaluated again at 15 years, were not significantly different from that of matched controls.[56] Similarly, Caksen et al. studied 47 preterm and 40 full-term infants with hypoglycemia.[17] Abnormal MRI findings were found in 4% of preterm infants and 32.5% of term infants. The MRI findings were normal in 96% of preterm infants with hypoglycemia. Abnormal MRI findings were statistically significantly more common in symptomatic infants (35.7%) compared to asymptomatic infants (15%). In this cohort of neonatal hypoglycemia, 50% of symptomatic and 57.5% of asymptomatic infants were healthy. Cerebral palsy with or without seizures occurred in 50% of symptomatic and 42.5% of asymptomatic infants.

In summary, although neonatal hypoglycemia poses a risk for neurologic sequelae, the data on the long-term neurologic consequences of symptomatic hypoglycemia remain, for the most part, inconclusive because of co-morbidities identified with each study.

Hyperglycemia

A high blood glucose concentration is less frequently observed in newborn infants than hypoglycemia. This partially results from the ability of normal infants, both preterm and full-term, to adapt to exogenous glucose administration by (1) decreasing or suppressing endogenous glucose production, and (2) increasing glucose uptake in the periphery. The net effect of such an adaptive response is the maintenance of normal blood glucose concentrations, even during high rates of glucose infusion. The definition of hyperglycemia in the newborn remains unclear. Obviously, hyperglycemia should be defined in the context of its clinical implications. Similar to other situations in older infants and adults, hyperglycemia increases blood osmolarity and may cause electrolyte disturbances, osmotic diuresis, and the associated loss of electrolytes in the urine. Because renal function in the neonate is significantly different from that in adults, all of the effects of hyperglycemia may not be seen. Specifically, the plasma glucose level at which renal glycosuria may occur is highly variable, depending on the maturity of renal function, so that renal glycosuria may be seen in extremely immature infants at plasma glucose levels that would be considered within the normal range. In general, most clinicians consider a plasma glucose range of higher than 180-200 mg/dL to represent hyperglycemia. Whether such hyperglycemia requires treatment depends on the associated abnormalities. Studies have demonstrated that even in the presence of significant hyperglycemia (a blood glucose concentration of 197 ± 15 mg/dL, mean ± SEM), the amount of glucose excreted or lost in the urine was less than 1% of the infused glucose. In addition, there was no significant diuresis, suggesting that such hyperglycemia (and minimum glycosuria) does not require the adjustment of intravenous fluids or insulin therapy. It should be emphasized that a change in blood glucose concentration from 90-180 mg/dL results in a change in blood osmolarity of 5 mOsm/L, which is relatively small compared with the normal range of plasma osmolarity (280-300 mOsm/L). The clinical circumstances in which hyperglycemia is observed in the newborn are described here.

Hyperglycemia in the infant with low birth weight is probably the most commonly observed perturbation of glucose metabolism in neonatal intensive care units. In the past, it was often attributed to the "immaturity" of glucose homeostasis in the infant with low birth weight or to the inability of the neonate to tolerate exogenous glucose infusion. However, studies have demonstrated that glucose metabolism, even in an infant with extremely low birth weight, is comparable to that in the full-term infant. These studies showed that (1) infants with low birth weight produce glucose at rates similar to those in full-term infants; (2) hepatic glucose production is regulated both by glucose and insulin and is suppressed in response to exogenous glucose infusion, hyperglycemia, or increased insulin levels; (3) hepatic glucose production is completely suppressed when glucose and amino acids are infused simultaneously, as in parenteral nutrition; (4) intravenous lipids do not cause any change in glucose production; and (5) peripheral glucose uptake increases normally in response to an increase in circulating insulin levels. The reasons for the observed hyperglycemia in the infant with low birth weight appear to involve stress related to the clinical problems.

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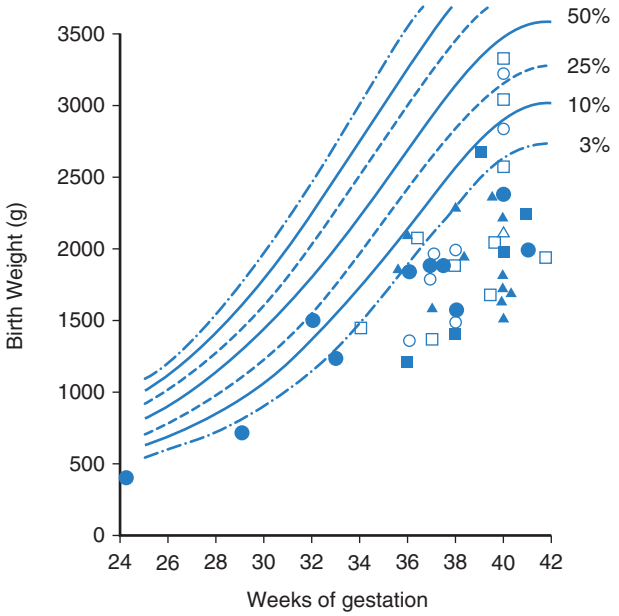
The circulating insulin levels in hyperglycemic infants were appropriately increased with a good linear correlation between plasma glucose and insulin levels in both normoglycemic and hyperglycemic infants.

In conclusion, hyperglycemia in the infant with low birth weight is most likely related to the secretion of glucose counter-regulatory hormones as a result of stress or to the release of cytokines in infected infants. In fact, the levels of circulating catecholamines were noted to be high in infants with low birth weight and were attributed to clinical manipulations such as ventilatory support. Therefore, a high glucose concentration in an infant with low birth weight should be considered an indicator of clinical problems such as sepsis not primarily related to glucose metabolism. In addition to having their blood glucose concentrations managed, these infants must be evaluated for the possible cause of hyperglycemia, which in most could be systemic septicemia.

Diabetes Mellitus in the Newborn

Neonatal diabetes mellitus (NDM) is a relatively rare condition caused by pancreatic beta-cell insufficiency or impaired insulin secretion/action, occurring between the second day after birth and 6 months of age. NDM does not show markers of autoimmune disease. Clinically, three subgroups are recognized: (1) transient NDM (TNDM) in approximately 50% of cases, (2) permanent NDM (PNDM) in approximately 50% of cases, and (3) syndromic NDM. Various genetic defects responsible for both permanent and transient neonatal diabetes have been identified. ATP-sensitive potassium (K_{ATP}) channels are strategic regulators of glucose-induced insulin secretion in pancreatic beta cells (see Fig. 86.8). Activating mutations of the K_{ATP} channel, which prevent closure of the channel and thus inhibit insulin secretion, are now known to be the predominant cause of permanent neonatal diabetes mellitus (PNDM). Transient neonatal diabetes (TND) has an incidence of 1:400,000-500,000.[54] It is defined as diabetes that starts within the first weeks of life and recovers by 18 months. Transient neonatal diabetes gets its name from the observation that remission occurs after a variable period, and the infants do not require insulin therapy. However, diabetes may manifest later, particularly around puberty. Three phases of TND are described: (1) neonatal diabetes, (2) apparent remission, and (3) relapse of diabetes. TND is usually owing to genetic or epigenetic aberrations at an imprinted locus on chromosome 6q24 and can be sporadic or inherited. Transient neonatal diabetes may also be associated with activating mutations of *KCNJ11* and *ABCC8* for the $Kir_{6.2}$ and SUR1 subunit of the K_{ATP} channel.

TNDM presents in a few days to weeks of life as hyperglycemia, glycosuria, dehydration, weight loss, and the presence or absence of ketonemia, ketonuria, or metabolic acidosis. The median age at diagnosis is 6 days (range, 1-81 days). Most of these infants are born SGA (Fig. 86.11). Plasma insulin levels during the basal state and in response to a glucose load have been reported to be low.



• **Fig. 86.11** Birth weight of 45 infants with neonatal diabetes mellitus. Closed symbols denote girls; open symbols denote boys; *circles*, transient diabetes; *triangles*, transient diabetes with later recurrence; *squares*, permanent diabetes. (From Von Muhlendahl KE, et al. Long-term course of neonatal diabetes. *N Engl J Med.* 1995;333:704.)

TNDM resolves in 12 weeks, but 50% of cases may relapse. Associated nondiabetic birth defects are also reported in some patients, including macroglossia, congenital heart defect, developmental delay, and hypothyroidism.[54]

Three genetic anomalies on chromosome 6 have been identified in 70% of cases of TNDM. They are paternal uniparental isodisomy of chromosome 6, unbalanced paternal duplications of 6q24, and methylation defects at 6q24, all implying a disorder of imprinting whereby the expression of a gene or genes is affected by parental origin.[54]

Patients with anomalies of chromosome 6 could be offered genetic counseling. With uniparental disomy, the risk for recurrence in a sibling or child of the index patient is small, whereas the risk for transmitting the disease to the children of a man with 6q trisomy would be high.

Mutations in the adenosine triphosphate (ATP) sensitive K^+ channel (KCNJ11 and ABCC8) account for the other 25% of cases of TNDM, but these are more commonly seen in PNDM.

Permanent neonatal diabetes presents a little later, usually within the first 3 months, and requires insulin treatment for life.[48] Mutations in about a dozen genes have been linked to the development of PNDM. The most frequent causes of PNDM are heterozygous mutations in the *KCNJ11*, *INS*, and *ABCC8* genes. Most cases of PNDM may be explained by a monogenic defect[48] (see Fig. 86.8). Patients with the molecular diagnosis of PNDM because of the *KCNJ11* and *ABCC8* gene mutations can be switched from insulin to oral sulfonylureas with an improvement in glycemic control. Patients with PNDM resulting from recessive *INS* mutations are characterized with even lower

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birth weight and an earlier age of diagnosis (first week of life); about 60% of them are the product of consanguinity and most remain on insulin therapy.[21]

Because K_{ATP} channels and their $Kir_{6.2}$ pore-forming subunits are expressed in the skeletal muscle and neurons throughout the brain, it was speculated that the severe developmental delay observed in some patients may be related to the altered activity of these channels in the brain and skeletal muscle.

Syndromic NDM can be associated with immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, Wolcott-Rallison syndrome, Wolfram syndrome and syndromes associated with mutations of *PDX/IPF1*, *PTF1A*, *GLIS3*, *NEUROD1*, and *HNF1B* genes.[42] IPEX presents with diabetes, thyroid disease, enteropathy, and exfoliative dermatitis in infancy due to autoimmune endocrinopathy. SNDM is considered when K-ATP channelopathies and other known mutations for NDM have been ruled out.

Diagnosis of monogenic NDM presenting in children less than 6 months of age requires molecular genetic analysis for K_{ATP} channel mutations. Treatment includes correction of fluid-electrolyte disturbances and hyperglycemia. These infants are often extremely sensitive to insulin and respond well to a daily insulin dose of 3-4 U/kg of body weight. Insulin dosage must be adjusted based on plasma glucose concentration, glycosuria, or both. Because of the risk for hypoglycemia, careful and frequent monitoring of plasma glucose levels should be performed. Sulfonylureas close the K_{ATP} channels and, therefore, most patients with these mutations (*KCNJ11* and *ABCC8*) are able to transition from insulin to oral sulfonylureas.

Diabetes mellitus owing to pancreatic lesions is extremely rare and is usually manifested soon after birth. The metabolic abnormalities are the result of either the absence of a pancreas (or pancreatic hypoplasia) or the congenital absence of insulin-secreting B cells. Both lesions result in a lack of insulin secretion. Because insulin is a primary growth-promoting hormone in utero, these infants are severely growth-restricted at birth. They rapidly become hyperglycemic soon after birth, often to extremely high levels, and require immediate insulin therapy. There may be other associated congenital abnormalities, such as congenital heart defects. In infants with pancreatic hypoplasia, insufficiency of the exocrine pancreas has also been reported. Very few infants have been reported to survive, primarily because of associated lethal congenital anomalies.

Insulin Therapy in the Baby With Low Birth Weight

Hyperglycemia is most commonly seen in extremely low birth weight infants at <26 weeks of gestation. Intravenous insulin in these infants has been used to (1) treat hyperglycemia and (2) enhance the delivery and assimilation of nutrients and consequently accelerate growth. When administering insulin to the neonate, frequent glucose monitoring and adjustment in the rate of glucose infusion are required to prevent hypoglycemia and its consequences. The rationale for such an approach is based on the observation that hyperglycemia and the inability to use glucose and other nutrients may be related to resistance to insulin action in those infants, resulting from either immaturity or a heightened counter-regulatory "stress" response.[11]

Insulin use increases glucose and total energy intake without affecting growth.[14] Use of insulin for hyperglycemia is not a widely utilized current practice because of suggested increase in mortality and adverse neurologic outcome in retrospective studies.[57]

Key Points

- Maternal glucose is the major substrate for fetal energy metabolism, facilitated by placental glucose transporters.
- Insulin is the major promoter of fetal growth.
- Hypoglycemia at levels of 25-40 mg/dL in the first 4 hours, and 35-45 mg/dL at 4-24 hours, requires intervention.
- Early feeding is critical to establish breastfeeding and maintain plasma glucose levels. Oral dextrose gel is recommended for early transitional hypoglycemia unresponsive to early feeds.
- Intravenous glucose infusions are begun at 6-8 mg/kg/minute and may need to be increased to maintain plasma glucose >50 mg/dL at <48 hours and >60 mg/dL at >48 hours of age.
- Hypoglycemia in IUGR infants results from multiple processes, including decreased glycogen stores and gluconeogenesis.
- Congenital hyperinsulinism (CHI) is an important cause of persistent and profound hypoglycemia. Diazoxide and octreotide are the first and second order drug treatments for hyperinsulinemic hypoglycemia.
- Transient asymptomatic hypoglycemia has a good prognosis. Severe symptomatic hypoglycemia may manifest brain injury, including occipital and parietal MRI lesions.

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87

Disorders of Calcium, Phosphorus, and Magnesium Metabolism in the Neonate

STEVEN A. ABRAMS AND DOV TIOSANO

Approximately 98% of the calcium, 80% of the phosphorus, and 65% of the magnesium in the body are in the skeleton; these elements, often referred to as the "bone minerals," are also constituents of the intracellular and extracellular spaces. The metabolism of these bone minerals and mineralization of the skeleton are complex functions that require the interaction of various parameters. These include an adequate supply of nutrients, including proteins for collagen matrix synthesis, and an adequate intake and absorption of calcium and phosphorus for full bone mineralization. During prenatal development, nutrients are transferred mainly across the placenta. From the analysis of stillbirths and deceased neonates, it has been calculated that during the last trimester of gestation, the daily accretion per kilogram of body weight represents approximately 100-130 mg of calcium, 60-70 mg of phosphorus, and 3 mg of magnesium.[65] Therefore, at birth, the whole-body content of a term infant represents about 30 g of calcium, 16 g of phosphorus, and 0.75 g of magnesium. After birth, nutrient intake from most enteral sources, especially unfortified human milk, is below the amount needed to achieve this level of mineral retention.[63] This can promote the occurrence of relative osteopenia or clinical rickets in preterm infants and in some high-risk, full-term infants. This risk is greatest in infants with chronic illnesses such as bronchopulmonary dysplasia.[1,34] In addition to their role in bone formation, the bone minerals play important roles in many physiologic processes, such as transport across membranes, activation and inhibition of enzymes, intracellular regulation of metabolic pathways, secretion and action of hormones, blood coagulation, muscle contractility, and nerve conduction. The 20% of phosphorus that is not complexed within bone is present mainly as adenosine triphosphate, nucleic acids, and cell and organelle membranes. Magnesium, an essential intracellular cation, is critical in energy-requiring metabolic processes, protein synthesis, membrane integrity, nervous tissue conduction, neuromuscular excitability, muscle contractility, hormone secretion, and intermediary metabolism.

Calcium, Phosphorus, and Magnesium Physiology

Calcium Physiology

Serum Calcium

Serum calcium represents a very small fraction of total-body calcium. Less than 1% of whole body calcium is present in extracellular fluid and soft tissues. In the circulation, calcium is distributed among three interconvertible fractions. About 50% of total serum calcium is in the ionized form at the normal serum protein concentration and represents the biologically active component of the total serum calcium concentration. Another 8%-10% is complexed to organic and inorganic acids (e.g., citrate, lactate, bicarbonate, sulfate, and phosphate). Together, the ionized and complexed calcium fractions represent the diffusible portion of circulating calcium. About 40% of serum calcium is protein bound, primarily to albumin (80%) but also to globulins (20%).[30] Ionized calcium is the only physiologically active fraction. The protein-bound calcium is not biologically active but provides a rapidly available reserve of calcium. Under normal circumstances, the serum calcium concentration is tightly regulated by parathyroid hormone (PTH) and calcitriol (1,25-dihydroxy vitamin D_3; $1,25[OH]_2D_3$), which increase serum calcium (Fig. 87.1), and by calcitonin, which decreases serum calcium.

Serum total and ionized calcium concentrations are relatively high at birth but decrease sharply during the first hours of life to reach a nadir at 24 hours and increase progressively thereafter up to the end of the first week of life (Table 87.1). Sudden changes in the distribution of calcium between ionized and bound fractions may cause symptoms of hypocalcemia even in children with functioning hormonal

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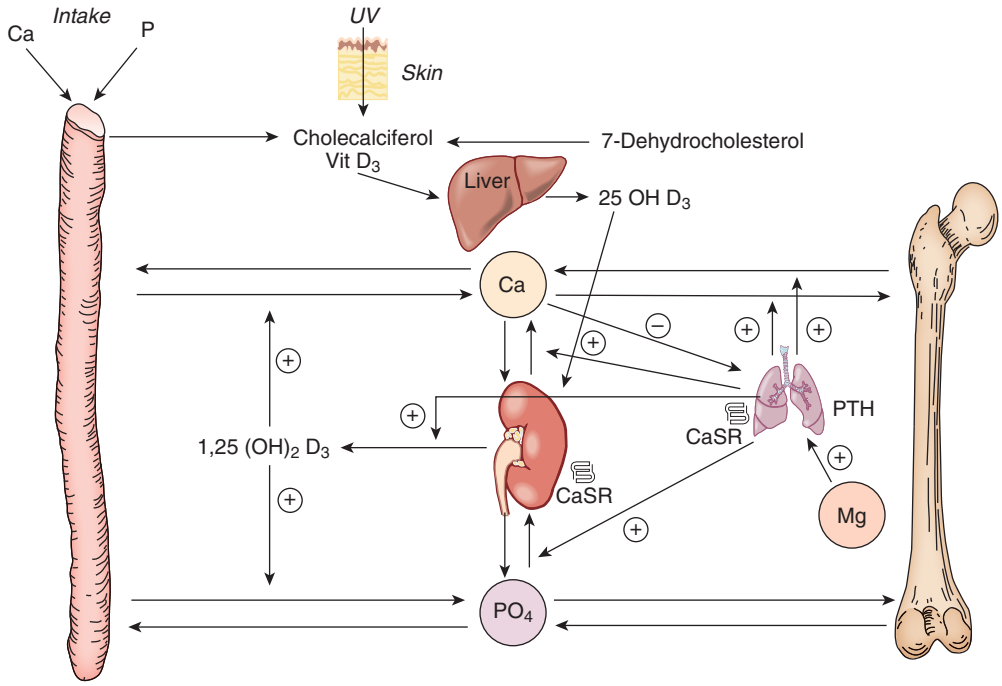
Abstract

The majority of the calcium, phosphorus, and magnesium in the body are in the skeleton. The metabolism of these bone minerals and mineralization of the skeleton are complex functions that require the interaction of various parameters. These include an adequate supply of nutrients, including proteins for collagen matrix synthesis, and an adequate intake and absorption of calcium and phosphorus for full bone mineralization. Key topics discussed in this chapter include intake recommendations, intestinal absorption, and excretion of these minerals, along with hormonal regulation of mineral metabolism in neonates.

Keywords

calcium
phosphorus
magnesium
neonate
newborn
infant

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• **Fig. 87.1** Regulation of calcium (Ca) and phosphate (PO_4) homeostasis. Parathyroid hormone (PTH) increases Ca release from bone, Ca resorption in the kidney, and $1,25(OH)_2D_3$ excretion from the kidney. PTH production is stimulated by low Ca and inhibited by low Mg and high $1,25(OH)_2D_3$. Vitamin D increases Ca release from bone and Ca and PO_4 absorption from the intestine. Vitamin D production is stimulated by high PTH and low PO_4. CaSR, Calcium-stimulating response; OH, hydroxylase; P, phosphorus; UV, ultraviolet light; Vit, vitamin.

TABLE 87.1 Early Life Changes in Serum Calcium, PTH, and Vitamin D Levels in Full-Term and Preterm Infants

	Cord Blood	24 Hr	48 Hr	96-120 Hr	30 Days
Calcium, nmol/L					
Full-term	2.42 ± 0.08	2.17 ± 0.10	2.16 ± 0.08	2.22 ± 0.12	2.52 ± 0.08
Preterm	2.28 ± 0.09	1.91 ± 0.06	1.86 ± 0.07	2.08 ± 0.11	2.43 ± 0.06
Intact PTH, pg/mL					
Full-term	5.1 ± 3	33 ± 8	30 ± 5	28 ± 16	
Preterm	4.5 ± 3	72 ± 17	56 ± 20	36 ± 14	
25(OH)D, ng/mL					
Full-term	13 ± 3	12 ± 2		12 ± 2	17 ± 1
Preterm	10 ± 3	8 ± 2		12 ± 2	17 ± 2
$1,25(OH)_2D$, pg/mL					
Full-term	38 ± 4	74 ± 9		100 ± 5	61 ± 4
Preterm	37 ± 6	62 ± 9		128 ± 29	108 ± 13

PTH, Parathyroid hormone.
Data from Hochberg Z, ed. *Vitamin D and rickets. Endocrine development* Vol 6. Basel, Switzerland: Karger; 2003:34-49.

mechanisms for the regulation of the ionized calcium concentration. Increases in the extracellular fluid concentration of anions such as phosphate, citrate, or bicarbonate increase the proportion of bound calcium and decrease ionized calcium. Alkalosis increases the affinity of albumin for calcium and thereby decreases the concentration of ionized calcium. In contrast, acidosis increases the ionized calcium concentration by decreasing the binding of calcium to albumin. Although it remains common to measure the total serum calcium concentration, more physiologically relevant information is obtained by direct measurement of the ionized calcium concentration. The total serum calcium

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decreases about 0.8 mg/dL, or 0.25 mmol/L, for each 1 g/dL of decrease in serum albumin, without any change in the ionized calcium.

Placental Transport

During pregnancy, calcium is actively transferred from the mother to the fetus. The normal fetus accumulates about 25-30 g of calcium by the end of gestation. Approximately 80% of this calcium accumulates during the third trimester, when the fetal skeleton is rapidly mineralized. To meet the high demand for mineral requirements of the developing skeleton, the fetus maintains higher serum calcium and phosphorus levels than the maternal levels. This process is the result of the active transport of calcium across the placenta by a calcium pump in the basal membrane that maintains a gradient of maternal-to-fetal calcium of 1 : 1.4.

The main regulator of fetal ionized calcium appears to be parathyroid hormone related protein (PTHrP), which is produced by the placenta as well as by the fetal parathyroid glands. Animal data suggest that both PTH and PTHrP act in the regulation of fetal mineral metabolism. PTH-ablated mice showed significant abnormalities in fetal bone formation, including decreased mineralization of the cartilage matrix and decreased vascular invasion of the growth plate, suggesting a role of PTH beyond simply regulating serum mineral ion concentration.[49] In contrast to the relatively mild phenotype of PTH-ablated mice, animals that lack PTHrP show major developmental abnormalities, particularly a significant acceleration of chondrocyte differentiation in the growth plates leading to a lethal skeletal dysplasia characterized by the premature mineralization of all bones that are formed through an endochondral process.[41]

Although vitamin D is critical for mineral ion homeostasis and bone development during adult life, fetal mineral ion homeostasis appears to be mostly independent of this hormone. $1,25(OH)_2D_3$ is produced by the fetal kidney, and the vitamin D receptor is present in many fetal tissues, including the placenta.[55]

However, neonates deficient in 1-alpha-hydroxylase are grossly normal from birth until weaning.[19] Additionally, the absence of the vitamin D receptor (VDR) either in the mother or the fetus does not affect placental calcium transfer or fetal serum levels of calcium, phosphorus, or magnesium during the first days after delivery, indicating that the VDR in either side of the placenta, on the maternal or at the fetal side, is not critical for placental calcium, phosphorus, or magnesium transfer.[39,42,68] Cord concentrations of 25(OH)D and $1,25(OH)_2D_3$ correlate significantly with those found in the maternal circulation, suggesting that the vitamin D pool of the fetus depends entirely on that of the mother. $1,25(OH)_2D_3$ found in fetal plasma is a result of fetal kidney and placental hydroxylation activity. The placenta synthesizes and metabolizes $1,25(OH)_2D_3$ through the activity of 25-hydroxyvitamin D-1α hydroxylase and 1,25-dihydroxyvitamin D-24 hydroxylase, two key enzymes for vitamin D metabolism. Bone mass of neonates may be partially related to the vitamin D status of the mother, although this relationship is not consistently found in either the United States or in developing countries.[44,73]

After the umbilical cord has been cut, the neonate loses the transplacental supply of calcium and must adapt rapidly to ensure normal calcium homeostasis and skeletal growth and mineralization. The neonate is dependent on intestinal absorption to supply calcium and therefore must quickly stimulate the synthesis of PTH and $1,25(OH)_2D_3$, which had been suppressed in utero. Total and ionized calcium levels decrease significantly within 24-48 hours after birth. Calcium concentrations usually return to normal by 5-8 days after birth. Serum PTH levels, which are low at birth, increase within the first 24-48 hours, probably in response to the decrease in serum calcium. Subsequently, $1,25(OH)_2D_3$ levels rise to adult levels within a few days. Serum calcitonin rises two- to tenfold over cord blood levels within the first 48 hours. Hypocalcemic premature and asphyxiated newborns have the highest levels of postnatal calcitonin.[52]

Intestinal Absorption

Calcium absorption occurs primarily in the small intestine by both active and passive processes. Ionization of calcium compounds, which require an acidic pH, develops in the stomach and is a prerequisite for absorption. Vitamin D is essential for the active absorption of calcium, which involves carriers such as calcium-binding proteins. However, the role of vitamin D and active transport early in life is uncertain.

The absorption rate of calcium is higher than that during other periods of life except for during pregnancy in populations with low mineral intake. The average absorption of calcium from human milk in infants is approximately 50%-60% of its intake. The absorption of calcium added to human milk with commercially available fortifiers generally parallels that of the calcium endogenous to human milk.[27]

Studies in vitamin D receptor–knockout (VDR-KO) mice have underscored the importance of an intact VDR for intestinal calcium absorption. The VDR-KO mice exhibit decreased calcium absorption with a concomitant reduction in the expression of transcellular calcium transport proteins. Vitamin D–dependent transcellular calcium transport involves three major components: transient receptor potential vanilloid type 6 (TRPV6), calbindin D_{9k}, and Ca^{+2}ATPase. VDR-KO mice exhibit decreased calcium absorption with a concomitant reduction in the expression of transcellular calcium transport proteins. However, recent studies revealed that TRPV6/calbindin D_{9k} double KO mice do not demonstrate impaired intestinal calcium transport when they have usual dietary calcium intake, indicating that other compensatory factors are involved in intestinal calcium transport. Several studies underscored the importance of the paracellular route and suggested that $1,25(OH)_2D_3$ regulates tight junction proteins, such as Caludin-2,3, Caludin-12, and Cadherin-17, which lead to increased paracellular calcium transport.[16]

Passive calcium transport is driven by chemical gradients that represent movement of calcium among the cells (paracellular transport). It may account for most of the calcium

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absorption very early in life, particularly in premature infants in whom the transport, which is transcellular and dependent on vitamin D, is not completely expressed.[13,39] In addition to vitamin D status, various other factors affect calcium absorption. Ionization of calcium compounds, which requires an acidic pH, occurs in the stomach and is a prerequisite for absorption. Therefore, low availability could be the result of an insoluble fraction of calcium intake or the precipitation of calcium in the gut. The quantity and quality of fat intake may influence calcium absorption through the formation of calcium soaps. Free palmitate content in the gastrointestinal tract after the hydrolysis of triglyceride may impair calcium absorption. Human milk contains a bile salt-stimulated lipase that is not specific to the Sn-1 and Sn-3 positions. The improvement of calcium absorption with the use of medium-chain triglycerides may be the result of the reduction of total saturated long-chain fatty acid content in formula. Relatively low gastrointestinal pH content or the lactose and casein content of the formula may also have an additional positive effect on calcium absorption.

Medications may also interfere with calcium absorption. For example, glucocorticoids inhibit intestinal absorption, and some anticonvulsants can also inhibit calcium absorption either directly (phenytoin) or indirectly through interference with vitamin D metabolism (phenobarbital and phenytoin). The clinical consequences of the use of these anticonvulsants in the neonatal period is not known but is unlikely to be a common major risk factor for low bone mineral accumulation in early life.

In infants, a significant amount of calcium is secreted in the intestinal lumen through digestive fluid. With the use of stable isotopes, endogenous fecal calcium excretion and true calcium absorption may be evaluated. Numerous metabolic balance studies have been performed in preterm infants fed human milk or a formula to evaluate apparent calcium absorption. In preterm infants fed human milk with or without fortification, calcium absorption ranges from 50%-70%. In formula-fed infants, the percentage of calcium absorption may be slightly less than that with human milk, although the difference does not appear to be large.[1]

Renal Excretion

Under normal circumstances, calcium status is maintained by a balance between its intestinal absorption and renal and endogenous fecal excretion with a small component of skin losses, especially with sweating. Although it is responsible for only 5%-10% of Ca^{2+} reabsorption, the major regulation of Ca^{2+} reabsorption occurs in the distal convoluted tubule by a mechanism independent of Na^{+} reabsorption but regulated by PTH and $1,25(OH)_2D_3$. Calcium reabsorption is increased by both PTH and $1,25(OH)_2D_3$. It is also regulated by ionized calcium concentration, phosphate concentration, and acid-base status. It increases with Ca^{2+} depletion and alkalosis but decreases with hypercalcemia, phosphate depletion, and acidosis. The effects of diuretics on renal calcium excretion vary considerably. Furosemide markedly increases renal calcium losses and is a risk factor for neonatal nephrocalcinosis.[24] Thiazides increase renal tubular calcium reabsorption, thereby reducing calciuria.

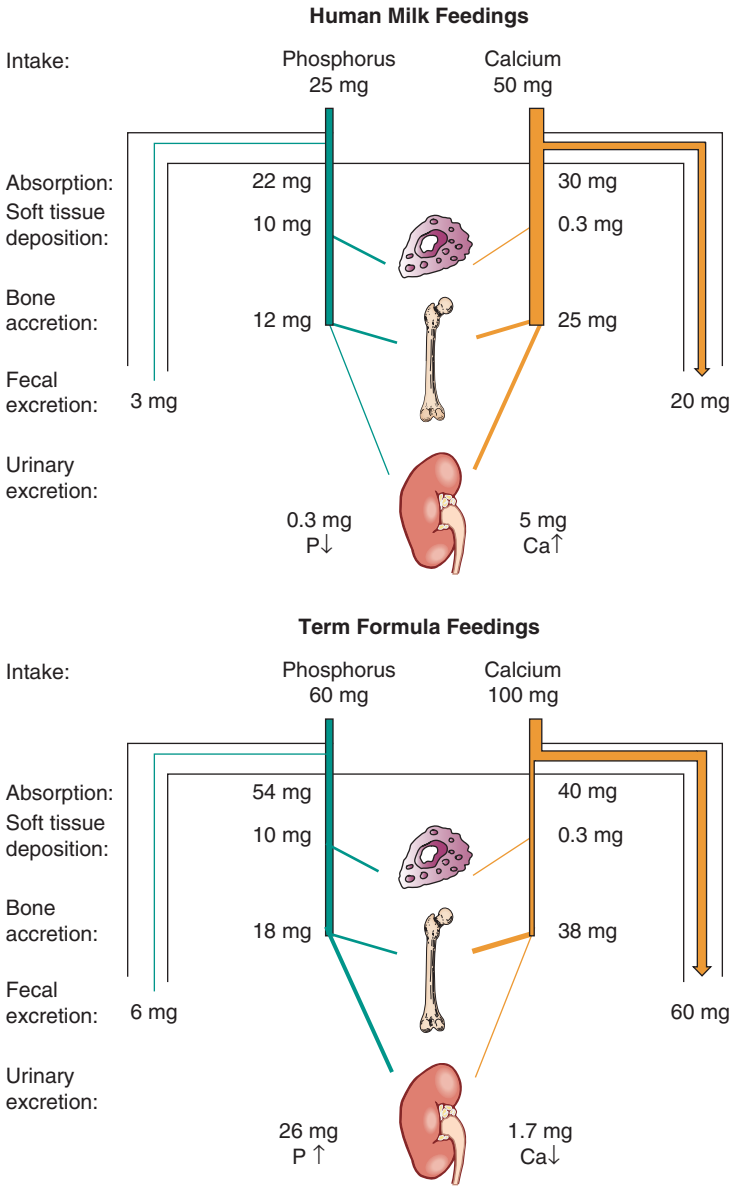
Nearly all filtered calcium (98%) is reabsorbed in the renal tubule. However, preterm and term infants differ from adults in three main aspects: (1) renal function is far from being completely developed; (2) mineral requirements for growth are very high; (3) renal calcium load results solely in the difference between net absorption and net bone and soft tissue retention. Considering that calcium soft tissue retention is negligible, renal calcium load is highly dependent on bone calcium deposition associated with phosphorus in the form of hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$ containing a molar calcium-to-phosphorus ratio of 1.67 (2.15 wt/wt). Therefore, the main determinant of the urinary loss of calcium in preterm and term neonates is phosphorus depletion and urinary excretion. When human milk is provided exclusively, there is an increase in the urinary excretion of calcium associated with very low urinary phosphate excretion. In contrast, when human milk is supplemented with phosphate, significant phosphaturia appears at the same time that calciuria decreases to a minimum level. Therefore, hypercalciuria can primarily be explained by a relative phosphate depletion that cannot meet the phosphate demand necessary for skeletal mineralization (Fig. 87.2).

Intake

Mature human milk contains approximately 260 mg of calcium per liter.[31] Considering the possibility of a lower efficiency (fraction) of calcium absorption from infant formulas compared with human milk, the guidelines of the Food and Drug Administration, the Life Sciences Research Office (LSRO),[36] and those of the Scientific Committee on Food of the European Commission for full-term infants during the first 6 months of life recommended a content of 50-140 mg of calcium per 100 kcal.[5] It should be noted that there are no comparisons of calcium absorption performed in the United States for infant formulas and human milk at the same calcium content, as the calcium content of human milk is uniformly less than the minimum mandated for infant formulas by the Infant Formula Act.[31] Typical 24-hour intake and retention values for human milk-fed infants are shown in Fig. 87.3.

The requirements for enteral calcium intake in preterm infants were reconsidered in an American Academy of Pediatrics (AAP) statement.[1] The AAP recommended a range of calcium intake of 150-220 mg/kg per day consistent with the LSRO recommendations for infants receiving 120 kcal/kg per day of feeding.[36] The AAP recommendations are slightly above those of the European authorities (Table 87.2).[5] In the United States, fortified human milk or preterm formula generally provides about 180-230 mg/kg per day of calcium at usual intakes (Table 87.3). There is no evidence that small variations among formulas within a class (e.g., different brands of preterm formulas marketed

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• **Fig. 87.2** Metabolism of calcium (Ca) and phosphorus (P) in term infants with feeding.

in the United States) in amount or source of calcium have a biologically meaningful impact on preterm infants.

Phosphorus Physiology

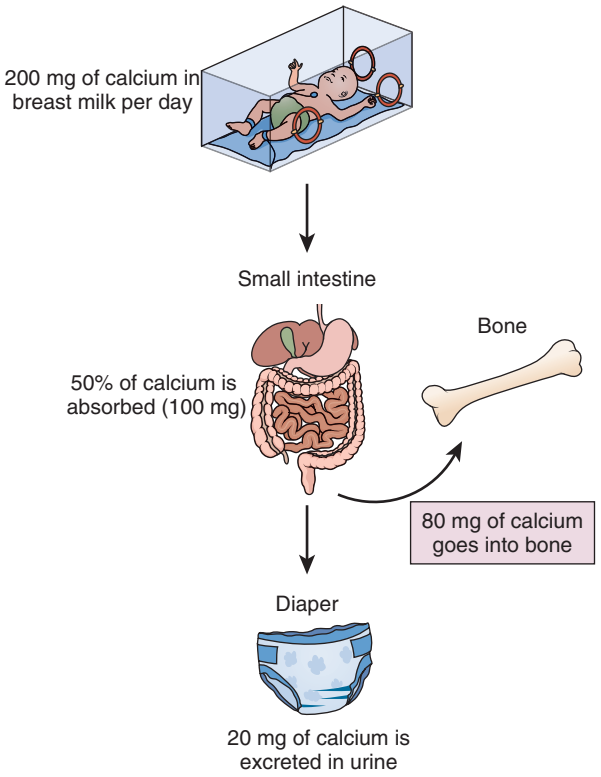
Unlike calcium, phosphorus is present in the soft tissues, mainly in the form of phosphate esters, and in extracellular fluid in the form of inorganic phosphate ions. This represents about 15% of the whole-body content. Given its widespread distribution, phosphorus plays a critical role in many biologic processes, including energy metabolism, membrane composition, nucleotide structure, cellular signaling, and bone mineralization. It is, therefore, not surprising that a deficiency of phosphorus results in clinical disease, including muscle weakness, impaired leukocyte function, and abnormal bone metabolism.

Serum Phosphorus

In serum, about two-thirds of phosphorus is organic (lipid phosphorus and phosphoric ester phosphorus) and one-third inorganic. In routine clinical practice, only inorganic phosphorus is measured. About 85% of the inorganic phosphorus is ionized, circulating as monohydrogen or dihydrogen phosphate; 5% is complexed with sodium, magnesium, or calcium; and 10% is protein bound. The serum concentration is conventionally expressed as the mass of the elemental phosphorus (mmol/L or mg/dL). In contrast to calcium, serum phosphorus concentration varies widely depending mainly on intake and renal excretion but is also influenced by age, gender, pH, and a variety of hormones. At birth, the mean serum phosphorus concentration is relatively low (2.6 mmol/L or 6.2 mg/dL) but thereafter rises rapidly to reach a typical value of 3.4 mmol/L, or

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8.1 mg/dL, owing to both endogenous phosphorus release and low renal excretion.[43] The diet partially determines the serum phosphorus content, with higher values usually seen in infant formula compared to human milk–fed infants. Serum phosphorus is inversely related to serum calcium concentration and to age during childhood. Hypophosphatemia prevents apoptosis in the hypertrophic cells in the growth plate. In the absence of apoptosis, the hypertrophic cells accumulate in the growth plate and form the rachitic bone. It follows that the primary common denominator of rickets is hypophosphatemia, thus the diagnosis of rickets should be based substantially on the etiologies of hypophosphatemia, although in preterm infants with rickets it is clear that significant deficiencies of both calcium and phosphorus occur.[69]



• **Fig. 87.3** Typical values for calcium for breastfed infants at term for an entire 24-hour period.

Placental Transport

During pregnancy, there is transfer of phosphorus from the mother to the fetus that reaches a peak rate of 60-75 mg/kg per day during the third trimester; 75% is retained for bone mineralization, and 25% is retained in other tissues. The transplacental transport of phosphorus is an active process against a concentration gradient and is sodium dependent. Both $1,25(OH)_2D_3$ and fetal PTH may be involved in the regulation of placental phosphorus transfer.

Intestinal Absorption

Intestinal phosphorus absorption takes place primarily in the duodenum and jejunum. It occurs by two mechanisms: an active, sodium-dependent transcellular process localized to the mucosal surface by sodium phosphorous cotransporter 2B (NaPi 2B), and passive diffusion through the paracellular pathway. It depends on both the absolute amount of dietary

TABLE 87.2 Recommendations for Enteral Nutrition for VLBW Infants

	Calcium (mg/kg per day)	Phosphorus (mg/kg per day)	Vitamin D (IU/day)
Tsang et al. (2005)	100-220	60-140	150-400
Klein (2002)	150-220	100-130	135-338[†]
Agostoni (2010)	120-140	65-90	800-1000
Abrams and AAP CON (2013)	150-220	75-140	200-400

[†]90-125 IU/kg (total amount shown is for 1.5-kg infant).
From Abrams SA, and the Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013; 131:e1676-1683.

TABLE 87.3 Intakes of Calcium, Phosphorus, and Vitamin D From Various Enteral Nutrition Feedings at 160 mL/kg per Day Used in the United States

	Unfortified Human Milk* (20 kcal/oz)	Fortified Human Milk* (24 kcal/oz)	Preterm Formula (24 kcal/oz)	Transitional Formula (22 kcal/oz)
Calcium (mg/kg)	37	184-218	210-234	125-144
Phosphorus (mg/kg)	21	102-125	107-130	74-80
Vitamin D (IU/day)[†]	2.4	283-379	290-468	125-127

*Human milk data based on mature human milk.
[†]Based on an infant weighing 1500 g.
Data from American Academy of Pediatrics, Committee on Nutrition, Kleinman RE, ed. *Pediatric nutrition handbook*. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009, and Abrams SA, and the Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013;131:e1676-1683.

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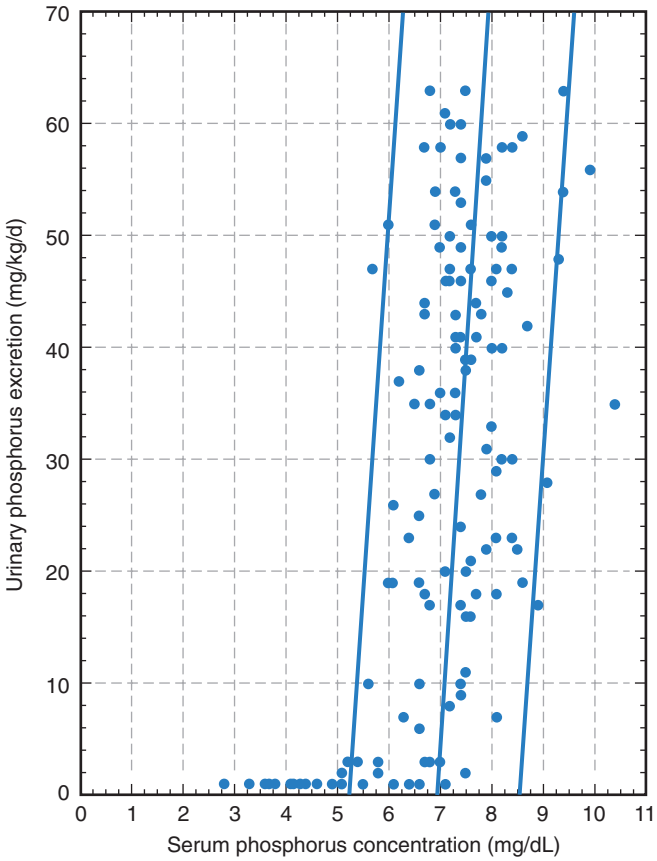
phosphorus and the relative concentrations of calcium and phosphorus (an excessive amount of either can decrease the absorption of the other). $1,25(OH)_2D_3$ stimulates NaPi 2B expression and active phosphorus absorption. In otherwise healthy intestines, the efficiency of this absorption is high (close to 90% of intake) regardless of the type of feedings provided to the infant.

Renal Excretion

The three major factors that control phosphorous reabsorption are high PTH activity, high FGF (fibroblast growth factor) 23, and renal defects that lead to inorganic phosphate (Pi) wasting. Hallmarks of high PTH activity are hypophosphatemia, phosphaturia, disturbance in vitamin D metabolism, and low calcium. The hallmarks of high FGF23 activity are hypophosphatemia and phosphaturia with inappropriately low $1,25\text{-}OH_2D$, and the hallmarks of renal rickets are hypophosphatemia and phosphaturia with high circulating $1,25\text{-}OH_2D$.

The kidney contributes to a positive phosphate balance during growth by the reabsorption of a relatively high fraction of filtered inorganic phosphate (99% in neonates, 95% in infants fed human milk, and 80% in adults). Preterm infants have an increased fractional excretion of phosphate and are at a greater risk for developing signs and symptoms of phosphate deficiency. The bulk of filtered phosphate is reabsorbed in the proximal tubule through sodium-dependent transporters, the Na-phosphate cotransporters 2A and 2C. A change from human milk with a low phosphate content to a formula with a higher content is associated with a rapid downregulation of Na-phosphate cotransporters mRNA and protein in the brush border membrane.

Because intestinal phosphorus absorption is very efficient and fairly unregulated, renal phosphorus excretion plays an important role in maintaining its balance. Filtered load depends on the plasma phosphorus level and glomerular filtration rate (GFR). Tubular reabsorption is an active and saturable process that gives rise to a maximal rate of tubular reabsorption (Tm). There is a plasma minimal threshold below which phosphorus reabsorption is almost complete and urinary excretion close to zero, and a maximal threshold above which all tubular reabsorptive systems are saturated, so each additional increment in filtered load is associated with a parallel increment in excretion.[43] In preterm infants, the minimal and maximal threshold levels are 1.75 mmol/L (5.4 mg/dL) and 2.45 mmol/L (7.6 mg/dL), respectively (Fig. 87.4). The three main factors responsible for Pi readsorption by the sodium/Pi cotransporter in the proximal tubule are urinary phosphorus, PTH, and FGF23. Renal handling of Pi is regulated by hormonal and nonhormonal factors. Changes in urinary excretion of Pi are almost invariably mirrored by changes in the apical expression of NaPi-IIa and NaPi-IIc in proximal tubules. Phosphate deprivation increases NaPi-IIa and NaPi-IIc expression in the proximal tubule. Both NaPi-IIa and NaPi-IIc, the main sodium/Pi cotransporters, are regulated in a similar fashion by PTH, FGF23, and dietary phosphate. Both PTH and FGF23 accelerate the cotransporter endocytosis, and FGF23 also accelerates cotransporters' degradation in the lysosome.



• **Fig. 87.4** Relationship between urinary excretion of phosphorus and serum phosphate level (N = 198) in preterm infants. Regression lines represent the minimal, mean, and maximal plasma phosphate concentration thresholds for tubular reabsorption of phosphate. Points to the left of the minimal threshold were considered hypophosphatemia associated with phosphorus depletion. Points to the right of the maximal threshold were considered hyperphosphatemia caused by low glomerular filtration rates and relative phosphorus overload.

During early postnatal life, the phosphate response to PTH is blunted, whereas PTH increases tubular calcium reabsorption. Together, these actions result in the retention of both calcium and phosphate in infants, which is favorable for growth and bone mineralization.

The level of FGF23 in cord blood is low, which might be caused by the low expression of FGF23 in fetal tissues. Measuring soluble α-Klotho and FGF23 levels in the cord blood reveals a negative correlation between the two.[54] The low FGF23 levels promote a relative hyperphosphatemia, and the relative increase in $1,25(OH)_2D_3$ promotes bone mineralization during early rapid growth in the neonatal period.

FGF23 functions principally as a phosphaturic factor. It is secreted by osteocytes and osteoblasts in response to high serum phosphate levels and $1,25(OH)_2D_3$. In the osteoblast, FGF23 post-translation undergoes O-glycosylation by GALNT 3. The glycosylation protects the molecule from degradation. Nonglycosylated FGF23 may be targeted

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for degradation by subtilisin/furin-like endopeptidases. Impaired FGF23 synthesis or action, owing to *FGF23* gene mutations; mutations in GALNT 3; or mutations in Klotho, which is required for the conversion of FGFR1(IIIc) into the FGF23 receptor, leads to severe hyperphosphatemia and tumoral calcinosis.[67]

FGF23 accelerates NaPi-2a and NaPi-2c cotransporters' endocytosis to reduce renal phosphate reabsorption and thereby increases urinary phosphate excretion. Furthermore, FGF23 suppresses the expression of 1-α-hydroxylase to reduce the production of the active vitamin D metabolite $1,25(OH)_2D_3$. The hallmark of all clinical entities that share high FGF23 activity is rickets or osteomalacia with hypophosphatemia owing to renal phosphate wasting and inappropriately low serum $1,25(OH)_2D_3$ levels. Moreover, FGF23 can also induce 24-hydroxylase, which degrades $1,25(OH)_2D_3$.[10,21]

Absorbed phosphate enters the extracellular phosphate pool, which is in equilibrium with bone and soft tissue. In growing infants, the amount of phosphorus excreted is less than the net amount absorbed owing to the deposition of phosphorus in soft tissues and bone. In infants, phosphorus will preferentially go to soft tissue with a weight-to-weight nitrogen-to-phosphorus ratio of 15 : 1 and to bone with a weight-to-weight calcium-to-phosphorus ratio of 2.15 : 1. The residual phosphorus constitutes the renal phosphorus load influencing plasma concentration and urinary excretion. In the face of a limited total phosphorus supply, bone mineral accretion may be limited, leading to significant calcium excretion associated with very low urinary excretion of phosphorus. This particular situation is illustrated in Fig. 87.2, showing calcium and phosphorus metabolism in term infants fed human milk or formula.

Because the amount of Pi filtered through the glomeruli greatly exceeds intestinal absorption, it is the tubular reabsorption that determines Pi serum level. Bedside assessment of Pi renal handling is done by fasting spot urine and serum measurements of Pi and creatinine, calculating the tubular reabsorption of phosphate (TRP) or the renal threshold for Pi ($TmPO_4$/GFR). The first is based on the concept that:

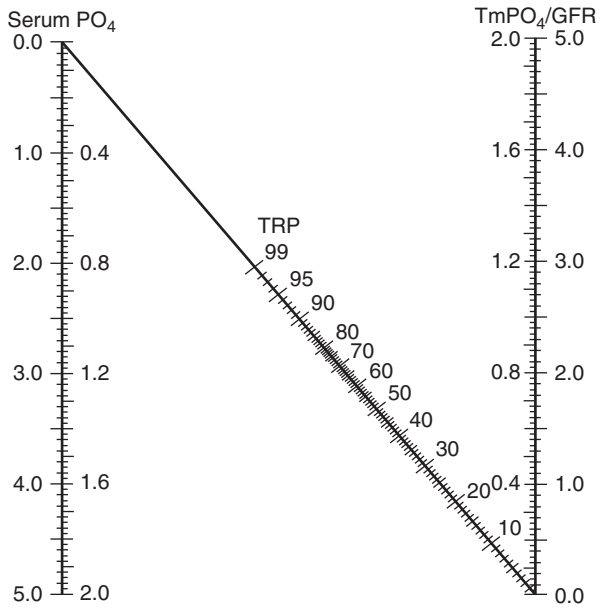
$$\text{TRP}\,(\%) = (1 - \text{Pi clearance}/\text{creatinine clearance}) \times 100$$

By dividing clearance / clearance, the time and volume are redundant, and

$$\text{TRP}\,(\%) = (1 - \text{Up} \times \text{Scr}/\text{Sp} \times \text{Ucr}) \times 100.$$

(Up, Urinary phosphorus; Scr, serum creatinine; Sp, serum phosphorus; Ucr, urine creatinine; Pi, inorganic phosphate.)

The normal range for TRP is 80%-90%; low values indicate phosphaturia, such as in hyperparathyroidism or hypophosphatemic rickets; high values designate enhanced Pi reabsorption, such as in hypo- or pseudohypoparathyroidism. In the presence of abnormally high or low serum Pi, renal reabsorption decreases or increases, respectively. The TRP becomes, therefore, a lesser value in such conditions, and $TmPO_4$/GFR is calculated. $TmPO_4$, the tubular threshold for Pi reabsorption, reflects the highest serum Pi levels that will result in complete reabsorption of the filtrated Pi load. The nomogram developed for that purpose almost four decades ago is still a useful bedside tool (Fig. 87.5).[71]



• **Fig. 87.5** Nomogram reflecting the highest serum inorganic phosphate (Pi) levels that will result in complete reabsorption of the filtrated Pi load. GFR, Glomerular filtration rate; TRP, tubular reabsorption of phosphate; $TmPO_4$, maximal rate of tubular reabsorption of phosphate. (From Walton RJ, Bijvoet OL. Nomogram for derivation of renal threshold phosphate concentration. *Lancet*. 1975;2(7929):309-310.)

Intake

Mature human milk contains about 140 mg of phosphorus per liter. To avoid the occurrence of hypocalcemia or hypercalcemia resulting from an unbalanced diet containing the minimal calcium combined with the maximal phosphorus content, or the inverse, the Life Sciences Research Office and the Scientific Committee on Food of the European Commission recommend that the calcium-to-phosphorus ratio be maintained at more than 1.1 : 1 but less than 2.0 : 1.[5,36] The AAP recommended intakes of 75-140 mg/kg per day of phosphorus for very low birth weight (VLBW) infants.[1] Infants and children receiving amino-acid-based elemental formula as their sole source of nutrition may be at risk for hypophosphatemia and skeletal disease.[25]

Magnesium Physiology

The skeleton represents the largest magnesium store (60%), which is divided into two compartments: one firmly bound to apatite and nonmobilizing, and the other absorbed to the surface of the mineral crystals and contributing to magnesium homeostasis. The remaining magnesium is distributed in skeletal muscle, the nervous system, and other organs

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with a high metabolic rate. Magnesium is the second-most abundant intracellular cation, playing a crucial role in many physiologic functions. It is critical in energy-requiring metabolic processes, protein synthesis, membrane integrity, nervous tissue conduction, neuromuscular excitability, muscle contraction, hormone secretion, and intermediate metabolism.

Serum Magnesium

In serum, about one-third of the magnesium is bound to protein, mainly albumin; the remaining two-thirds is ultrafilterable, being about 92% free and 8% complexed to citrate, phosphate, and other compounds. The plasma magnesium concentration is elevated in preterm and term infants (0.8 ± 0.16 mmol/L, or 2.0 ± 0.4 mg/dL) and decreases soon after infancy to adult values. The sum of ionized and complexed magnesium constitutes its diffusible or ultrafilterable form. Although the concentration of this form of magnesium in plasma remains almost constant (0.45 ± 0.1 mmol/L, or 1.1 ± 0.2 mg/dL), the proportion of this diffusible form in relation to total magnesium increases progressively with age (preterm newborn infants, 52%; term newborn infants, 62%; infants, 66%).

Placental Transport

Magnesium freely crosses the placental barrier and accumulates in the fetus mainly during the first trimester of pregnancy. Placental transfer continues throughout gestation at a daily rate of 3-5 mg. The transfer of magnesium across the placenta depends on an active transport mechanism different from that of calcium, which is necessary to maintain higher fetal than maternal concentrations. Situations of magnesium excess or deficiency in the mother are also reflected in the fetus.

Intestinal Absorption

About 40% of ingested magnesium is absorbed in the intestine, mainly in the proximal parts. There are two mechanisms of absorption: one is passive and the other active and saturable. Passive absorption occurs by means of a paracellular pathway, following a favorable electrochemical gradient as a function of water and solute movement, and appears to be proportional to dietary intake. Regulated, active transport depends on a saturable carrier present in the luminal membrane and operates only under conditions of low magnesium intake. The factors regulating the intestinal absorption of magnesium are largely unknown. The magnesium concentration in the digestive tract is the most important determinant of the amount of magnesium absorbed, nevertheless. Substances that increase magnesium solubility favor its absorption, whereas substances that form insoluble complexes decrease its likelihood. Magnesium absorption in the gut is not regulated by $1,25(OH)_2D_3$.

Renal Excretion

The kidney plays a major role in magnesium homeostasis. It conserves magnesium in response to a deficiency and increases excretion in proportion to the load presented to the kidney. About 70%-80% of serum magnesium is filtered through the glomerular membrane, but only 5%-15% of the filtered magnesium is reabsorbed along the proximal tubule, which is considerably less than the amount of fractional reabsorption of sodium or calcium. The primary site for magnesium reabsorption is the thick ascending limb of the loop of Henle, where about 65% of the filtered magnesium is reabsorbed. When the magnesium intake is severely restricted in humans with normal kidney function, urine output decreases. Supplementing a normal intake increases urinary excretion without altering normal serum levels as long as renal function is normal and the amounts given are not excessive. Overall, the tubular reabsorption of magnesium is a process that is quantitatively limited; the maximal rate of this reabsorption appears to be lower than that of calcium and phosphorus.

Renal homeostasis of magnesium is regulated by many hormonal and nonhormonal factors. The hormonal factors interact to modify the transepithelial electric gradient, tubular permeability at the level of the loop of Henle, or mechanism of active transport at the level of the distal convoluted tubule. Calcitonin, glucagon, vasopressin, PTH, and insulin all increase the tubular reabsorption of magnesium. The nonhormonal factors include the concentration of magnesium in the tubular lumen, acid-base equilibrium, and plasma concentrations of potassium and inorganic phosphate. The tubular reabsorption of magnesium is closely linked to that of calcium. It has been recently shown that epithelial cells of the loop of Henle and the distal convoluted tubule have receptors that sense the extracellular concentrations of both Mg^{2+} and Ca^{2+}. Metabolic acidosis also increases the urinary excretion of magnesium. Daily urinary excretion in normal children oscillates between 1.6 and 2.8 mg/kg of body weight daily. An increased value observed during infancy does not represent a higher excretion of magnesium but is related to the diminished excretion of creatinine per unit of lean body mass during this age period.

Intake

Mature human milk contains about 26 mg of magnesium per liter.[32] Guidelines for infant formulas during the first 6 months of life recommend minimal and maximal contents of 4-5 mg and 15-17 mg/100 kcal, respectively. For preterm infants, the recommendations are based on fetal accretion rates, and values similar to those at term have been suggested (6.8-17 mg/100 kcal and 7.9-15 mg/kg per day, respectively).[5,32,36,59,70]

Hormonal Regulation of Mineral Metabolism

Parathyroid Hormone

The parathyroid glands, through the secretion of PTH, regulate serum calcium concentrations and bone metabolism.

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PTH is synthesized as a larger (115-amino acid) precursor (prepro-PTH) but is stored and secreted mainly as an 84-amino acid peptide, with the 1-34,N-terminal portion conferring bioactivity.[46]

Effects

Parathyroid hormone increases serum calcium concentrations directly by increasing bone resorption and renal calcium reabsorption and indirectly by increasing renal synthesis of $1,25(OH)_2D_3$, thereby increasing intestinal calcium absorption. In addition, PTH lowers serum phosphorus concentrations through its phosphaturic action on the renal proximal tubule. This action minimizes the possibly adverse effect of hyperphosphatemia related to bone resorption on calcium homeostasis.

Regulation of Hormonal Secretion

Serum calcium concentration regulates PTH secretion; high concentrations inhibit the secretion of PTH, and low concentrations stimulate it. Low or falling serum calcium concentrations act within seconds to stimulate PTH secretion, initiated by means of a calcium-sensing receptor on the surfaces of parathyroid cells. This receptor is expressed in the parathyroid glands, where it regulates PTH secretion, and in the kidneys, where it regulates tubular calcium reabsorption. Decreases in ionized calcium of as little as 0.4 mmol/L stimulate PTH secretion, and increases suppress it. Acute decreases in magnesium concentrations also stimulate PTH secretion, and increases depress it. However, chronic magnesium deficiency paradoxically decreases PTH secretion, probably by altering the calcium-sensitive, magnesium-dependent adenylate cyclase involved in PTH secretion.[40]

Vitamin D and its metabolites 25-OHD and $1,25\text{-}OH_2D$, acting through vitamin D receptors, decrease the level of PTH mRNA. The human calcium receptor gene contains six exons and is located at 3q13.3-21 (*Online Mendelian Inheritance in Man*, OMIM, 601199). In the parathyroid gland, the calcium receptor mediates inhibition by extracellular Ca^{2+} concentration of PTH secretion, of *PTH* gene expression, and of parathyroid cellular proliferation. In the kidney, the receptor mediates the direct inhibition of the reabsorption of divalent cations in the thick cortical ascending limb of the loop of Henle.[62] Inactivating or activating mutations of this receptor cause inherited human conditions.

Both activating and inactivating calcium-sensing receptor (CaSR) mutations have been identified. Loss-of-function CaSR mutations lead to familial hypocalciuric hypercalcemia, which is an autosomal dominant condition usually characterized by mild degrees of hypercalcemia, inappropriately normal PTH levels, and low (or inappropriately low) urinary calcium excretion. Gain-of-function CaSR mutations are associated with dominant hypocalcemic hypercalciuria. Some cases of nonfamilial idiopathic hypoparathyroidism may also be caused by gain-of-function CaSR mutations.

Fetal Parathyroid Function

Maternal immunoreactive PTH, like other polypeptide hormones, does not cross the placenta. Concentrations of PTH increase from the first to the second trimester, declining again in the third trimester to the levels of the first trimester. However, PTH is significantly increased postpartum. In contrast, PTHrP concentrations increase continuously throughout pregnancy and lactation. Human parathyroid glands are functionally active as early as 12 weeks of gestation. However, fetal parathyroid glands are functionally suppressed by high intrauterine calcium concentrations, and PTH levels in cord blood are frequently below the detection limit. Loss of PTH has no effect on overall fetal growth (crown-rump length, weight); loss of PTHrP has a modest effect on fetal growth; loss of PTH and PTHrP has a more pronounced effect on fetal growth; and loss of the PTH1 receptor causes the most marked fetal growth restriction.

Maternal hyperparathyroidism results in maternal hypercalcemia, which leads to fetal hypercalcemia and suppression of fetal and neonatal parathyroid glands. Conversely, untreated maternal hypoparathyroidism leads to maternal hypocalcemia, fetal hypocalcemia, and secondary fetal and neonatal hyperparathyroidism.

Neonatal Parathyroid Function

After birth, with the abrupt termination of the maternal calcium supply, serum calcium in the newborn decreases, and serum PTH increases correspondingly. Both term and preterm infants may show a PTH response to falling serum calcium. Infants with VLBW have a decreased PTH surge compared with full-term infants. Infants of diabetic mothers may have impaired PTH production during the beginning days of life. Infants with severe perinatal depression may also have decreased PTH responses to hypocalcemia.

Parathyroid Hormone Reference Values

Current assays for serum PTH are conducted at two sites that are designed to detect both amino-terminal and carboxy-terminal epitopes of the peptide. PTH molecules that are reactive in these two-site immunoassays are considered intact.

In full-term newborn infants, serum PTH concentrations tend to be low in cord blood but increase within the first 48 hours of life in response to the decrease in serum calcium. In preterm infants, PTH concentrations increase immediately after birth, indicating that, in them, the secretion of the hormone responds physiologically to the hypocalcemic stimulus. This increase in PTH concentration could be blunted when premature infants receive calcium by infusion, with the calcium load buffering the postnatal depression of serum calcium. By day of life 10, the serum concentrations of intact PTH return to euparathyroid values (Table 87.4). The multiplication factor for serum PTH from picograms per deciliter to picomoles per liter (pg/dL to pmol/L) is 0.11.

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TABLE 87.4 Evolution of Intact Parathyroid Hormone (1-84), Carboxy-Terminal Parathyroid Hormone, and Vitamin D–Binding Protein Concentrations in 15 Preterm Infants

	PTH (1-84) (pmol/L)	cPTH (pmol/L)	DBP (μmol/L)
Cord serum	11 ± 3	48 ± 8	4.43 ± 0.37
Day 1	66 ± 11*	125 ± 15*	4.40 ± 0.34
Day 2	87 ± 11*	168 ± 5*	4.96 ± 0.23
Day 5	67 ± 9*	152 ± 16*	6.21 ± 0.26*
Day 10	23 ± 4	69 ± 6	6.03 ± 0.30*
Day 30	38 ± 7	80 ± 11	5.16 ± 0.23

cPTH, Carboxy-terminal PTH; DBP, vitamin D-binding protein; PTH, parathyroid hormone.
*Significantly different from cord serum, $P < .05$.
Data from Salle BL, et al. Perinatal metabolism of vitamin D. *Am J Clin Nutr*. 2000;71:1317S.

Vitamin D

Synthesis and Metabolism

Vitamin D is synthesized endogenously in the skin (cholecalciferol or vitamin D_3) after sunshine exposure to high-energy ultraviolet photons (ultraviolet B, 290-315 nm) or is absorbed from dietary sources in the duodenum and jejunum as either vitamin D_3 (from animal sources) or vitamin D_2 (ergocalciferol, from vegetable sources). Regardless of its origin, vitamins D_2 and D_3 are transported bound to the vitamin D–binding protein to the liver, where it is hydroxylated at carbon 25 to form vitamin D_3 (25(OH)D_3, or calcidiol), the most abundant vitamin D metabolite. The generation of calcidiol is regulated by CYP2R1.[14] Circulating concentrations of 25(OH)D_3 provide a useful index of vitamin D status (reflecting both dietary intake and sunshine exposure). Subsequently, 25(OH)D_3 is further hydroxylated at carbon 1 to form the final active metabolite, 25-hydroxyvitamin D_3-1α-hydroxylase (1α-hydroxylase), which is classically expressed in the kidney. However, 1,25$(OH)_2D_3$ can also be synthesized by various cells, including monocytes and skin cells, as well as by the placenta during pregnancy.

Effects

Normal vitamin D status is necessary to maintain calcium and phosphorus homeostasis. The effects of 1,25$(OH)_2D_3$ (calcitriol) on target tissues are initiated by its binding to a steroid receptor (vitamin D receptor) distributed in numerous tissues, leading to the synthesis of a variety of proteins. Therefore 1,25$(OH)_2D_3$ acts on the small intestine, increasing the absorption of calcium and phosphorus by the synthesis of calcium-binding (calbindin-D) proteins; on bone, mobilizing calcium and phosphorus by increasing the number of osteoclasts; and on the kidney, increasing calcium reabsorption in the distal nephron segments by increasing the expression of the epithelial calcium influx channel.

Regulation of Secretion

Renal 1-hydroxylation, which leads to the active metabolite, is tightly regulated. The main factors increasing the synthesis of calcitriol through stimulation of renal 25(OH)D_3-1α-hydroxylase are PTH, PTHrP, hypocalcemia, hypophosphatemia, and other hormonal factors such as IGF-1, estrogen, prolactin, and growth hormone. The production of calcitriol is inhibited by elevated serum levels of calcium and phosphorus and by FGF23.[58]

Fetal Vitamin D Function

Serum 25(OH)D concentration depends on vitamin D intake and production. The production of vitamin D is influenced by geographic location, season, skin pigmentation, and latitude. Vitamin D deficiency is very common during pregnancy, especially in areas with a prolonged winter season.[35] It is lower in African-American pregnant women in contrast to Caucasian pregnant women. In the United States, nearly half of African-American pregnant women are vitamin D deficient with a serum 25(OH)D less than 37.5 nmol/L, as opposed to less than 30% of Caucasian women.[12,31]

The serum 1,25-dihydroxyvitamin D concentration increases from the beginning of pregnancy. In humans, a proportion of the circulating active metabolite appears to be derived from maternal decidual cells, but increased 1,25$(OH)_2D$ synthesis by the mother's kidneys is not excluded. In addition, serum concentrations of vitamin D–binding protein increase during pregnancy.

Cord concentrations of the major vitamin D metabolites are consistently lower than those measured in the mother's serum. Placental venous 25(OH)D concentrations correlate significantly with those found in the maternal circulation, suggesting that calcidiol easily diffuses across the placental barrier and that the vitamin D pool of the fetus depends entirely on that of the mother. Most of the 1,25$(OH)_2D$ in fetal plasma is owing to fetal kidney activity, as suggested by studies in fetal plasma from infants with renal agenesis.

In undernourished populations with vitamin D deficiency, osteomalacia in the mother and abnormal skeletal metabolism in the fetus and infant have been reported. Infants of severely malnourished mothers may be born with rickets and can suffer fractures during the neonatal period. Therefore, bone mass of the newborn infant may be related to the vitamin D status of the mother. Comparison of the results of dual-energy x-ray absorptiometry (DEXA) from different countries shows that infant whole-body bone mineral content values are lower in countries in which milk products are not supplemented with vitamin D than in those in which milk products are supplemented. In contrast, vitamin D supplementation of malnourished mothers results in improved growth of the fetus and child in terms of both birth weight and subsequent linear growth during infancy. Moreover, maternal vitamin D status during

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pregnancy may have influence on the fetal skeletal development starting as early as 19 weeks' gestation and can persist long after infancy.[45] At the age of 9 years, children whose mothers had deficient or insufficient concentrations of 25-OHD in late pregnancy had a reduced bone size and bone mineral content.[33]

Maternal vitamin D deficiency and insufficiency during pregnancy have been associated with an increased risk for preeclampsia, insulin resistance and gestational diabetes mellitus, and primary cesarean delivery.[2,15,48]

Current guidelines from the Institute of Medicine as endorsed by the American Academy of Pediatrics recommend a total dietary and supplement intake (RDA) of 600 IU/day of vitamin D during pregnancy and lactation.[8,31] Although some, including the Canadian Paediatric Society,[26] have suggested higher doses may be preferred, more safety and efficacy research is needed regarding high-dose vitamin D supplementation in pregnancy and lactation. Practitioners seeking to ensure that an adequate dose of vitamin D is transferred via breast milk without providing any supplementation directly to the breastfed infant recommend doses of about 6400 IU/day for mothers. Further studies are needed before this becomes routine policy, but limited data support this approach, especially for women who are breastfeeding and are unwilling or do not desire to give their infant a supplement.[28]

Neonatal Vitamin D Function and Recommendations

Serum or plasma 25(OH)D concentration is a useful vitamin D biomarker reflecting vitamin D supply (exposure) over a period of time. Nevertheless, several surveys show a high rate of poor maternal vitamin D status throughout the world, particularly in countries without vitamin D supplementation, with poor sun exposure, extensive clothing, or with deeply pigmented skin. Thus, the rate of cord blood vitamin D deficiency (<20 nmol/L; <8.3 ng/mL) may reach up to 70% in European populations.[56]

Vitamin D content in human milk is usually low.[31] A daily intake of 400 IU (10 micrograms/day) of vitamin D is recommended by the Institute of Medicine and endorsed by the American Academy of Pediatrics for all infants beginning soon after birth.[8] In addition, vitamin D is metabolized in the liver, and anticonvulsants such as phenobarbital and diphenylhydantoin increase its hepatic catabolism and requirements. There are some questions about what is meant in terms of timing of initiation by the available statements. In most practices, it is considered ideal to begin healthy full-term infants who are being partly or wholly breastfed on vitamin D supplements prior to their hospital discharge or not later than a week of age for those with longer initial hospitalizations.

In preterm infants, as a result of the decrease in serum calcium during the first days of age, the postnatal surge in PTH induces increased synthesis of $1,25(OH)_2D_3$ during the first days of life. Provision of vitamin D_3 increases the 25(OH)D pool of the newborn infant at birth, followed by rapid renal synthesis of $1,25(OH)_2D$ during the early postnatal days. In preterm infants, immaturity of the vitamin D activation pathway, either alone or in combination with other abnormalities, particularly transient hypoparathyroidism, hypercalcitoninemia, and end-organ resistance to its hormonal effects, may promote late neonatal hypocalcemia.

Reference Values

At the present time, consensus has not been reached with regard to the concentration of plasma 25(OH)D to define vitamin D insufficiency. The Institute of Medicine considered a value of 20 ng/mL (50 nmol/L) to be sufficient, and that is the value most commonly used.[31] The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition in 2013 supported a value of 50 nmol/L as defining sufficiency and a concentration below 25 nmol/L (10 ng/mL) as representing severe deficiency in all age groups.[11] Although some groups recommend a minimum 25(OH)D target of 30-32 ng/mL, there are no data to suggest any clear benefit in infants to this higher target.[4] Achieving a plasma 25(OH)D level in all infants above 32 ng/mL would require careful monitoring of blood levels and dosing of some infants with more than 1000 IU/day, which is the currently established safe upper limit in infants less than 6 months of age.[4,23] In contrast, the vast majority of infants will achieve a plasma 25(OH)D of 20 ng/mL with a dose of 400 IU/day.[3] The risk:benefit and cost:benefit ratios of frequent monitoring of blood 25(OH)D levels in large groups of preterm or full-term infants are unclear at this time.[1,53]

Calcitonin

Synthesis and Metabolism

Calcitonin is a 32-amino acid peptide secreted by the thyroidal C cells, which also produce the calcitonin gene-related protein (CGRP). Calcitonin is also produced in other tissues, notably pituitary cells and other neuroendocrine cells in which calcitonin has a local paracrine effect but does not contribute to its peripheral effect. Both the *calcitonin/CGRP* and *PTH* genes are located on chromosome 11. CGRPα is produced throughout the central and peripheral nervous systems, acting as a vasodilator and a neuromodulator. The physiologic effects of CGRPα on bone are unclear.

Effects

The CaSR regulates serum calcium by suppressing the secretion of PTH; it also regulates renal tubular calcium excretion. The CaSR has a dual physiologic response to acute increases in ionized calcium, which includes the inhibition of PTH release, the stimulation of calcitonin release, and the reverse effects in response to a decrease in calcium.

The effects of calcitonin are independent of PTH and vitamin D action. The principal effect of calcitonin is to decrease osteoclastic bone resorption and the amount of calcium and phosphorus released from bone. Additionally,

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calcitonin increases calcium and phosphorus excretion, so the overall effect of calcitonin is to decrease serum calcium and phosphorus concentrations. With regard to magnesium, calcitonin may decrease both its release from bone and renal tubular reabsorption. In humans, serum calcitonin rises during pregnancy, growth, and lactation. It is during these periods of calcium stress that a tonic antiresorptive hormone will best exert its effects to limit skeletal loss and promote mineral accretion. Calcitonin has a very short half-life and is cleared mainly by the kidney.

Fetal Calcitonin Function

Calcitonin is expressed by human thyroidal C cells early in gestation, and it circulates in fetal blood at levels that are higher than those in the mother. In a study using a *calcitonin/CGRP* gene knockout model in mice, McDonald and colleagues suggested that calcitonin and CGRP are not needed for normal fetal calcium metabolism.[47] They may instead regulate some aspects of fetal magnesium metabolism.

Neonatal Calcitonin Function

At birth, serum calcitonin concentrations are higher in cord blood than maternal blood, and they increase further in the first 24 hours of life. Serum calcitonin may be higher in preterm than full-term infants and higher in hypocalcemic preterm infants than normocalcemic ones. Serum calcitonin is also higher in asphyxiated than nonasphyxiated full-term infants. The physiologic importance of the postnatal increase of calcitonin is unclear. It may protect the skeleton from excessive bone resorption; however, it may contribute to neonatal hypocalcemia in some infants. It is uncertain whether calcitonin plays a specific role in neonatal hypocalcemia. Excess calcitonin would not explain the hyperphosphatemia commonly associated with neonatal hypocalcemia.

Bone Development

Ontogenesis

The perinatal development of bone occurs through two separate but interrelated processes: intramembranous and endochondral. Bone is formed in a precursor area occupied by fibrous mesenchyme or in an area of cartilaginous tissue. Intramembranous bone is the first to begin ossification. The elaborated bony trabeculae fuse to form the primary spongiosa. Osteoblasts cover the surface of the spongiosa and deposit new layers of the bone matrix, while new bone is being removed from other surfaces by a special group of multinucleated phagocytic cells called *osteoclasts*.

In contrast, all bones of the appendicular and axial skeleton grow by the transformation of growth plate cartilage into bone through a series of cell and matrix changes referred to as *endochondral ossification*. Calcium salts precipitate in the matrix partitions separating the hypertrophic cells, and capillary buds penetrate the perichondrium and begin to invade the hypertrophic cell area. The hypertrophic cells undergo apoptosis, which is phosphorous dependent and enables capillary invasion and osteoblasts to lay down a thin collar of osteoid around the midsection of the cartilage model.

Therefore, a medullary cavity is formed in the area that will become the midshaft of the long bone, establishing the first center of ossification. The perichondrium is called the *periosteum*. In this vascularized environment, the osteoblasts deposit layers of osteoid on the residual calcified cartilage, and bone tissue gradually replaces the formerly solid mass of cartilage.

Histomorphometric data from femoral metaphyses in fetuses and newborns with gestational ages ranging from 16-41 weeks established morphometric reference data and provided the opportunity to gain insight into long-bone growth in humans. Despite a rapid rate of net bone gain, osteoid indexes were relatively low, indicating that mineralization occurred very rapidly after bone deposition, and then suggesting that modeling, not remodeling, is the predominant mechanism responsible for the development of femoral metaphyseal cancellous bone in utero. Therefore, during fetal life, various environmental factors are specifically oriented to promote growth, high mineral transfer, and increases in the physical mineral density of the skeleton.

Factors Affecting Growth and Mineralization

During gestation, the fetus receives an ample provision of nutritional supply through the placenta. Nitrogen, energy, minerals, and vitamins allow a high velocity of body length growth, representing about 1.2 cm per week during the last trimester of gestation. The fetus maintains its hypercalcemic state in a high calcitonin and estrogen environment, promoting the modeling-to-remodeling ratio in favor of modeling and thus increasing endocortical bone. In addition, according to the mechanostat theory of bone development, fetal bone is also driven by the mechanical force applied to the fetal skeleton during the intrauterine resistance training provided by regular fetal kicks against the uterine wall.[60] Consequently, at term, the newborn skeleton has a high physical density (bone mass divided by bone volume), with elevated cortical thickness and relatively small marrow cavities.

Various factors influence the processes of growth, mineralization, and bone structure. Growth is directly related to protein and energy supplies but also to the hormonal environment comprising insulin, IGF-1, and IGF-2, among others. Bone formation, mineralization, and structure are related to mineral supply and hormonal factors such as PTH, vitamin D, and calcitonin, as well as others, such as genetics and physical activity. Several factors have been found to have a significant impact on newborn bone mineral content and developing fetal bone.[52] Reduced calcium supply, vitamin D deficiency, ethanol consumption, and smoking during pregnancy are all factors affecting fetal skeletal development in addition to low weight related to gestation and diabetes in the mother.

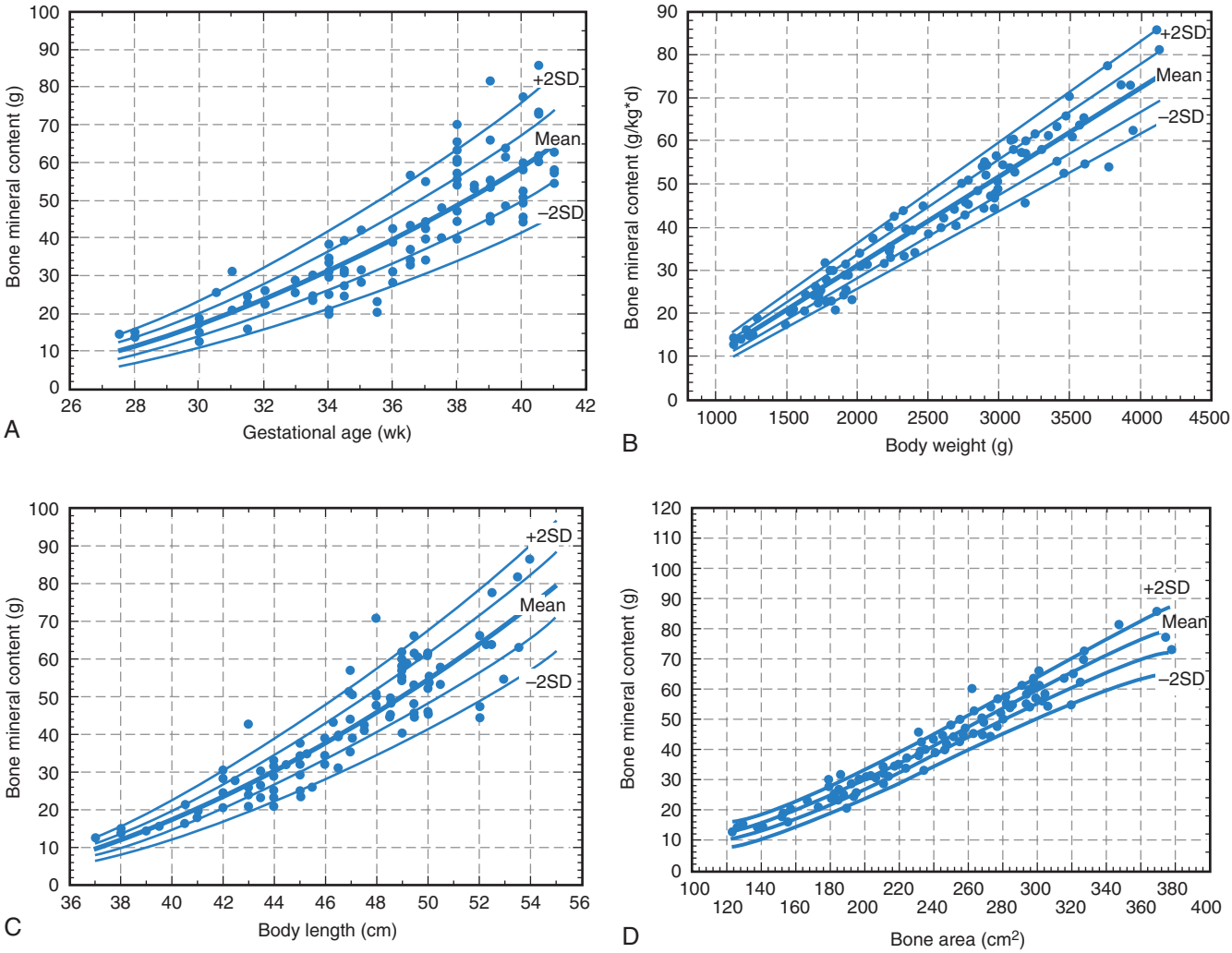
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Evaluation of Fetal Mineral Accretion

From studies in stillborn infants and other cadavers, it appears that in preterm and term infants who are appropriate for gestational age, whole-body calcium accretion is exponentially related to gestational age and linearly related to body weight. Similar values have been obtained with the use of neutron activation techniques.[20]

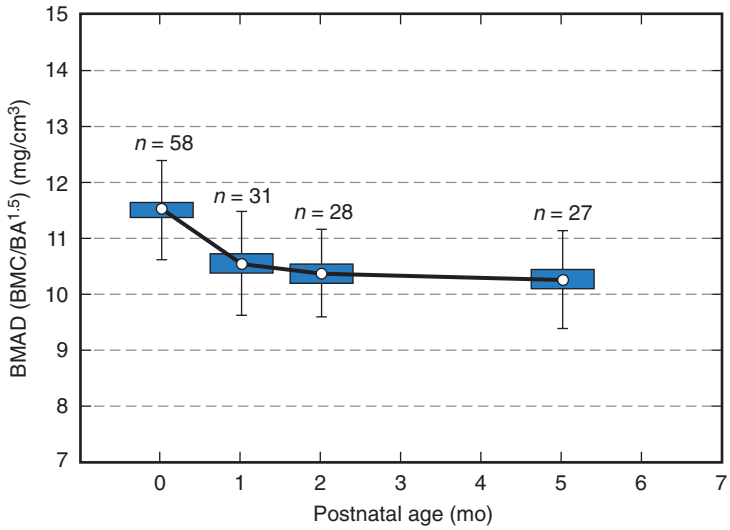
Dual-energy x-ray absorptiometry is becoming the most accurate and precise noninvasive technique for assessing bone mineralization in vivo. Normative data for bone mineral content (BMC) and projected bone area in 106 healthy preterm and term infants near birth have been established (Fig. 87.6).[61] Bone area and BMC are positively related to body weight, body length, and gestational age. However, in multivariate analysis, body weight was the major and also the only significant predictor of those parameters. The high level of agreement between the in vivo calcium estimations and reference values suggests that the translation equation calculated in newborn piglets may generally be applied to newborn infants scanned with identical equipment soon after birth. Normative data for preterm and newborn full-term infants are extremely limited and the results frequently difficult to compare because of the different equipment and software used.[38]

Quantitative ultrasound (QUS) has been proposed as a diagnostic tool to evaluate bone mineralization in newborn infants. It measures the speed of sound (SOS) propagation through the bone, which reflects mainly the cortical bone density. Advantages of QUS include being nonionizing, inexpensive, and portable. At birth, there is a significant correlation between tibial SOS values and gestational age, birth weight, and birth length. The SOS values are significantly lower in preterm infants at birth compared with term infants and appear to fall when measured longitudinally in preterm infants. The relationship between SOS values and biochemical markers of osteopenia of prematurity is uncertain. QUS may have potential uses to assess bone health in



• **Fig. 87.6** Reference values for bone mineral content related to gestational age (**A**), body weight (**B**), body length (**C**), and projected bone area (**D**) determined at birth in preterm and term infants (N = 106). (From Rigo J, et al. Reference values of body composition obtained by dual energy X-ray absorptiometry in preterm and term neonates. *J Pediatr Gastroenterol Nutr*. 1998;27:184.)

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• **Fig. 87.7** Change in bone mineral apparent density (BMAD) according to postnatal age in healthy term infants (*N* = 144). BMC, Bone mineral content; BA, bone area.

the newborn, but it is not widely available, nor has it gained traction in clinical use.[9]

Physiologic Skeletal Changes in the Early Postnatal Period

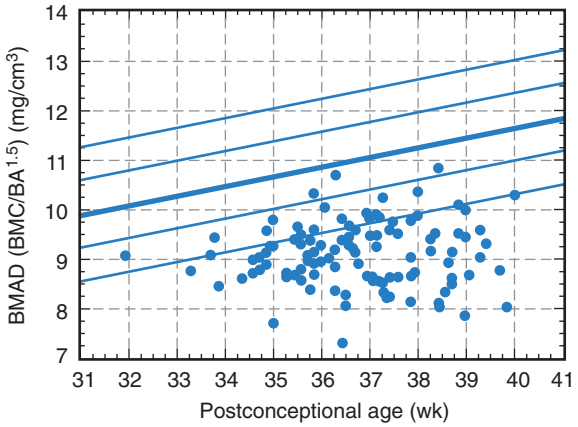
Term Infants

After birth, the switch from placental to dietary minerals causes the relatively hypercalcemic fetus to become a relatively hypocalcemic neonate, inducing a stimulation of PTH secretion. This leads to a large reduction in calcium availability for bone mineralization compared with the prenatal situation. The hormonal environment changes postnatally, because the placental supply of estrogen and many other hormones has been cut off. In addition, mechanical stimulation is likely to be lower postnatally. Therefore, there is a need for postnatal adaptation of the skeleton, and some of the factors implied in the fetal modeling-to-remodeling ratio disappear, inducing an increase in endosteal bone resorption. The physical density of long bones such as the femoral diaphysis decreases by about 30% during the first 6 months of life. This change is mostly the result of an increase in marrow cavity size, which is faster than the increase in the cross-sectional area of the bone cortex.

In term infants, these postnatal changes have been classically called *physiologic osteoporosis of infancy*, but they appear to occur without an increase in bone fragility. This phenomenon is well illustrated by the evolution of bone mineral apparent density (BMAD, g/cm^3) during fetal life, in which there is a continuous increase that contrasts with that obtained from birth to the first months of life, at which time a rapid reduction in BMAD is observed (Fig. 87.7).

Very Low Birth Weight Infants

The goal of feeding regimens for VLBW infants is to obtain a prompt postnatal resumption of growth to a rate approximating intrauterine growth. Postnatal adaptations of the skeletal system to extrauterine conditions also occur in premature infants, with the difference being that they take place earlier than they do in term babies. The process of birth interrupts fetal bone mineralization and, combined with the reduction in calcium availability, contributes to a reduction in bone physical density. These postnatal changes have been classically called osteopenia of prematurity, and these changes can be accompanied by an increase in bone fragility and the risk for fracture. In this situation, there is a sharp postnatal decrease in bone mineral areal density during the early postnatal weeks of life up to discharge near term (Fig. 87.8). Radiologically, however, identifying "osteopenia" is difficult and its clinical interpretation is uncertain. Thus, an emphasis on clearly defining infants as having rickets may be more clinically relevant.[1]



• **Fig. 87.8** Comparison between bone mineral apparent density (BMAD) at discharge in infants with very low birth weight (•, *N* = 108) and reference values (regression lines, *N* = 106). BMC, Bone mineral content; BA, bone area.

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Clinical Conditions Associated With Calcium Disturbances

Neonatal Hypocalcemia

Neonatal hypocalcemia has been variously defined as a total serum calcium level of less than 2 mmol/L (8 mg/dL), less than 1.87 mmol/L, or less than 1.75 mmol/L. This variance in definition is at least partially due to the lack of clinical signs in many neonates, even at a very low serum total calcium concentration.

A better definition of neonatal hypocalcemia would be based on the metabolically active component of calcium, ionized calcium, because changes in ionized calcium concentration are more likely to have physiologic significance. Under conditions of normal acid-base status and normal albumin levels, the serum total calcium level and Ca^{2+} are linearly correlated, so total serum calcium measurements remain useful as a screening test. However, because Ca^{2+} is the physiologically relevant fraction, in sick infants, it is preferable to directly determine Ca^{2+} in freshly obtained blood samples.

Neonates at the greatest risk for symptomatic or asymptomatic neonatal hypocalcemia, such as the infants of diabetic mothers or preterm or asphyxiated neonates, are frequently sick for a multitude of reasons, and the contribution of neonatal hypocalcemia to signs related to their primary illness can be easily obscured. From a clinical viewpoint, because Ca^{2+} concentrations are maintained within narrow ranges under normal circumstances, the potential risk for disturbances of physiologic function increases as the Ca^{2+} concentration decreases. A useful approach to the classification of neonatal hypocalcemia is by time of onset. The early and late forms of hypocalcemia have different causes and occur in different clinical settings.

Early Hypocalcemia

See Box 87.1 and Box 87.2.

Term Infants

Early neonatal hypocalcemia occurs during the first 4 days of life and represents an exaggeration of the normal fall in serum calcium concentration that occurs during the first 24-48 hours of life. At birth, there is an interruption of maternal calcium supply, and the serum calcium concentration in infants is maintained by either the increased calcium flux from bone or sufficient exogenous calcium intake. Trabecular bone, which is richly vascularized, represents the main source of potentially rapidly mobilized calcium. Because intestinal calcium absorption is correlated with intake, and dietary calcium is usually low on the first day of life, the serum calcium concentration decreases on the first day of life.[30]

Normal serum concentrations for Ca^{2+} in full-term newborns reach a nadir at about 24 hours of age (1.10-1.36 mmol/L or 4.4-5.4 mg/dL) and rise slowly thereafter. In full-term infants, hypocalcemia is usually defined as an ionized calcium concentration of less than 1.10 mmol/L (4.4 mg/dL), which is the standard nadir in normal infants. This concentration represents two standard deviations below the mean at 24 hours. This definition is a statistical one and is based on assumptions of normal distributions of

• BOX 87.1 Causes of Neonatal Hypocalcemia

Early Hypocalcemia (1-4 Days of Age)

- Prematurity
- Maternal diabetes
- Perinatal stress, asphyxia
- Intrauterine growth restriction
- Maternal anticonvulsants

Late Hypocalcemia (5-15 Days of Age)

- Hyperphosphatemia (high phosphate load, advanced renal insufficiency)
- Hypomagnesemia
- Vitamin D deficiency
- Parathyroid hormone resistance (transient neonatal pseudohypoparathyroidism)
- Hypoparathyroidism
- Primary: parathyroid agenesis, 22q11 deletion, parathyroid hormone gene mutation
- Secondary: maternal hyperparathyroidism
- Calcium-sensing receptor defects, autosomal dominant hypocalcemic hypercalciuria
- Acquired or inherited disorders of vitamin D metabolism
- Neonatal hypocalcemia associated with skeletal dysplasia
- Other causes (alkalosis, citrated blood transfusions, phototherapy, viral gastroenteritis, lipid infusions)

• BOX 87.2 Diagnostic Steps for Hypocalcemia

History

- Family
- Pregnancy (diabetes mellitus, hyperparathyroidism, intrapartum events, fetal distress, asphyxia)
- Nutritional supplies of the newborn infant

Physical Examination

- Jitteriness, apnea, cyanosis
- Seizures
- Associated features (prematurity, dysmorphism, congenital heart defect)

Investigations

- Total serum and ionized calcium, magnesium, phosphorus, glucose
- Acid-base balance
- Chest radiograph (e.g., thymic shadow, aortic arch position)
- Urinary calcium, magnesium, phosphorus, creatinine, drug screen
- Vitamin D metabolites
- Parathyroid hormone
- Calcitonin
- Others (e.g., malabsorption, lymphocyte count, T-cell numbers and function, maternal and family screening, molecular genetic studies)
- Genetic studies for chromosome 22q11 deletion

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physiologic variables. Further investigation needs to define physiologically important limits for term and preterm neonates. Characteristically, early neonatal hypocalcemia occurs most frequently in preterm infants, infants with evidence of respiratory depression at birth, infants of diabetic mothers, infants with significant growth restriction, and infants of mothers treated with anticonvulsants during pregnancy.

In preterm infants, the reference values for ionized calcium are available only for moderately premature infants who show values very similar to those for full-term infants. These cutoff values might not apply to smaller infants. Clinical symptomatology is rarely, if ever, identified in a VLBW infant with an ionized calcium greater than 0.80 mmol/L, although few recent data are available regarding this issue.

Preterm Infants

The frequency of hypocalcemia varies inversely with birth weight and gestational age. In preterm infants, the postnatal decrease in the serum calcium level typically occurs more rapidly than it does in term infants, the magnitude of the depression being inversely proportional to gestation. The fall in Ca^{2+} is not proportional to that in total calcium concentration, and the ratio of ionized to total calcium is higher in these infants. The reason for the maintenance of Ca^{2+} is uncertain but is probably related to low serum protein concentration and pH associated with prematurity. The sparing effect of Ca^{2+} may partially explain the frequent lack of signs in preterm infants with low total calcium levels.

Early neonatal hypocalcemia apparently results from the abrupt interruption of the placental supply and the low intake provided by oral and parenteral nutrition and also by the insufficient release of PTH by immature parathyroid glands or the inadequate responsiveness of the renal tubular cells to PTH. An exaggerated rise in calcitonin secretion in premature infants may play a contributory role.[30] In VLBW infants, the high renal sodium excretion probably aggravates calciuric losses, and relative end-organ resistance to $1,25(OH)_2D_3$ may exist.

Hypocalcemia is temporary, and usually the serum calcium concentration gradually reverts to normal after 1-3 days. Factors contributing to serum calcium normalization include increased calcium intake with feedings, increased renal phosphorus excretion, and improved parathyroid function.

Maternal Diabetes

Infants of diabetic mothers (IDMs) (see Chapter 18) have an exaggerated postnatal drop in circulating calcium levels compared with controls of gestational age. Prematurity and birth asphyxia are frequently associated problems that independently increase the risk for hypocalcemia. In IDMs, hypocalcemia may be related to hypomagnesemia, the maternal form of which is caused by urinary magnesium losses with diabetes and leads to fetal magnesium deficiency and secondary functional hypoparathyroidism in the fetus and newborn. Hypocalcemia in IDMs is also correlated with the severity of maternal diabetes. The natural history is usually similar to that of early neonatal hypocalcemia in preterm infants, but hypocalcemia sometimes persists for several additional days. Improved metabolic control for pregnant diabetic women has markedly diminished the occurrence and severity of early neonatal hypocalcemia in IDMs. As with IDMs, infants of gestational diabetic mothers are at increased risk of hypocalcemia related to hypomagnesemia.

Severe Cardiorespiratory Depression at Birth

In these infants, the following factors may contribute to early hypocalcemia: a decreased calcium intake owing to delayed feedings, an increased endogenous phosphorus load resulting from the reduction of the glomerular filtration rate, and an increased serum calcitonin concentration. Hyperphosphatemia may induce relative PTH resistance. Theoretically, the correction of acidosis with alkali may further aggravate hypocalcemia by inducing decreased calcium flux from bone to the extracellular fluid and by lowering the ionized calcium concentration.

Late Hypocalcemia

Hypocalcemia is conventionally considered late when it occurs after the first 3 days of life. Late neonatal hypocalcemia usually develops at about 4-7 days of age (see Box 87.1) and more frequently in term than preterm infants. It is not correlated with maternal diabetes, birth trauma, or asphyxia.

Phosphate Loading

Hypocalcemia induced by an elevated phosphorus supply usually occurs at the end of the first week of life. Late-onset hypocalcemia is considered to be a manifestation of relative resistance of the immature kidney to PTH. In these infants, the renal tubular cells are unable to respond appropriately to PTH, leading to renal retention of phosphorus and hypocalcemia. These biochemical features strongly resemble those of pseudohypoparathyroidism.[30] The normally low neonatal GFR may also play a role in limiting the ability to excrete the phosphorus load. Late hypocalcemia was frequently observed in infants fed cow milk or evaporated milk because of their high phosphorus content. With the introduction of adapted infant formulas, late hypocalcemia, although not abolished, has become uncommon, although it appears to occur more frequently in the Southwestern part of the United States. It may also be more common among Hispanic and male infants, but further information is needed regarding these possibilities.[6,66]

Even using currently marketed infant formulas, formula-fed infants have lower serum ionized calcium and higher serum phosphorus in the first week of life than breastfed infants. These differences correlate with the absolute phosphorus amount but not with the different calcium-to-phosphorus ratios in formulas. The phosphate load increases calcium bone deposition, leading to hypocalcemia. The normal response to hypocalcemia is an increase in PTH secretion, inducing an increase in both the urinary excretion

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of phosphate and the tubular resorption of calcium. The pathogenesis of this transient hypoparathyroidism in late neonatal hypocalcemia is poorly understood. The inadequate secretion of PTH, immaturity of PTH receptors, or transient change in the threshold of CaSR may play an important role. Serum calcium levels frequently increase when these infants are given human milk, lower-phosphate formulas, and calcium supplements. After several days to weeks, serum PTH usually increases, and the infants are able to tolerate a higher dietary phosphate load and routine infant formulas without calcium supplements.

Hypomagnesemia

Neonatal hypocalcemia usually accompanies hypomagnesemia, because magnesium deficiency inhibits the secretion of PTH and reduces responsiveness to its action. Depression of the serum magnesium levels in newborns is caused by primary hypomagnesemia with secondary hypocalcemia or transient hypomagnesemia.

Primary hypomagnesemia with secondary hypocalcemia presents in infancy with persistent hypocalcemia and seizures that cannot be controlled with anticonvulsants or calcium gluconate. It is a rare autosomal recessive disorder resulting from primary defects in the intestinal transport of magnesium. The gene has been segregated to chromosome 9. Serum magnesium is frequently less than 0.8 mg/dL (normally, 1.6-2.8 mg/dL), and circulating levels of PTH are low despite the presence of hypocalcemia. The administration of magnesium to these infants leads to spontaneous parallel increases in serum PTH levels, serum calcium levels, and renal phosphate clearance.

Transient neonatal hypomagnesemia often occurs in association with hypocalcemia. The decrease in the serum magnesium level is usually less severe (0.8-1.4 mg/dL) than that in magnesium transport defects. In many infants with transient hypomagnesemia, the serum magnesium level increases spontaneously as the serum calcium level returns to normal after the administration of calcium supplements.

Transient hypomagnesemia secondary to renal magnesium wasting can be caused by the administration of loop diuretics, aminoglycosides, amphotericin B, urinary tract obstruction, or the diuretic phase of acute renal failure. The disorder may be mistaken for a form of neonatal hypoparathyroidism because of tetany and hypocalcemia or confused with Bartter syndrome (hypokalemic alkalosis with hypercalciuria) because of secondary potassium wasting. The diagnosis can be made by finding low serum magnesium levels with inappropriately high urinary magnesium excretion. A common laboratory feature of magnesium depletion is hypokalemia. Attempts to restore the potassium deficit with potassium therapy alone are usually not successful without simultaneous magnesium therapy.

Neonatal Hypoparathyroidism

The biochemical characteristics of hypoparathyroidism are hypocalcemia and hyperphosphatemia in the presence of normal renal function. Serum PTH concentrations are low or undetectable. The causes of hypoparathyroidism are diverse, representing disruptions of one or more of the steps in the development and maintenance of PTH secretion.

Secondary Hypoparathyroidism Related to Maternal Diseases. This transient condition may occur in the offspring of mothers with hyperparathyroidism or hypercalcemia from any cause. Maternal history may not be contributory, because the maternal disease (usually a benign adenoma) may be asymptomatic and discovered only after the diagnosis is made in the newborn. Maternal hypercalcemia leads to fetal hypercalcemia and secondary fetal hypoparathyroidism. This condition resolves spontaneously in days to weeks, and supportive therapy with calcium, $1,25(OH)_2D_3$, or both, usually suffices, but it may be temporally exacerbated by the feeding of high-phosphate diets.

Developmental Defects in the Parathyroid Glands. The isolated absence of parathyroid gland development may be inherited in an X-linked or autosomal recessive fashion. The most well described example is DiGeorge syndrome. DiGeorge syndrome, or velocardiofacial syndrome, is caused by an embryologic defect in the development of the third, fourth, and fifth branchial pouches and results in hypoparathyroidism. It is also characterized by cardiac defects, cleft palate, dysmorphic facial features, renal and ocular defects, and hypoplasia or agenesis of the thymus in addition to the parathyroid glands. The mutation isolated that causes DiGeorge syndrome is a de novo heterozygous deletion of chromosome 22q11 that includes the gene *TBX1*, which encodes a transcription factor necessary for thymic and parathyroid gland development. The constellation of abnormalities in DiGeorge syndrome has been referred to as CATCH 22 (*c*ardiac defects, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, and *h*ypocalcemia). DiGeorge syndrome is usually sporadic; however, autosomal dominant transmission has also been reported.[37]

Hypoparathyroidism has also been described in the hypoparathyroidism-deafness-renal dysplasia syndrome. In this syndrome, an autosomal dominant mutation leads to reductions in GATA3, a transcription factor essential for parathyroid, renal, and otic vesicular development.

Two other syndromes that include hypoparathyroidism, Kenny-Caffey syndrome and Sanjad-Sakati syndrome, have been described. The former is associated with short stature and ocular and bony abnormalities. Both syndromes have been linked to autosomal recessive loss of function mutations of *TBCE*, a gene involved in microtubule assembly in target tissues. Both syndromes are referred to generally as hypoparathyroidism-retardation-dysmorphism syndrome.[26]

Maternally inherited mitochondrial DNA defects have been associated with hypoparathyroidism in addition to other features as seen in the MELAS syndrome, as well as other disorders including the mitochondrial trifunctional protein deficiency syndrome, and the Kearns-Sayre syndrome.[46] An isolated hypoparathyroid defect has been described caused by mutations in the PTH glial cells missing

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the homolog B (*GCMB*) gene. The *GCMB* gene regulates the development of the parathyroid glands.

Defects in the Parathyroid Hormone Molecule. A few cases of familial hypoparathyroidism have been described in which the cause was a mutation in the gene for PTH that resulted in the synthesis of a defective PTH molecule and undetectable amounts of PTH in serum.

Defective Regulation of Parathyroid Hormone Secretion. Hypocalcemia and hypercalciuria are the chief features of autosomal dominant hypercalciuric hypocalcemia, which is caused by activating mutations of the parathyroid and renal CaSR. These mutations cause excessive calcium-induced inhibition of PTH secretion. Hypocalcemia is usually mild and asymptomatic. When it is mild, it should be treated cautiously, if at all, because raising serum calcium concentrations further increases urinary calcium excretion and may cause nephrocalcinosis.[57]

Hypocalcemia Resulting From Vitamin D Disorder

Maternal vitamin D deficiency is the major risk factor for neonatal vitamin D deficiency presenting as hypocalcemia. Vitamin D deficiency is unusual in countries in which it is common practice to supplement the diet with vitamin D dairy products and other foods. However, it occurs in women in whom both sunlight exposure and the dietary intake of vitamin D are inadequate. At high risk are immigrants from the Middle East or South Asia who continue to wear traditional clothing. Daily supplementation of 400 IU for infants and 600 IU for pregnant and lactating women is recommended in most cases, although this is a topic of ongoing research and controversy and some populations may benefit from higher intakes.[31]

Infantile Osteopetrosis

Osteopetrosis is a rare congenital disorder related to bone resorption abnormalities that may be fatal without hematopoietic stem cell transplantation. Impaired bone remodeling associated with the dysregulated activity of osteoclasts for such a condition may cause bony narrowing of the cranial nerve foramina, which typically results in cranial nerve (especially optic nerve) compression. Abnormal remodeling of primary woven bone to lamellar bone results in brittle bone that is prone to fracture. Therefore, fractures, visual impairment, and bone marrow failure are the classic features of this disease. A number of heterogeneous molecular or genetic defects can result in impaired osteoclastic function. These genetic defects include mutations in the following genes: *Tnfrsf11a* gene (OMIM 259710) that encodes RANK; *OSTM1* (OMIM 607649) that encodes osteopetrosis-associated transmembrane protein 1; *ATP6iTCIRG1* (OMIM 604592) gene that encodes the a3 subunit of the vacuolar proton pump, which mediates the acidification of the bone-osteoclast interface, the chloride channel-7 protein CLCN7 (OMIM 602727), and carbonic anhydrase IICA2 (OMIM 611492). Given that the trabecular bone represents the main source of potentially rapidly mobilized calcium by osteoclasts, osteopetrosis can present as late neonatal hypocalcemia (mean age at presentation, 12 days) and is diagnosed easily based on its typical radiographic features.

Other Causes of Neonatal Hypocalcemia

Bicarbonate therapy, as well as any form of metabolic or respiratory alkalosis, decreases ionized calcium levels and bone resorption of calcium. Transfusion and plasmapheresis with citrated blood can form nonionized calcium complexes, thus decreasing Ca^{2+}. Furosemide and xanthine therapy promotes calciuresis as well as nephrolithiasis. Phototherapy appears to be an additional possible cause of neonatal hypocalcemia, although the mechanism is still uncertain. Lipid infusions may increase serum free fatty acid levels, which form insoluble complexes with calcium. Most of these effects are transient, and cessation of therapy is associated with a return to normal serum calcium levels.

Clinical Manifestations of Hypocalcemia

The clinical manifestations of neonatal hypocalcemia in infants may be easily confused with other neonatal disorders (e.g., hypoglycemia, sepsis, meningitis, asphyxia, intracranial bleeding, narcotic withdrawal). The neonate with hypocalcemia may be asymptomatic; the less mature the infant, the more subtle and varied are the clinical manifestations. In the neonatal period, the main clinical signs of hypocalcemia are jitteriness (increased neuromuscular irritability and activity) and generalized convulsions, although focal seizures have also been reported. Infants may also be lethargic, eat poorly, vomit, and have abdominal distention.

The degree of irritability does not appear to correlate closely with serum calcium values. Furthermore, hypocalcemia may be asymptomatic. Therefore, suspicion of hypocalcemia should be confirmed by the measurement of Ca^{2+}. The diagnostic workup for hypocalcemia (see Box 87.2) includes a history, physical examination, and relevant investigations. In clinical practice, the diagnosis of hypocalcemia is based on the determination of ionized calcium. Serum magnesium should also be measured because hypomagnesemia may coexist and cause identical signs. The measurement of calcium-regulating hormones is not routinely recommended unless hypocalcemia is prolonged, refractory, or recurrent. Chest radiographic examination for a thymic silhouette is indicated if DiGeorge syndrome is suspected. The measurement of QT intervals, corrected for heart rate, has not been shown to be useful for the prediction or management of neonatal hypocalcemia. Assays of calciotropic hormones and plasma 25(OH)D may be useful in the diagnosis of uncommon causes of neonatal hypocalcemia, such as primary hypoparathyroidism, malabsorption, and disorders of vitamin D metabolism but are not routinely needed in many settings such as with VLBW infants who respond to calcium therapy. Molecular genetic studies may be needed to confirm a specific diagnosis and have potentially important clinical relevance for the patient's clinical outcome.

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Other investigations, which are listed in Box 87.2, may be important in the differential diagnosis and understanding of the pathophysiology of hypocalcemia.

Treatment

Early Neonatal Hypocalcemia

The choice of treatment for early neonatal hypocalcemia is complicated by several factors, among them that (1) the condition may coexist with other neonatal complications (e.g., asphyxia, hypoglycemia) that cause similar signs; (2) it may be associated with seizures, which may have a different etiology; and (3) it may remain asymptomatic and in most newborn infants is a self-limited disorder.

Symptomatic Hypocalcemia. The treatment of symptomatic hypocalcemia consists of the administration of calcium salts, either calcium gluconate (usual) or, if more readily available in an emergency, calcium chloride. A 10% solution of calcium gluconate contains about 9.4 mg of elemental calcium per milliliter. In case of seizures, 1-2 mL/kg of calcium gluconate (about 18 mg/kg of elemental calcium) is given intravenously over 10 minutes accompanied by continuous heart rate monitoring. After the resolution of seizures, intravenous calcium solution may be continued at a dose of up to 1.87 mmol/kg (75 mg/kg) of elemental calcium per day until the serum calcium concentrations have remained consistently in the normal range. Thereafter, the intravenous calcium solution can be reduced in a stepwise fashion (e.g., 50% for 4-12 hours, 25% for another 4-12 hours) and then discontinued.

Complications of intravenous calcium therapy include extravasation into soft tissues (with calcium deposition and sometimes cutaneous necrosis) and bradycardia. Because of the many potential risks, arterial infusions of calcium should not be done. However, parenteral nutrition solutions containing standard mineral (including calcium) content can be safely infused through appropriately positioned umbilical venous catheters or percutaneous centrally placed catheters. The direct administration of calcium preparations with bicarbonate results in precipitation and must be avoided.

As an alternative, if infants can tolerate oral fluids and are not actively having seizures, the intravenous form of calcium gluconate can be given orally at the same dose after the initial correction. All calcium preparations are hypertonic, and there is the theoretical potential for precipitating necrotizing enterocolitis in infants at risk for this condition. Calcium absorption in neonates from calcium carbonate may be limited by the higher pH of the neonatal stomach, and other forms, such as calcium glubionate, are commonly used in the neonatal period. The duration of supplemental calcium therapy varies with the course of hypocalcemia. As few as 1-3 days of therapy are usually required. The serum ionized calcium concentration should be assessed frequently during the first few days of treatment and for 1 or 2 days after its discontinuation until the serum total calcium and Ca^{2+} concentrations are stabilized. Persistent hypocalcemia needs further investigation. A poor response to calcium therapy may often result from concurrent magnesium deficiency.

Asymptomatic Hypocalcemia. In asymptomatic hypocalcemia, opinions vary on the need for and intensity of therapy. Some do not favor treatment because, in most cases, hypocalcemia resolves spontaneously with time. However, hypocalcemia has potentially adverse effects on both the cardiovascular system and the central nervous system.

Late Neonatal Hypocalcemia

Because serum calcium is not routinely measured after the first few days of life, late hypocalcemia is usually symptomatic when diagnosed. In phosphorus-induced hypocalcemia, a relatively low-phosphorus infant formula (or human milk) and oral calcium supplementation are indicated to decrease phosphorus absorption and increase calcium absorption.

In hypomagnesemia, the magnesium deficiency usually has to be corrected before hypocalcemia can be treated successfully. Magnesium may be administered intravenously as a 50% solution of magnesium sulfate in a dose of 25 mg/kg with continuous ECG monitoring. The magnesium dose may be repeated every 12 hours, depending on the clinical response and the (monitored) serum magnesium levels. Many infants with transient hypomagnesemia respond sufficiently to one or two doses of intravenous magnesium.

True hypoparathyroidism requires therapy with vitamin D metabolites; $1,25(OH)_2D_3$ (or 1 alpha-hydroxyvitamin D_3, a synthetic analogue that undergoes hepatic 25-hydroxylation) has the advantage of a shorter half-life, and treatment may be more easily tailored to the individual patient. In the CaSR mutation the need for therapeutic correction of hypocalcemia remains an open question, considering that hypercalciuria and nephrocalcinosis may be deleterious to renal function. Attention should be directed toward a number of concomitant treatments. Because thiazide diuretics can increase renal calcium reabsorption, the inadvertent institution or discontinuation of these drugs may increase or decrease, respectively, the plasma calcium level. In contrast, furosemide and other loop diuretics can increase the renal clearance of calcium and depress serum calcium levels. The administration of glucocorticoids antagonizes the action of vitamin D (and the analogues) and may also precipitate hypocalcemia. The development of hypomagnesemia may also interfere with the effectiveness of treatment with calcium and vitamin D.[30]

Prevention of Neonatal Hypocalcemia

The most effective prevention of neonatal hypocalcemia includes the prevention of prematurity and birth depression, including the judicious use of bicarbonate therapy and the prevention of severe maternal vitamin D deficiency. In current clinical practice, early use of intravenous nutrition including protein and calcium for VLBW and other high-risk infants has decreased the need for additional therapy, including boluses of IV calcium. In most cases in which intravenous nutrition including protein is not needed (e.g.,

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• BOX 87.3 Causes of Neonatal Hypercalcemia

Iatrogenic
- Calcium salts, vitamin A
- Hypophosphatemia (prematurity)
- Hypervitaminosis D
- Thiazide diuretics

Disorders of parathyroid function
- Maternal hypocalcemia, hypoparathyroidism
- Mutation of the parathyroid hormone–related protein receptor
- Jansen metaphyseal chondrodysplasia
- Calcium-sensing receptor defects
- Familial hypocalciuric hypercalcemia
- Neonatal severe hyperparathyroidism

Idiopathic infantile hypercalcemia
Hyperprostaglandin E syndrome
Severe infantile hypophosphatasia
Other causes
- Congenital carbohydrate malabsorption
- Distal renal tubular acidosis
- Tumor-related hypercalcemia
- Congenital hypothyroidism
- Williams syndrome
- Subcutaneous fat necrosis
- Blue diaper syndrome

• BOX 87.4 Diagnostic Steps in Hypercalcemia

History
- Familial or maternal calcium or phosphorus disease
- Traumatic birth
- High maternal or neonatal supplies of vitamin D and/or A
- Drugs during pregnancy (thiazide, lithium)

Physical Examination
- Growth restriction
- Lethargy, dehydration
- Seizures, hypertension
- Associated features (e.g., elfin facies, congenital heart disease, mental retardation, subcutaneous fat necrosis)

Investigations
- Total and ionized calcium, phosphorus, magnesium, alkaline phosphatase
- pH, total protein, creatinine
- Urinary calcium, phosphorus, creatinine, cyclic adenosine monophosphate
- Chest and long-bone radiographs
- Renal ultrasound
- Parathyroid hormone, 25-OH vitamin D, 1,25-OH vitamin D
- Ophthalmologic evaluation, electrocardiography (QT interval)
- Others: parathyroid hormone related protein, parental serum calcium and phosphorus concentrations, vitamin A
- Molecular genetic studies

larger preterm infants), it is not necessary to routinely add calcium to glucose-containing solutions from birth.

Neonatal Hypercalcemia

Hypercalcemia is defined as a pathologic elevation in plasma ionized Ca^{2+} concentration greater than 1.45 mmol/L.[30,62] Neonatal hypercalcemia is relatively uncommon in infants greater than 1000 g birth weight, but it needs to be recognized, because it can result in significant morbidity. The clinical symptoms of sustained hypercalcemia are not specific. Infants with mild increases in ionized calcium (<1.60 mmol/L) often fail to show specific symptoms of hypercalcemia. Nonspecific signs and symptoms such as anorexia, vomiting, and constipation, but rarely diarrhea, may occur with moderate to severe hypercalcemia. The presence of seizures, bradycardia, or arterial hypertension is rare. On physical examination, infants may appear dehydrated, lethargic, and hypotonic. Those with chronic hypercalcemia may present with failure to thrive as the principal source of physical distress. Renal function is generally impaired, and polyuria and hypercalciuria are observed. However, renal complications such as nephrocalcinosis, nephrolithiasis, and hematuria may be the earliest clinical manifestations of hypercalcemia.

Iatrogenic Hypercalcemia

Iatrogenic hypercalcemia (Box 87.3 and Box 87.4) is the most common type of hypercalcemia in the newborn and should be considered before starting extensive investigation of rare syndromes. It may result from excessive intravenous calcium administration during total parenteral nutrition or exchange transfusion. Other causes of iatrogenic hypercalcemia are the use of extracorporeal membrane oxygenation, which can cause transient hypercalcemia in up to 30% of infants, and vitamin D intoxication from the administration of excessive vitamin D supplements. It has been shown that idiopathic infantile hypercalcemia (IIH) or "vitamin D intoxication" is a result of mutations in the *CYP24A1* gene (MIM 126065) encoding $25(OH)D_3$. The enzyme 24-hydroxylase is primarily responsible for $1,25(OH)_2D_3$ degradation.[64] The *CYP24A1* gene mutation leads to the increased sensitivity of the patients to even prophylactic doses of vitamin D and to the development of severe symptomatic hypercalcemia in patients with IIH. Conservative therapy includes parenteral rehydration, diuretics, corticosteroids, bisphosphonates, and vitamin D prophylaxis withdrawal. Clinical symptoms generally resolve rapidly after normalization of serum calcium levels.

Vitamin A toxicity is rare and can cause severe hypercalcemia. Because vitamin A is metabolized by the kidney, renal insufficiency may cause toxic accumulation, which probably acts directly on bone to cause increased resorption and hypercalcemia. Moderate hypercalcemia may also be the result of phosphorus deficiency in premature infants receiving unbalanced calcium and phosphorus regimens in oral and parenteral nutrition. In this situation, hypercalcemia is accompanied by hypophosphoremia.

The low phosphorus concentration in human milk causes phosphorus deficiency in very premature infants, leading to a mildly increased calcium concentration and

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hypercalciuria. The absorbed phosphorus is preferentially oriented for soft tissue formation, whereas the remaining phosphorus is insufficient to allow calcium deposition. Hypophosphatemia stimulates renal synthesis of calcitriol, which activates the intestinal absorption and skeletal resorption of calcium and phosphorus. Phosphorus supplementation and the use of human milk fortifiers can prevent hypophosphatemia and hypercalcemia. Similar situations have been reported in infants on parenteral nutrition, providing an unbalanced calcium-to-phosphorus ratio. Additionally, thiazide diuretics reduce renal calcium excretion and may represent a contributing factor.

Congenital Hyperparathyroidism

Neonatal hyperparathyroidism is defined as symptomatic hypercalcemia with skeletal manifestations of hyperparathyroidism during the first 6 months of life. It may present in the first few days of life with PTH-dependent hypercalcemia, hypotonia, constipation, and respiratory distress.

Secondary Hyperparathyroidism

Most of the cases are caused by poorly treated maternal hypoparathyroidism, pseudohypoparathyroidism, or clinically unsuspected hypocalcemia, as seen in mothers with renal tubular acidosis that had induced severe secondary hyperparathyroidism in the developing fetus during pregnancy. Secondary hyperparathyroidism is a transient condition with a good prognosis provided that supportive measures are instituted. Bone disease usually resolves by 6 months of age.

Primary Hyperparathyroidism

In other cases, heterozygous or homozygous loss-of-function mutations in the *CASR* gene cause neonatal hyperparathyroidism.[57] The main forms of primary familial hyperparathyroidism presenting in infancy are autosomal dominant familial hypocalciuric hypercalcemia and sporadic neonatal hyperparathyroidism owing to a de novo heterozygous *CASR* mutation that results from an inactivating mutation of the *CASR* gene.

Familial hypocalciuric hypercalcemia is characterized by lifelong and generally asymptomatic, modest elevations in serum calcium levels, with relative hypocalciuria and PTH levels that are not suppressed by hypercalcemia and are inappropriately normal. Hypercalcemia is accompanied by borderline hypermagnesemia and hypophosphatemia. The low urinary excretion of calcium is inappropriate considering the presence of hypercalcemia.

Neonatal Severe Hyperparathyroidism. In contrast, individuals who are homozygous for *CASR* mutations or double heterozygous mutations have neonatal severe hyperparathyroidism (NSHPT). This condition is characterized by marked hypercalcemia, skeletal demineralization, and parathyroid hyperplasia, which can be fatal without parathyroidectomy.

Generally, NSHPT is manifested in the first few days of life with failure to thrive, hypotonia, constipation, and respiratory distress. Bony abnormalities are major and include undermineralization, subperiosteal erosion, metaphyseal destruction, and multiple fractures of both the long bones and ribs. It is often a life-threatening disorder, with a mortality rate of more than 25% in historical series. Children who survive NSHPT but remain hypercalcemic may feed poorly, with resulting failure to thrive, hypotonia, and developmental delay, and may be at risk for subsequent neurodevelopmental deficits. After the infant is rendered aparathyroid by surgical treatment, there is a dramatic fall in the serum calcium level, necessitating vitamin D and calcium therapy. Constitutional symptoms quickly reverse, with resolution of the bony abnormalities over about 6 months. Subtotal parathyroidectomy is often ineffective. Total parathyroidectomy with partial autotransplantation could be performed, leaving a minimal amount of parathyroid tissue necessary for normal calcium homeostasis. The use of pamidronate may be helpful to stabilize life-threatening demineralization before parathyroidectomy in rescue situations.

Williams Syndrome

Williams syndrome (also known as Williams-Beuren syndrome) is a multisystem disorder now recognized to be caused by a microdeletion of chromosome 7. It is present at birth and affects boys and girls equally. Williams syndrome is characterized by dysmorphic, elfin facies (100%); cardiovascular disease (most commonly supravalvar aortic stenosis, 80%); mental retardation (75%); developmental delay (90%); and idiopathic hypercalcemia (15%). The microdeletion codes for the structural protein elastin explain some of the characteristics of Williams syndrome. The pathogenesis of other characteristics, such as hypercalcemia, mental retardation, and unique personality traits, remains unexplained. In a fascinating piece of medical history, Dr. J.C.P. Williams, a registrar in New Zealand after whom the syndrome is named, disappeared after being offered a job in the United States, and his ultimate fate was never determined (http://www.whonamedit.com/doctor.cfm/56.html, accessed January 8, 2018).

Subcutaneous Fat Necrosis

Subcutaneous fat necrosis is common in full- or late-term newborn infants who experience a traumatic or difficult delivery.[18] Fat necrosis occurs in tissues that sustain direct trauma, such as those on which forceps or vacuum extraction is used. It is characterized by multiple indurated plaques or nodules with or without erythema on the cheeks, buttocks, posterior trunk, or extremities. Many lesions become calcified or fluctuant with liquefied fat. The cause of this disorder is unknown, but it may be initiated by ischemic injury, hypoxia, or hypothermia. Subcutaneous fat necrosis may be clinically occult, with spontaneous resolution over several weeks to as long as 6 months.[18] Hypercalcemia is uncommon, but it is the most frequently reported and serious complication of subcutaneous fat necrosis. Hypercalcemia usually appears when the subcutaneous fat necrosis

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begins to resolve, but it has been associated with long-term intellectual impairment and may be fatal if unrecognized, requiring the need for long-term monitoring of total and ionized calcium levels after the onset of skin lesions.[18]

The pathogenesis of hypercalcemia is not fully understood. Three hypotheses have been proposed. In the first, the calcium is released from the resolving subcutaneous plaques, but most individuals do not develop hypercalcemia or have calcium deposition in the subcutaneous fat necrosis lesions. In the second, the elevated levels of PTH and prostaglandin E_2 stimulate bone resorption, but most patients have levels within the normal range. Elevated prostaglandin levels may be the result of emesis and therapy with furosemide. The third, the most widely accepted theory, proposes that the elevated $1,25(OH)_2D_3$ secreted from the granulomas of subcutaneous fat necrosis lesions stimulates intestinal calcium uptake. Normally, PTH stimulates the production of $1,25(OH)_2D_3$ from $25(OH)D_3$ by the kidney. The findings of low-normal PTH concentrations and elevated $1,25(OH)_2D_3$ support the hypothesis of the extrarenal production of $1,25(OH)_2D_3$.

Other Causes of Hypercalcemia

Congenital carbohydrate malabsorption can cause hypercalcemia during the first few months of life. Congenital lactase, glucose-galactose, or sucrase-isomaltase deficiency may be associated with hypercalcemia and nephrocalcinosis. The etiology of hypercalcemia is unclear, but it is thought to be related to an increase in intestinal calcium absorption secondary to increased gut lactose or galactose or to metabolic acidosis, or both.

Distal renal tubular acidosis is another disorder associated with hypercalcemia and nephrocalcinosis. Metabolic acidosis also has a significant effect on calcium homeostasis. In chronic metabolic acidosis, the buffering of acidosis by bone salts is markedly enhanced. Bone demineralization results from the release of calcium carbonate from the bone to neutralize excess hydrogen ions. In addition to its other effects, metabolic acidosis reduces the urinary citrate concentration and increases the risk for the formation of insoluble calcium oxalate or phosphate crystals.

Severe infantile hypophosphatasia is an autosomal recessive disorder associated with a marked deficiency in serum and tissue alkaline phosphatase, skeletal demineralization and bone deformity, and hypercalcemia. One of the main actions of alkaline phosphatase is to split the pyrophosphate molecule in the extracellular space into two phosphate molecules. Given that pyrophosphate is the main inhibitor of mineralization, in the absences of alkaline phosphatase activity, pyrophosphate constantly inhibits mineralization. This disorder presents with a spectrum of clinical manifestations. The most severe form presents with polyhydramnios, extreme skeletal hypomineralization, short deformed limbs, and fetal death. Less severe forms are carried to term, but the infant has hypercalcemia, severe rachitic-like/undermineralized bone on radiograph. These less severe forms are generally lethal early in life. An additional clinical form, transmitted as an autosomal dominant trait characterized by perinatal symptoms but a better clinical course, has been described. Enzyme replacement therapy has been shown to improve the findings on skeletal radiographs and to improve pulmonary and physical function in infants and young children with life-threatening hypophosphatasia.[72]

Blue diaper syndrome is a rare familial disease in which hypercalcemia and nephrocalcinosis are associated with a defect in the intestinal transport of tryptophan. The mechanism of hypercalcemia is uncertain, although oral tryptophan loading in humans and experimental animals produces an increase in the serum calcium level. The bacterial degradation of tryptophan in the intestine leads to excessive indole production, which is converted to indican in the liver and causes indicanuria. The oxidative conjugation of two molecules of indican forms the water-insoluble dye indigo blue (indigotin), which causes a peculiar bluish discoloration of the diaper. The clinical course is characterized by failure to thrive, recurrent unexplained fever, infections, marked irritability, and constipation. Treatment consists of glucocorticoid administration and low calcium and low vitamin D diets.

Tumor-related hypercalcemia has been found in infants with increased levels of PTHrP, which is thought to be the causative agent of hypercalcemia.

Clinical Manifestations

Most infants are asymptomatic when diagnosed. Those with mildly elevated levels of calcium often fail to manifest specific symptoms of hypercalcemia. Infants with chronic hypercalcemia may present with failure to thrive as the principal source of physical distress. There are nonspecific signs and symptoms such as anorexia, vomiting, and constipation (but rarely diarrhea); polyuria may occur with moderate to severe hypercalcemia. In severe hypercalcemia, infants are often dehydrated, lethargic, and hypotonic. Alternatively, they may present with seizures. Clinically, these infants can have bradycardia, a short QT interval, and hypertension. However, renal complications such as nephrocalcinosis, nephrolithiasis, and hematuria may be the earliest clinical manifestations of hypercalcemia. Otherwise, the physical examination is usually normal except for the infants with subcutaneous fat necrosis, Williams syndrome, Jansen metaphyseal chondrodysplasia, and hypophosphatasia.

In clinical practice, the following approach may be useful. First, the possibility of iatrogenic hypercalcemia should be excluded. Second, a maternal history of calcium-phosphorus disease or excessive vitamin D intake during pregnancy should be investigated. Third, the signs of clinical syndromes associated with hypercalcemia, such as blue diapers, fat necrosis, and elfin facies, should be sought. Fourth, the initial laboratory evaluation should include serum calcium, phosphorus, alkaline phosphatase, PTH, the urinary calcium-to-creatinine ratio, and tubular reabsorption of phosphorus. In most cases, these tests allow the differentiation of hypercalcemia caused by parathyroid disorders from nonparathyroid conditions. In

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hyperparathyroidism, the serum phosphorus concentration is low; renal tubular phosphorus reabsorption is decreased, usually to less than 85%; and the serum PTH concentration is elevated. Finally, additional tests may be performed. Serum $25(OH)D_3$, $1,25(OH)_2D_3$, and $24,25(OH)_2D_3$ determination may be useful when mutation in 24 hydroxylase vitamin D is suspected; long-bone radiographs identify demineralization, osteolytic lesions, or both (hyperparathyroidism), or osteosclerotic lesions; measurements of serum and urinary calcium in parents allow a diagnosis of familial hypocalciuric hypercalcemia; and renal sonography detects nephrocalcinosis.

Treatment

The treatment of neonatal hypercalcemia depends on the severity of the presentation. Conservative management is appropriate in the case of mild hypercalcemia in a preterm infant resulting from an inappropriate mineral supply, hypoalbuminemia, or chronic acidosis, with special emphasis on the phosphorus supply when hypercalcemia is associated with hypophosphatemia. Hypercalcemia seen in newborn infants exposed to maternal hypocalcemia is usually mild and transient, and treatment consists of no more than supplying the appropriate amounts of calcium and phosphorus in the milk.

Infants with moderate to severe hypercalcemia need more aggressive treatment. The initial steps are not specific: (1) Discontinue oral and intravenous calcium and vitamin D supplementation and dietary restriction; (2) increase the urinary excretion of calcium by maximizing glomerular filtration with the administration of intravenous fluids, which consist of standard saline at about twice the maintenance requirements, and encourage calcium excretion with furosemide after rehydration but with particular attention to maintaining electrolyte homeostasis; and (3) be aware that more specific therapy comprises the use of glucocorticoids, calcitonin, bisphosphonate, dialysis, and total parathyroidectomy.

Glucocorticoids (2 mg/kg of prednisone) decrease intestinal calcium absorption, decrease bone resorption, and increase renal excretion. They may be useful during a short period, mainly in cases of an excess of vitamin D, but are relatively ineffective in cases of hyperparathyroidism. Bisphosphonate therapy is limited in newborn infants. However, pamidronate (0.5-2.0 mg/kg) has been used in the treatment of subcutaneous fat necrosis and could be an ideal agent to stabilize cases of NSHPT, as recently suggested. A calcimimetic drug that reduces PTH secretion, approved by the US Food and Drug Administration for chronic secondary hyperparathyroidism in dialyzed patients, could be of major interest in primary hyperparathyroidism but needs to be evaluated during infancy. Dialysis could be prescribed with a low-calcium dialysate (1.25 mmol/L) in the face of severe and unremitting hypercalcemia. Total parathyroidectomy with partial autotransplantation could be a rescue treatment in the severe form of NSHPT.

In the chronic phase, dietary restriction with the use of a special formula without vitamin D supplementation is the mainstay of treatment. If the dietary regimen is insufficient, corticosteroids can be used with caution. Cellulose phosphate binders have been occasionally used in children, but there is limited experience in neonates, in whom they may not be safe to use, in part because they may contain unwanted free phosphate.

Nephrocalcinosis in Preterm Infants

Nephrocalcinosis refers to deposits of calcium crystals diffusely located in the parenchyma of the kidney. The incidence is particularly high in infants with VLBW and ELBW (extremely low birth weight). However, it varies widely between 1.7% and 64% depending on different study populations, ultrasonographic criteria, and equipment.[29] Ultrasonography has been found to be a sensitive and reliable method for the detection of nephrocalcinosis. It shows either bright reflections of 1 ± 2 mm without acoustic shadowing, defined as white flecks, or bright reflections larger than 2 mm with or without acoustic shadowing, defined as white dots. The etiology of nephrocalcinosis in preterm neonates has not been fully clarified. It develops as the result of an imbalance between stone-inhibiting and stone-promoting factors. Because of its hypercalciuric effect, furosemide therapy is most frequently mentioned as a provocative factor. Treatment with aminoglycosides, corticosteroids, and xanthines may also contribute to stone formation, and neonates with lower birth weight, shorter gestational age, and transient renal failure appear to run a higher risk. Immature kidneys have relatively better-developed deep nephrons, with a long Henle loop and probably a low urinary flow velocity. Therefore, conditions are favorable for the formation of crystals, which then stick to the surface and grow. Preterm neonates who develop nephrocalcinosis may have a high urinary calcium-to-creatinine ratio, and an accompanying high intake of ascorbic acid might contribute to the high urinary oxalate-to-creatinine ratio, which is a potent lithogenic factor. In contrast, a low urinary citrate-to-calcium ratio, considered a lithoprotective factor, may be seen in infants with ELBW, suggesting that supplementation with alkaline citrate may have a beneficial effect in the prevention of nephrocalcinosis.

The short- and long-term evolution of nephrocalcinosis has not been clearly defined. Ultrasonographic abnormalities that develop during the first months of life disappear in most patients within months to years. Although proximal tubular function is unaffected in children with neonatal nephrocalcinosis, high blood pressure and impaired glomerular and distal tubular function might occur more frequently than in healthy, term children.

The long-term outcome of nephrocalcinosis in preterm neonates has not been defined. Nephrocalcinosis was not a prognosis factor for long-term (3-18 years) renal disease in infants with ELBW who had neonatal renal failure.

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Clinical Conditions Associated With Magnesium Disturbances

Hypomagnesemia

Hypomagnesemia occurs when serum magnesium concentrations fall below 0.66 mmol/L (1.6 mg/dL), although clinical signs often do not develop until they fall below 0.49 mmol/L (1.2 mg/dL). The signs of hypomagnesemia are the same as those of hypocalcemia: irritability, tremors, and seizures. Because serum magnesium does not reflect total-body magnesium, there is no strict correlation between the clinical signs and serum magnesium concentrations. Hypomagnesemia and hypocalcemia frequently coexist.

Etiology

See Box 87.5.

Maternal Diabetes

In diabetes, glycosuria causes polyuria and increased urinary magnesium losses. The severity and prevalence of hypomagnesemia in infants of insulin-dependent diabetic mothers are directly related to the severity of maternal diabetes, which is thought to reflect the severity of maternal magnesium deficiency. The incidence of hypomagnesemia is also increased in infants of gestational diabetic mothers. Hypomagnesemia in IDMs (and infants of gestational diabetic mothers) is associated with neonatal hypocalcemia and decreased parathyroid function. Cord serum magnesium concentrations and its stores are decreased. Magnesium supplementation improves both serum calcium and PTH.

Intrauterine Growth Restriction

Some infants with IUGR manifest hypomagnesemia at birth. This manifestation may represent conditions in which maternal supply, placental transfer of magnesium, or both, are deficient. Hypomagnesemia is seen especially in infants with IUGR born from young, primiparous, toxemic mothers.

Neonatal Hypoparathyroidism

Serum magnesium and PTH concentrations are interrelated, so it may not be clear whether hypomagnesemia is the cause or the effect of hypoparathyroidism. A magnesium infusion test may help resolve the issue. If PTH increases after the magnesium load, magnesium deficiency with secondary functional hypoparathyroidism is likely. If PTH does not increase, hypoparathyroidism is probably unrelated to the deficiency.

Inherited Disorders of Renal Magnesium Handling

The genetic basis and cellular defects of a number of primary magnesium-wasting diseases have been elucidated during the past decade.

Primary Hypomagnesemia With Secondary Hypocalcemia. This is a rare autosomal recessive disorder resulting from primary defects in the intestinal transport of magnesium, with the responsible gene mapping to the long arm of chromosome 9. It presents in early infancy with persistent hypocalcemia and seizures that cannot be controlled with anticonvulsants, calcium gluconate, or both. Serum magnesium is frequently less than 0.8 mg/dL (normal, 1.6-2.8 mg/dL), and circulating levels of PTH are low despite the presence of hypocalcemia. In older children with inadequate magnesium control, clouded sensorium, disturbed speech, and choreoathetoid movements have been observed. The administration of magnesium to these infants leads to spontaneous parallel increases in serum PTH levels, serum calcium levels, and renal phosphate clearance. The prognosis is favorable if a diagnosis is made early enough.

Infantile Isolated Renal Magnesium Wasting (Dominant). Hypomagnesemia as the result of isolated renal magnesium loss is an autosomal dominant condition associated with few symptoms other than chondrocalcinosis. Patients always have hypocalciuria and variable, but usually mild, hypomagnesemic symptoms.

• BOX 87.5 Neonatal Hypomagnesemia and Hypermagnesemia

Neonatal Hypomagnesemia

Decreased Magnesium Supply

- Maternal magnesium deficiency
- Intrauterine growth restriction
- Maternal diabetes, insulin-dependent and gestational
- Malabsorption syndrome
- Extensive small intestine resection
- Intestinal fistula or diarrhea
- Hepatobiliary disorders
- Defect of intestinal magnesium transport: primary hypomagnesemia with hypocalcemia

Magnesium Loss

- Exchange transfusion with citrated blood
- Decreased renal tubular reabsorption
- Primary:
  - Infantile isolated renal magnesium washing (dominant and recessive)
  - Hypomagnesemia with hypercalciuria and nephrocalcinosis
- Secondary:
  - Extracellular fluid compartment expansion, osmotic diuresis
  - Drugs (e.g., loop diuretics, aminoglycosides)
- Other causes
  - Increased phosphate intake
  - Maternal hyperparathyroidism

Neonatal Hypermagnesemia

Increased Magnesium Supply

- Maternal treatment with magnesium sulfate
- Neonatal magnesium therapy: asphyxia, pulmonary hypertension
- Parenteral nutrition
- Antacids, enema

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Infantile Isolated Renal Magnesium Wasting (Recessive). There is evidence of a variant form of hypomagnesemia that is more consistent with isolated renal magnesium loss with autosomal recessive inheritance. Patients also have variable symptoms, but they usually have normal urinary calcium excretion.

Hypomagnesemia With Hypercalciuria and Nephrocalcinosis. A distinct syndrome of hypomagnesemia with hypercalciuria and nephrocalcinosis (HHN) has been described. The HHN syndrome is an autosomal recessive disorder that is characterized by renal magnesium wasting and results in persistent hypomagnesemia and marked hypercalciuria, leading to early nephrocalcinosis. It is distinguished from other conditions by the absence of infantile hypocalcemic tetany and normal plasma potassium.

Other Causes of Hypomagnesemia

Secondary defects in the renal tubular reabsorption of magnesium may result from extracellular fluid expansion caused by excessive glucose, sodium, or fluid intake or by osmotic diuresis. Loop diuretics such as furosemide and high doses of aminoglycosides such as gentamicin may cause magnesuria. Any severe malabsorption syndrome can cause magnesium deficiency. In the neonatal period, multiple exchange blood transfusions with citrate as an anticoagulant result in the complexing of citrate with magnesium, which leads to hypomagnesemia.

Clinical Manifestations

Hypomagnesemia in the neonatal period is usually transient (except for malabsorption syndromes) and asymptomatic, but it can cause hyperexcitability and occasionally severe, intractable hypocalcemic seizures that are unresponsive to calcium infusion and anticonvulsants. Hypomagnesemia should be considered in any patient with hypocalcemia who does not respond clinically or biochemically to calcium or vitamin D therapy.

Treatment

Hypomagnesemia should not be treated with calcium or vitamin D, which may cause a further decrease in serum magnesium. The administration of magnesium salts is the treatment of choice. The average amount of magnesium sulfate required in the neonate is a 50% solution of magnesium sulfate, 0.05-0.1 mL/kg (0.1-0.2 mmol/kg, or 2.5-5.0 mg/kg of elemental magnesium), given by slow intravenous infusion over 30-60 minutes. Repeated doses may be required every 8-12 hours. Possible complications of intravenous infusion include systemic hypotension and prolongation or even blockade of sinoauricular or atrioventricular conduction.

Concomitant oral magnesium supplements can be started if oral fluids are tolerated. A 50% solution of magnesium sulfate can be given at a dose of 0.2 mL/kg per day. In specific magnesium malabsorption, daily oral doses of 1 mL/kg per day may be required. Daily serum magnesium concentrations should be measured until the values are stable to evaluate efficacy and safety. Oral magnesium salts are not well absorbed, and large doses may cause diarrhea due to hyperosmolarity. The maintenance magnesium supplement should be diluted fivefold to sixfold to allow for more frequent administration, maximizing gut absorption, and minimizing side effects.

Neonatal seizures caused by hypocalcemia and hypomagnesemia do not have a uniformly favorable outcome, although the outcome is generally better than many other causes of neonatal seizures.

Hypermagnesemia

Hypermagnesemia is defined as a serum magnesium concentration greater than 1.15 mmol/L (2.8 mg/dL). Hypermagnesemia is invariably an iatrogenic event caused by excessive magnesium administration to mother or infant. Because magnesium balance is regulated primarily by the kidneys, decreased renal function can be a contributing factor.

Etiology

See Box 87.5.

Maternal Treatment With Magnesium Sulfate

Magnesium sulfate is used to prevent seizures in preeclampsia and as a tocolytic agent. Maternal hypermagnesemia results in fetal and neonatal hypermagnesemia. Concomitant maternal hypocalcemia may also occur secondary to decreased serum PTH concentrations. With the current treatment of preeclampsia, the neonatal serum magnesium concentration usually does not rise to a potentially dangerous level and gradually returns to normal after a few days.

Excessive Magnesium Administration

Treatment with magnesium-containing antacids for the prevention and treatment of stress ulcers has been reported to cause hypermagnesemia. Excessive magnesium administration with total parenteral solution is a potential cause of hypermagnesemia, especially in sick neonates.

High doses of intravenous magnesium sulfate have been used in the treatment of persistent pulmonary hypertension in the newborn. At high doses, magnesium appears to reverse the hypoxia-induced increase in pulmonary arterial pressure.

Clinical Manifestations

Hypermagnesemia should be suspected in depressed infants born to mothers who have been treated with magnesium sulfate. In most cases, hypermagnesemia is associated only with hypotonia. However, in extreme cases, severe neuromuscular depression (a curare-like effect) and respiratory failure (CNS depression) may occur. In adults, the signs may include neuromuscular depression and hypotension (usually at magnesium concentrations of greater than 1.64-2.46 mmol/L, or 4-6 mg/dL), difficult urination (greater than 2.05 mmol/L, or 5 mg/dL), CNS

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depression (greater than 2.46-3.28 mmol/L, or 6-8 mg/dL), and respiratory depression and coma (greater than 4.92-8.33 mmol/L, or 12-17 mg/dL).

Serum calcium concentrations may be normal, decreased, or increased in hypermagnesemic neonates. Hypermagnesemia may suppress PTH and $1,25(OH)_2D_3$ production and may result in lower serum calcium concentrations. Rickets has been reported when maternal magnesium therapy is prolonged (e.g., in tocolysis to prevent preterm delivery).

Treatment

In most cases of neonatal hypermagnesemia, supportive treatment is sufficient, because an excess of magnesium is gradually removed through urinary excretion. Calcium is a direct antagonist of magnesium, and intravenous calcium given at the same dosage as that given for the treatment of hypocalcemia may be useful for acute therapy. Optimal hydration is important to ensure adequate urinary flow. Loop diuretic therapy may increase magnesium excretion. Citrated donor blood is particularly useful, because the complexing action of citrate expedites the removal of magnesium from the infant. Peritoneal dialysis and hemodialysis may be considered in refractory patients. Supportive measures such as cardiorespiratory assistance and adequate hydration may be needed.

Osteopenia of Prematurity

Premature babies are at increased risk for developing bone disease by reduced bone mineral content. Increased survival of infants with VLBW has been associated with an increased incidence of osteopenia of prematurity, which is also called *metabolic bone disease* or *rickets of prematurity*. The incidence is inversely proportional to gestational age and birth weight, and two decades ago, it was estimated to be 50% in infants weighing less than 1000 g and 23%-32% in infants weighing less than 1500 g; however, the current incidence is difficult to estimate, because the nutritional strategy has changed. Maximizing calcium and phosphorus intake from parenteral and enteral nutrition, early initiation of feeding, and decreased use of paralysis during mechanical ventilation probably have decreased the incidence of the disease.

Etiology

From birth, premature babies begin the process of physiologic postnatal adaptation, which is characterized by an increase in bone remodeling, with a progressive increase in marrow cavity size and a concomitant reduction in physical density. Primarily, the mineral supplies, especially calcium and phosphorus, may be low, whereas length and skeletal growth rates remain relatively high during the last trimester. In utero mechanical stimulation is likely to be higher, although there is inadequate information about the effects of this on bone mineral development after birth in VLBW infants.[60] Finally, the hormonal situation is different postnatally, because the placental supply of estrogen and many other hormones has been cut off.

Although vitamin D deficiency can cause rickets, it is not the primary cause in most cases in preterm infants, and provision of vitamin D supplementation alone does not reduce the incidence of rickets in preterm infants. The role of maternal vitamin D status in the development of osteopenia of prematurity is not clear, although low maternal vitamin D status is associated with reduced bone mineralization in term infants.[17]

Additional risk factors for bone disease in preterm infants include prolonged parenteral nutrition, feeding with unsupplemented human milk, fluid restriction, chronic illness, and the use of hypercalciuric drugs such as furosemide for the treatment of bronchopulmonary dysplasia and methylxanthines for the treatment of apnea and bradycardia, both of which increase calcium loss. The use of postnatal steroids can decrease bone formation. In addition, immobility, especially for prolonged periods of sedation during mechanical ventilation, could enhance calcium loss and demineralization. There is evidence that placental insufficiency has a role in increasing the risk of low bone mass as well. There may be an increased incidence of rickets in growth-restricted infants.

Development of osteopenia of prematurity or overt rickets in preterm infants may be associated with genetic polymorphisms. Candidate genes associated with adult osteoporosis have been evaluated for bone disease in infants with VLBW. A summary of the risk factors that contribute to the development of severe osteopenia of prematurity and rickets is illustrated in Fig. 87.9.

Diagnosis

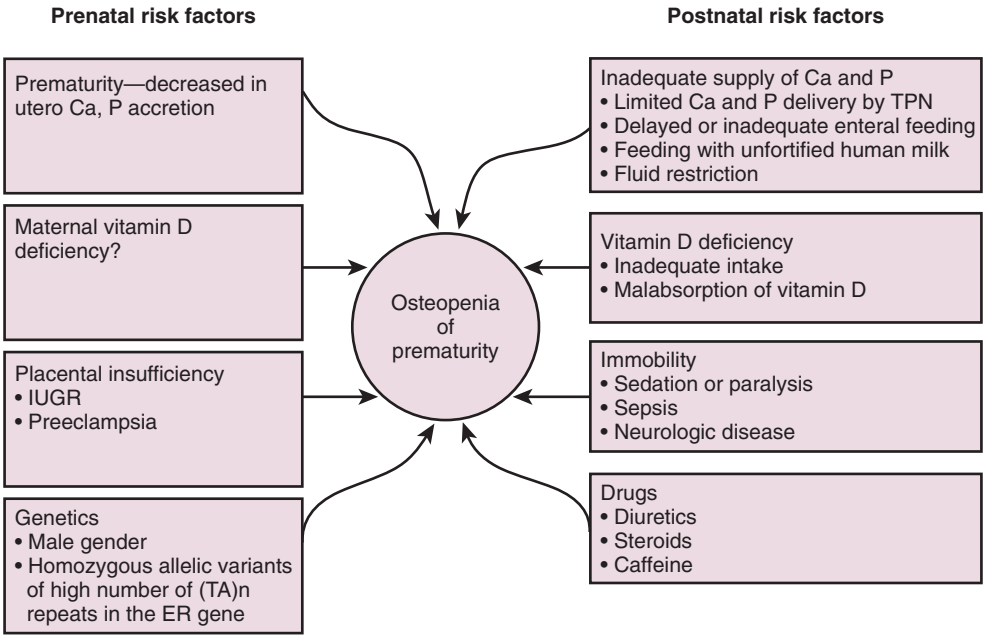
Clinical Symptoms

Clinical symptoms of osteopenia are rare in infants with VLBW because of the widespread use of well-balanced parenteral solutions, human milk fortifiers, and preterm formulas. Fractures and rickets, which represent the major symptoms, have diminished, although they remain a concern in the smallest infants, especially those less than 1000 g.[50]

Biochemical Features

Biochemical features are relatively nonspecific. Usually serum calcium concentrations are within the normal range and serum phosphorus concentrations are normal or low at the time of diagnosis. The occurrence of a prolonged reduction of serum phosphorus during the early weeks of life could be predictive of the occurrence of rickets and osteopenia, because infants with ELBW are at risk for low renal phosphate reabsorption (tryptophan and GFR values), leading to urinary phosphate excretion even in the presence of low serum phosphate levels. Therefore, the absence of, or very low, urinary phosphate excretion also needs to be considered as an indicator of phosphate depletion. Alkaline phosphatase is frequently used to screen for osteopenia of prematurity despite conflicting evidence about its sensitivity

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• **Fig. 87.9** Prenatal and postnatal risk factors for development of osteopenia of prematurity. Ca, Calcium; IUGR, intrauterine growth restriction; P, phosphorus; (TA)n, thymine-adenine repeat; TPN, total parenteral nutrition; VDR, vitamin D receptor.

and specificity.[1] The peak alkaline phosphatase level is inversely related to the serum phosphorus concentration. Therefore, the combination of alkaline phosphatase and serum phosphorus concentration could be more useful to screen for osteopenia of prematurity than alkaline phosphatase alone. An alkaline phosphatase level higher than 900 IU/L has predicted radiographic osteopenia by DEXA scan with 88% sensitivity and 71% specificity, but the sensitivity is much higher with concomitant lower serum phosphorus concentrations (<1.8 mmol/L).[22]

Hormonal Features

In preterm infants, the serum PTH, serum $25(OH)D_3$, and serum $1,25(OH)_2D_3$ concentrations increase during the first month of life. Both 25- and 1,25-hydroxylation mechanisms are functionally active in preterm infants. The $25(OH)D_3$ and $1,25(OH)_2D_3$ levels are related to the mother's vitamin D status at birth as well as to the vitamin D supply to the newborn during the first weeks of life. In infants with VLBW supplemented with vitamin D, osteopenia does not appear to be related to the hormonal status.

Radiologic Features

Standard radiographs do not allow an accurate assessment of bone demineralization. Bone mineral density must decrease by 30% or more to be diagnosed by this method, and interobserver variability is considerable. However, standard radiographs can detect fractures, and a wrist or knee radiograph at or after 4-5 weeks of age in a high-risk infant remains a practical assessment of the presence of overt rickets. Currently, DEXA is the standard in whole-body mineral measurement, and normative data are available. The DEXA equipment is not portable, so performing a scan involves transportation of the infant, which may not be feasible for very small and sick infants who are at the greatest risk for metabolic bone disease.

Prevention and Treatment

A management strategy for rickets that is evident radiologically is shown in Box 87.6. Calcium and phosphorus requirements in preterm infants are usually based on demands for matching intrauterine bone mineral accretion rates and the maintenance of serum calcium and phosphorus concentrations comparable to those of normal term infants. However, more recent consideration of bone physiology suggests that the process of postnatal adaptation could modify the requirement, considering that the remodeling stimulation by itself provides part of the mineral requirement necessary for postnatal bone turnover. Under extrauterine conditions, the care of premature infants should not necessarily aim to achieve intrauterine calcium accretion rates. Subsequently, the skeletons of these infants will adapt to the mechanical requirements, whether intrauterine calcium accretion rates are achieved or not.

Parenteral Nutrition

Inadequate calcium and phosphorus intake has been associated with diminished bone mineralization in parenterally nourished premature infants. This deficiency occurs when protein and energy are adequate for growth, but calcium and phosphorus are insufficient to sustain appropriate skeletal mineralization. Calcium and phosphorus cannot be provided through parenteral solutions at the concentrations

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needed to support in utero accretion because of precipitation. The solubility of calcium and phosphorus in parenteral solutions depends on the temperature, type, and concentration of amino acids; dextrose concentrations; pH of the calcium salt; sequence of the addition of calcium and phosphorus to the solution; calcium-to-phosphorus ratio; and presence of lipids. More acidic pediatric amino acid solutions improve calcium and phosphorus solubility. With a range of fluid intake of 120-130 mL/kg per day, it is advisable to supply a calcium content of 1.5-2.0 mmol/dL and a calcium-to-phosphorus ratio of 1.3 : 1 by weight and 1 : 1 by molar ratio in the total hyperalimentation solution. This quantity of calcium provided by the parenteral route is about 60%-80% of that deposited by the fetus during the last trimester of gestation.[51]

• BOX 87.6 Management Approach for Enterally Fed Preterm Infants With Radiologic Evidence of Rickets

1. Maximize nutrient intake. Consider increasing human milk fortifier and/or feeding volume of preterm formula, as clinically indicated. If unable to tolerate human milk fortifier or preterm formula, then will likely need elemental minerals added as described below.
2. If no further increases in these can be made, add elemental calcium and phosphorus as tolerated. Usually beginning at 20 mg/kg per day of elemental calcium and 10-20 mg/kg per day elemental phosphorus and increasing, as tolerated, usually to a maximum of 70-80 mg/kg per day of elemental calcium and 40-50 mg/kg per day elemental phosphorus.
3. Evaluate cholestasis and vitamin D status. May consider measuring 25-OH-D concentration, targeting serum 25-OH-D concentration of >20 ng/mL (50 nmol/L).
4. Follow serum phosphorus concentration and serum alkaline phosphatase weekly.
5. Recheck radiographs for evidence of rickets at 5- to 6-week intervals until resolved.
6. Advise caregiving team to be cautious in handling of infant.
7. Limit use of steroids and furosemide, as clinically feasible.

From Abrams SA, Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013;131:e1676-1683.

Enteral Nutrition

The exclusive use of human milk without phosphorus and mineral fortification promotes the occurrence of osteopenia and rickets in infants with VLBW. Both liquid and powdered human milk fortifiers are commercially available. Their use has dramatically reduced the incidence of fractures and radiographically diagnosed osteopenia. A similar reduction has also been observed in preterm infants fed preterm formulas.[7]

Although both the absorption and retention rates of calcium and phosphorus are higher in infants than adults, intestinal absorption of minerals remains a limiting factor of mineral accretion. In contrast, phosphorus is generally well absorbed, but phosphorus retention is related to calcium and protein accretion. Absorption of calcium is currently best evaluated using stable isotope techniques, taking into consideration the endogenous intestinal calcium secretion (Table 87.5).

Monitoring Mineral Supplementation

There are very few markers of adequate bone mineralization during the early weeks of life in newborn infants. Bone mineral content can be measured accurately by DEXA, but in clinical practice it is performed in very few centers.

An ideal approach to assess the adequacy of mineral intake in VLBW or other very high-risk infants may involve the following recommendations[1]:

1. Preterm infants, especially those less than 27 weeks' gestation or with birth weight less than 1000 g with a history of multiple medical problems, are at high risk of rickets.
2. Routine evaluation of bone mineral status using biochemical testing is indicated for infants with birth weight less than 1500 g but not those with birth weight greater than 1500 g. Biochemical testing should usually be started 4-5 weeks after birth.
3. Serum alkaline phosphatase greater than 800-1000 IU/L or clinical evidence of fractures should lead to a radiographic evaluation for rickets and management focusing on maximizing calcium and phosphorus intake and minimizing factors leading to bone mineral loss.

TABLE 87.5 Approximate Calcium Balance in a Typical Infant Receiving 120 kcal/kg per Day Intake*

	Calcium Concentration (mg/dL)	Intake (mg/kg per Day)	Absorption %	Total Absorption (mg/kg per Day)	Approximate Retention (mg/kg per Day)
Human milk	25	38	60	25	15-20
Preterm formula/fortified human milk	145	220	50-60	120-130	100-120

*Human milk assumed to be 20 kcal/oz, and preterm formula and fortified human milk assumed to be 24 kcal/oz.
Data from Abrams SA, and the Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics*. 2013;131:e1676-1683.

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4. A persistent serum phosphorus concentration less than approximately 4.0 mg/dL should be followed, and consideration should be given for phosphorus supplementation.
5. Routine management of preterm infants, especially those with birth weight less than 1800-2000 g, should include human milk fortified with minerals or formulas designed for preterm infants.
6. At the time of discharge from the hospital, VLBW infants will often be provided higher intakes of minerals than are provided by human milk or formulas intended for term infants through the use of transitional formulas. If exclusively breastfed, a follow-up serum alkaline phosphatase at 2-4 weeks after discharge from the hospital may be considered.
7. When infants reach a body weight greater than 1500 g and tolerate full enteral feeds, vitamin D intake should generally be approximately 400 IU/day, up to a maximum of 1000 IU/day.

Outcome

Catch-up growth occurs after discharge in VLBW infants. At 6 months of corrected age, spine and total bone mineral density, corrected for anthropometric values, is in the range of normal term newborn infants. Nevertheless, peak bone mass may be less during adulthood. In older children, formerly preterm infants were shorter, lighter, and had lower bone mineral content (BMC) than controls. Of note is that long-term data do not demonstrate a relationship between feeding type in preterm infants and long-term bone mineral content.[22]

In most cases, prematurity-associated rickets appears to spontaneously resolve, although the potential long-term consequences on the attainment of peak bone mass are not clearly known. Even if BMC improves spontaneously in most infants, this discovery does not imply that a period of demineralization is acceptable. Although the long-term consequences are unclear, the benefits of prevention and treatment include avoidance of fractures and possibly improved linear growth and peak bone mass. Severe rickets may also limit pulmonary status, because historically it was thought that rickets was, in part, a pulmonary disease caused by poor lung expansion in the absence of a normal rib cage.

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Key Points

- The metabolism of calcium, phosphorus, and magnesium and subsequent mineralization of the skeleton are complex functions that require the interaction of numerous factors such as supply of nutrients, daily accretion in utero, and transport across membranes.
- After birth, the switch from placental to dietary minerals causes the relatively hypercalcemic fetus to become a relatively hypocalcemic neonate that leads to PTH secretion, leading to a reduction in calcium availability for bone mineralization.
- Neonatal hypercalcemia is defined as an elevation in plasma ionized calcium concentration greater than 1.45 mmol/L (5.8 mg/dL). Iatrogenic hypercalcemia is the most common and is often caused by excessive intravenous calcium administration during parenteral nutrition or exchange transfusion, use of extracorporeal membrane oxygenation.
- Causes of hypomagnesemia (<1.6 mg/dL) may include maternal diabetes, intrauterine growth restriction, neonatal hypoparathyroidism, inherited disorders of renal magnesium handling, primary hypomagnesemia with secondary hypocalcemia, infantile isolated renal magnesium wasting, or hypomagnesemia with hypercalciuria and nephrocalcinosis.

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Thyroid Disorders in the Neonate

JANET CHUANG AND IRIS GUTMARK-LITTLE

Thyroid hormone is critical for linear growth and maturation of thyroid-dependent tissues, including the brain. Many physiologic factors influence fetal and neonatal thyroid function, including fetal–maternal relationships and the dynamic alteration of thyroid function with birth. Understanding the action of thyroid hormones, the synthesis and transport of these hormones, and mechanisms regulating thyroid function is also important in the evaluation and management of thyroid disorders. This chapter begins with a review of thyroid physiology and laboratory tests. Thyroid hormone abbreviations are defined in Box 88.1. Embryology and fetal development of thyroid function are then described. Finally, clinical conditions of altered thyroid function are discussed.

Physiologic Action of Thyroid Hormones

Functions of the Thyroid Gland

The principal functions of the thyroid gland are to synthesize, store, and release the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) into the circulation. The major secretory product of the thyroid is T_4. Thyroidal secretion of T_3 accounts for only about 20% of its production. The remaining 80% is derived from peripheral deiodination of T_4. Therefore, T_4 acts as a prohormone for T_3, because T_4 has negligible intrinsic metabolic activity in most tissues. Most of the physiologic effects of thyroid hormone are mediated by T_3 through its interaction with the thyroid response element on DNA.

Neurologic Effects

Prenatal and postnatal maturation of the brain, retina, and cochlea is thyroid hormone dependent.[22] Thyroid hormone modulates expression of thyroid hormone–responsive target genes at precise times during development, controlled by an interplay of deiodinases, thyroid receptor expression, transporters, cofactors, and transcription factors.[41,58] T_3 promotes the neural differentiation of embryonic stem cells at the dendritic level, and both T_3 and T_4 impact cerebral vascular development.[9,61] Genes that control neural migration are also regulated by thyroid hormone.

As normal levels of thyroid hormone are essential for neuronal migration, myelination, and other structural changes in the fetal brain, congenital thyroid hormone deficiency results in cretinism (severe mental retardation) if not treated. This effect is prevented by thyroid hormone replacement early in life. Early detection of congenital hypothyroidism occurs through newborn screening, which was initiated in the 1970s. Intellectual development is normal in children with congenital hypothyroidism who are treated early and aggressively.[8,51] The degree of mental retardation in cretinism is related to the severity and duration of the hypothyroid state of the infant. The brain is susceptible to a lack of thyroid hormone during its rapid growth and maturation. Defective growth and permanent damage do not occur if hypothyroidism begins after morphologic maturation of the brain is completed (after a postnatal age of 3 years).

Basal Metabolic Rate

Thyroid hormone stimulates basal metabolic rate primarily by increasing ATP production for metabolic processes and by maintaining ion gradients (Na/K^+ and Ca^{2+}), which consume ATP. Thyroid hormone is a key driver of thermogenesis. It uncouples oxidative phosphorylation in mitochondria and reduces activity of shuttle molecules that transfer reducing equivalents into the mitochondria. Thyroid hormone also increases sensitivity to catecholamine effect, which is required for maintenance of core body temperature.[36]

Clinically, the calorigenic action of thyroid hormone affects circulation by increasing heart rate, stroke volume, and cardiac output. The pulse pressure is widened mainly by a decrease in the diastolic pressure and by some elevation in the systolic pressure. Circulation time is also shortened.

Protein and Lipid Metabolism

Negative nitrogen balance occurs in hyperthyroidism unless the patient is protected by adequate caloric intake to provide for the increased energy requirements. Hypothyroidism results in increased serum total cholesterol and low-density lipoprotein (LDL) cholesterol. Thyroid hormone stimulates

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Abstract

Thyroid hormone is critical for linear growth and for maturation of thyroid-dependent tissues, including the brain. Many physiologic factors influence fetal and neonatal thyroid function. They include embryogenesis of the thyroid, fetal–maternal relationships and the dynamic alteration of thyroid function with birth, the action of thyroid hormones, the synthesis and transport of these hormones, and mechanisms regulating thyroid function. For purposes of review, this chapter will provide a summary of thyroid hormone physiology and the use of laboratory and imaging studies to define thyroid function. Embryology and fetal development of the thyroid gland will also be reviewed. Thyroid pathology in the fetus and neonate are then discussed, with emphasis on diagnosis and treatment of congenital hypothyroidism and neonatal Graves disease.

Keywords

TSH
T4
T3
congenital hypothyroidism
neonatal Graves disease
levothyroxine
goiter
iodine

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• BOX 88.1 Abbreviations Related to Thyroid Hormones

- ACTH, adrenocorticotropic hormone
- DIT, diiodothyronine (diiodotyrosine)
- FT_4, free T_4
- FT_3, free T_3
- GH, growth hormone
- IGF-1, insulin-like growth factor 1
- IQ, intelligence quotient
- KI, potassium iodide
- LDL, low density lipoprotein
- MIT, monoiodothyronine (monoiodotyrosine)
- MTZ, methimazole
- PTU, propylthiouracil
- rT_3, reverse T_3 (3,3′,5′-L-triiodothyronine)
- SGA, small for gestational age
- T_4, thyroxine (tetraiodothyronine)
- T_3, triiodothyronine (3,5,3′-L-triiodothyronine)
- TBG, thyroid (thyroxine)-binding globulin
- TBII, TSH-binding/inhibiting immunoglobulins
- TG, thyroglobulin
- TGAb, thyroglobulin antibodies
- TPOAb, thyroid peroxidase (formerly microsomal) antibodies
- TRAb, TSH-receptor antibodies
- TRH, thyrotropin-releasing hormone, TSH-releasing hormone (L-pyroglutamyl-L-histidyl-L-proline amide)
- TSH, thyrotropin; thyroid-stimulating hormone
- TSI, TSH receptor-stimulating immunoglobulins
- TTR, transthyretin (formerly T_4-binding prealbumin)

the expression of LDL receptors and in hypothyroidism the number of hepatic LDL receptors is reduced, leading to the decreased clearance of circulating LDL. Apolipoprotein B and lipoprotein (a) are also increased in hypothyroidism.[28]

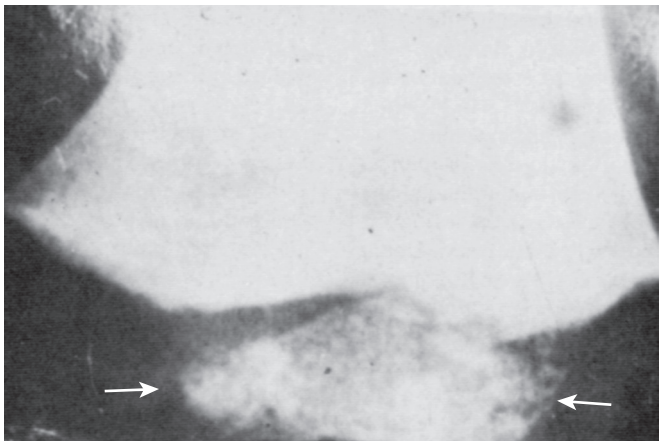
Carbohydrates, Liver Function, Water Balance, and Calcium Metabolism

The rate of gluconeogenesis, glucose absorption, and use is increased by thyroid hormone. In hypothyroidism, the glucuronic acid conjugation mechanism of the liver may be impaired. In infants, hyperbilirubinemia associated with primary hypothyroidism is almost entirely indirect; in hypothalamic-pituitary hypothyroidism, it is both direct and indirect. Retention of water in the extracellular compartment occurs in hypothyroidism, producing deposition of myxedematous fluid in soft tissue.

In hyperthyroidism, calcium balance tends to be negative. Urinary and fecal calcium excretion is enhanced. Demineralization of bone also occurs. The efflux of calcium from the bones leads to higher plasma ionized calcium and phosphate and lower circulating $1,25(OH)_2D_3$, which in turn results in decreased calcium absorption from the intestine.

Growth and Skeletal Development

A principal action of thyroid hormone is its effect on growth and skeletal development. These effects may be tissue specific and synergistic with other hormones. Prenatal growth is highly dependent on nutrition and insulin secretion. Postnatal linear growth is dependent on thyroid hormone and growth hormone (GH), which are mediated through insulin-like growth factor type 1 and its receptor. Similar synergistic effects between thyroid hormone and growth hormone can be observed in skeletal maturation. When primary hypothyroidism occurs, dental eruption, linear growth, and skeletal maturation are retarded. Retardation of skeletal maturation may be severe and is associated with immature skeletal proportions and facial contours, which contribute to the characteristic body configuration of hypothyroidism (long torso compared to short length of arms and legs). Ossification of cartilage is also disturbed in hypothyroidism, leading to epiphyseal dysgenesis in radiographs of the ossifying epiphyseal centers (Fig. 88.1). Growth rate and adult height are normal in children with congenital hypothyroidism who are diagnosed in early infancy by newborn screening and treated appropriately.[17]



• Fig. 88.1 Epiphyseal dysgenesis of the distal femoral center.

Synthesis, Release, Transport, and Use of Thyroid Hormones

The biologically active thyroid hormones T_4 and T_3 are iodinated amino acids. Their synthesis starts within the follicular cells.

Iodine Metabolism

Iodine is supplied to the body mainly through dietary intake. Although some organic iodine compounds, including T_4 and T_3, can be absorbed unchanged from the gastrointestinal tract, most are reduced and absorbed as inorganic iodide. One-fourth to one-third of ingested iodide is taken up by the thyroid. Iodine can be absorbed readily from the skin, lungs, and mucous membranes. Application of iodine-containing ointment or lotion to the skin, common during procedures with premature or sick infants, causes very high levels of iodide in circulation and promptly blocks thyroid hormone release from the thyroid gland.

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Iodide-trapping involves an active transport process through a sodium/iodide symporter that requires oxidative phosphorylation. Iodine uptake through the sodium/iodide symporter is a major rate-limiting step in thyroid hormone biosynthesis, and when it is defective, it is a rare cause of congenital goitrous hypothyroidism.[55] The iodide pump is present at both the basal and apical surfaces of follicular cells. At the basal cell surface, the pump concentrates iodide in the cells by transporting them from the extracellular space. At the apical cell surface, the pump pushes iodide into the follicular lumen as a secondary reservoir. The mechanism is capable of maintaining intrathyroidal iodide concentration at a 20- to 100-fold higher level than that of serum. Some anions—bromide (Br^{2-}), nitrate (NO_2^{2-}), thiocyanate (SCN^{2-}), perchlorate (ClO_4^{2}), and technetium pertechnetate (TcO_4^{2-})—are capable of competitively inhibiting iodide transport.

Iodide is immediately oxidized to an active form for iodination of thyroglobulin (TG) by a peroxidase enzyme system. Thyroglobulin, a glycoprotein, is synthesized by the ribosomes of the follicular cells. Iodination of TG (organification) appears to occur at the cell colloid-lumen interface. Almost all the iodine taken up by the thyroid is rapidly incorporated into the 3′ and the 5′ positions of the many tyrosyl residues of TG to form monoiodothyronine (MIT) and diiodothyronine (DIT). Once it is organically bound to tyrosyl residues, iodine can no longer be readily released from the thyroid. Defects in iodide oxidation or organification can be seen in several types of goitrous congenital hypothyroidism.[55]

Synthesis of Triiodothyronine and Thyroxine

The synthesis of T_3 requires the coupling of an MIT and a DIT molecule; T_4 is formed by the coupling of two DIT molecules. These reactions occur within the structure of TG and involve oxidative processes, probably catalyzed by thyroid peroxidase as well.

Secretion of Triiodothyronine and Thyroxine

Secretion of T_4 and T_3 into the circulation requires the liberation of these moieties from TG. Thyroglobulin molecules pass from the lumen of the follicles into the follicular cells (endocytosis), where colloid droplets are ingested by lysosomes and undergo proteolysis. After proteolysis of TG, the freed MIT and DIT are deiodinated by iodotyrosine deiodinase, and the liberated iodide is recycled by the thyroid for reiodination of new TG. Congenital hypothyroidism can result from both abnormal TG synthesis or defect in the deiodination of freed iodotyrosines, which results in iodine depletion through urinary losses.[55]

Serum Protein Binding and Transport

The thyroid is the only source of T_4, and its blood concentration is 50-100 times greater than that of T_3. T_4 and T_3 secreted into the circulation are transported by loose attachment, through noncovalent bonds, to three plasma proteins, which include thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin. TBG has the highest affinity for thyroid hormone and carries about 70% of T_4 in plasma. TTR and albumin have lower affinity than TBG, but together they still provide significant binding capacity because of their higher plasma concentration.[50] The free T_4 (FT_4) concentration more accurately indicates the metabolic status of the individual than total T_4 or T_3 does, because only the free hormones can enter the cells to exert their effects. If the capacity of thyroid binding proteins is increased or decreased, a concurrent change in the concentration of total hormones will follow, but the concentration of free hormones will be maintained.

Monodeiodination of Thyroxine

Monodeiodination of T_4 occurs in many tissues through the action of three distinct deiodinase enzymes. Type I and II deiodinase through is found in peripheral tissues such as the liver and kidney. Deiodination at the 5′ position of T_4 in peripheral tissues generates T_3, the iodothyronine that mediates the metabolic effects of thyroid hormone. Eighty percent of circulating T_3 is produced by the monodeiodination of T_4. However, the relative serum levels of T_4 and T_3 do not reflect the intracellular proportions of the hormones. The tissue distribution of T_3 may differ greatly from that of T_4 from tissue to tissue. The plasma half-life of T_3 is 1 day, compared with 6.9 days for T_4. However, the plasma half-life of T_4 is much shorter (3.6 days) in neonates. Most T_3 is localized in cells, whereas T_4 is found mainly in the extracellular space. The metabolic effects of T_3 are mediated through binding to specific receptors in the DNA response element that regulates transcription. T_3 also interacts with membranous, mitochondrial, and cytosolic binding sites.

Neural tissue requires T_4 (and does not bind T_3). Thyroid hormone availability to neurons mainly takes place through astrocytic delivery. T_4 is taken up by astrocytes at the blood–brain barrier, and T_4 is converted to T_3 by astrocytic type II deiodinase; T_3 is then transported to neurons by transmembrane transporters.[21,60] Type III deiodinase regulates peripheral deiodination of T_4 at the 5 position on the thyronine molecule instead of 5′ and generates reverse T_3 (rT_3). Serum rT_3 concentration parallels that of T_3 in normal circumstances but not in fetal life, starvation, or patients with severe nonthyroidal illnesses (e.g., euthyroid sick syndrome, non-thyroidal illness syndrome). Reverse T_3 is generally metabolically inactive, although weak nuclear binding activity has been reported.

Regulation of Thyroid Function

Control of thyroid hormone secretion is centered in the hypothalamic-pituitary-thyroid axis. Basophilic cells of the anterior pituitary gland synthesize and store thyrotropin (TSH), a glycoprotein capable of rapidly increasing

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intrathyroidal cyclic adenosine monophosphate (cAMP). TSH release from the pituitary causes an increased uptake of iodine by the thyroid, accelerates iodothyronine synthesis and release, and increases the size and vascularity of the thyroid. These changes are mediated by activation of adenylate cyclase and tyrosine kinase. Human chorionic gonadotropin (hCG) weakly competes with TSH for receptors on thyroid follicular cells. Hyperthyroidism seen in patients with choriocarcinoma can be explained by this mechanism. Similarly, certain immunoglobulins—TSH-binding inhibiting immunoglobulins (TBII) and TSH receptor-stimulating immunoglobulins (TSI) found in autoimmune thyroid diseases like Graves disease compete with TSH for binding to TSH receptors.

Secretion and plasma levels of TSH are inversely related to circulating levels of FT_3 and FT_4. The inhibitory feedback action of FT_3 and FT_4 involves a direct action of these hormones on the pituitary gland without involving the hypothalamus. Therefore, secretion of TSH is regulated directly by the ambient intrapituitary T_3 concentration and intrapituitary deiodination of T_4 to T_3 by type II monodeiodinase activity.

The hypothalamus secretes thyrotropin releasing hormone (TRH) that enters the portal system to reach the pituitary and stimulate synthesis and release of TSH from thyrotrophs. TRH is under negative feedback control by thyroid hormone, but other factors like nutritional status, external temperature, and circadian cycle regulate TRH independently of thyroid hormone level.[25]

A circadian variation of circulating TSH has been found in normal children and adults. A peak TSH concentration (≈3-4 mU/L) develops between 10:00 PM and 4:00 AM and is about 50%-300% higher than the afternoon (2:00-6:00 PM) nadir values. This nocturnal TSH surge is not directly related to sleep; it is blunted or absent in central (secondary or tertiary) hypothyroidism but maintained in primary hypothyroidism. The circadian pattern of TSH is not yet present in neonates but has been noted to be present in infants as young as 4 months of age. In children age 1 year and older, the AM to PM TSH ratio can be useful in identifying mild primary hypothyroidism and in differentiating this from central hypothyroidism.[49]

In addition to hypothalamic-pituitary regulation, the thyroid is under autoregulatory control that adjusts the degree of iodide trapping, thyroid hormone production, and release in response to changes in iodine exposure. This helps to maintain a euthyroid state despite fluctuation in dietary iodine intake.

Laboratory and Imaging Tests Used in the Diagnosis of Thyroid Disease in Infancy and Childhood

Thyroxine (T_4)

The plasma pool of T_4 constitutes a large protein-bound reservoir; this pool turns over slowly. Therefore, T_4 measurement usually reflects the adequacy of the hormonal supply. The normal level of T_4 is age dependent in infancy and childhood. T_4 reaches a peak concentration shortly after birth and declines slowly, gradually approaching the adult normal range in puberty.[18] The range of normal levels for each age group is also wide (Fig. 88.2). However, it should be kept in mind that more than 99% of circulating T_4 is bound to serum thyroid hormone–binding proteins. Any change or abnormality in the concentration of these proteins, particularly TBG, can affect the T_4 level. Several clinical situations and pharmacologic agents can alter the levels of TBG or TTR**.** Certain anticonvulsants not only bind competitively to TBG but also interfere with T_4 assays without greatly influencing the TSH level in a person with an otherwise normal thyroid reserve. These drugs include phenytoin, valproate, primidone, and carbamazepine. Other drugs, such as furosemide, salicylate, and L-asparaginase, compete with thyroid hormone for binding with plasma proteins and can alter the levels of T_4, T_3, FT_4, and FT_3.

Triiodothyronine

When TSH becomes elevated, the percentage of T_3 produced by the thyroid gland is increased. Serum concentration of T_3 can vary from day to day. Because of the overall small quantity of T_3 in serum, its level may not fall below the normal range until T_4 is critically low. Therefore, serum T_3 is not very useful in evaluation of patients for possible hypothyroidism. T_3 is physiologically low in the fetus and cord blood, but rises promptly after birth to levels greater than those in older children and adults.

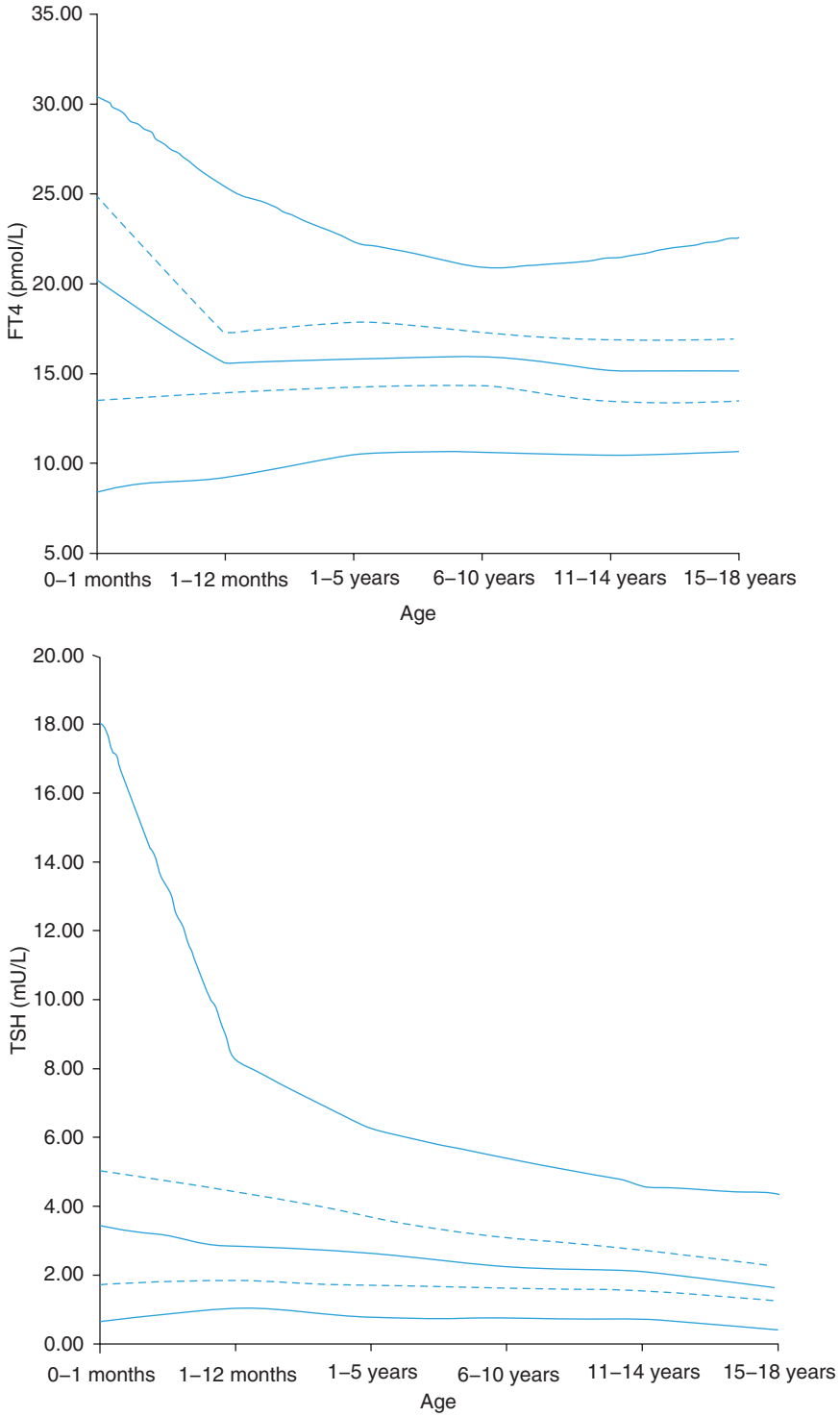
Reverse Triiodothyronine

Hormonally inactive rT_3 is derived primarily from deiodination of T_4. Serum half-life is very short, less than one-half that of T_3. Concentration of rT_3 usually parallels that of T_3. However, rT_3 is disproportionately high in the fetus, in the early neonatal period, and in severe nonthyroidal illness, probably reflecting altered tissue metabolism of T_4.[6,11]

Free Hormones

Because concentrations of T_4 and T_3 are affected by those of thyroid hormone–binding proteins and the degree of their saturation at the binding site, the simplest approach to determine thyroid hormone levels is to measure free T_4 (FT_4) and not measure T_4 at all. In clinical settings, FT_4 does not depend on the T_4-binding capacity, because a change in such a capacity is soon compensated for by a change in the amount of T_4 released from the thyroid. The gold standard for measuring FT_4 in serum is by direct dialysis. Serum is placed in a dialysis cell on one side of a semipermeable dialysis membrane, with a buffer solution on the other side. T_4 equilibrates across the membrane and bound T_4 remains with serum. Unbound FT_4 that crosses

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• **Fig. 88.2** Age-related reference values for thyrotropin (TSH) and free T_4 (FT4). The central 95% range (2.5th, 25th, 50th, 75th, and 97.5th percentiles) is shown. Because of resolution reasons, lines start at zero, although no samples were taken within the first hours after birth. (From Kapelari K, et al. Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. *BMC Endocrine Disorders*. 2008;8:15; doi:10.1186/1472-6823-8-15.)

the dialysis membrane can then be measured by radioimmunoassay or tandem mass spectrometry. FT_3 levels in the serum can be measured in the same dialysate as that used for FT_4.

Labeled analogue or antibody methods are also available to measure FT_4. They can be performed more rapidly and are less expensive than measurement of free hormone by direct dialysis. The principle of labeled analogue or antibody methods is that the rate of binding of labeled hormones to antibodies depends on the FT_4 concentration during a timed incubation. They are acceptable for routine testing in children. However, these methods may not provide an accurate assessment of FT_4 at extremes of thyroid hormone binding capacity or with significant changes in T_4 binding protein affinity.[12]

Measurement of FT_3 is not currently part of standard care. In the future, FT_3 measurements may be shown to be useful in assessing hypothyroidism. Currently, FT_3 may be

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useful when the diagnosis of thyrotoxicosis is suspected and TSH is suppressed but values for T_4, T_3, or both are normal.

Proteins That Bind to Thyroid Hormones

Serum thyroxine-binding globulin (TBG) is determined by radioimmunoassay in commercial laboratories, and its measurement is useful in the quantitation of abnormal levels of TBG. Because most T_4 is bound to TBG, these measurements give a good approximation of the T_4-binding protein capacity. Increased TBG levels may be caused by pregnancy, hypothyroidism, liver disease, acute intermittent porphyria, or human immunodeficiency virus. Pharmacologic agents that increase TBG levels include estrogens, methadone, and heroin. The concentration of TBG may be decreased in preterm infants, acute illness, nephrotic syndrome, kidney failure, severe liver disease, malnutrition, hyperthyroidism, and acromegaly. Drugs that decrease TBG levels include androgens, danazol, glucocorticoids, and L-asparaginase. Pharmacologic agents that compete with T_4 for TBG-binding sites include salicylates, phenytoin, and possibly other anticonvulsants, hypolipemic agents, sulfonylureas, diazepam, heparin, and fenclofenac. These agents give falsely low T_4. TSH and FT_4 determinations by direct dialysis method are usually normal.

Thyrotropin

Measurements of TSH and FT_4 are the most important tools for screening thyroid function. Serum TSH is measured by specific competitive-binding isotopic and nonisotopic methods. TSH is the most sensitive test for primary hypothyroidism at any age and is used in many neonatal thyroid screening programs. Serum TSH is also an indicator of the adequacy of thyroid hormone replacement therapy and is used in assessment of the hypothalamic-pituitary-thyroid axis. TSH is elevated in primary hypothyroidism. A surge of TSH release occurs at parturition and reaches a peak within 2 hours after birth. TSH in the cord serum and a term infant's serum after the 1st day of postnatal life is usually less than 20 mU/L. Therefore TSH is the most important test to screen for primary congenital hypothyroidism. The target range for TSH during thyroid hormone therapy for primary hypothyroidism is 0.5-2 mU/L.

AM to PM Thyroid-Stimulating Hormone Ratio, Thyroid-Stimulating Hormone Surge Test

Central hypothyroidism is diagnosed in infants who have low or low-normal FT_4, no TSH elevation, and other common features of hypopituitarism (e.g., hypoglycemia, microphallus). More subtle central hypothyroidism (FT_4 in the lowest third of the normal range) can be confirmed in children older than 1 year by the AM to PM TSH ratio or the TSH surge test.[49] This test is not useful in infants before development of the circadian pattern of TSH secretion.

The TSH surge test is performed by obtaining blood for TSH assay at the usual time of the nadir of the circadian variation of TSH (the mean of two or three samples between 10:00 AM and 6:00 PM) and again at the usual time of peak TSH secretion (the mean of the three highest sequential samples between 10:00 PM and 4:00 AM). The mean nadir and peak TSH values are calculated. Normal night-time peak TSH values are 50%-300% higher than the nadir values obtained during the day. Blunting or absence of this rise confirms central hypothyroidism.[49]

Thyroid Autoantibodies

Numerous methods have been used for detection of a variety of thyroid antibodies. Assays for thyroglobulin antibodies (TGAb) and thyroperoxidase (microsomal) antibodies (TPOAb) are widely available. These antibodies are found in Hashimoto thyroiditis and in about 2% of the adult population. TSH receptor stimulating and blocking antibodies may be detected in the sera of patients with autoimmune thyroid diseases and are known as TSH receptor antibodies (TRAb). TRAb that are stimulatory are found in the sera of patients with active Graves disease and are known as thyroid-stimulating immunoglobulins (TSI); TRAb that are inhibitory are called TSH-binding/inhibiting immunoglobulins (TBII).

Mothers with primary hypothyroidism and Hashimoto thyroiditis may have circulating serum TBII or antibodies that block the TSH receptor. These mothers give birth to children with a transient form of congenital hypothyroidism as a result of the transplacental transfer of TBII. The half-life of immunoglobulins in the neonate is about 2 weeks, and TRAb usually disappear from the serum of affected infants by 6-8 weeks of age. The disease may recur in infants of subsequent pregnancies if the high-affinity antibody persists in the mother's circulation.

Mothers with Graves hyperthyroidism may have TBII but more commonly have TSI. These mothers give birth to children with a transient form of hyperthyroidism as a result of the transplacental transfer of TSI. Hyperthyroidism in the affected infant may persist for 2-6 months.

Thyroglobulin

Small amounts of thyroglobulin (TG) are co-secreted with T_4 and T_3 and are detectable in the serum with levels roughly correlating with thyroid size and TSH level. In complete thyroid aplasia, TG is not detectable. Therefore, TG level is helpful to determine if thyroid tissue is present. In autoimmune congenital hypothyroidism caused by antibodies that block the TSH receptor, TG may be detectable even when the radioactive iodine scan suggests an absent thyroid gland; ultrasound should then identify the thyroid gland. TG levels may be elevated when the thyroid gland is hyperactive, as in endemic goiter, subacute thyroiditis, toxic nodular goiter, and Graves disease. TG cannot be reliably measured when there are TGAb present, as these antibodies

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interfere with the immunometric assays and often lead to falsely low results.

Thyroid Imaging

Ultrasonography of the thyroid gland is useful for visualization of eutopic thyroid glands and can provide information on size, homogeneity/heterogeneity, vascularity, and presence of nodules. Ultrasonography can also identify dysgenetic thyroid glands but does not appear to be as sensitive for detecting ectopic thyroid tissue as a radioiodine uptake scan. Ultrasonography should be used as the first imaging tool, with a scan performed to distinguish agenesis from ectopia.[13] When a scan is necessary, ^{123}I or ^{99m}Tc should be used to reduce radiation exposure to the child. ^{123}I or ^{99m}Tc does not emit beta particle gamma radiation, and their half-lives are much shorter compared to ^{131}I.

Radioiodine uptake studies are invaluable for diagnosing certain inborn errors of thyroid hormone synthesis, such as defects in iodide-trapping, iodide oxidation, and organification. In addition to the thyroid gland, the salivary glands, gastric mucosa, small intestine, mammary glands, and placenta are capable of concentrating iodine. In patients with goitrous congenital hypothyroidism, the inability of salivary glands to trap iodide can help identify defects in the sodium/iodide symporter. The perchlorate discharge test can also be performed during the radioiodine uptake test to detect the presence of a defect in iodide oxidation or organification.[13]

Embryogenesis

Factors such as FOXE1, NKX2-1, PAX8, TBX1, HOXA3, FGF10, and HHEX are involved in stem cell differentiation into thyroid follicular cells (Table 88.1).[5,19] Activin A, insulin, and IGF-1 are among the hormones required for generation of thyroid cells.[16] The major portion of the human thyroid originates from the median anlage, the tissue that arises from the pharyngeal floor (toward the back of the future tongue) and is identifiable in the 17-day-old embryo.[19] The median anlage is initially in close contact with the endothelial tubes of the embryonic heart. With the descent of the heart, the rapidly growing median thyroid is progressively pulled caudally until it reaches its final position in front of the second to sixth tracheal ring by day 45-50 of gestation. Abnormal descent leads to ectopic location of the thyroid gland. The pharyngeal region contracts to become a narrow stalk called the *thyroglossal duct*, which subsequently atrophies. The median anlage usually grows caudally so that no lumen is left in the tract of its descent. An ectopic thyroid gland or persistent thyroglossal duct or cyst results from abnormalities of thyroid descent. The lateral parts of the descending median anlage expand to form the thyroid lobes and the isthmus.

The second source of thyroid tissue is composed of a pair of ultimobranchial bodies arising from the caudal extension of the fourth pharyngeal pouch. These bodies are initially connected to the pharynx by the pharyngobranchial duct. The pharyngeal connection is subsequently lost, and the ductal lumen becomes obliterated. The ultimobranchial bodies are incorporated into the expanding lateral lobes of the median anlage. They contribute little to the future size of the thyroid, and their differentiation appears to require the influence of the median anlage. Parafollicular or C cells arise from the ultimobranchial bodies in mammals and are the source of calcitonin.

By the latter part of the 10th week of gestation, the histogenesis of the thyroid is virtually complete, although the follicles do not contain colloid.[19] A single layer of endothelial cells surrounds the follicular lumen. By the beginning of the second trimester, the fetal thyroid is capable of trapping and oxidizing iodide.[24] Therefore the fetal thyroid begins to secrete thyroid hormone and contributes to the fetal circulation of thyroid hormone.

At the same time as the development of the thyroid gland, the fetal pituitary and hypothalamus are also forming and beginning to function. The anterior pituitary gland is derived from the Rathke pouch, which originates at the roof of the pharynx. Histologic differentiation of pituitary cells can be observed by 7-10 weeks of gestation, and TSH can be detected in fetal blood by 10-12 weeks. The hypothalamus develops from the ventral portion of the diencephalon. Thyrotropin-releasing hormone has been found in fetal whole-brain extracts by 30 days and in the hypothalamus by 9 weeks of gestation.

Thyroid Function: Fetal–Maternal Relationship

In considering the fetal–maternal relationship, the placenta is of major importance. Thyroid stimulating hormone does not cross the placental barrier, whereas TRH does. Maternal-to-fetal transport of T_4 is highest in the first trimester. Rapid placental deiodination of T_4 into biologically inactive rT_3 and DIT limits transfer of maternal T_4 during later stages of pregnancy. However, maternally derived thyroid hormone continues to be important even in the third trimester. This third trimester T_4 placental transfer to a fetus with a total inability to synthesize T_4 results in a fetal T_4 concentration that is 25%-50% of that found in normal neonates.[59] Therefore, in a mother with normal thyroid function, the hypothyroid fetus is somewhat protected. It has been well documented that overt maternal hypothyroidism poses risk to the maternal–fetal unit. Untreated maternal hypothyroidism not only results in negative impact on neurocognitive development in offspring,[23] but there is also increased risk for gestational hypertension, premature birth, low birth weight, and pregnancy loss.[3,33] To prevent significant untreated maternal hypothyroidism, it is now recommended that upon confirmation of pregnancy, certain high-risk groups will be screened.[2]

Maternal dietary iodine deficiency results in impaired maternal and fetal thyroid hormone synthesis. Consequent maternal and fetal hypothyroidism can lead to increased TSH and goiter in both the mother and fetus and also

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TABLE 88.1 Inherited Disorders of Thyroid Metabolism

	Gene	Inheritance
Hypothalamic-Pituitary Development		
Combined pituitary hormone deficiency	Mutations of *LHX3*, *LHX4*, *HESX1*, *PROP1*, *POU1F1*	AR or AD
Isolated TSH deficiency	*TRH, TSH beta-subunit, TRHR* mutations	AR
TSHR	Loss-of-function TSHR mutation Resistance to TSH with normal TSHR Gain-of-function TSHR mutation *GNAS1* mutations	AR or AD AD AD
Thyroid Gland Development		
	Mutations of *NKX2* (prior *TTF1*), *FOXE1* (prior *TTF2*), *PAX8, TBX1, HOXA2, HHEX, BCL2, SHH*	AR or AD
Organification		
Iodide transport, Pendred syndrome	*SLC5A5, SLC26A4*	AR
TPO	*TPO* mutations	AR
Thyroid NADPH oxidase	*DUOX1* and *DUOX2* mutations	
TG	*TG* mutations	AR or AD
Iodide cycling	Defect not known	?AR
Deiodinase	*DEHAL1*	AR
Thyroid Hormone Transport		
TBG	*TBG* deficiency, partial or complete X-linked recessive *TBG* excess	X-linked recessive X-linked recessive
TTR	*TTR* mutations	AD
Albumin	Albumin mutations	AD
Thyroid Hormone Action		
	THR-beta *MCT8* *SECISBP2*	AD X-linked AR
Generalized Thyroid Hormone Resistance		
	THR mutations	AD

AD, Autosomal dominant; AR, autosomal recessive; GNAS, gene encoding G_s-protein alpha subunit; NADPH, reduced nicotinamide-adenine dinucleotide phosphate; TBG, thyroxine-binding globulin; TG, thyroglobulin; THR, thyroid hormone receptor; TPO, thyroid peroxidase; TRHR, thyrotropin-releasing hormone receptor; TSH, thyrotropin; TSHR, TSH receptor; TTR, transthyretin.
Adapted from Knobel M, Medeiros-Neto G. An outline of inherited disorders of the thyroid hormone generating system. *Thyroid*. 2003;13:771.

adverse neurocognitive development in the fetus.[14] Iodine requirements increase more than 50% during pregnancy, and it is recommended that all pregnant women ingest about 250 mcg of iodine daily.[2] Maternal iodine excess can also cause fetal goiter and hypothyroidism. Iodides and iodine, when given in large quantities, produce a transient inhibition of T_4 synthesis through an autoregulatory mechanism known as the Wolff-Chaikoff effect. Following several days of continued high exposure to iodine, there is escape from the Wolff-Chaikoff effect due to decreased active transport of iodine into the thyroid gland, and thyroid hormone production resumes. The fetal thyroid appears to be more susceptible to this inhibitory effect of iodine and has decreased ability to escape.[20] Maternal administration of medications containing iodides (expectorants, topical antiseptics, amiodarone) can cause neonatal goitrous hypothyroidism. Sustained iodine intake should not exceed 500 mcg daily to avoid potential for fetal thyroid dysfunction.[2]

Other clinically important compounds that can affect fetal thyroid function by crossing the placenta from the mother to the fetus are antithyroid drugs, environmental goitrogens, endocrine disruptors, and thyroid antibodies. Antithyroid drugs include propylthiouracil and methimazole. Transplacental transfer of these drugs can result in fetal goiter with or without hypothyroidism. Transfer of TSI across the placenta to the fetus can cause transient neonatal thyrotoxicosis; the placental transfer of TBII can cause transient neonatal hypothyroidism.

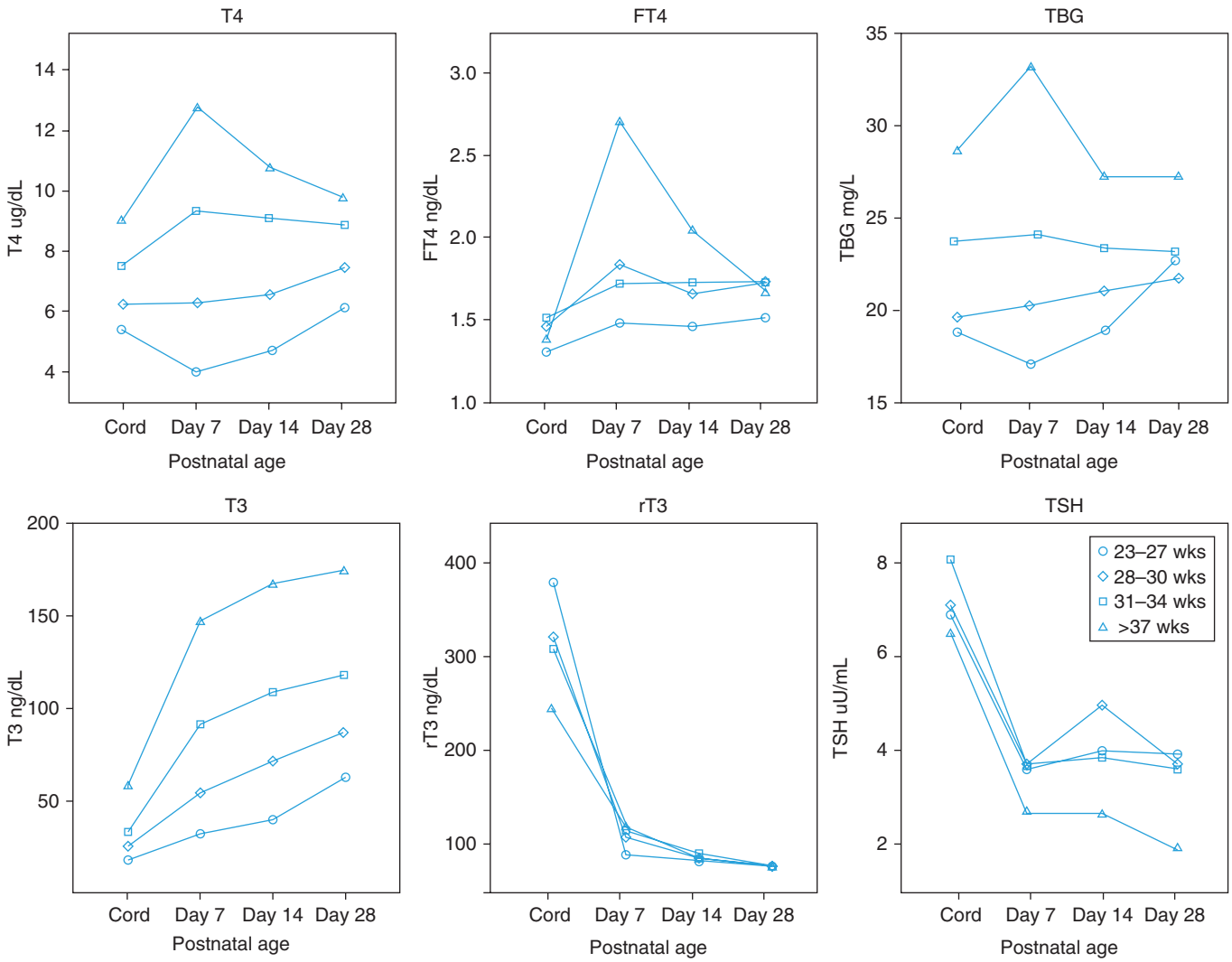
Fetal T_4 and T_3 metabolism differs markedly from that of postnatal life. TSH can be detected in fetal blood by

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10-12 weeks. As a result of maturation of the HPT axis, fetal hypothalamic expression of TRH and production of TSH and T_4 progressively rise from mid gestation to peak during the month prior to term. TSH then remains higher than maternal levels, possibly reflecting a higher set-point for feedback.[30] T_3 levels in fetal blood remain low until 26-30 weeks of gestation, a consequence of high levels of type III deiodinase activity (which converts T_4 to inactive reverse T_3) in peripheral fetal and placental tissues.[41]

T_4-binding proteins can also be detected in the 12-week-old fetus. During early fetal life, T_4 appears to be bound mainly to TTR and albumin. Fetal TBG increases rapidly and by midgestation reaches a level approaching that in a full-term infant. The binding capacity of TBG in premature and full-term infants is about 1.5 times that in the normal adult but lower than that in the mother. The high TBG in the neonate is caused by transplacental transfer of estrogens from the mother and to a large extent accounts for the high T_4 in infants. TTR is low in both newborn and maternal sera and plays a minor role after midgestation.

Shortly after birth, transient but marked hyperactivity occurs in the thyroid function of neonates (Fig. 88.3). Within the first minutes of life, there is a dramatic release of TSH, reaching a peak level of about 100 mU/L at 30 minutes of age. This hypersecretion of TSH persists during the next 6-24 hours. Evidence shows that this acute rise in TSH may be stimulated at least partially by a drop in the body temperature of the fetus with birth. In response to the postnatal TSH surge, T_4, FT_4, and T_3 increase progressively during the first hours of extrauterine life, reaching a peak at about 48 hours of age. The increases in T_3 and FT_3 are more marked than those of T_4 and FT_4 during this period because of increased peripheral conversion of T_4 to T_3. Therefore neonates experience a physiologic



• **Fig. 88.3** Postnatal changes in T4, free T4, thyroxine-binding globulin (TBG), T3, rT3, and thyrotropin (TSH) according to gestational age. Note the increase in T4, free T4, and TBG in the full-term infant in the 1st week of life. T3 also rises strikingly, whereas rT3 and TSH decline. The increase in T4 and free T4 is blunted in infants less than 35 weeks and not seen at all in very premature infants in whom thyroid hormone levels may actually decline. (Reproduced with permission from *Disorders of the Thyroid Gland in Infancy, Childhood and Adolescence,* by Maria Segni, MD, in http://www.thyroidmanager.org/, the free online Thyroid Web-book, version April 4, 2017, published by Endocrine Education, Inc., South Dartmouth, MA.)

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hyperthyroid state during the first few days of life. Concentrations of thyroid hormone remain elevated during the first 2 weeks of life and fall gradually thereafter, with FT_4 reaching high-normal adult values by 4-6 weeks of age. True adult levels of T_4 and T_3 are not reached until puberty, probably because TBG levels in children remain elevated compared with adults until mid-puberty (see Fig. 88.3).

The postnatal TSH surge occurs even in preterm infants and those who are small for gestational age (SGA), although the changes in TSH and iodothyronines are less than those in healthy full-term infants. In preterm infants, T_4 concentrations may decline for a week and then gradually rise, remaining lower than those of full-term infants during the first weeks of life. Thyroid-stimulating hormone returns to normal adult values after 3-10 days of postnatal life regardless of gestational age (see Fig. 88.3).

In human milk, T_4 is present in very small amounts. The concentrations of T_3 and rT_3 in human milk vary from specimen to specimen. The T_3 concentration in breast milk is insufficient to prevent the detrimental effects of hypothyroidism, although it may alleviate the symptoms in certain cases.

Congenital Hypothyroidism

Congenital hypothyroidism is a deficiency in thyroid hormone present at or before birth. Prompt diagnosis is critical, because a delay in treatment can lead to irreversible brain damage. However, overt signs of hypothyroidism are rarely present at birth, and 95% of affected babies are asymptomatic. Dynamic changes in thyroid function after birth, deprivation of maternal hormones, and antibodies acquired by transplacental transfer contribute to the difficulty in establishing a diagnosis. Newborn screening for hypothyroidism was first performed and consequently established in 1972 in Quebec, Canada, to permit early identification of infants at risk and allow prompt institution of thyroid hormone replacement therapy.

Etiology and Pathogenesis

The etiologic classification of congenital hypothyroidism:

1. Primary hypothyroidism
   - a. Defective embryogenesis of thyroid
     - i. Agenesis (athyreosis)
     - ii. Dysgenesis
       - (a) Thyroid remnant in normal location (hypoplasia)
       - (b) Maldescent or ectopic thyroid gland (ectopia)
   - b. Inborn error of hormone synthesis or metabolism (familial dyshormonogenesis)
     - i. Iodide-trapping defect
     - ii. Iodide organification (oxidation) defect
       - (a) Without deafness
       - (b) With deafness (Pendred syndrome)
     - iii. Deiodination defect
       - (a) Generalized
       - (b) Limited to thyroid gland
       - (c) Limited to peripheral tissues
     - iv. Thyroglobulin synthetic defect
     - v. Peripheral tissue resistance to thyroid hormone
2. Central hypothyroidism
   - a. Genetic mutation or deletion (see Table 88.1)
     - i. Isolated deficiency of TSH alpha-subunit
     - ii. Abnormality of hypothalamic-pituitary development, with multiple pituitary hormone deficiencies
   - b. Midline congenital defect (septo-optic dysplasia, holoprosencephaly, cleft lip, single central incisor)
   - c. Acquired birth injury (usually hypothalamic TRH deficiency; birth injury, hemorrhage, hydrocephalus, meningitis, trauma, nonaccidental injury)

Defective Embryogenesis of the Thyroid

In contrast to the clear preponderance of thyroid disorders in females compared with males during childhood and adult life, the gender difference in incidence of congenital hypothyroidism is much less obvious. In North America, the female-to-male ratio is about 2:1, as detected by neonatal screening programs.[4] The relative incidences of each type of congenital hypothyroidism vary widely in different geographic locations, but overall, congenital hypothyroidism occurs in 1:3000 to 1:4000 newborns.

In nongoitrous regions, defective embryogenesis of the thyroid accounts for 80%-90% of nonendemic congenital hypothyroidism. Most cases of thyroid dysgenesis are sporadic, but there is evidence of a familial or genetic component in some patients. Loss-of-function mutations of the TSH receptor gene lead to hypoplasia of the thyroid gland and TSH elevation (see Table 88.1).[10] Mutations in transcription factors (e.g., *PAX8* and *FOXE1*) may be responsible for some cases of congenital hypothyroidism.[19] Failure in the anatomic development of the thyroid gland may be complete or partial. Residual thyroid tissue in the normal position or in ectopic location is detected in 60%-80% of infants and children with hypothyroidism. An ectopic thyroid is usually composed of a remnant of undescended thyroid tissue that is usually situated in the midline. Undescended thyroid is located at the base of the tongue in about half of the cases, between the tongue and the hyoid bone in about one-fourth, and between the hyoid bone and the normal location in the remaining one-fourth. Ectopic tissue is often capable of undergoing compensatory hypertrophy when hormone production becomes inadequate, and thus may be found as a midline mass.

Familial Dyshormonogenesis

Genetically determined errors of T_4 synthesis or metabolism involve a deficiency of one or more enzymes necessary at various stages of the biosynthetic and metabolic pathways. Impaired secretion of T_4 and T_3 results in hypersecretion of TSH, usually leading to compensatory hyperplasia of the

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thyroid. The familial forms of congenital hypothyroidism are usually referred to as *familial dyshormonogenesis*. Hypothyroidism, goiter, or both may be present in the newborn and infant, depending on the degree and time of onset of the hormonal deficiency.

Hypothyroidism caused by a defect in the trapping of iodide is due to a mutation in *SLC5A5*, the sodium-iodide symporter. *SLC5A5* mutations are inherited in an autosomal recessive manner. Infants will typically have a normal-sized or enlarged thyroid gland by ultrasonography and elevated serum thyroglobulin levels. Patients with iodide trapping defects can be confused with athyreosis because of the failure of administered radioiodine to be concentrated in the neck; however, there will also be lack of other physiologic iodine uptake (i.e., in the salivary glands, gastric mucosa, nasopharynx). The severity of hypothyroidism is variable and may depend on the amount of dietary iodine present.[22]

There are specific types of defects in the oxidation or organification of iodide. Among them, thyroperoxidase enzyme deficiency (due to mutations in thyroperoxidase) is the most frequent cause of dyshormonogenesis. Thyroperoxidase mutations are inherited in autosomal recessive manner and can result in severe hypothyroidism with large goiter. Impairment of normal generation of hydrogen peroxide caused by mutations in *DUOX1* and *DUOX2* also can result in congenital hypothyroidism. *DUOX* gene mutations demonstrate variable phenotype with the presence of some residual activity in one of the alleles, resulting in more mild or transient hypothyroidism.

In Pendred syndrome, patients have congenital sensorineural hearing loss and goiter, which typically develops later in childhood or adolescence. Incidence of this disorder is estimated to be about 1.5-3 per 100,000 schoolchildren. Affected individuals are either euthyroid or have mild hypothyroidism. Many will have an abnormal radioiodide discharge from the thyroid after perchlorate administration, indicative of defective iodide organification. Pendred syndrome is caused by biallelic inactivating mutations of the *SLC26A4* gene, located on chromosome 7 (7q31). The *SLC26A4* gene encodes the protein pendrin, which is expressed in the apical membrane of the thyroid and facilitates passive iodide efflux into the lumen. Pendrin is also expressed in the inner ear and is important for maintaining normal acid–base homeostasis of the endolymphatic fluid. The thyroid phenotype in Pendred syndrome is affected by nutritional iodide intake. With adequate dietary iodide, about 90% of patients remain clinically and biochemically euthyroid; in the other 10%, the TSH level is elevated and goiter is present.[22]

In patients with iodothyronine deiodinase defects, there is a rapid turnover of thyroid iodine and wasting of iodotyrosines into the urine. The defect may be generalized, or it may be limited to intrathyroidal or peripheral deiodination. The onset of goiter and hypothyroidism in these patients is variable and may be caused by dietary iodine intake and presence of partial activity of protein.

Defects in thyroglobulin synthesis can result in moderate to severe congenital hypothyroidism with goiter. These patients will have low or absent TG levels and abnormal iodoproteins in their sera. Mutations in the TG gene (8q24, stopping synthesis or causing conformational changes in the molecule) have been reported in these patients.[22]

Defects in TSH or Thyroid Hormone Action

Resistance to thyroid hormone is caused by mutations in thyroid hormone receptors, primarily point mutations in the thyroid hormone receptor-β. It is rare, with incidence of about 1:40,000. Patients have high serum T_4, free T_4, and T_3 with normal or mildly elevated serum TSH. In childhood, there may be development of tachycardia, failure to thrive, and attention deficit disorder. The severity of hormone resistance varies among tissues because of differences in relative expression of the two thyroid hormone receptors—β and α—with some tissues such as cardiac exhibiting more hyperthyroid state due to predominant expression of the α isoform of the thyroid hormone receptor.[37]

Unresponsiveness of the thyroid gland to TSH has been reported in some children with congenital hypothyroidism without goiter. Serum TSH was elevated, and exogenous TSH stimulation caused no increased radioiodine uptake or serum iodothyronine levels. Loss-of-function germline mutations of both alleles of the gene for the TSH receptor have been reported to cause resistance to the action of TSH and hypothyroidism.[10] The mutations were located in the extracellular, TSH-binding domain of the TSH receptor. The TSH receptor is coupled to the protein that binds to guanine nucleotide, or G protein. In these mutations, the TSH receptor does not activate G protein, and the effector adenylate cyclase (cAMP) signaling pathway remains inactive (*GNAS* mutations).

Iodine Deficiency

Endemic goiter and cretinism are still prevalent in large geographic areas where dietary iodine is deficient. Iodide deficiency results in decreased thyroid hormone production in both the mother and fetus. Iodine deficiency also causes preferential production of T_3 relative to T_4. Reduced maternal T_4 levels early in gestation may deprive the developing fetal brain of T_4, which may be the essential iodothyronine for early brain maturation. Severe iodine deficiency that remains untreated can result in two severe types of endemic cretinism: myxedematous cretinism with metabolic symptoms of hypothyroidism and neurologic cretinism with dominant neurologic disorders (severe mental deficiency, deaf-mutism, and motor spasticity).

Significant progress has been made to reduce iodine deficiency through programs of universal salt iodization. About 70% of households worldwide have access to iodized salt, but 30 countries have mild or moderate iodine deficiency. There is recent data that US women are mildly iodine deficient. Iodine deficiency has re-emerged in parts of the

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developed world and may be related to initiatives to lower population sodium consumption.[43] Iodine supplementation before or during pregnancy improves thyroid function in the mother and newborn. The recommended daily iodine intake for all pregnant women is 250 mcg.[2]

Central Hypothyroidism

Secondary (pituitary) and tertiary (hypothalamic) hypothyroidism are not commonly recognized in neonates. Infants with central hypothyroidism can be detected through neonatal thyroid screening programs when T_4 measurements are included with TSH as the neonatal screening test. However, many infants with central hypothyroidism have normal TSH and are missed until they are older than 1 year.[38] A low FT_4 by direct dialysis is the confirmatory test that determines the need for continued treatment when the diagnosis is suspected on the basis of initial tests.

Overall, the prevalence of central congenital hypothyroidism is reported to be higher than previously thought (1 in 20,000 to 1 in 30,000).[1] Autosomal recessive disorders that cause severe hypothyroidism as a result of congenital central hypothyroidism have been reported. Mutations have been identified in the β subunit of TSH, the TRH gene, and the TRH receptor gene.[7,10] Multiple pituitary hormone deficiencies suggest a genetic defect in the signaling cascade leading to fetal pituitary formation, such as *PROP1*, *LHX3*, or *POU1F1*. When present, pituitary aplasia may be associated with anencephaly or other severe malformations of the brain.

Midline facial, cranial, or intracranial defects may also indicate the possibility of hypopituitarism. Septo-optic dysplasia, often associated with pituitary hormone deficiencies, can be manifested as secondary or (more commonly) tertiary hypothyroidism. A genetic mutation in *HESX1* has been described in septo-optic dysplasia. Clinical symptoms of hypopituitarism, such as neonatal hypoglycemia (from growth hormone and ACTH deficiencies), polyuria (from antidiuretic hormone deficiency), or a small phallus in boys (from gonadotropin deficiency), whether or not accompanied by the presence of blindness, congenital nystagmus, or midline defects of the brain, should alert the physician to suspect septo-optic dysplasia.

Diagnosis of Congenital Hypothyroidism

Neonatal Screening for Hypothyroidism

Every state in the United States and every province in Canada has legislatively mandated the screening of newborns for congenital hypothyroidism.[4] Screening programs have also been established in Western Europe, parts of Eastern Europe, Japan, Australia, and parts of Asia, South America, and Central America. However, many countries still do not have a nationwide program for neonatal thyroid screening, despite clear evidence that early detection and treatment of congenital hypothyroidism prevents neurodevelopmental disability.[32]

Most programs currently use the filter paper spot technique. Capillary blood specimens from a heel stick are obtained at 24 hours to 5 days of age. Most programs throughout the world screen for primary hypothyroidism with the measurement of TSH only. In some US states and some Canadian provinces, initial screening measures T_4. Those samples with T_4 values that fall within the lowest 10th percentile are tested for TSH. These methods effectively screen for congenital hypothyroidism for the following reasons: (1) they are easily incorporated into the existing metabolic-genetic screening programs (e.g., phenylketonuria screening); (2) primary T_4 with confirmatory TSH screening (T_4 + TSH) also rapidly identifies those infants with central hypothyroidism or TBG deficiency; (3) selectivity is high because TSH measurements discriminate between affected and nonaffected infants, with a low recall rate (0.3%-1%); and (4) cases of mild congenital hypothyroidism are identified by primary TSH screening and most cases are also identified by T_4 + TSH screening.

Both methods of screening (primary TSH and primary T_4 + TSH) appear to be capable of detecting almost all infants with primary congenital hypothyroidism, the only form of congenital hypothyroidism that carries a high risk for mental retardation if not detected early and treated adequately. Although a TSH level of greater than 40 mU/L is highly suggestive of congenital hypothyroidism, some affected infants have TSH values between 25 and 40 mU/L. These infants require prompt serum confirmation testing, because many will be shown to have primary congenital hypothyroidism. The practice of early hospital discharge (before 48 hours of age) has led to a higher rate of indeterminate results. Infants screened before 48 hours of age require recheck of the newborn screen by the primary care physician at 2 weeks. Infants who are preterm, of low and very low birth weight, ill, the result of a multiple gestation (particularly same sex), or have had sample collection done within the first 24 hours of life should have a second specimen collected and analyzed at 2 weeks of age or 2 weeks after initial sample collection. These infants may be categorized incorrectly based on initial screening due to multiple factors.[32,53]

From mass screening programs in multiple nations, the overall incidence of congenital hypothyroidism appears to be about 1 in 2000-3000 births. There is a female preponderance of 2:1 in the incidence of congenital hypothyroidism in North America, with ectopic thyroid tissue occurring in roughly half of congenital hypothyroidism cases. Aplastic or hypoplastic thyroid glands are found in about one-third of the cases. The prevalence of nonendemic, goitrous congenital hypothyroidism (typically thyroid dyshormonogenesis) depends on frequency of the defective gene in the population but usually occurs in 10% of infants with primary hypothyroidism. In the United States, the combined incidence of secondary and

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tertiary hypothyroidism is about 1 in 80,000-100,000 births.

The prevalence of transient neonatal hypothyroidism differs by geographic location, related to variability in iodine intake. In areas with an adequate iodine supply, most infants with transient hypothyroidism were born to mothers who received goitrogens during pregnancy. Some cases result from placental transmission of maternal blocking antibodies or from exposure of the fetus or newborn to high doses of iodine (e.g., amiodarone, iodine-containing contrast, or topical absorption of iodine-containing antiseptic compounds).[56]

Incidence of congenital hypothyroidism (including dyshormonogenesis) is greatly increased in Down syndrome. Obvious congenital hypothyroidism occurs in about 2% of those with Down syndrome, and thyroid hormone replacement should be implemented in those individuals, followed by prudent and selective reassessment of the need for replacement at an older age (typically >3 years of age).[45] Many additional children with Down syndrome have mildly elevated TSH (5-15 mU/L). The underlying etiology of this observation is unclear, though thyroid-stimulating hormone bioactivity appears to be normal. It has been suggested that this may be reflective of a nonpathologic shift in the normal range of TSH, though this notion, as well as whether these individuals warrant intervention, is unclear. In a single randomized controlled study of infants and toddlers with Down syndrome, early replacement therapy resulted in modest growth and developmental benefits. However, these differences did not clearly persist in the follow up of this population at age 10 years.[35]

Screening programs that measure T_4 also identify infants with TBG deficiency. This predominantly X-linked trait (Xq22.2) occurs as frequently as 1 in 5000-10,000 births. Thyroxine-binding globulin deficiency has no clinical importance and, therefore, requires no intervention but leads to abnormal laboratory tests. T_4 concentrations are low, in the context of normal TSH and FT4 concentrations. Diagnosis can be confirmed by low TBG concentration on specific radioimmunoassay.

Clinical Manifestations

Even in athyreotic infants, classic clinical features of congenital hypothyroidism are usually absent at birth, resultant from some maternal T4 crossing the placenta, with umbilical cord levels of T4 reaching 25%-50% of those of normal newborns. Birth length and weight are generally normal, and manifestations appear gradually over several weeks in infants who do not receive thyroid hormone replacement. These manifestations include lethargy; inactivity; hypotonia; periorbital edema; large anterior and posterior fontanelles; feeding difficulty, including needing to be awakened to feed; respiratory distress; pallor; prolonged jaundice; perioral cyanosis; mottled skin; poor or hoarse crying; constipation; and hypothermia. In patients with a functional remnant of thyroid tissue and in those with familial dyshormonogenesis, clinical manifestations may be delayed several months or years, depending on the functional state of the thyroid.

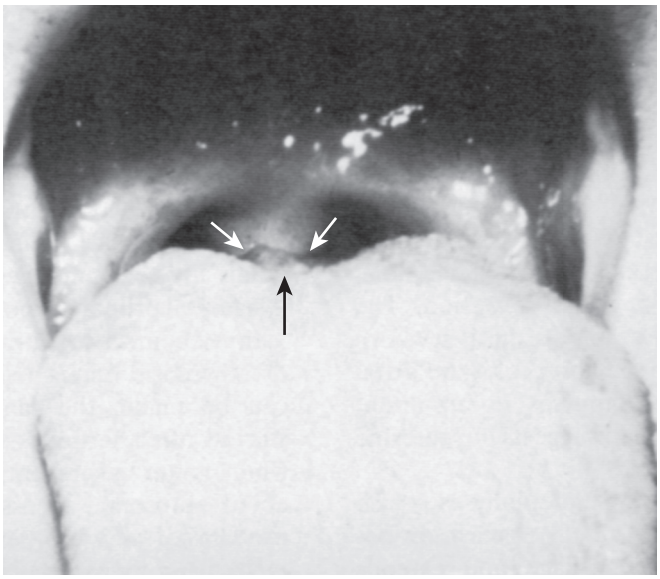
Respiratory distress associated with myxedema of the airway is characterized by noisy breathing, nasal stuffiness, and intermittent cyanosis, especially in the perioral area. Respiratory symptoms may lead to suspicion of congenital anomalies of the airway or congenital heart disease. After the 1st week of life, prolonged physiologic jaundice may be an indication of hypothyroidism. In primary hypothyroidism, indirect hyperbilirubinemia predominates, whereas in central hypothyroidism, there is a mixture of indirect and direct hyperbilirubinemia. Serum creatinine may be elevated.

Classic features of congenital hypothyroidism in the infant usually become apparent after about 6 weeks of age (Fig. 88.4). They include typical facies, characterized by a



• **Fig. 88.4** Three-month-old male with features of hypothyroidism. (Reproduced with permission from Maria Segni. Disorders of the thyroid gland in infancy, childhood and adolescence. In: DeGroot LJ, ed. *Thyroid disease manager*. Figure drawn on data from Fiona L. R. Williams, et al., Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. *The Journal of Clinical Endocrinology & Metabolism* 2004;89(11):5314-5320.)

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• **Fig. 88.5** Visualization of a lingual thyroid.



• **Fig. 88.6** Iodine-induced goiter in a neonate. The lateral bulging of the neck is caused by enlarged lateral lobes of the thyroid.

depressed nasal bridge, a relatively narrow forehead, puffy eyelids, dry and cold skin, long and abundant coarse hair, large tongue, abdominal distention, umbilical hernia, hyporeflexia, bradycardia, hypotension with narrow pulse pressure, anemia, and widely patent cranial sutures.

Lingual thyroid tissue can occasionally be seen in infants and children as a discrete round mass at the base of the tongue (Fig. 88.5). The base of the tongue must be firmly depressed to visualize the lingual thyroid. Because ectopic thyroid tissue may function normally at birth, the ectopic gland of a child may not be detected by newborn screening and may present during childhood or adolescence with a lingual mass associated with speech and feeding problems. In some instances, the sublingual thyroid is palpable as a round midline mass deep under the mandible or is visualized by ultrasonography.

Neonatal goiters may be extremely large, asymmetric, and confused with hygroma or other cervical masses (see Fig. 88.6). Alternatively, the goiter may be quite small and escape notice. The thyroid can be palpated in infants by placing them in the prone position, gently extending the neck, identifying the thyroid cartilage, and palpating inferiorly and laterally for the thyroid isthmus and lobes. The normal size of each thyroid lobe is about equal to the volume of the distal segment of the patient's thumb.

In infants with central hypothyroidism, there is no thyroid enlargement. Onset of symptoms tends to be gradual because some T_4 production continues. As a result, prognosis for mental development remains good. However, signs of other pituitary hormone deficiencies, congenital midbrain defects, or both are typically present. These signs may include neonatal hypoglycemia, a small penis, hypospadias, undescended testes, wandering nystagmus, cleft lip or palate, and combined direct and indirect hyperbilirubinemia. Growth failure gradually becomes evident in these patients.

Infants with congenital hypothyroidism are at higher risk to have certain comorbid congenital malformations, including cardiac malformations (such as septal defects) and renal anomalies, and a careful clinical evaluation of these infants should be done.

Laboratory Manifestations

When the diagnosis of congenital hypothyroidism is suspected, thyroid function tests should be performed (see Box 88.2). It is advisable to assess FT_4 and TSH, and in selected patients, TG levels.[34] Measurements of T_3, rT_3, FT_3, and T_3U are not currently indicated. Elevated serum TSH value is the most sensitive and specific test to confirm the diagnosis of primary hypothyroidism. The normal value for TSH in cord blood is higher than that at any other age (see Fig. 88.3). The physiologic TSH surge occurs during the first 6 hours of life, as noted earlier, and concentration of TSH may remain higher than 10 mU/L during the first 24-48 hours of life. Infants whose specimens were collected before 24 hours of life and who have mildly elevated TSH values very likely will have normal thyroid function tests on repeated testing.[53]

The typical laboratory findings for primary hypothyroidism are an elevated TSH, with T_4 and FT_4 values in the

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• BOX 88.2 Laboratory Tests Used for the Diagnosis of Thyroid Disorders and Assessment of Thyroid Function in Infancy and Childhood

Serum Tests

- Thyrotropin (TSH)
- Thyroid hormones: thyroxine (T_4), free T_4 (FT_4) by analogue methods (initial screen), and direct dialysis (definitive method), triiodothyronine (T_3)
- Thyroid hormone-binding protein: thyroxine-binding globulin (TBG)
- Thyroid autoantibodies: thyroglobulin antibodies (TGAb), thyroperoxidase (microsomal) antibodies (TPOAb), TSH-receptor antibodies (TRAb) by TBII or TSI methods
- Thyroglobulin (TG)

Imaging Tests

- Thyroid scan with ^{99m}Tc-pertechnetate or ^{123}I-iodide
- Thyroid ultrasound

Miscellaneous Tests

- AM to PM TSH ratio
- Assessment of skeletal maturation
- Thyrotropin-releasing hormone (TRH) stimulation test
- Urinary iodine excretion

low or low-normal range. Occasionally, TG may be used as an adjunct to distinguish between etiologies of primary hypothyroidism if imaging is equivocal. A low or undetectable TG concentration with TSH elevation confirms a dysgenetic or absent thyroid gland, whereas a high TG with TSH elevation suggests an organification defect. In central hypothyroidism, TSH is usually normal or may be frankly low, T_4 is low or low-normal, and FT_4 is low or low-normal. Confirmation of suspected central hypothyroidism requires interrogation of the remainder of pituitary function and anomalies in pituitary anatomy.

In infants with acute or chronic illness, the euthyroid sick syndrome or nonthyroidal illness syndrome may be present and affects thyroid function test results but does not produce hypothyroidism. Typical laboratory findings in nonthyroidal illness are low or normal serum T_4, normal FT_4 by direct dialysis, and normal TSH. Total T_3 can be very low, and rT_3 is elevated.

Retardation of bone maturation is present in about half of the newborns with primary hypothyroidism and may suggest the fetal age at which a deficiency developed in the delivery of thyroid hormone to responsive tissues.[4] This assessment has been reported as a predictive indicator of persistent developmental delays, even in the setting of early intervention. Retardation of bone maturation in neonates is best assessed by radiographs of the knee and foot. The ossification centers of the calcaneus and talus appear at about 26-28 weeks of gestation, and those of the distal femur at about 34-36 weeks. The proximal tibial epiphyses appear at about 35 weeks of gestation. Absence of the distal femoral epiphyses in a newborn weighing 3000 g or more, or absence of the distal femoral and proximal tibial epiphyses in an infant weighing 2500-3000 g at birth, suggests an intrauterine thyroid hormone deficiency. Ossification of the cartilage of the epiphyses is also disturbed in hypothyroidism and normally begins from the center of the cartilage and extends peripherally in an orderly manner. In hypothyroidism, calcification of epiphyseal centers starts from multiple irregular foci scattered within the developing cartilage. The irregular calcification pattern appears on the radiograph as stippled or fragmented ossification centers and is referred to as *epiphyseal dysgenesis*, a finding that is highly characteristic of hypothyroidism (see Fig. 88.1). Stippled epiphyses may also occur in thyroid hormone resistance and also in multiple epiphyseal dysplasia, although thyroid function is normal in this familial disease.

Interpretation of Scanning Results

An enlarged, lingual, or dysgenetic thyroid may be identifiable by ultrasound.[54] Thyroid ultrasonography is highly user-dependent and also limited in its ability to detect lingual and sublingual ectopy.

The use of ^{123}I or ^{99m}Tc-pertechnetate is recommended, when practical, to distinguish dysgenesis from ectopia, as well as detect a large gland or one with high levels of uptake. Tracer uptake is obviously decreased or absent in hypoplastic or aplastic thyroid glands. A decrease in uptake may also be indicative of maternal blocking antibodies or acute iodine excess. Avid or high uptake is suggestive of iodine deficiency, or certain forms of dyshormonogenesis with defects downstream of iodine uptake or trapping (e.g., defects in thyroid peroxidase, dual oxidase 2, thyroglobulin, pendrin, or dehalogenase).

A perchlorate discharge test, which assesses the discharge of ^{123}I following the administration of perchlorate, may aid in the diagnosis of an organification defect. When rapid oxidation and organification of inorganic iodide fails to take place in the thyroid (i.e., a lack of conversion to iodine), an anion such as perchlorate can competitively inhibit the iodide accumulation, leading to a net loss of iodide from the gland. ^{123}I-iodide uptake is measured at 2 hours, immediately after which sodium or potassium perchlorate is given orally in doses of 10 mg/kg of body weight. Thyroid uptake is measured every 15-30 minutes for 2 hours. If the uptake decreases by more than 10% of the initial value, a defect in iodide oxidation or organification is confirmed.

Imaging should never delay the initiation of treatment in infants with suspected congenital hypothyroidism. Scintigraphy can be performed within 7 days of starting levothyroxine.[32] Patients can also be treated for a few years, with a definitive study undertaken at a later date. Ultimately, the findings of imaging studies can help to further guide diagnostic evaluation (i.e., molecular genetic testing) to confirm the presence of true congenital hypothyroidism and its etiology.

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Differential Diagnosis

Errors in diagnosis of congenital hypothyroidism usually result from a failure of the newborn screening program (no specimen collected or a laboratory error), from a clinical failure to suspect the condition, or from the misdiagnosis of other disorders as hypothyroidism. These errors typically arise when the diagnosis is based on a few suggestive clinical features, and laboratory data are incorrectly interpreted. It is necessary to perform newborn screening even in sick newborns so that clear-cut abnormalities cannot be missed. Repeated screening is then indicated as the illness resolves.

During the early neonatal period, respiratory difficulty, pallor, and cyanosis in hypothyroid infants must be differentiated from other common causes of respiratory distress and from congenital heart disease. Lethargy, inactivity, hypotonia, and feeding difficulty may be mistaken for manifestations of sepsis or brain damage from a variety of causes. The prolonged jaundice in hypothyroidism must not be confused with icterus caused by hemolytic anemia, septicemia, or hepatic disease. The coarse facial features, macroglossia, and dry skin of hypothyroidism can mislead one to suspect Hurler syndrome, chondrodystrophy, or Down syndrome (see Fig. 88.4). A large goiter must not be confused with a hygroma, cyst, or tumor of the neck. A lingual thyroid, when visible or obstructing the airway, may be mistaken for a tumor of the pharyngeal area (see Fig. 88.5). Although epiphyseal dysgenesis may resemble osteochondritis deformans in its radiographic appearance (see Fig. 88.1), the latter does not occur during the neonatal period.

Transient Disorders of Thyroid Function

Transient neonatal thyroid dysfunction must be distinguished from permanent disorders of thyroid function. The results of neonatal screening tests from these patients may mimic those found in permanent hypothyroidism and may lead to an erroneous diagnosis and prolonged treatment. About 24%-36% of children diagnosed with congenital hypothyroidism by newborn screening are later determined to have transient hypothyroidism.[29]

In mothers with Graves disease, the transplacental passage of antithyroid drugs may cause transient hypothyroidism with goiter in the neonate. These drugs are rapidly cleared from the neonate within days.

Transplacental transfer of maternal inhibiting TSH-receptor antibodies (TRAb) can rarely result in transient neonatal primary hypothyroidism. These antibodies may persist in the infant's circulation for 2-3 months. No goiter is present, and absent or decreased uptake is seen on thyroid scintigraphy, although thyroid tissue can be seen on an ultrasonogram.

Premature neonates have many aberrations in thyroid status, including a delay and blunting of their postnatal TSH surge. In some very preterm infants (<31 weeks), T_4 concentrations do not rise and may fall within the first 1-2 weeks, termed transient hypothyroxinemia of prematurity. Free T_4 levels tend to be less affected, and the laboratory profile reflects abnormal protein binding or decreased TBG levels (affecting infants <30 weeks of gestation). Many other factors are thought to affect thyroid status in premature neonates, including immaturity of the hypothalamic-pituitary axis. In addition, given the prevalent neonatal morbidities in premature infants, laboratory anomalies consistent with the euthyroid sick syndrome are common. It is recommended that thyroid screening in preterm infants be repeated at 2 weeks of age or 2 weeks after initial screening was done.

Whether or not preterm infants should receive thyroid hormone replacement remains controversial. An association between hypothyroxinemia in preterm infants and neurodevelopmental problems and intellectual disability has been documented; however, these were observational studies that did not establish causality. Efficacy of thyroid hormone therapy has also not been established. A Cochrane review did not support use of thyroid hormone to treat transient hypothyroxinemia in preterm infants.[39] It was recommended that future controlled trials should be of adequate size to detect clinically significant differences in neonatal outcomes.

The incidence of transient primary hypothyroidism is higher in geographic areas where the dietary supply of iodine is insufficient, and premature infants are more susceptible, with incidence increasing with decreasing gestational age. Low urinary iodine concentration suggests this as the causative factor, and iodine supplementation may successfully correct hypothyroidism and goiter in these infants.

Conversely, iatrogenic iodine overload may also cause transient hypothyroidism, and premature infants appear to be more susceptible to iodine-induced transient hypothyroidism. Radiocontrast agents or the excessive application of iodine-containing antiseptics to mucous membranes (e.g., omphalocele) or intact skin can be sources of excessive iodine exposure.[31]

Heterozygous or homozygous DUOX2 mutations, impacting enzymes involved in iodine oxidation, may result in transient primary hypothyroidism in the neonate.

Finally, neonates who are the product of pregnancies complicated by uncontrolled hyperthyroidism during pregnancy may also be transiently centrally hypothyroid.

Euthyroid Sick Syndrome

Acutely ill patients commonly have alterations in thyroid function testing. The current hypothesis is that these alterations occur as an adaptive response to decrease basal metabolic rates in severely ill patients. The syndrome has been recognized in sick infants and children, with both acute and/or chronic illness.[52]

In the neonatal period, preterm infants with respiratory distress syndrome are the most frequently encountered patients with euthyroid sick syndrome.[42] An alteration in T_4 metabolism favors production of rT_3 over T_3, which appears to occur rapidly. The prevalence and severity of the euthyroid sick syndrome increases with decreasing gestational

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age. The consistent finding is an abnormally low serum T_3 level, often accompanied by an increase in the rT_3 level. T_4 may be low or normal and FT_4 may be normal, depending on the metabolic clearance rate of T_4. Serum TBG may be low or normal, and TSH may be low or normal. In preterm infants, T_4, FT_4, and T_3 levels are typically lower than those in term infants, and rT_3 is high.[42] Therefore, thyroid tests in preterm infants may present a confusing situation when the infants are ill from nonthyroidal diseases.

Abnormal thyroid function gradually reverts to normal function as the patient's primary illness improves. During recovery, TSH may be transiently elevated (up to 15 mU/L). Treatment with thyroid hormone is not indicated in these patients. However, preterm infants at risk should be monitored by serial determinations of FT_4 and TSH, and T_4 treatment should be initiated if there is a progressive increase in serum TSH and decrease in FT_4.

Treatment of Hypothyroidism

Transplacental transfer of maternal T_4 during gestation initially offers some protection of brain development in the hypothyroid neonate. Serum T_4 concentrations at term in athyreotic babies are 25%-50% of those found in normal neonates. For this reason, the majority of newborns with congenital hypothyroidism are asymptomatic or have only mild symptoms. However, the half-life of serum T_4, including T_4 acquired from the mother, is short in infants (3-4 days) compared with adults (about 6 days), and within 1-2 weeks the infant's serum T_4 level will have dropped significantly. A delay in the initiation of thyroid hormone therapy can result in a decrease in IQ score, and replacement is recommended within the first 2 weeks of life.[32] Thyroid hormone replacement therapy for neonatal congenital hypothyroidism must be started as soon as blood is collected for serum confirmation tests.[4] Therefore, all hypothyroid infants, with or without goiter, should be rendered euthyroid as promptly as possible with replacement therapy. Those with mild TSH elevation and normal FT_4 may be monitored with serial TSH and FT_4 tests and not treated for up to 4 weeks. However, if TSH remains elevated, thyroid hormone therapy should be started. In rare instances in which the diagnosis of congenital hypothyroidism cannot be established expeditiously because of confounding laboratory results, it is the safest course to fully treat the infant for the first 3 years of life. At 3 years of age, after the brain has substantially completed its growth, treatment can be withdrawn or decreased by 50% and the patient re-evaluated 4-6 weeks later.

Asymptomatic infants and those with minimal clinical manifestations of congenital hypothyroidism can be given sodium-L-thyroxine, 10-15 μg/kg per day (administered orally once per day), beginning as soon as the diagnosis is established (optimally by 2 weeks of age).[4] There is no evidence that sole or combination therapy with L-T3 is superior to therapy with L-T4 alone and, therefore, it is not recommended. Bioavailability of brand L-T4 may be higher than generic and, therefore, generally preferred in use in athyreotic infants. The pill should be crushed and suspended in a small amount of formula, breast milk, or water (not the whole bottle). Human breast milk does not contain enough T_4 to alter thyroid hormone levels in the infant, and therefore breastfeeding can continue with appropriate replacement of L-T4. The suspension can be provided by way of a cross-cut nipple and followed later by the feeding. Administration can be either before or with feedings, although should be in the same way with every dose. Separation from intake of soy, iron, or calcium is advised, and in the first few weeks of life, from vitamin D administration.

The initial dose of T_4 need not exceed 50 μg/day. TSH and FT_4 values should be initially rechecked 1-2 weeks after initiation of therapy, and then at 2-week intervals until normalization of TSH. The thyroid hormone dose may need to be decreased to 37.5 μg/day or on rare occasions to 25 μg/day if FT_4 exceeds 2.5 ng/dL, TSH suppression occurs, or clinical symptoms of thyrotoxicosis develop. The target for TSH concentrations should be in the normal range for age during thyroid hormone replacement therapy, with FT_4 levels in the upper half of normal for age. Age-appropriate levels in children differ from those in adults (see Fig. 88.2).

In preterm infants, the same starting dose of T_4 (10-15 μg/kg per day) is recommended to promptly increase T_4 to normal. The dose may need to be decreased, as described, once free T_4 (FT_4) or total T_4 (TT_4) values reach the desired normal level. No adverse effects from this dose of T_4 replacement therapy were found in infants during their 1st year of life as long as they were frequently monitored, including FT_4 and TSH determinations.

In treatment of infants with severe myxedema with fluid retention, possible complications should be kept in mind. Cardiac insufficiency caused by pericardial effusions or overloading of the myxedematous heart through too rapid a mobilization of the myxedema fluid into the circulation is well-known in the adult. This complication in older children and adults is prevented by administering a small dose of thyroid hormone at first and gradually increasing the dosage. However, infants generally tolerate a rapid restoration to the euthyroid state better than adults, and a prompt restoration of T_4 to a normal value is important for the recovery of brain development and maturation. Nevertheless, excessive thyroid hormone therapy must be avoided, and the dose must be adjusted judiciously (starting at ~50% of the target dose, and increasing gradually after 2 weeks) if there is evidence of severe myxedema, particularly of the heart. Aspiration of food can occur in cases of severe myxedema resulting from impairment in swallowing (caused by myxedema of the pharyngeal area), compounded by an increased appetite as the euthyroid state is restored. Therefore, when myxedema is severe, the infant should be fed carefully and slowly during the early phase of treatment.

During the first years of life, patients should be monitored frequently—at least every 2 months during the first

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6 months of life, every 3-4 months during the next 2 years, and then twice a year—to assess clinical progress and adjust levothyroxine to maintain FT_4 and TSH in target range.[4] Thyroid hormone requirement based on weight (μg/kg per day) will gradually decrease from a dose of 8-10 μg/kg per day at age 3-6 months to 2-3 μg/kg per day in adolescents. In adults, thyroid hormone requirement is approximately 1.7 μg/kg per day.

Goitrous cretinism caused by the maternal ingestion of goitrogens is a self-limited condition. The blocking effect of antithyroid drugs usually disappears several days after birth. Therefore, if the goiter is small, TSH is not elevated, and the patient is euthyroid, no treatment is required. However, if the patient is hypothyroid and TSH is elevated or if the goiter is large, it is safer to treat the infant until the age of 3 years, as described previously.

In nursing mothers with Graves disease, both propylthiouracil (PTU) and methimazole (MTZ) are secreted in breast milk in small concentrations. However, studies of breastfed infants of mothers taking these medications have demonstrated normal thyroid function and intellectual development.[26]

Prenatal diagnosis and intrauterine treatment of congenital hypothyroidism have been successful in only a number of cases. Optimal methods for monitoring fetal thyroid state still need to be established. Imaging studies alone are not sufficient, because goiter can result from hypothyroid or hyperthyroid states. Measurements of accurate TSH levels (compared to gestational age norms) are done by cordocentesis, but this increases the risk of fetal loss and should therefore only be done when intervention is contemplated. In utero treatment with intra-amniotic L-thyroxine injection is effective for reducing fetal goiter size, which may be considered for a fetus with progressive hydramnios, a risk for premature delivery, and/or concerns for tracheal occlusion. However, there are no clear recommendations for dosing regimens or outcome data to show neurodevelopmental benefit from therapy, because the number of cases treated in utero is small. Prenatal diagnosis and treatment of congenital hypothyroidism await further developments.

Prognosis for Congenital Hypothyroidism

Shortly after adequate substitution therapy is instituted, clinical manifestations of hypothyroidism resolve. If growth restriction was present before treatment, accelerated linear growth occurs. After a period of catch-up growth, an optimal rate of growth is maintained. Goiter or a hypertrophied ectopic thyroid gradually shrinks in size when the patient is properly treated. If there was a delay in skeletal maturation at diagnosis, treatment is associated with acceleration in bone maturation after a latent period of a few months, with subsequent osseous development that parallels chronologic age. Overtreatment should be avoided, because this can result in rapid epiphyseal closure and craniosynostosis. With substitution therapy, epiphyseal dysgenesis (see Fig. 88.1), present in ossification centers that failed to calcify while the patient was hypothyroid, develops calcification that coalesces to form a normal epiphysis.

Age of initiation of thyroid hormone therapy is a major determinant of neurodevelopmental outcome. Review of a number of studies comparing treatment at an earlier age (day of life 12-30) versus at a later age (>30 days of life) found that infants started at the earlier age averaged 15.7 IQ points higher. Initial starting dose of levothyroxine is also important. The majority of studies have found that children started on doses of 10-15 μg/kg per day had the best IQ outcome. Severity of hypothyroidism was also thought to contribute to poor outcome in prior studies. However, it appears that inadequate starting dose likely explains the association in these studies, and titrating levothyroxine dose to severity of hypothyroidism greatly improves outcome.[47] Last, continued compliance of thyroid hormone therapy during infancy and childhood is vital; recurrent episodes in childhood of insufficiently suppressed TSH are associated with school delay.

Current follow-up studies of patients treated within the first few weeks of postnatal life after identification by neonatal screening indicate that neurologic function overall is normal, with a few minor exceptions. Residual defects may include visual–spatial processing, sensorimotor defects, attention problems, and selective memory. There are only minor differences in intelligence, school achievement, and neuropsychologic test scores in affected congenital hypothyroidism adults treated early with thyroid hormone compared with control groups of classmates and siblings. Poor attention can also be seen in patients who have been overtreated.[32] Overall, intellectual and neurologic prognosis for patients with congenital hypothyroidism has greatly improved since the advent of newborn screening. We may still expect further improvement in the future, because thyroid hormone treatment regimens used today are more aggressive in targeting the early correction of TSH than the regimens used 15-30 years ago.

Neonatal Graves Disease

Etiology and Pathogenesis

Maternal Graves disease is the most common cause of neonatal hyperthyroidism and results from transplacental transfer of stimulating TSH-receptor antibodies (TRAb) from the mother to newborn. The disease can occur in the neonate of a mother known to have active Graves disease and also in mothers with a history of Graves disease previously treated with thyroidectomy or radioiodine ablation. Neonatal Graves disease occurs in 1%-5% of at risk pregnant mothers. There is an increased likelihood of neonatal Graves hyperthyroidism if there is higher maternal stimulatory TRAb concentration during the third trimester. The highest risk occurs when maternal TSI is greater than 5 index units.[44]

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Clinical Manifestations

When neonatal thyrotoxicosis occurs in the infant born to a mother with untreated, active Graves disease, clinical manifestations of hyperthyroidism may become apparent within the first 24 hours of life. Infants may be born prematurely from such a mother. Clinical features that may be seen include hyperkinesis, diarrhea, poor weight gain, hepatosplenomegaly, jaundice, thrombocytopenia, craniosynostosis, tachycardia, exophthalmos, and goiter. Although a goiter is inevitably present in neonatal thyrotoxicosis, its size varies considerably; it may be small and escape notice on a cursory examination, or it may be large enough to cause tracheal compression. Exophthalmos is usually mild when present. In severe neonatal thyrotoxicosis, hyperthermia, arrhythmia, and high-output cardiac failure may occur. If the condition remains untreated, death may result. In most cases, the course of neonatal hyperthyroidism is self-limited because of the gradual depletion of transplacentally acquired stimulating TRAb. The signs and symptoms subside spontaneously after 3 weeks to 6 months; rapid resolution of symptoms occurs when the initial titer of serum-stimulating TRAb in the neonate is lower. However, goiter may persist for some time after all signs of hyperthyroidism disappear. The thyroid gradually returns to its normal size. In rare instances, neonatal thyrotoxicosis may not be a transient disorder and may persist for years, usually indicating the presence of activating mutations of the TSH receptor.

In the infant born to a mother who received antithyroid medications for the treatment of Graves disease during the latter part of pregnancy, the onset of clinical manifestations may be modified by transplacental acquisition of the antithyroid agent as well as stimulating TRAb. At birth, the infant may be euthyroid or even hypothyroid, and the presence of a goiter may be the only abnormal feature. Because the plasma half-life of antithyroid agents is short compared with the half-life of stimulating TRAb, the typical manifestations of neonatal thyrotoxicosis may appear several days to 2 weeks after birth. Although neonatal Graves disease is a disease mediated by monoclonal antibodies, polyclonal antibodies are sometimes produced by the mother and cause atypical disease in the infant. Hyperthyroidism may not develop until 1-2 months of age if a high-affinity TSH-binding/inhibiting immunoglobulin (TBII) in low concentrations initially predominates; once it is metabolized, a second population of stimulating TRAb prevails to cause late-onset hyperthyroidism.

Diagnosis and Differential Diagnosis

A maternal history of Graves disease before or during pregnancy is important to identify infants at risk for neonatal Graves disease. Information concerning both prior and current treatment of maternal hyperthyroidism must also be obtained. The infant should be examined sequentially for signs of thyrotoxicosis, and the neck should be palpated carefully to detect a goiter. Determination of stimulating TRAb in infant serum or cord blood should be obtained. A higher titer of TRAb in cord blood or neonatal serum strongly supports the diagnosis of neonatal Graves in a thyrotoxic infant. Serial measurements of TRAb in the infant also help monitor disease activity and aid the decision to decrease or terminate therapy. It is recommended that in at-risk infants, TSH and FT_4 be measured at day 3-5 of life or earlier if there is clinical concern. If these levels are normal, they should be repeated again at day of life 10-14. If there are no lab abnormalities after 2 weeks of life, routine testing can be discontinued as the majority of infants are diagnosed by 2 weeks. At-risk infants should continue to be assessed clinically at 4 weeks, 2 months, and 3 months of life to identify a minority of patients with delayed presentation.[57] Lab measurements should be interpreted in relation to age-appropriate reference ranges.

In the euthyroid or hypothyroid neonate born to a mother who received antithyroid medication during the latter part of pregnancy, it is almost impossible to predict whether thyrotoxicosis will ensue. Therefore, serial examinations of the infant must be undertaken during the first 10 days of life. Although neonatal thyrotoxicosis can be confused with various neurologic disorders, narcotic withdrawal in the infant of an addicted mother, congenital heart disease, or sepsis, a positive maternal history of Graves disease and presence of goiter should readily alert the physician to the correct diagnosis. In normal neonates and infants, the thyroid gland is difficult to palpate. Therefore, an easily palpable thyroid in such an infant should generally be regarded as a goiter.

More rarely, neonatal hyperthyroidism may result from defects in the TSH receptor or the downstream mediators, and unlike neonatal Graves disease, these forms of hyperthyroidism are persistent and are not mediated by TRAb. These germline mutations demonstrate autosomal dominant inheritance (see Table 88.1) and occur in the transmembrane domains of the receptor or affect receptor coupling to stimulatory G protein, which leads to constitutive activation of the adenylate cyclase.[46] Because of disease severity and frequent relapse, definitive therapy with surgery or radioactive iodine is eventually indicated when the patient is older.

Treatment

The treatment of thyrotoxicosis in a neonate is similar to that in an older child and involves use of antithyroid drugs. Care should be exercised not to induce hypothyroidism with excessive medication. Iodine (Lugol solution) and an antithyroid drug, methimazole (MTZ), are typically used. Lugol solution can be given at a dose of one drop three times daily. Although iodine rapidly inhibits the release of T_4 from the thyroid, its effects tend to disappear after several weeks. Iodine should be given at least 1 hour after methimazole to avoid exacerbating hyperthyroidism acutely. Methimazole is given in doses of 0.2-1 mg/kg per day in

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one to three divided doses. Propylthiouracil (PTU) is no longer recommended for use in children because of association with liver failure.[48] Most symptoms of hyperthyroidism are closely related to increased adrenergic response. Therefore, beta-adrenergic blocking drugs can alleviate many of the potentially life-threatening manifestations of neonatal thyrotoxicosis. In contrast to antithyroid drugs, these agents can rapidly diminish the severity of thyrotoxicosis, and their effects are evident within a few hours. Propranolol, together with iodine and MTZ, may be used in the treatment of severe neonatal thyrotoxicosis. Propranolol is given orally in a dose of 0.5-2 mg/kg per day in two or more divided doses. In critically ill newborns, a short course of pharmacologic glucocorticoids, which inhibits thyroid hormone secretion and impairs peripheral conversion of T_4 to T_3, may be needed to help stabilize the infant.

Circulating T_4 has a half-life of 3-4 days in neonates and about 6 days in adults. Therefore, little or no clinical response to antithyroid drugs can be expected during the first few days of therapy. The TSH response to a hypothyroid state induced by the excessive treatment of thyrotoxicosis may be diminished for several months or longer in these infants. Therefore, lack of TSH elevation cannot be relied on to indicate the excessive treatment of thyrotoxicosis. It is recommended that thyroid function be measured weekly until FT_4 concentrations are stable and then every 2 weeks.[48] MTZ should be decreased and eventually discontinued when FT_4 concentrations have normalized. Monitoring of TRAb titers may facilitate decision making about when to discontinue therapy as well. Depending on the initial TRAb titers, neonatal Graves disease typically resolves by 6 months of age; treatment duration usually lasts about 1-2 months.

The hypothyroid infant born to a mother who received antithyroid medications during pregnancy should be managed as described in the section on congenital hypothyroidism. If the infant has already received thyroid hormone, such therapy should be decreased as soon as thyrotoxic manifestations occur, and the appropriate management of hyperthyroidism must be initiated.

Prenatal therapy is possible with the use of oral maternal antithyroid drugs and adjustment of the dose to normalize fetal TSH and cardiac function. It is recommended that when a pregnant woman has uncontrolled hyperthyroidism or elevated TRAb greater than three times the upper limit of normal, serial fetal ultrasounds should be performed.[2] Ultrasound can detect fetal tachycardia, rapid bone maturation, and goiter, which indicate a fetal hyperthyroid state. If fetal hypothyroidism results from maternal overtreatment with antithyroid drugs, serial ultrasound of the fetal thyroid can also be helpful to determine if subsequent dose reduction of antithyroid drug is sufficient.

Prognosis

Most infants diagnosed promptly and treated appropriately for neonatal Graves disease will improve quickly. However, it has been reported that some patients on long-term follow-up are found to have lower IQs. Craniosynostosis, hyperactivity, and other behavioral problems have also been seen.[15] There have also been cases described associating neonatal Graves disease and/or poorly controlled maternal hyperthyroidism with development of central hypothyroidism in the infant.[27,34] It seems as if fetal or neonatal exposure to high thyroid hormone concentrations can impair neurodevelopment and specifically the maturation of the hypothalamic-pituitary-thyroid axis. These findings highlight the importance of close monitoring of both maternal and neonatal thyroid function and drug management.

Familial Abnormalities of Thyroxine-Binding Proteins

Genetic disorders resulting in either increased or decreased levels of T_4-binding proteins have been reported. Affected individuals are healthy and asymptomatic because a change in the level of T_4-binding proteins does not lead to an alteration of FT_4. The disorders are usually discovered fortuitously by the measurement of T_4, which reveals unexpectedly high or low values. Therefore, the only clinical significance of these conditions lies in the abnormal T_4 level, possibly leading to an erroneous diagnosis. The TSH levels are normal in these individuals.

Thyroxine-Binding Globulin (TBG) Defects

TBG is one of the major serum transport proteins for thyroid hormone. TBG is encoded by one gene copy on the long arm of the X chromosome (Xp22.2). Inherited TBG defects typically follow an X-linked pattern. Complete TBG deficiency occurs in 1/15,000 newborns and partial deficiency in 1/4,000 newborns. Males with complete deficiency have undetectable TBG and heterozygous females typically have half the normal TBG concentration. In TBG excess, affected males have TBG concentration 2-4 times the mean level, and carrier females have levels slightly above half of affected males. TBG excess and deficiency are usually diagnosed incidentally with lab work, demonstrating abnormal T_4 with normal free T_4.[40]

Increased Transthyretin (TTR)

Families with increased levels of TTR have been reported and specific gene mutations identified. Serum T_4 is elevated, but FT_4 is normal. Only a small amount of T_4 is bound to TTR; therefore, T_4 level is only significantly elevated in variants with much higher binding affinity for thyroid hormone.[40]

Familial Dysalbuminemic Hyperthyroxinemia

Familial dysalbuminemic hyperthyroxinemia is caused by gain-of-function mutations in the human serum albumin

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gene resulting in enhanced binding of T_4 by abnormal serum albumin. Its prevalence varies from 0.01%-1.8% depending on the ethnicity with frequency being highest in Hispanics.[40] Affected individuals typically have elevated T_4 or T_3 depending on the specific mutation. Free T_4 concentration measured by direct dialysis is normal, but if analogue methods are used, there may be interference from abnormal albumin, resulting in falsely elevated levels.

Key Points

- Maintenance of normal thyroid hormone levels is important for metabolism, linear growth, and brain development during infancy and childhood.
- The hypothalamic-pituitary axis along with iodine metabolism exert primary control over thyroid hormone production.
- In utero, maternal and fetal relationships have significant impact on thyroid hormone adequacy in the fetus.
- Early detection of congenital hypothyroidism by newborn screening has dramatically improved outcomes and reduced negative impact of hypothyroidism on neurocognitive development.
- Neonatal Graves disease is the most common cause of neonatal hyperthyroidism; even mothers who have already been treated for Graves disease are at risk for having offspring with neonatal Graves disease.
- Clinical awareness of abnormalities in thyroxine-binding proteins is important to avoid erroneous diagnosis of hypo- or hyperthyroidism.

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89

Disorders of Sex Development

JULIA CATHERINE SORBARA AND DIANE KATHERINE WHERRETT

Genetic sex is determined at the time of fertilization, but carrying out the steps of sexual differentiation takes place over 14 weeks of embryonic and fetal development. An error in this process may result in a disorder of sex development (DSD), defined as a discrepancy in the genetic, gonadal, or genital makeup of an individual. This chapter reviews normal fetal sexual differentiation; the approaches to the recognition and diagnosis of neonates who may have a DSD; and the classification, clinical features, and general management principles of DSDs, with the focus on perinatal issues.

Fetal Sexual Determination and Differentiation

Genetic Control of Fetal Gonadal Determination and Differentiation

The embryo and early fetus, regardless of genetic sex (i.e., 46,XX or 46,XY), are bipotential with respect to sexual differentiation, having the anatomic and biochemical components necessary for both male and female development. For normal male differentiation to occur, a succession of genetic and hormonal signals must be intact and occur correctly.[14] The classic teaching is that there is an innate tendency of the embryo and early fetus to differentiate along female lines; that is, female differentiation is the default setting, occurring when signals for male differentiation are absent. However, there is growing evidence supporting female differentiation as an active process, induced and maintained by specific genes and signaling pathways.[5] The biopotential gonad begins to differentiate at 7 weeks of gestation under the direction of both sex and autosomal chromosome gene products, which function primarily as transcription factors.

Sex Chromosomes and Role of the SRY Gene

The presence of the *SRY* gene on the Y chromosome causes the bipotential gonad to differentiate as a testis, and male phenotypic development follows. The presence of one, two, or more X chromosomes does not alter this process. However, the presence of more than one X chromosome (e.g., 47,XXY syndrome, also known as Klinefelter syndrome) results in eventual meiotic failure, loss of germ cells, and infertility. Although autosomal factors that drive ovarian differentiation have been identified, an X-linked female-determining factor analogous to SRY has not yet been discovered.[5]

On the other hand, early ovarian differentiation does not require two X chromosomes and can proceed in 45,X fetuses. Later stages, however, of ovarian differentiation do require two X chromosomes, as this is necessary for normal formation of primordial follicles. From 15 weeks' gestation onwards, ovarian development will start to fail if part or all of the second X chromosome is missing as primordial follicles and oocytes degenerate rapidly. The resulting gonad appears as an elongated, whitish streak that microscopically demonstrates whorls of fibrous tissue without germ cells or epithelial elements. This "streak" gonad is characteristic of the gonadal dysgenesis syndromes.

Fetuses with Y chromosome material that fail to undergo normal testicular differentiation are believed to develop streak gonads through similar changes. Unlike gonadal dysgenesis in individuals without Y chromosome material, these structures carry a high risk for the development of gonadal tumors.[1] These tumors may result from the persistence of residual XY germ cells that did not degenerate or from tumorigenic loci on the Y chromosome.

Autosomal and X-Linked Genes

Although the presence or absence of the *SRY* gene determines the fate of the bipotential gonad, additional autosomal and X-linked genes, located upstream and downstream from the *SRY* gene, are involved in gonadal development and differentiation (Fig. 89.1).[80] Several of these genes encode transcription factors or transcription regulatory proteins, which activate or repress the expression of additional target genes, often in multiple tissues, influencing or controlling a diverse program of cellular differentiation and proliferation during embryonic and fetal development. When gene mutations occur, the functional domain of the transcription factor becomes altered, leading to abnormal or contrary regulation (e.g., from a repressor to an activator) of downstream genes. This results in abnormal cell differentiation or growth or neoplastic transformation. It is the occurrence of such mutations and the resulting pathologic conditions that have led to the identification and functional understanding

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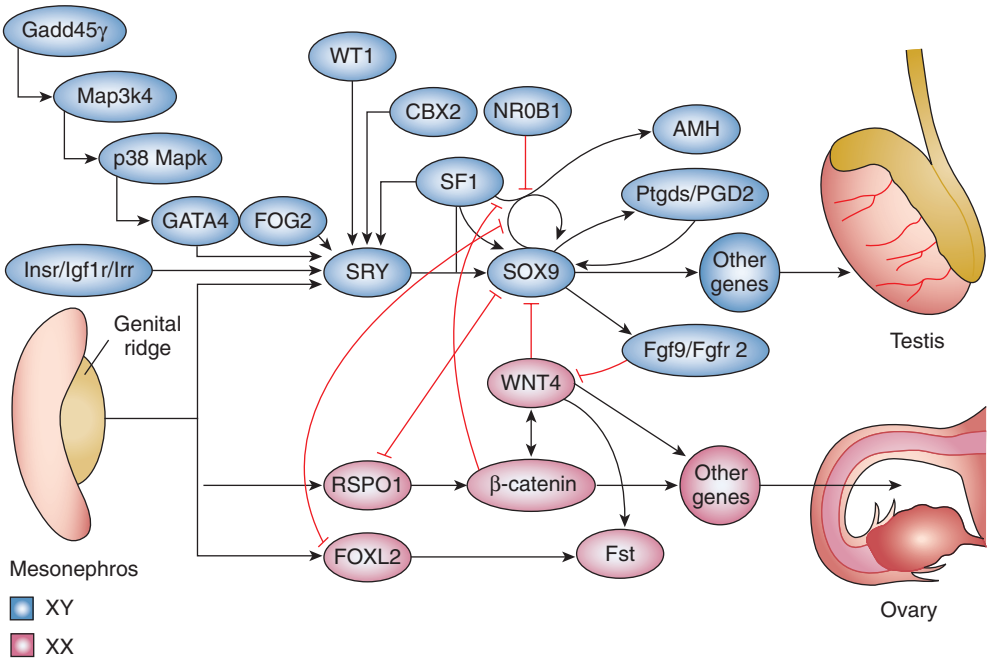
Abstract

Genetic sex is determined at the time of fertilization, but carrying out the genetic directives that lead to steps of sexual differentiation takes place over 14 weeks of embryonic and fetal development. An error or fault in this process may result in a disorder of sex development (DSD), defined as a discrepancy in the genetic, gonadal, or genital makeup of an individual. This chapter reviews (1) normal fetal sexual differentiation; (2) an approach to the recognition and diagnosis of neonates who may have a DSD; and (3) the classification, clinical features, and general management principles of DSDs, with the focus on perinatal issues.

Keywords

disorders of sex development
congenital adrenal hyperplasia
sexual differentiation
gonadal dysgenesis
micropenis
clitoromegaly
cryptorchidism

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• **Fig. 89.1** Gene regulatory networks in embryonic gonadal development. Genes shown are known to have a role in sex development on the basis of studies in humans and mice (*uppercase*) or in mice only (*lowercase*). Testis-related genes (*blue*) and ovary-related genes (*red*) are depicted in regulatory pathways leading to Sertoli- and granulose-cell specification, respectively. In XY gonads, SOX9 expression is subsequently upregulated by SRY and SF-1 binding to TESCO. SOX9 is a key hub gene for testis development. SOX9 maintains its own expression through binding to TESCO with SF-1. SOX9 also regulates expression of genes required for testis formation such as AMH, FGF9, PTGDS, and probably other genes. SOX9 also suppresses the expression of ovarian genes such as RSPO1 and FOXL2. Sexual dimorphism in the XX genital ridge is triggered by R-spondin-1 (encoded by RSPO1) and FOXL2. WNT4, β-catenin, and Fst are also expressed in a female-specific manner, promoting ovarian development. Additionally, R-spondin-1, FOXL2, WNT-4, and β-catenin have roles in preventing differentiation of testis by repressing SOX9 expression. (From Ono M, Harley VR. Disorders of sex development: new genes, new concepts. *Nat Rev Endocrinol.* 2013;9:79-91.)

of many of these genes. Examples of gene mutations that affect sex determination in 46,XY and 46,XX DSDs are listed in Table 89.1.[80]

Embryology and Endocrinology

The bipotential gonads as well as the anlagen for the genital ducts and external genitalia are derived from the mesodermal germ layer; the exception is the urogenital sinus epithelium, which is of endodermal origin. The bipotential gonadal and genital tissues undergo morphogenesis during the embryonic period, which extends from the end of the third week, or about 20 days gestational age, through the 7th to 8th week of gestation. Fetal sexual differentiation begins in the 7th week, when the bipotential gonad begins to differentiate as either a testis or an ovary. This process continues until 12-14 weeks of fetal age, at which point differentiation of the internal genital ducts and external genitalia along male or female lines is largely complete.

Development of the Gonads

The initial step in gonadal development is the formation of paired, bipotential genital ridges, which occurs at 4-4.5 weeks' gestational age on the medial aspect of each mesonephros. The somatic component of the gonad originates from coelomic epithelium and the underlying mesenchyme or adjacent mesonephros.[109] The germinal component comprises the primordial germ cells, which migrate from the yolk sac endoderm at 24 days to reach the genital ridge at 4.5-6 weeks. Following migration, there is ongoing proliferation up until 9 weeks' gestational age, which completes the formation of the indifferent gonad (Fig. 89.2).[72,109] Normal development of the potential gonads is directed by key transcription factors. Genetic changes to their encoding regions may lead to the development of streak gonads, having significant implications for further sexual differentiation.[30]

Testicular Differentiation

The expression of the *SRY* gene in XY gonads initiates testicular differentiation at 7 to 8 weeks' gestational age. Anatomical differentiation begins when the sex cords form loops in the cortex and differentiate as the seminiferous cords. In the hilum, they anastomose to form the rete cords. From 8 weeks on, the seminiferous cords become coiled and thickened and contain eight to ten layers of Sertoli cells. Spermatogonia, however, remain located near the basement

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membrane of the cords. Under the influence of signals from Sertoli cells, Leydig cells appear in the interstitium between the seminiferous cords at 7.5-8 weeks. They increase strikingly in number during the third month, occupy half the volume of the testis at 13-14 weeks, and then show a significant fall in number. Some Leydig cells are present postnatally but histologically disappear after 3-6 months because of the physiologic decline in gonadotropin stimulation. As the fetus elongates, the testis descends and occupies a more caudal position. In the 6th and 7th months, the cremaster muscle differentiates in the caudal testicular ligament to form the testicular gubernaculum, which penetrates the inguinal canal and is anchored to the connective tissue of the scrotum. The testis descends behind the peritoneum and

TABLE 89.1 Examples of Gene Mutations That Affect the Sex Determination, Clinical Phenotype, and Associated Anomalies

Gene (Locus)	Gonadal Development and External Genital Phenotype(s)	Müllerian Structures	Associated Disorders
Gene Mutations Described in 46,XY DSD			
WT1 (WT33) (11p13)	Dysgenetic testis Undervirilized ♂; EG or normal ♀; EG	±	Wilms tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash, and Fraser syndromes)
MAP3K1 (5q11.2)	Dysgenetic testis Normal/undervirilized ♂; EG or normal ♀; EG	±	None
ARX (Xp22.13)	Dysgenetic testis Undervirilized ♂; EG	–	Lissencephaly, epilepsy, temperature instability
ATRX (Xq13.3)	Dysgenetic testis Normal/undervirilized ♂; EG or normal ♀; EG	–	α-Thalassemia, developmental delay, dysmorphic facial features
WWOX (16q23.3-q24.1)	Dysgenetic testis Normal ♀; EG	–	—
AMH or Type II receptors (19p13.3-13.2) (12q12-13)	Normal gonadal development Normal ♂; EG	+	—
NROB1 (DAX1) (Xp21.3)	Dysgenetic testis Normal/undervirilized ♂; EG or normal ♀; EG	±	Congenital adrenal hypoplasia, hypogonadotropic hypogonadism
DHH (12q13.1)	Dysgenetic testis Normal ♀; EG	+	Minifascicular neuropathy
DMRT1 (9p24.3)	Dysgenetic testis Normal/undervirilized ♂; EG	±	Facial abnormality, developmental delay, microcephaly
CBX2 (17q25)	Normal ovaries Normal ♀; EG	+	None
GATA4 (8p23.1– p22)	Dysgenetic testis Normal/undervirilized ♂; EG	–	Congenital heart disease
AR (Xq12)	Normal/undervirilized ♂; EG or normal ♀; EG	–	Spinal and bulbar muscular atrophy (SBMA) and prostate cancer
HHAT	Partial/complete gonadal dysgenesis Normal ♀; EG	±	Chondrodysplasia
Gene Mutations Described in 46,XX DSD			
SOX3 duplication (Xq27.1)	Atrophic change in testis with loss of normal spermatogenesis Normal/virilized ♀; EG	Data unavailable	Microcephaly, developmental delay, growth restriction
RSPO1 (1p34.3)	Testis or ovotestis Virilized ♀; EG or undervirilized ♂; EG	–	Palmoplantar hyperkeratosis, squamous cell carcinoma of the skin

Continued

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TABLE 89.1 Examples of Gene Mutations That Affect the Sex Determination, Clinical Phenotype, and Associated Anomalies—cont'd

Gene (Locus)	Gonadal Development and External Genital Phenotype(s)	Müllerian Structures	Associated Disorders
Gene Mutations Described in 46,XY or 46,XX DSDs			
SOX9 duplication (17q24q25)	46,XY DSD: Dysgenetic testis or ovotestis Undervirilized ♂; EG or normal ♀; EG	±	Campomelic dysplasia
	46,XX DSD: Gonadal histologic phenotype: not determined Virilized ♀; EG or undervirilized ♂; EG	–	None
SRY translocation (Yp11.3)	46,XY DSD: Dysgenetic testis or ovotestis Undervirilized ♂; EG or normal ♀; EG	±	None
	46,XX DSD: Testis or ovotestis	–	None
MAMLD1 (Xq28)	46,XY DSD: Isolated hypospadias	–	None
	46,XX DSD: Streak or dysgenetic gonads Abnormal ♀; EG	+	None
NR5A1 (SF-1) (9p33)	46,XY DSD: Dysgenetic testis Normal/undervirilized ♂; EG or normal ♀; EG	±	± Adrenal insufficiency
	46,XX DSD: Dysgenetic gonads Normal ♀; EG	+	None
WNT4 (1p35)	46,XY DSD: Dysgenetic testis Undervirilized ♂; EG	–	Cleft lip, cleft palate, IUGR, tetralogy of Fallot, developmental delay, microcephaly
	46,XX DSD: Ovary or ovotestis Normal/virilized ♀; EG or normal ♂; EG	–	Mayer-Rokitansky-Küster-Hauser, SERKAL syndromes

EG, External genital; IUGR, intrauterine growth restriction; SERKAL, sex reversion, kidneys, adrenal and lung dysgenesis; WAGR, Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.
Modified from Ono M, Harley VR. Disorders of sex development: new genes, new concepts. *Nat Rev Endocrinol.* 2013;9:79-91.

reaches the scrotum by the 8th or 9th month. The inguinal canal closes after testicular descent is complete.[44]

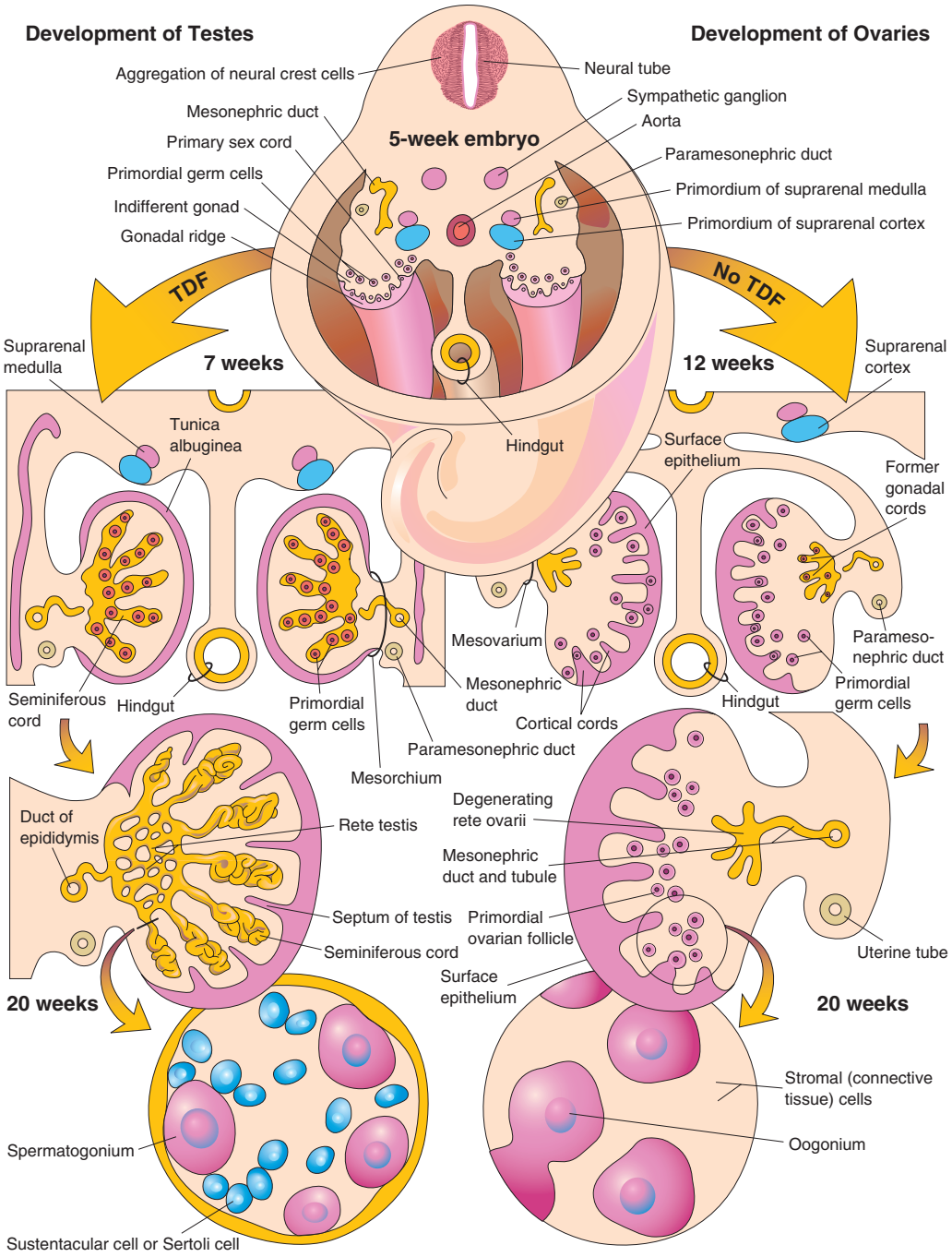
Ovarian Differentiation

Ovarian differentiation begins at 7 weeks, as outlined previously and in Table 89.2. Unlike in testicular differentiation, the presence of germ cells in an XX gonad is required for normal ovarian follicular development. The sex cords in the ovary show germ cells (oogonia) undergoing repeated mitotic divisions from 7 weeks through about the 5th month. Most oogonia differentiate into primary oocytes between about 10 and 24 weeks. During this process, they enter meiosis, proceeding through the first meiotic prophase. After reaching the meiotic prophase, from about 21 weeks until term, many oocytes become surrounded by a single layer of granulosa cells to form primordial follicles. Two X chromosomes are needed for differentiation of the primordial follicle into a mature follicle. Oocytes degenerate if they are not enclosed in a mature follicle. During ovarian differentiation, the number of germ cells greatly increases to several million oogonia and oocytes by the 5th month. Most germ cells degenerate thereafter, either before or during the primordial follicle stage, leaving about 150,000–295,000 follicles in each ovary at birth.[104] Theca cells, the ovarian steroid hormone–producing cells, first appear in midgestation.[109]

Development of the Genital Ducts

The internal genital ducts, unlike the gonads, develop from the mesonephric or wolffian ducts in the male and from the paramesonephric or Müllerian ducts in the female. The wolffian ducts are formed in 26- to 32-day-old embryos. The Müllerian ducts begin development at about 37 days in close association with the wolffian ducts, which serve as

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• **Fig. 89.2** Schematic illustration showing differentiation of the indifferent gonads of a 5-week embryo (*top*) into ovaries or testes. The left side of the drawing shows the development of testes resulting from the effects of the testis-determining factor (TDF) located on the Y chromosome. Note that the gonadal cords become seminiferous cords, the primordia of the seminiferous tubules. The parts of the gonadal cords that enter the medulla of the testis form the rete testis. In the section of the testis at the bottom left, there are two kinds of cells: spermatogonia, derived from primordial germ cells, and sustentacular or Sertoli cells, derived from mesenchyme. The right side of the drawing shows the development of ovaries in the absence of TDF. Cortical cords have extended from the surface epithelium of the gonad, and primordial germ cells have entered them. They are the primordia of the oogonia. Follicular cells are derived from the surface epithelium of the ovary. (From Moore KL, Persaud TVN. *The developing human: clinically oriented embryology.* 10th ed. Philadelphia: Saunders; 2015.)

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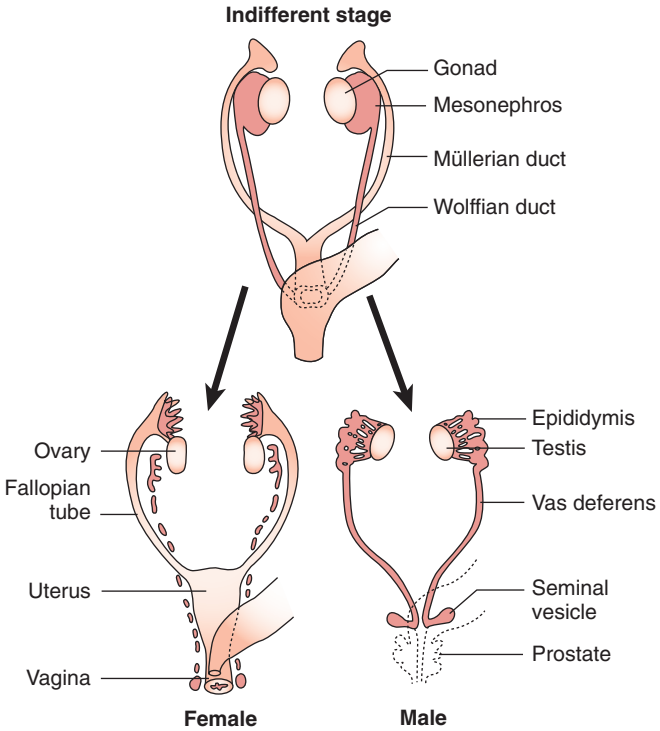
TABLE 89.2 Descriptive Features of Testicular and Ovarian Differentiation at 7 Weeks of Gestation

Gonadal Cells	Testicular Differentiation	Ovarian Differentiation
Cord somatic cells	Differentiate as Sertoli cells Synthesize anti-Müllerian hormone (AMH) at 7½ weeks Unable to aromatize androgens to estrogens	Differentiate as granulosa cells Do not synthesize AMH at this age Able to aromatize androgens to estrogens
Germ cells	Reduced mitotic activity results in small number of spermatogonia Meiosis is inhibited until puberty	High mitotic activity results in large number of oogonia Meiosis is promoted within several weeks
Interstitial cells	Differentiate as Leydig cells Synthesize testosterone de novo at 8 weeks	Remain undifferentiated until 15 weeks Lack steroidogenic capability at this age
Outer cortex	Sex cords lose connection with surface epithelium Mesenchymal tissue forms tunica albuginea that lacks germ cells	Sex cords retain connection with surface epithelium Thickened zone that contains germ cells

a guide to the caudal progression of the Müllerian ducts. In the absence of the wolffian ducts, the Müllerian ducts do not develop.

In the male fetus, the Müllerian ducts begin to regress at 7-7.5 weeks, shortly after the Sertoli cells have differentiated and begun to produce anti-Müllerian hormone (AMH), also known as *Müllerian-inhibiting substance* (MIS). This occurs before the onset of local testosterone production by Leydig cells and regression is complete by 9 weeks. Differentiation of the wolffian ducts into the male internal genitalia is testosterone dependent and begins at about 8.5 weeks. The wolffian ducts differentiate into the epididymis and vas deferens, and beginning at 10.5 weeks, the seminal vesicles and their ejaculatory ducts develop at the caudal end from lateral outpouchings (Fig. 89.3).

In the female fetus, Müllerian duct differentiation occurs in the absence of AMH and does not require the presence of any ovarian hormone. Beginning in the 3rd month, the Müllerian ducts form the fallopian tubes, uterus, and upper portion of the vagina, stimulated in part by epidermal growth factor. The wolffian ducts degenerate in the absence of local testosterone and disappear by 13 weeks (see Fig. 89.3). The fallopian tubes later descend with the ovaries and are included in a fold of peritoneum called the *broad ligament*. At birth and until puberty, the position of the uterus is vertical, and uterine development is disproportionate with the cervix being twice as large as the fundus. Maternal estrogens stimulate uterine growth in utero and, consequently, its size at birth is larger than at several months of age. Endometrial hyperplasia may occasionally result in transient neonatal uterine bleeding. The development of the vagina depends on the caudal Müllerian ducts contacting the endodermal epithelium of the urogenital sinus. At this junction, a multilayered, solid epithelial cord known as the *vaginal plate* is formed and it disintegrates beyond 4 months to form the vaginal lumen. It is not clear whether the lower portion of the vagina is derived from the urogenital sinus, with the upper portion of Müllerian origin, or if the vagina originates entirely from the urogenital sinus.

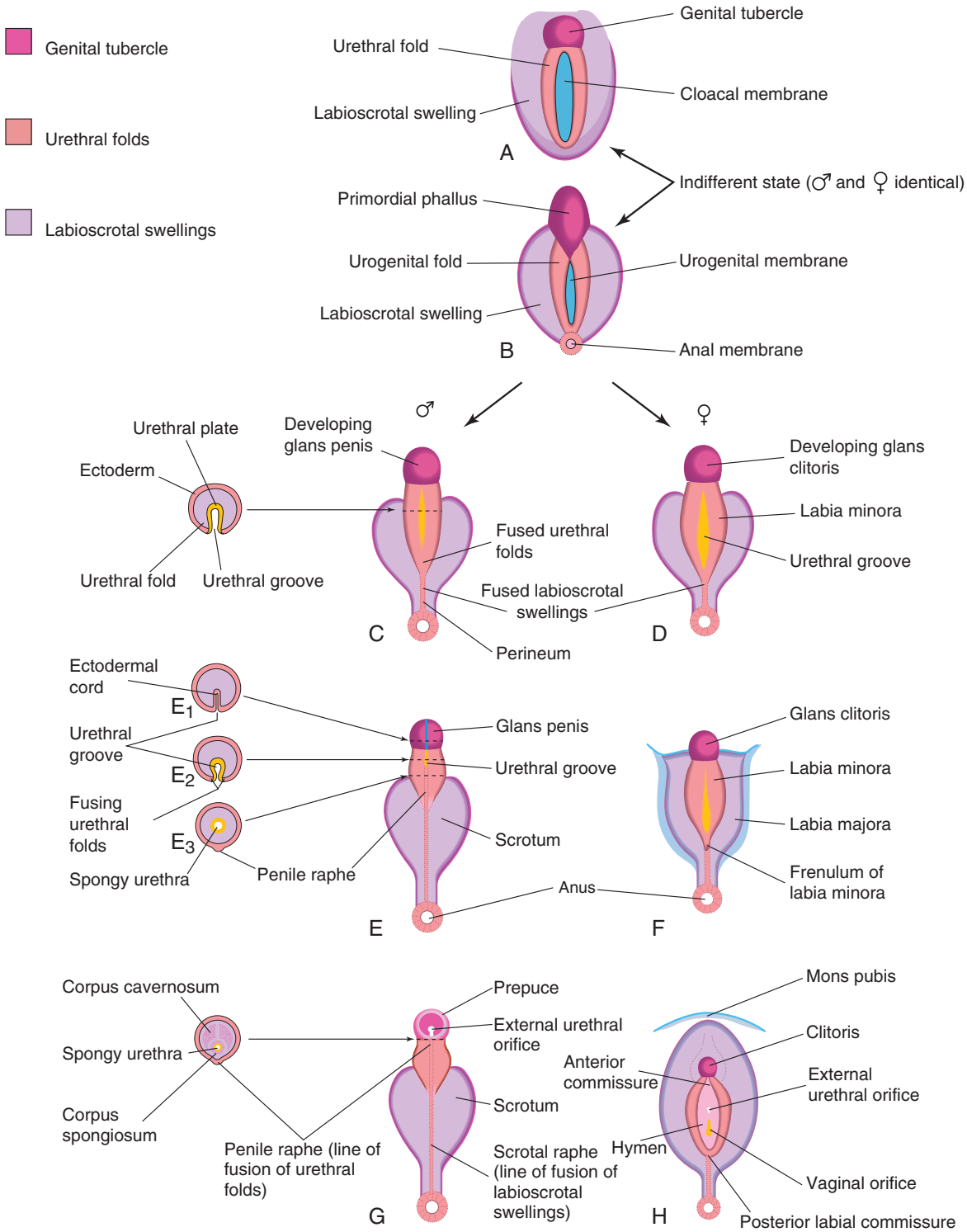


• **Fig. 89.3** Embryonic differentiation of female and male genital ducts from wolffian and Müllerian primordial tissue before descent of the testes into the scrotum. In females, Müllerian structures persist to form the fallopian tubes, uterus, and upper portion of the vagina. The lower portion of the vagina and urethra are derived from the urogenital sinus. In males, wolffian structures develop into the epididymides, vasa deferentia, and seminal vesicles, whereas the prostate and prostatic urethra are derived from the urogenital sinus. In some cases, a small Müllerian remnant can persist in males as a testicular appendage. (From Kronenberg H, et al. *Williams' textbook of endocrinology.* Philadelphia: Saunders; 2011.)

Development of the External Genitalia

The external genitalia in both sexes, like the gonads, are derived from common anlagen (Fig. 89.4). The inherent development is along female lines unless systemic androgens, specifically dihydrotestosterone (DHT), induce male

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• **Fig. 89.4** Development of the external genitalia. **A** and **B**, Diagrams illustrating the appearance of the genitalia during the indifferent stage (4th to 7th weeks). **C**, **E**, and **G**, Stages in the development of the male external genitalia at 9, 11, and 12 weeks, respectively. To the left are schematic transverse sections of the developing penis illustrating formulation of the spongy urethra. **D**, **F**, and **H**, Stages in the development of the female external genitalia at 9, 11, and 12 weeks, respectively. The mons pubis is a part of the fatty tissue over the symphysis pubis. From Moore KL, Persaud TVN. *The developing human: clinically oriented embryology.* 10th ed. Philadelphia: Saunders; 2015.

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differentiation. The genital tubercle forms early in the 4th week at the cranial end of the cloacal membrane and, on each side, the labioscrotal swellings and urogenital folds develop. Fusion of the urorectal septum with the cloacal membrane in the 7th week creates a dorsal anal membrane and a ventral urogenital membrane, which rupture in the 8th week to form the anus and urogenital orifice. Abnormal development of the urorectal septum results in anorectal malformations.

In the male fetus, the indifferent stage of the external genitalia lasts until the 9th week when, in the presence of systemic androgens, masculinization begins with lengthening of the anogenital distance (see Fig. 89.4). Androgens also drive the urogenital and labioscrotal folds to fuse in the midline, beginning caudally and progressing anteriorly. The urethra develops with fusion of the urogenital folds, which form both the membranous urethra in the perineum and the penile urethra along the ventral surface of the phallus. Midline fusion of the labioscrotal folds forms the scrotal raphe, whereas the penile raphe represents the fused portions of the urogenital folds. These processes are complete by 14 weeks' gestation.

In the 9-week female fetus, without the presence of systemic androgens, the anogenital distance does not increase, and the urogenital folds and labioscrotal swellings do not fuse (see Fig. 89.4). The labioscrotal swellings develop predominantly in their caudal portions but less so than in male fetuses. They remain unfused as they are transformed into the labia majora. The unfused urogenital folds develop into the labia minora. The epithelium of the vaginal vestibule between the labia minora and the hymen is endodermal, derived from the urogenital sinus, whereas the epithelium between the labia minora and majora is ectodermal in origin.[73]

Hormonal Control of Fetal Sex Differentiation

The fetal testes play a major role in male sex differentiation by producing two hormones, AMH and testosterone, which are important determinants of internal and external genital differentiation. In contrast, the fetal ovaries play a negligible role or no role in female sex differentiation, although they may have some steroidogenic capacity.

Fetal Gonadal Endocrine Function

Anti-Müllerian hormone is a large glycoprotein. It is produced by the fetal Sertoli cells beginning at 7.5 weeks that induces irreversible involution of the Müllerian ducts. Regression of the Müllerian ducts can occur only during a fetal age of 8-9 weeks as, by 10 weeks' gestation, the Müllerian ducts become insensitive to AMH. The gene coding for AMH is located on chromosome 19p13.3 and for the AMH receptor on chromosome 12.[91]

The other major hormone produced by the fetal testis is testosterone (Fig. 89.5). It is synthesized by the Leydig cells beginning at 8 weeks, with peak testicular testosterone production occurring at 10-15 weeks. In the second half of gestation, serum testosterone levels decline in males and rise in females such that, by the third trimester, males have similar or only slightly higher levels than females.[95]

Between 8 and 14 weeks, the control of fetal testicular synthesis of testosterone is under the control of placental or fetal human chorionic gonadotropin (hCG). In the second and third trimesters, fetal serum luteinizing hormone (LH) stimulates testosterone synthesis and LH levels correlate with the maintenance and subsequent decline of serum testosterone.[9] Follicle-stimulating hormone (FSH) receptors are present in fetal testes from 8 weeks and FSH is involved in the proliferation of both Sertoli and germ cells during the second trimester. However, the degree to which FSH is required for these processes, independent of LH and testosterone, remains unclear.[81]

The fetal ovary in the first trimester is hormonally quiescent, lacking hCG and FSH binding sites as well as the enzymes necessary for steroid hormone synthesis. Starting at 8 weeks, the fetal ovary develops aromatase activity and is capable of converting androstenedione or testosterone to estrone or estradiol. However, actual steroidogenesis at this time has not been demonstrated. The majority of fetal estrogen is produced by placental aromatase. Amniotic fluid levels of estradiol at 12-16 weeks are slightly higher in females, raising the possibility of ovarian synthesis of estrogen.

Control of Genital Differentiation: Roles of Anti-Müllerian Hormone and Testosterone

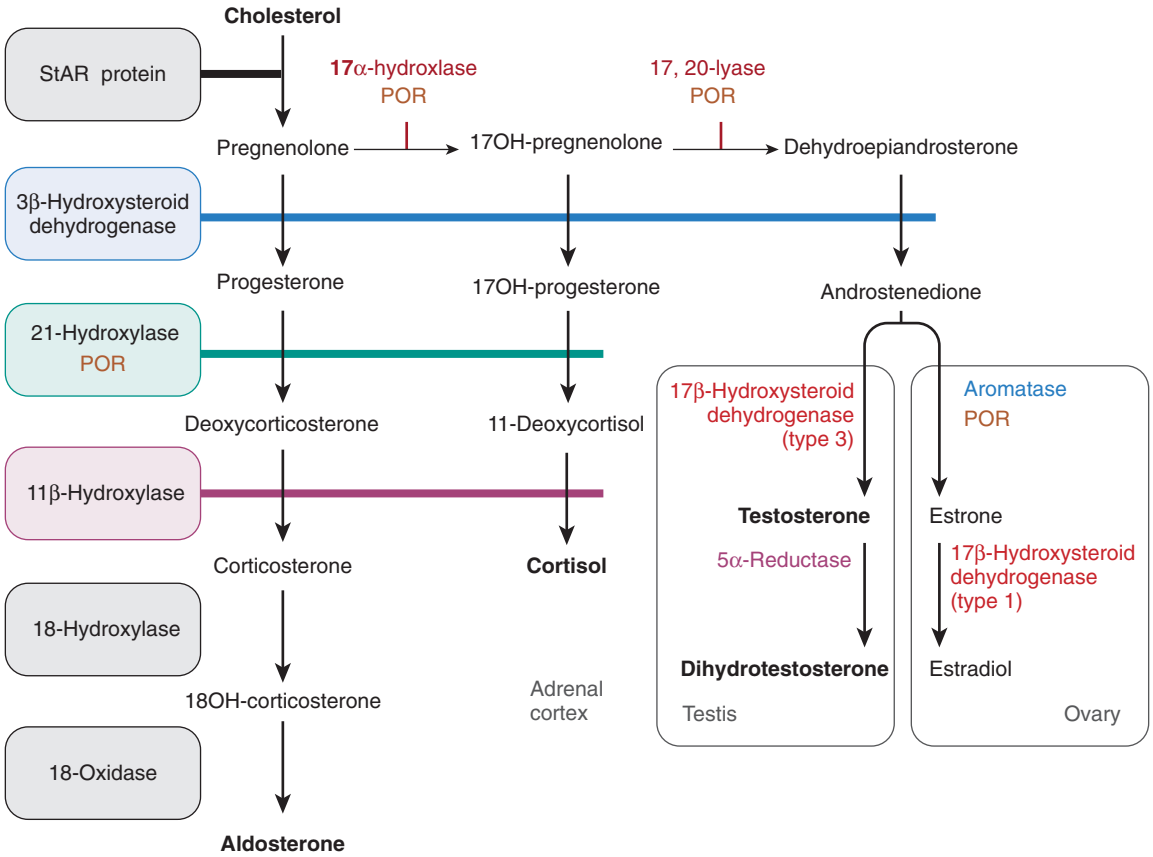
In the absence of testes, female sex differentiation occurs regardless of whether a functional ovary is present or not. This activity is in keeping with the inherent tendency of the fetus to develop along female lines.

Normal male sex differentiation requires bilateral testes that produce AMH from the Sertoli cell and testosterone from the Leydig cells. Anti-Müllerian hormone acts locally to induce regression of the ipsilateral Müllerian duct. If only one testis is present, Müllerian duct structures persist on the contralateral side. Testosterone does not cause Müllerian duct regression. A 46,XX female with Müllerian duct regression resulting from a *WNT4* mutation suggests that proteins other than ß-catenin, are important mediators of Müllerian duct regression.[51]

Testosterone produced by the fetal testes is secreted both locally, where it stimulates differentiation of the ipsilateral wolffian duct, and systemically, where it serves as a prohormone in the masculinization of the external genitalia. If only one testis is present, the contralateral wolffian duct fails to differentiate, indicating that systemically circulating testosterone levels are insufficient for the development of wolffian duct structures.

Although the wolffian ducts are stabilized through the effects of testosterone, the external genitalia and urogenital sinus are stimulated to undergo male differentiation by dihydrotestosterone (DHT). This potent androgen is synthesized in peripheral tissues (external genitalia, liver, kidney, and bone marrow) through the action of 5α-reductase on testosterone. As testosterone is a weaker androgen than

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• **Fig. 89.5** Diagrammatic representation of steroidogenesis pathway. POR, P450 oxoreductase; StAR, steroidogenic acute regulatory. (From Murphy C, et al. Ambiguous genitalia in the newborn: an overview and teaching tool. *J Pediatr Adolesc Gynecol.* 2011;24:236-250.)

DHT, it does not drive male external genital differentiation and serves instead as a prohormone for DHT in these tissues. Systemic testosterone derived from the fetal adrenals, as in CAH, or from maternal sources can induce variable masculinization of the external genitalia when it is metabolized to DHT.

Congenital absence of one testis (anorchia) is usually associated with incomplete masculinization of the external genitalia, suggesting that two testes are generally required to provide adequate systemic levels of testosterone substrate for conversion to DHT. The period in which DHT can induce male differentiation extends up to 12-14 weeks' gestation.

A Clinical Approach to the Infant With Suspected Disorder of Sex Development

The evaluation of the neonate with a suspected DSD requires prompt attention and a multidisciplinary team approach. Depending on the institution, the team may include neonatology, pediatric endocrinology, genetic counseling, pediatric urology, pediatric gynecology, pediatric surgery, psychology, psychiatry, nursing, and social work. Appropriate initial assessment and management of the newborn with a DSD is essential to helping the family cope with this difficult situation. This evaluation needs to begin as soon as possible and should be approached systematically.

Clinical Indications for Evaluation for a Possible Disorder of Sex Development

Most individuals with a DSD have some abnormality of their external genitalia that makes them identifiable at birth. An evaluation of a possible DSD should be considered for patients who have male-appearing external genitalia with defects, including isolated micropenis, severe hypospadias (perineal), bilateral cryptorchidism, or the presence of two defects such as hypospadias and unilateral cryptorchidism. In an infant with female-appearing external genitalia, the presence of posterior labial fusion, clitoromegaly, labial or inguinal mass that might represent a gonad, and difficulty in visualizing a separate vaginal introitus and urethra warrant evaluation for possible DSD, as does the finding of discordance of the prenatal karyotype with postnatal external genital phenotype.[3,58,59] Examples of conditions that can cause genital abnormalities are listed in Table 89.3.

Medical History

Most DSDs are isolated occurrences or inherited as autosomal recessive or X-linked traits. The family may not know

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TABLE 89.3 Associations of Genital Abnormalities

Abnormal Characteristics	Examples of Associated Disorders
Male-Appearing Genitalia	
Micropenis	Growth hormone or luteinizing hormone deficiency Testosterone deficiency (in second and third trimesters) Partial androgen insensitivity Syndrome: idiopathic
Hypospadias (more severe)	Disorders of gonadal development 46,XX DSD Ovotesticular DSD 46,XX or 46,XX DSD Syndrome: idiopathic
Impalpable gonads	Anorchia Persistent Müllerian duct syndrome 46,XX DSD with 21- or 11β-hydroxylase deficiency Cryptorchidism
Small gonads	47,XXY, 46,XX DSD Dysgenetic or rudimentary testes
Inguinal mass (uterus or tube)	Persistent Müllerian duct syndrome, dysgenetic testes
Female-Appearing Genitalia	
Clitoromegaly	XX with 21- or 11β-hydroxylase or 3β-hydroxy dehydrogenase deficiency Other 46,XX DSD Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD 46,XY DSD Tumor infiltration of clitoris Syndrome: idiopathic
Posterior labial fusion	As for clitoromegaly
Palpable gonad(s)	Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD 46,XY DSD
Inguinal hernia or mass	As for palpable gonad(s)

the specifics about other family members with DSDs but may be aware of a family history of a trait that could be a manifestation of a DSD such as infertility, amenorrhea, or hypospadias or infants with unexplained deaths in the family. History of parental consanguinity, maternal intake of drugs during pregnancy (such as androgen or progestins), use of assisted reproductive technologies, and the results of prenatal tests should be explored. A history of maternal virilization during pregnancy, especially if assessing a virilized female infant, raises the possibility of aromatase deficiency or maternal androgen-secreting tumors such as luteoma.[106]

• BOX 89.1 Findings That Constitute a Normal Genital Examination in the Newborn

Female Newborn

- Vaginal opening fully visible: 3- to 4-mm slit or stellate orifice with heaped-up mucosa (i.e., no posterior labial fusion)
- Clitoris width 2-6 mm
- Absence of gonads in labia majora or inguinal region

Male Newborn

- Urethra at tip of glans (which may be inferred by a fully developed foreskin)
- Penis of normal stretched length (2.5-5 cm) and diameter (0.9-1.3 cm)
- Bilateral testes of normal size (8-14 mm) in the scrotal sacs

Physical Examination

Considerable information can be obtained by performing a careful physical examination. The findings of a normal newborn external genital examination are listed in Box 89.1. The clinical findings do not need to be overtly ambiguous to qualify for a diagnostic evaluation for DSDs. Inferences can be made regarding gonadal development and status and the degree of androgen effects. When evaluating a newborn for possible DSD, the clinical features of the external genitalia that require examination include evidence for any asymmetry; presence of palpable gonads in the labioscrotal folds or inguinal canals; pigmentation and extent of labioscrotal fold fusion and rugosity; phallus length, breadth, and amount of erectile tissue; number of orifices in the perineum and their topography; and the position and patency of the anus (Table 89.4). A useful tool to describe and grade the extent of female genitalia virilization is the Prader scale (Stage I-V) (Fig. 89.6), whereas calculating the external masculinization score (EMS: scale 0-12) provides an objective aggregate score to describe the extent of masculinization of genitalia in boys (Fig. 89.7).[3]

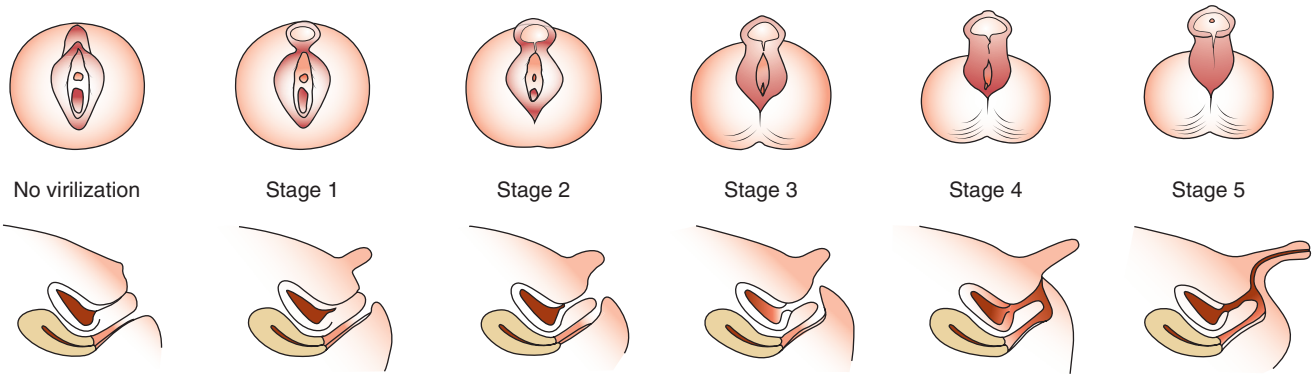
Delivery Room or Nursery Examination of All Newborns

Every newborn must have a careful genital examination in the delivery room or nursery. The purposes of the examination are to verify the gender assignment; to avoid missing the diagnosis of a DSD, particularly in females with CAH; and to recognize mild abnormalities that are not likely to affect gender assignment but that require follow-up, such as mild hypospadias or unilateral cryptorchidism. Neonates with overtly ambiguous genitalia should have gender assignment deferred.

Gonadal Descent and Size

Gonads should be carefully palpated in the scrotum or labial area and along the inguinal canal. Only a gonad containing testicular tissue (testis or ovotestis) can descend to a position where it is palpable (an ovary almost never descends). A small gonad (longest diameter <8 mm) may be dysgenetic,

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• **Fig. 89.6** Prader scale reflecting the degree of virilization of the external genitalia. The internal genitalia reflect the changes in the urogenital sinus that may be seen with a 46,XX DSD such as congenital adrenal hyperplasia. (From Allen L. Disorders of sexual development. *Obstet Gynecol Clin North Am.* 2009;36:25-45.)

TABLE 89.4 Initial Assessment of Disorder of Sex Development in the Newborn

History

Maternal History

Virilization during pregnancy, antenatal exposure to drugs (progestins and steroids), assisted reproductive technologies

Perinatal History

Prematurity, intrauterine growth restriction, results of prenatal investigations

Family History

Parental consanguinity, unexplained infant death, infertility, amenorrhea, gonadal or urogenital malformation

Physical Examination

General

Signs of dysmorphic features, hyperpigmentation, associated anomalies including skeletal malformations

External Genitalia

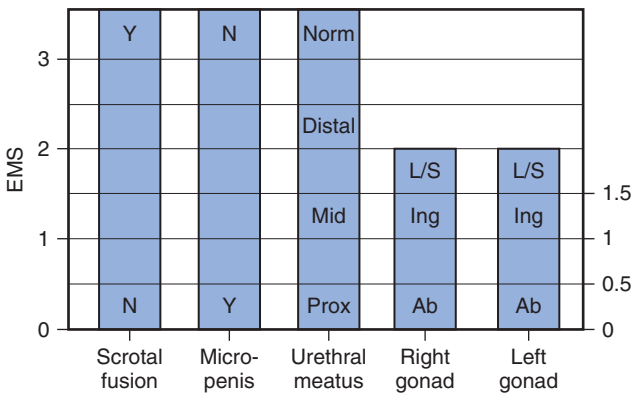
Symmetry of virilization
Gonads: location and size
Phallic structure: stretched length, breadth, and amount of erectile (corpora) tissue
Labioscrotal folds: degree of fusion, rugation, and pigmentation
Perineal orifices: number and topography
Anus: patency and anogenital distance

Prader Classification

Commonly used to stage virilization of female external genitalia (see Fig. 89.6)

External Masculinization Score

Helpful tool to grade male masculinization (see Fig. 89.7)



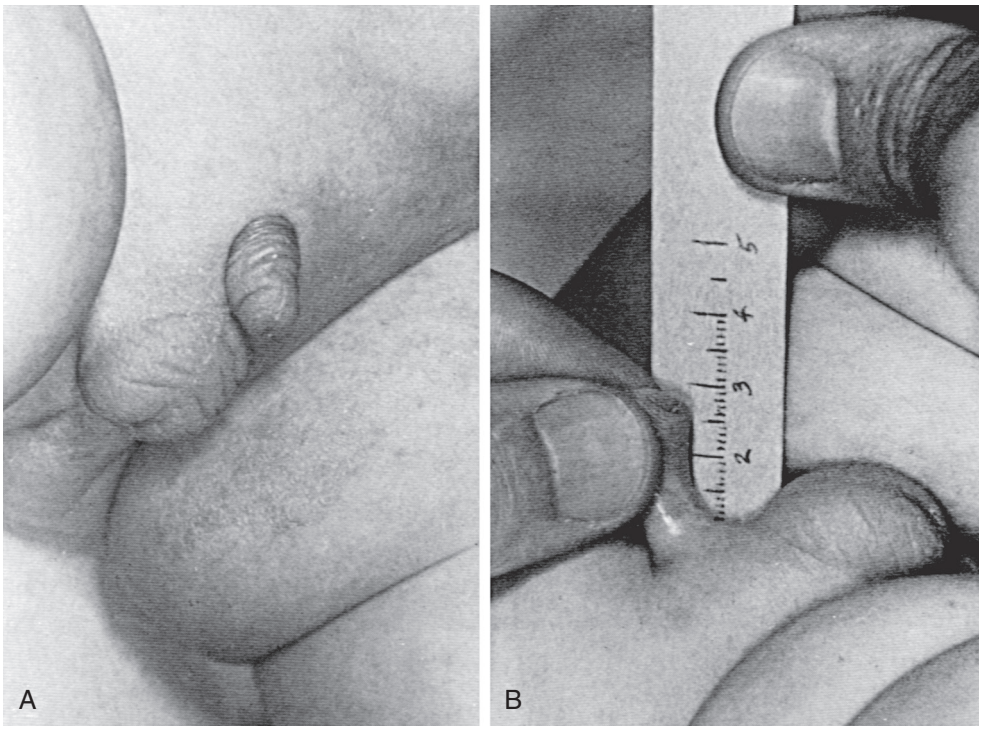
• **Fig. 89.7** External masculinization score (EMS) provides an objective aggregate score of extent of masculinization of external genitalia. Each individual feature of genitalia (phallus size, labioscrotal fusion, site of the gonads, and location of urethral meatus) is individually scored to provide a score out of 12. *Micropenis* refers to a phallus below the male reference range. Ab, Abdominal or absent on examination; Ing, inguinal; L/S, labioscrotal; Prox, proximal. (From Ahmed SF, et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development. *Clin Endocrinol.* 2011;75:12-26.)

rudimentary, or result from lack of gonadotropin stimulation. The ability to detect gonads in the inguinal area can be enhanced by applying soap or oil to the skin and the examiner's fingers to decrease friction. With the infant supine, glide two or three fingers with gentle to firm pressure along the inguinal canal toward the scrotum, repeating this action numerous times if necessary. The gonad will be felt "popping" under the fingers. With this technique, less accessible or small gonads can be palpated that would otherwise be missed. Additionally, sit the infant in a frog-leg position and, particularly with crying or increased intra-abdominal pressure, the testis may descend into the lower inguinal or scrotal region.

Penis Size

It is important to assess both the length and the amount of erectile tissue of the penis. A penis that appears small must

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• **Fig. 89.8 A,** A 2-month-old boy with micropenis and cryptorchidism caused by luteinizing hormone and follicle-stimulating hormone deficiency. The scrotum is compact or "unlived in," and the testes are inguinal. **B,** Centimeter markings are inked on a wooden tongue blade, which is placed near the penis and depressed down on the pubic ramus. The penis is maximally stretched, with the measurement made to the tip of the glans (measurement here is 1.7 cm).

be measured fully stretched, pressing the ruler down against the pubic ramus, depressing the suprapubic fat pad completely, and measuring to the tip of the glans only, ignoring any excess foreskin (Fig. 89.8). An excellent ruler can be made by placing marks 0.5 cm apart on a wooden stick such as a tongue blade or a flexible strip. The width is measured at the midshaft of the stretched penis. A micropenis is arbitrarily defined as a penis with a normally formed urethra that opens at the tip of the glans in which the stretched length is less than 2.5 cm in the full-term neonate. The length criteria must be adjusted to take into account the smaller phallus in the premature neonate (Fig. 89.9).[33] The definition of a micropenis can also be used to describe a rare condition in which the penile corpora cavernosa are absent or severely deficient in size, resulting in an abnormally thin penis (Table 89.5).[58]

Clitoris Size

A clitoris that appears enlarged is best assessed by measurement of the width (diameter) of the paired corpora cavernosa that compose the erectile shaft of the clitoris. With clitoral enlargement caused by edema or birth trauma, a normal corporal width (<6 mm) is present, whereas clitoral enlargement caused by androgen stimulation (occurring in the second and third trimesters) results in increased corporal growth (>6 mm). The width of the clitoris is measured by gently but firmly pressing the shaft of the clitoris between the thumb and forefinger to exclude excess skin and subcutaneous tissue, thereby measuring predominantly the width of the corpora cavernosa.[78]

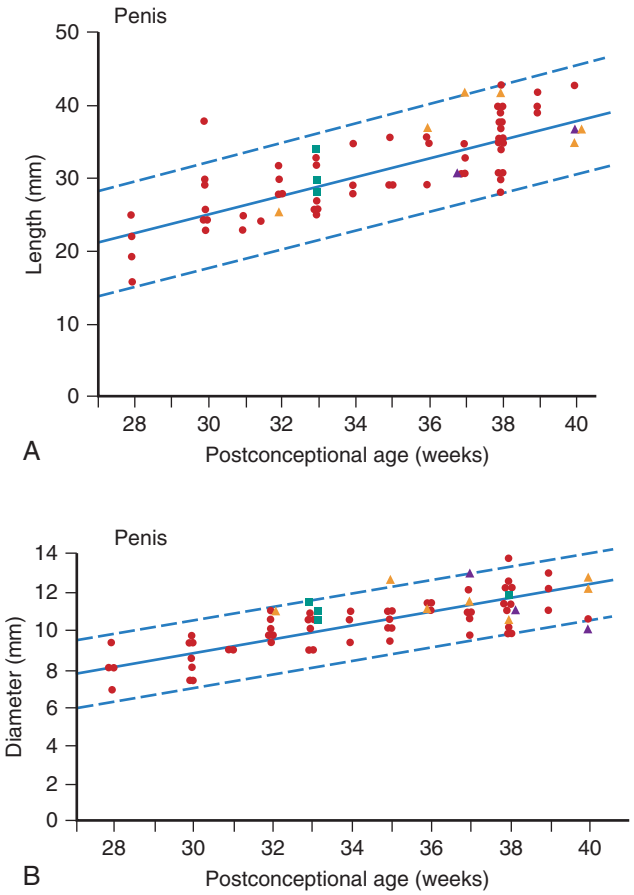
Urethral Opening

If the foreskin is fully formed, the urethra is almost always at the tip of the glans; on rare occasions, the foreskin covers hypospadias on the glans. Hypospadias can vary from mild (off the center of the glans) to severe (at the base of the penis or on the perineum) (Fig. 89.10). The prepuce in the hypospadiac penis is usually deficient ventrally and thus appears hooded. Chordee (ventral curvature of the penis) is caused by fibrotic contracture in the area of failed urethral development. The presence of severe hypospadias in a male infant indicates deficient testosterone or DHT action in the first trimester. In girls, the urethral meatus is normally a 1-mm pinhole-like or flat opening located just ventral to the vagina. Androgen exposure at 8-14 weeks of fetal age moves the urethral meatus ventrally on the perineum or the shaft of the phallic structure.

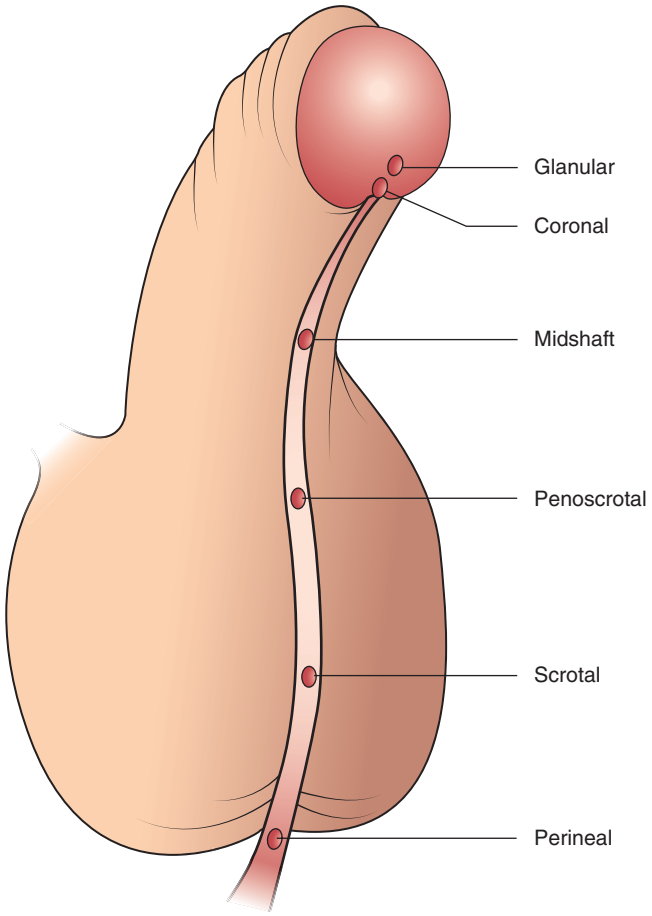
Vaginal Opening

The vaginal orifice, a 3- to 4-mm slit or stellate opening surrounded by heaped-up mucosa, is normally visible when the examiner lifts up the labia majora. The presence and direct visualization of the vaginal opening indicate the absence of androgen effects and the presence of a distal vagina (of urogenital sinus origin); whether a uterus (of Müllerian duct origin) is also present cannot be inferred from this finding. Conversely, at 8-14 weeks of fetal age, exposure of the female fetus to androgens or incomplete androgen stimulation of the male fetus results in variable masculinization. This process can be mild to moderate, with

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• **Fig. 89.9** Stretched penile length (mean ± 2 SD) (**A**) and penile diameter (mean ± 2 SD) (**B**) in 63 normal premature and full-term male infants (●), two infants who were small for gestational age (▲), seven infants who were large for gestational age (▲), and four twins (■). (From Feldman KW, et al. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr.* 1975;86:395.)



• **Fig. 89.10** Hypospadias classification based on the location of the abnormal urethral meatus. Proximal (glandular and subcoronal), middle (distal penile, midshaft, and proximal penile), and distal (penoscrotal, scrotal, and perineal) hypospadias. (From Barcat J. Current concepts of treatment. In: Horton CE, ed. *Plastic and reconstructive surgery of the genital area.* Boston: Little, Brown; 1973:249-262.)

posterior midline fusion of the labia majora that partially or completely covers the vaginal opening, thereby preventing its direct visualization. With more severe masculinization, there is formation of a common urogenital sinus (resulting from the internal junction of the vagina and urethra) that is seen as a single 1- to 2-mm flat orifice on the perineum or shaft of the phallus.

Labioscrotal Development

The labia majora are normally unfused in the female. Partial or complete midline fusion indicates androgen exposure at 8-14 weeks of fetal age and predicts ventral placement of the urethral meatus on the perineum or phallus. The scrotum in the male is normally completely fused, with a midline raphe. A compact or "unlived-in" scrotum indicates the lack of testes or undescended testes. In the male, incomplete or absent midline fusion indicates deficient or absent androgen effects at 8-14 weeks of fetal age and predicts a perineal location of the urethral meatus.

Associated Dysmorphology

A thorough physical examination should be done to identify any other dysmorphic features. Genital abnormalities are often part of dysmorphic syndromes and are frequently associated with midline defects.[45] Examples include the presence of the Turner phenotype in gonadal dysgenesis and campomelic dwarfism (bowing and angulation of the lower limbs, flat facies, shortened vertebrae) in XY gonadal dysgenesis. Some DSD patients appear phenotypically normal at birth, including many (but not all) cases of gonadal dysgenesis, XX male, 46,XY male with persistent Müllerian ducts, and complete androgen insensitivity syndrome (cAIS).

Discussion With Family and Professional Staff

It is important to recognize that the birth of an infant with a DSD is a major stress for the family. A physician

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TABLE 89.5 Anthropometric Measurements of the External Genitalia

Sex	Population	Age	Stretched Penile Length, Mean ± SD, cm (Males), or Clitoral Length, Mean ± SD, mm (Females)	Penile Width, Mean ± SD, cm (Males), or Clitoral Width, Mean ± SD, mm (Females)	Mean Testicular Volume, mL (Males), or Perineum Length, Mean ± SD, mm (Females)
M	United States	30 weeks' GA	2.5 ± 0.4		
M	United States	Term	3.5 ± 0.4	1.1 ± 0.1	0.52 (median)
M	Japan	Term to 14 years	2.9 ± 0.4 – 8.3 ± 0.8		
M	Australia	24-36 weeks' GA	2.27 ± (0.16 GA)		
M	China	Term	3.1 ± 0.3	1.07 ± 0.09	
M	India	Term	3.6 ± 0.4	1.14 ± 0.07	
M	North America	Term	3.4 ± 0.3	1.13 ± 0.08	
M	Europe	10 years	6.4 ± 0.4		0.95-1.20
M	Europe	Adult	13.3 ± 1.6		16.5-18.2
F	United States	Term	4.0 ± 1.24	3.32 ± 0.78	
F	United States	Adult nulliparous	15.4 ± 4.3		
F	United States	Adult	19.1 ± 8.7	5.5 ± 1.7	31.3 ± 8.5

GA, Gestational age.
Data from Lee PA. International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*. 2006;118:e488.

experienced in the evaluation of DSD should meet with the family as soon as possible to discuss the situation, ensuring confidentiality and privacy. Both parents should be present if possible. As part of the discussion, the infant's genitalia should be examined with the parents. Parents are frequently afraid to look at their child's genitalia. Showing the anatomic abnormalities to the family in a calm and professional manner helps the family bond with their child. Outline what will happen (procedures, consultations) and the time frame in which the results will be available. Review with the parents what they plan to tell relatives and friends, which is often a source of great anxiety. Many families and cultures have strong feelings about gender assignment, and these feelings must be known by the health professionals. Reassure the family that when the data from the tests are available, there will be much more information that will help determine the appropriate gender assignment. In most cases, the correct gender assignment will be apparent when the test results become available; in some cases, the gender assignment is not clear, and the options will need to be discussed with the parents.

Following are examples of scripts for answering questions commonly asked by families with children with a new diagnosis of a DSD. These are taken largely from the *Clinical Guideline for the Management of DSD in Childhood*, published by the Consortium on the Management of Disorders of Sex Development.[46]

Q: Is my child a boy or a girl?

A: Your question is very important. We wish we could tell you right this minute, but we really can't tell yet. We will have more information after we conduct some tests. It's hard for parents to wait for these test results, so we will try to update you every day, and you can call (give contact person's name). Although your baby has a condition you probably haven't heard much about, it isn't that uncommon. We've encountered this before, and we'll help you through this time of confusion. As soon as the tests are completed, we will be able to talk with you about the gender in which it makes most sense to raise your child, and we'll give you a lot more information, too, because quite a lot is known about these variations, and we are learning more each day. We want to reassure you that our focus is on supporting you and your child in this time of uncertainty.

Q: What do we tell our friends and family while we wait for the gender assignment?

The following script may be most appropriate for talking to close family and friends. When discussing the situation with others, you may feel more comfortable just letting them know that the baby is in the hospital for tests.

A: This is important. We strongly recommend being open and honest with your friends and family about your child's situation. Even if you don't intend to, lying or withholding information will create a sense of shame and secrecy. Although it can be awkward to talk with family and friends about a

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child's sex development, being honest signals that you are not ashamed—because you have nothing to be ashamed of—and it also allows others to provide you with the love and support you may need. Isolating yourself at this time will probably make you feel unnecessarily stressed and lonely. Talking about it will help you feel connected with others. So here is what you can tell people: Our baby was born with a kind of variation that happens more often than you hear about. Our doctors are doing a series of tests to figure out whether our baby is probably going to feel more like a boy or a girl. We expect to have more information from them within (specify realistic time frame), and then we'll send out a birth announcement with the gender and the name we've chosen. Of course, as is true with any child, the various tests the doctors are doing are not going to tell us for sure who our baby will turn out to be. We're going to go on that journey together. We appreciate your love and support, and we're looking forward to introducing you to our little one in person soon.

It also helps to let your friends and family know whether your baby is healthy or whether there are some health concerns. Finally, take some pictures of your baby's face, and share those pictures with others!

Because of the stress produced by having a child with DSD, support from a behavioral scientist (social worker, psychologist, or psychiatrist) may be helpful for the family. It may be helpful for families to be informed about relevant credible resources listed at the end of this section.[105]

In addition to discussions with the family, it is important to keep the hospital staff who have contact with the family fully informed about the information that has been given to the parents. This professional candor reduces the possibility of insensitive comments made by hospital personnel to family members and is especially important in cases in which gender assignment must be delayed.

Initial Diagnostic Evaluation

In cases in which gender assignment is pending, all relevant tests should be obtained as soon as possible. A summary of the initial workup for DSD evaluation in newborns is shown in Box 89.2.

Chromosomes

Fluorescence in situ hybridization (FISH) or QF-PCR for X and Y markers may be available within 24-48 hours. Results reveal the number of X and Y chromosomes present. Most cytogenetic laboratories can provide a peripheral blood karyotype result within 2 or 3 days for cases of DSD. In cases in which the gender assignment is not clear, the laboratory should be personally contacted and asked to expedite the chromosome result.

Biochemistry

Interpretation of biochemistry tests is dependent on the timing of the sample and understanding of the normal levels of hormones at that time. A blood sample should be obtained after 24-48 hours of life, after the time of the neonatal surge of androgens, for measurement of testosterone and 17-hydroxyprogesterone (17-OHP). It is desirable to draw extra blood so that the laboratory can save the serum for analysis of other hormones that may be indicated as the evaluation continues. Increased serum levels of testosterone occur physiologically in neonates with functioning testes at 12-36 hours and at 2 weeks to 4-6 months of age.[110] The level may also increase pathologically at any time from the adrenal secretion of androgens in cases of CAH. Decreased levels of testosterone occur if Leydig cells are deficient or absent, LH activity is impaired, or there is a testosterone biosynthetic defect. Blood samples are also diagnostically useful at 1 or 2 months of age to assess the peak of hypothalamic-pituitary-testicular axis function in infancy.

An increased level of 17-OHP suggests 21- or 11β-hydroxylase deficiency and implies that any increased levels of testosterone were of adrenal rather than testicular origin in a 46,XX patient. The 17-OHP levels in premature infants are higher than those in full-term infants.[57] In CAH with 21-hydroxylase deficiency, the levels of 17-OHP are often 10-50 times the upper limit of the normal level, making the test virtually diagnostic.

The measurement of serum AMH has been shown to correlate with Sertoli cell function.[12] Similarly, inhibin B

• BOX 89.2 Initial Diagnostic Evaluation of Disorder of Sex Development in the Newborn

First-Tier Tests

- Chromosomes
- Karyotype and FISH or QF-PCR for X and Y chromosomes
- Additional blood work based on the presence or absence of palpable gonads
  If gonads palpable:
  - Testosterone, androstenedione, and dihydrotestosterone (DHT)
  - Luteinizing hormone and follicle-stimulating hormone
  If no gonads palpable:
  - 17OH-progesterone, testosterone, and androstenedione
- Renin and serum electrolytes (to be measured after 48 hours of life)
- Imaging
- Ultrasound: adrenal, kidneys, pelvis, inguinal regions, and labioscrotal folds
- Genitogram

Second-Tier Tests

- DHEA, 11-deoxycorticosterone, progesterone, 17OH-pregnenolone, anti-Müllerian hormone
- Stimulation tests: hCG (human chorionic gonadotropin) and ACTH (adrenocorticotropic hormone) tests
- Molecular androgen receptor studies
- Specific molecular testing for genetic disorders
- Microarray
- Whole exome sequencing
- Cystoscopy, vaginoscopy
- Laparoscopy/gonadal biopsy

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levels have been shown to rise in males in the first week of life. Its measurement is, therefore, useful for identifying the presence of Sertoli cells and of functional testes in newborn boys with nonpalpable gonads.[12] Other tests that may be useful, depending on the clinical presentation, are measurements of LH, FSH, estradiol, precursors of testosterone, and DHT.

Ultrasonography

Ultrasound examination can usually determine the presence or absence of the uterus. If no uterus is seen, it suggests that there is testicular tissue producing AMH. If a uterus is present, it suggests bilateral ovaries, dysgenetic gonads that failed to produce AMH, or an AMH receptor defect. Intrapelvic gonads can sometimes be located. Fetal ultrasonography can identify abnormal genitalia in utero.[82] Adrenal ultrasonography has a sensitivity of 92% and a specificity of 100% for diagnosing CAH when read by an experienced pediatric radiologist.[4] Ovaries may be difficult to identify on ultrasound.

Genitography

Genitography is used to determine the presence or absence of a urogenital sinus and the anatomy of the urethra and vagina. Visualization of the cervix confirms the presence of Müllerian duct structures. If radiographs show filling of a fallopian tube, the gonad on that side has failed to produce AMH. Endoscopy may be needed to direct where the radiopaque contrast material is to be injected; otherwise, small vaginal openings into the urethra may be missed.

Human Chorionic Gonadotropin Stimulation Test

A short hCG stimulation test can be used to determine whether functioning Leydig cells are present and to detect disorders of androgen biosynthesis. One example of a protocol for doing the test is as follows: for full-term infants, 1000 units of hCG is given intramuscularly every day for three injections.[3] The testosterone level is measured on the day after the last injection and compared with the baseline value. There are a number of protocols but no consensus about the best way to do the test. Normal or low levels of testosterone in response to hCG should be interpreted in relation to LH, FSH, and AMH values.[3] A significant rise in testosterone concentration confirms the presence of Leydig cells and, by implication, testicular tissue.

Refining the Diagnosis

After the chromosome results are available, the initial diagnosis can be confirmed or refined. An approach that can be used to arrive at a final (differential) diagnosis is shown in Figs. 89.11 and 89.12. The use of microarray and next-generation sequencing are increasing, improving diagnostic accuracy.[2] Details of the specific diagnoses are discussed later.

Gender Assignment in Newborns

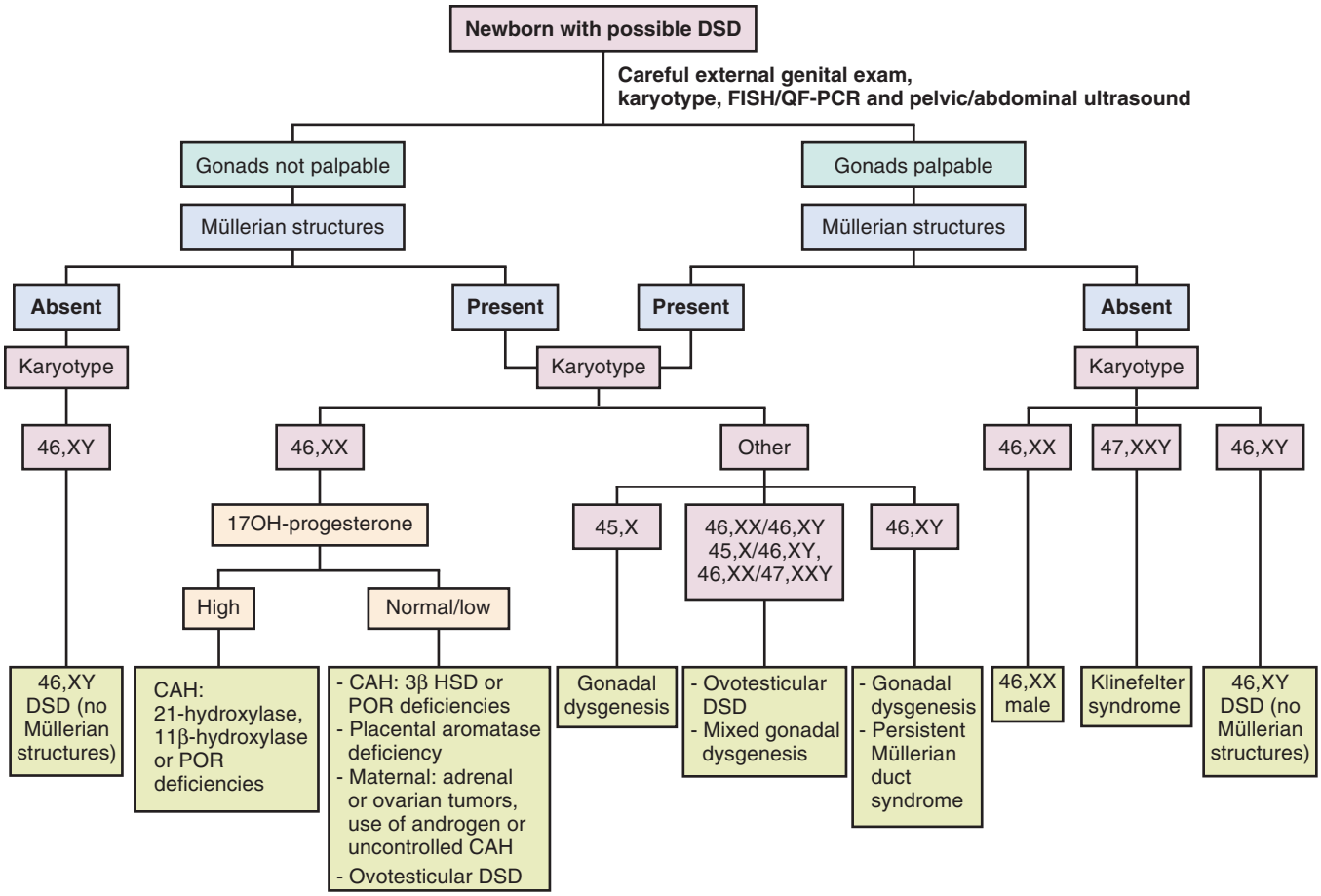
The decision about gender assignment is complex and stressful. It should, therefore, be made expeditiously by a thorough assessment of a multidisciplinary team, including the family and health care staff representing medical genetics; gynecology; pediatric urology; endocrinology; nursing; and psychiatry, psychology, or social work.[84] Guiding factors include the diagnosis, appearance of the genitals, internal genital and gonadal development, surgical options, need for lifelong sex-hormone replacement therapy, potential for fertility, and the views of the family and their cultural practices.[59] In addition, the prospect for a gender identity congruent with sex of rearing and good sexual function are very important.

In general, most patients with disorders of sex development identify with their gender of rearing as adults, but there are higher rates of gender dysphoria than in the general population.[20] Most 46,XX patients with CAH identify as females regardless of degree of genital virilization.[11] Sex of rearing decisions are difficult in patients with 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency, as up to 60% of those assigned female in infancy without gonadectomy, and all those assigned male, identify as males.[68] For individuals with cAIS assigned female in infancy, the vast majority continue to live as female.[27] Among both males and females with partial AIS (pAIS) and partial gonadal dysgenesis, about 75% were satisfied with their initial sex assignment.[111] In the case of infants with markedly ambiguous genitalia, including a micropenis and perineoscrotal hypospadias, the decision about sex of rearing should be made after thorough discussion of the results of all investigations, diagnosis, etiology, prognosis, and surgical options.[59] The gender assignment in XY infants with small phalluses remains controversial, but these infants are increasingly being assigned male gender because of lack of need for medical or surgical intervention and potential for fertility.[52,59] The availability of intracytoplasmic sperm injection has also created the possibility of fertility for males with a very low sperm count. If the phallus is small and associated with hypospadias, partial androgen resistance is a possible diagnosis. Androgen sensitivity can be assessed by the response of the penis to an intramuscular injection of testosterone. If the response is poor, the choice of gender assignment becomes very difficult and must be approached on a case-by-case basis, with extensive discussion with the family.

Nomenclature of Disorders of Sex Development

An improved understanding of the molecular and genetic causes of DSDs and increased awareness about patient sensitivity led to the development of an updated nomenclature for this group of disorders (Table 89.6).[58]

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• **Fig. 89.11** General diagnostic algorithm for disorders of sex development (DSD). Differential diagnosis is based on the presence or absence of palpable gonads, Müllerian structures, karyotype, and serum 17-OH progesterone level. CAD, Congenital adrenal hyperplasia; HSD, hydroxysteroid dehydrogenase; POR, P450 oxidoreductase.

Disorders of Sex Development

Sex Chromosome Disorder of Sex Development

Abnormality in number or parts of sex chromosomes leads to failure of testes or ovaries to undergo normal development. This group can be classified into four main categories, including 45,X (Turner syndrome and variants); 47,XXY (Klinefelter syndrome and variants); 45,X/46,XY (mixed gonadal dysgenesis); and 46,XX/46,XY (chimerism).

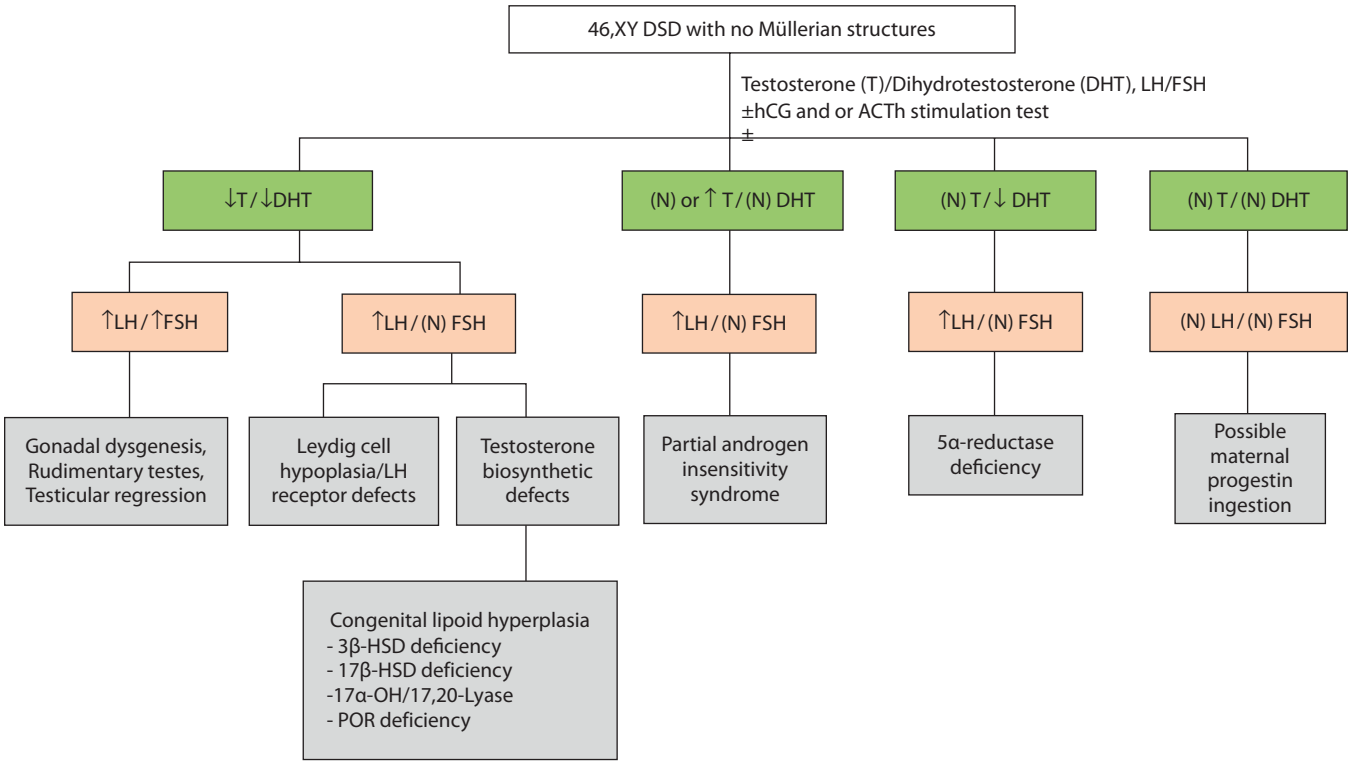
45,X (Turner Syndrome and Variants)

Loss of the second X chromosome results in a syndrome consisting of a phenotypic female with bilateral streak gonads and accompanying somatic abnormalities. Variant forms include partial deletions of the second X chromosome, such as deletion of the short arm of the X chromosome (XXp−) or the long arm of the X chromosome (XXq−) or various forms of X chromosome mosaicism (e.g., 45,X/46,XX).

In fetuses with 45,X gonadal dysgenesis, normal ovarian differentiation occurs at up to 13-15 weeks of gestation, followed by rapid degeneration of the primordial ovarian follicles. In affected neonates and infants, the late stages of this process are usually evident, with scattered primordial ovarian follicles in varying states of degeneration. The final result is the streak gonad, a whitish streak consisting of whorls of connective tissue, suggestive of ovarian stroma, that contain no germinal elements or endocrine or other epithelial elements.

Affected patients have normal Müllerian duct development, an absence of wolffian ducts, and phenotypically female external genitalia. Because the genitalia are normal, the identification of neonates is limited to those who have the accompanying Turner somatic abnormalities, as listed in Box 89.3. The cardiovascular and lymphatic abnormalities, particularly lymphedema of the dorsa of the feet or hands, are diagnostically the most useful and may be pathogenetically related. In the 45,X fetus, impaired drainage of the lymph channels leads to stasis of lymph fluid, with distention of lymphatics, peripheral lymphedema. Large

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• **Fig. 89.12** Clinical diagnostic algorithm for disorders of sex development (DSD) in 46,XY infant with absent Müllerian structures. The differential diagnosis is based on the results of testosterone, dihydrotestosterone (DHT), LH, and FSH. Further diagnostic investigations are then based on the most probable diagnosis.

• BOX 89.3 Features of Turner Phenotype in the Neonate

- Intrauterine growth restriction
- Head and facies: low-set ears, low nuchal hairline, asynchronous growth of scalp hair, epicanthus, folds below lower lids, micrognathia, high palate
- Lymphatic: lymphedema of dorsa of hands and feet, hypoplasia of nails, loose neck folds (cutis laxa) or cystic hygroma, ascites, pleural or pericardial effusion, gross edema
- Cardiovascular: coarctation of aorta, bicuspid aorta, aortic stenosis, hypoplastic left heart, partial anomalous pulmonary venous drainage, ventricular septal defect, patent ductus arteriosus, and secundum atrial septal defect
- Urinary tract: rotated or horseshoe kidneys, renal hypoplasia, duplications
- Skeletal: short fourth metacarpals, shield chest

Modified from Gordon RR, et al. Turner's infantile phenotype. *Br Med J*. 1969;1:483.

nuchal cystic hygromas and generalized edema occur frequently in utero. Distention of the cardiac lymphatics is hypothesized to compress the ascending aorta, altering flow in the left atrioventricular canal and affecting pulmonary venous return and consequently resulting in cardiovascular malformations. A strong association is observed between the presence of a webbed neck and the occurrence of aortic coarctation, partial anomalous pulmonary venous drainage, a hypoplastic left heart, and secundum atrial septal defect.

The mean maternal and paternal ages are not raised, so nondisjunction is not thought to be important; a postfertilization abnormality is thought to be the most likely etiology. The single X is of maternal origin in about 75% of cases.[43] The clinical features of Turner syndrome seem to be related to the haploinsufficiency of the short stature homeobox-containing gene (*SHOX*) and to the lymphogenic gene that causes lymphatic hypoplasia and, as a result, soft tissue and visceral anomalies.[79] The incidence of the 45,X karyotype in spontaneous abortuses is very high, generally estimated to be 6%-10%. However, the mean incidence of living 45,X newborns is only about 1 in 5000 female births, suggesting that more than 99% of 45,X fetuses abort. The reasons for this high mortality rate are unclear, but dysfunction of the 45,X placenta or fetal hypoalbuminemia, generalized edema, serous effusions, and cardiovascular abnormalities may play a role.

Individuals with X chromosome mosaicism or partial deletion of the second X chromosome tend to have fewer somatic and gonadal manifestations than those with the 45,X karyotype. In cases of mosaicism, the relative proportions of 46,XX to 45,X cells do not correlate well with the clinical phenotype.[61] Individuals having only a partial deletion of the X chromosome may also manifest a modified phenotype, depending on the part of the X chromosome that is deleted. Genes related to ovarian development

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TABLE 89.6 A Proposed Classification of Causes of Disorders of Sex Development (DSDs)

Sex Chromosome DSD	46,XY DSD	46,XX DSD
A: 47,XXY (Klinefelter syndrome and variants) B: 45,X (Turner syndrome and variants) C: 45,X/46,XY (mixed gonadal dysgenesis) D: 46,XX/46,XY (chimerism)	A: Disorders of gonadal (testicular) development 1. Complete or partial gonadal dysgenesis (e.g., *SRY*, *SOX9*, *SF1*, *WT1*, *DHH*) 2. Ovotesticular DSD 3. Testis regression B: Disorders in androgen synthesis or action 1. Disorders of androgen synthesis LH receptor mutations Smith-Lemli-Opitz syndrome Steroidogenic acute regulatory protein mutations Cholesterol side-chain cleavage (*CYP11A1*) 3β-Hydroxysteroid dehydrogenase 2 (*HSD3B2*) 17α-Hydroxylase/17,20-lyase (*CYP17*) P450 oxidoreductase (*POR*) 17β-Hydroxysteroid dehydrogenase (*HSD17B3*) 5α-Reductase 2 (*SRD5A2*) 2. Disorders of androgen action Androgen insensitivity syndrome Drugs and environmental modulators C: Other 1. Syndromic associations of male genital development (e.g., cloacal anomalies, Robinow, Aarskog, hand-foot-genital, popliteal pterygium) 2. Persistent Müllerian duct syndrome 3. Vanishing testis syndrome 4. Isolated hypospadias (*CXorf6*) 5. Congenital hypogonadotropic hypogonadism 6. Cryptorchidism (*INSL3, GREAT*) 7. Environmental influences	A: Disorders of gonadal (ovarian) development 1. Gonadal dysgenesis 2. Ovotesticular DSD 3. Testicular DSD (e.g., *SRY +, dup SOX9*, RSP01) B: Androgen excess 1. Fetal 3β-Hydroxysteroid dehydrogenase 2 (*HSD3B2*) 21-Hydroxylase (*CYP21A2*) P450 oxidoreductase (*POR*) 11β-Hydroxylase (*CYP11B1*) Glucocorticoid receptor mutations 2. Fetoplacental Aromatase (*CYP19*) deficiency Oxidoreductase (*POR*) deficiency 3. Maternal Maternal virilizing tumors (e.g., luteomas) Androgenic drugs C: Other 1. Syndromic associations (e.g., cloacal anomalies) 2. Müllerian agenesis, hypoplasia (e.g., MURCS) 3. Uterine abnormalities (e.g., MODY5) 4. Vaginal atresia (e.g., McKusick-Kaufman) 5. Labial adhesions

From Hughes IA. Disorders of sex development: a new definition and classification. *Best Pract Res Clin Endocrinol Metab*. 2008;22:119.

and Turner somatic abnormalities are located on both Xp and Xq. The combined incidence of 45,X, partial deletion, and mosaic Turner syndrome is about 1 in 2000 female newborns.[39]

About 40%-50% of patients with this diagnosis have a partial deletion or mosaicism of the X chromosome; at least 20 cells should be assessed for the possibility of mosaicism.[39] Those with XYp− gonadal dysgenesis and structural abnormalities of the Y chromosome may also have a Turner somatotype but carry a different prognosis. Y chromosome material is associated with about a 10% risk for gonadoblastoma.[39] About 10%-12% of patients with Turner syndrome have Y chromosome material.[39]

The antenatal diagnosis of Turner syndrome has been made after ultrasound identification of a cystic hygroma and pleural effusion.[17] Clinical practice guidelines exist that outline the suggested screening investigations in individuals with a new diagnosis of Turner syndrome.[39] These include a cardiovascular evaluation, renal ultrasound, hearing evaluation, and referral to appropriate support groups.[3] A 15%-35% incidence of heart anomalies is found. The most common are left-sided and include bicuspid aortic valve in 14%-34% and aortic coarctation in 7%-14%.[39] The most common renal/urinary tract abnormalities are horseshoe kidney and duplex/abnormal collecting system. Feeding difficulties in infancy, caused by oral-motor dysfunction, may result in a lower rate of weight gain. Patients who are not recognized in infancy come to medical attention later, usually because of short stature or failure of secondary sexual development. Most girls demonstrate absence of any ovarian function, but 5%-15% of patients do show variable secondary sexual development; a very small number of pregnancies have been reported.

47,XXY (Klinefelter Syndrome and Variants)

The major clinical manifestations of Klinefelter syndrome develop with the onset of puberty, and most patients are recognized at that time or later, at presentation with infertility. The constant features are small testes with histologic evidence of impaired spermatogenesis. Infants with 47,XXY

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Klinefelter syndrome occasionally have small testes or a micropenis that might permit their recognition, and cases with hypospadias have been reported. Other congenital abnormalities seen in this syndrome included cleft palate, cryptorchidism, and inguinal hernia.[40] The fetal testes at midgestation are normal. Testicular histology in the first year of life has varied from normal to abnormal, with decreased to absent spermatogonia.

The incidence of the 47,XXY karyotype in live newborn males is about 1 in 1000; if Klinefelter variants are added, the overall incidence is about 1 in 6600. Increased maternal age is associated with an additional X chromosome, although this effect is not as marked as it is in autosomal trisomies. Among the variant forms of Klinefelter syndrome, patients with 48,XXXY and 49,XXXXY karyotypes are more likely to be recognized early in life. All have somatic abnormalities and cognitive disability, and many have a hypoplastic penis. All males with the 49,XXXXY karyotype have cryptorchidism, and 14% have cardiac defects.

45,X/46,XY (Mixed Gonadal Dysgenesis)

This group of disorders is characterized by the presence of dysgenetic and often asymmetric gonads. The streak gonad represents the end result of failed gonadal (ovarian or testicular) differentiation. *Mixed gonadal dysgenesis* is a term used to describe individuals with a unilateral, functioning testis and a contralateral streak gonad (Fig. 89.13).

Ninety percent of prenatally diagnosed cases have a normal male phenotype, whereas those diagnosed postnatally show variable phenotypes.[100] Most have some degree of virilization of the external genitalia, ranging from clitoromegaly or partial labial fusion to normal male external genitalia. Slightly more than half have a urogenital sinus. All have some Müllerian development consisting of an upper vagina, a hemiuterus, and a fallopian tube, usually on the side with the streak or absent gonad. An epididymis or vas deferens is present on the testicular side in 50% of cases, and the testis is most frequently located in the inguinal canal. Normal to diminished or absent testosterone responses have been reported with hCG stimulation, and gonadotropins are normal or elevated.[63] Gonadal tumors occur in approximately 20%-30% but have been found in as many as 50% in those with severe genital ambiguity, affecting either the testis or the streak gonad.[26] This condition differs from ovotesticular DSD, previously referred to as *true hermaphroditism*, because of the presence of abnormal gonadal tissue.

In 45,X/46,XY, Turner somatic features such as lymphedema, cardiovascular abnormalities, or short stature are frequently seen and reflect the presence of 45,X cell lines. The prevalence of the XY cell line in the gonad and the extent of structural abnormality of the Y chromosome determine the degree of testicular development and masculinization.

Appropriate gender assignment in the newborn period should be based on functional considerations and fertility. Removal of dysgenetic gonads should be considered in infancy because of the increased risk for tumor formation.[64]



• **Fig. 89.13** A 45,X/46,XY neonate with sex chromosome disorder of sex development was noted at birth to have a male-appearing external genitalia with a phallus measured at 2.5 cm × 1.2 cm and penoscrotal hypospadias. The left gonad was palpable in incompletely fused scrotum, whereas the right gonad was not palpable. Gonadal biopsy revealed a testis on the left side and streak gonad on the right. The diagnosis was mixed gonadal dysgenesis.

The scrotal testis may be normal prepubertally, but many adults show a loss of germ cells and accompanying tubular sclerosis; a few have spermatocytes.

46,XX/46,XY (Chimerism)

The most common phenotype is that seen in ovotesticular DSD, discussed next.

Ovotesticular Disorder of Sex Development

Formerly known as true hermaphroditism, ovotesticular DSD is defined as the coexistence of normal ovarian and testicular tissue either in the same gonad or in opposite gonads. The ovarian tissue must contain ovarian follicles or corpora albicantia as fibrous stroma alone does not define ovarian tissue. The testicular tissue must contain seminiferous tubules or spermatozoa. Several karyotypes are seen in ovotesticular DSD. Karyotype distribution has ethnic variability. On average, around 60% are 46,XX; 20% have Y chromosome-containing mosaic or chimeric karyotypes (45,X/46,XY, 46,XX/47,XXY), with the most common

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being 46,XX/46,XY; only 7% have 46,XY karyotypes.[54] The most frequently occurring gonadal combinations are an ovary and a testis or an ovary and an ovotestis. An ovotestis accounts for 44%-50% of all gonads in this condition, an ovary 20%-30%, and a testis 12%-20%. Less than 1% of patients have a unilateral streak gonad or a tumor. Ovarian tissue occurs more often on the left side, and gonads with any amount of testicular tissue are more often on the right.[54,102]

The internal genital ducts reflect the gonadal constitution. On the side with an ovary, a fallopian tube is almost always seen, and on the side with a testis, the vas deferens and epididymis are almost always present. On the side with an ovotestis, a vas deferens is seen 35% of the time and a fallopian tube, often closed at the fimbriated end is seen, 65% of the time. A uterus is described in about 86% of patients, but is usually hypoplastic, unicornuate, or otherwise underdeveloped.[102]

The external genitalia are usually ambiguous, although some cases have been reported with normal male or female appearances. The urethra most often opens on the perineum as a urogenital sinus. The phallus is usually larger than a normal clitoris and often has chordee; it is frequently of sufficient size to give the genitalia a masculine appearance. Gonads are descended or palpable in 61% of patients, more frequently on the right side. About 60% of palpable gonads are ovotestes, with the majority of the remainder being testes. An ovary will rarely descend past the inguinal canal. The ovotestis is more likely to descend if it contains a greater proportion of testicular tissue. The ovarian portion of the ovotestis tends to be firm and convoluted and is histologically normal except for a reduction in the number of primordial follicles. The testicular portion tends to be soft, smooth, and histologically normal in infants. However, it becomes abnormal in more than 90% of adults, marked by tubular atrophy with undifferentiated germ cells and the absence of spermatogenesis. The histology of an intact testis is similar, with spermatogenesis seen in only 12% of patients. The testosterone response to hCG stimulation is usually low but can be normal depending on the amount of testicular tissue present. Gonadal tumors occur in 3%-5% of patients with ovotesticular DSD and are more frequent in those who are Y chromosome positive.[54,102] Renal abnormalities have been noted in 5% of 150 cases.

Most cases of ovotesticular DSD are 46,XX and on karyotype have no separate Y chromosome material. Autosomal or X-linked mutations in genes downstream of *SRY*, such as several of the *SOX*-family genes, have been shown to induce testicular differentiation. Mutations in *RSPO1* and *WNT4* have also been associated with 46,XX DSD.[80] Other mechanisms include the translocation of Y chromosome material to an autosome and chromosome mosaicism in gonadal tissue. Familial cases of 46,XX DSD with male phenotype, and 46,XX ovotesticular DSD, show phenotypic similarity, typically having ambiguous genitalia and lacking the *SRY* gene or other Y sequences, indicating that these conditions are closely related.

Ovotesticular DSD may be identified in the neonatal period because of the finding of ambiguous genitalia. Definitive diagnosis requires a gonadal biopsy, but this is preferably delayed until after the neonatal period. Fertility is often impaired in this condition for both males and females. Gender assignment is guided by the same principles outlined for other DSDs.

46,XY Disorder of Sex Development

This can be classified further into disorders of gonadal development, androgen synthesis or action, and others.

Disorders of Gonadal (Testicular) Development

Complete and Partial Gonadal Dysgenesis

In testicular dysgenesis, the underlying defect is disordered testicular differentiation or development that results in anatomically or histologically abnormal testes and secondary impairment of hormonogenesis or spermatogenesis. Dysgenetic testes are defined by the following characteristics: a failure to induce regression of the ipsilateral Müllerian duct structures, an association with incomplete masculinization of the genitalia, variably abnormal histology, and an increased predisposition toward the development of tumors originating from the germinal structures. The testes may be of normal or small size and are usually cryptorchid. The karyotype is typically 46,XY, but other karyotypes are also seen. Dysgenetic testicular tissue can be seen in ovotesticular DSD.

Individuals with complete gonadal dysgenesis (Swyer syndrome) have a 46,XY karyotype and no testes but instead have streak gonads, female-appearing external genitalia, and normal Müllerian structures, and as a result, the condition is rarely diagnosed in infancy unless there is a known XY karyotype from prenatal testing.[50] A mutation in the *SRY* gene has been reported in 10%-20% of those with complete gonadal dysgenesis.[50] XY gonadal dysgenesis occurring in families has been described and attributed to mutations in the *SRY* gene that resulted in the reduction rather than loss of DNA binding. The reduced binding presumably leads to variability in phenotype, allowing some individuals to have near-normal gonadal development.

The clinical recognition of 46,XY partial gonadal dysgenesis may be possible in the newborn period in infants with clitoromegaly. There is a very high risk for the development of gonadal tumors in XY gonadal dysgenesis. Prophylactic removal of the streak or dysgenetic gonads is indicated in infancy. The gender assignment is most commonly female. Gonadal dysgenesis associated with a Y chromosome is significantly different from the Y-negative forms described previously. Both forms have in common the presence of bilateral or unilateral streak gonadal tissue but differ in tumor risk.

The causes of Y-positive gonadal dysgenesis are heterogeneous and include a small deletion of distal Yp (the short arm of chromosome Y) with loss of the *SRY* gene, an X chromosome or autosomal mutation that interferes

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with or prevents testicular differentiation, and Y chromosome abnormalities or mosaicism. Causative genes include *NR5A1* (SF-1), *SOX9*, *MAP3K1*, *ARX*, *ATRX*, *DHH*, *DMRT1*, *GATA4*, *MAMLD1*, *NROB1*, *WNT4*, *WT1,* and *WWOX*.[80] A structurally abnormal Y chromosome frequently results in 45,X/46,XY or 45,X/47,XYY mosaicism. When the result is two streak gonads, a female phenotype is usually seen. Varying degrees of testicular development, reflecting the relative prevalence of the XY cell lines, may result in ambiguous or predominantly male genital development. The finding of genital ambiguity with asymmetry of the labioscrotal folds, Turner somatic stigmata, or associated malformations allows many patients to be identified in the neonatal period.

Yp gonadal dysgenesis is caused by an abnormal X-Y recombination involving the distal ends of Xp and Yp. This may result in translocation and thus loss of the *SRY* gene from the Y to the X chromosome. The resulting XYp– individual has bilateral streak gonads and a female phenotype; most have lymphedema or other Turner somatic features thought to be caused by the loss of certain Yp genes. Y autosome translocations may also result in loss of the *SRY* gene.

The risk for tumor development in those with 46,XY complete gonadal dysgenesis is 37%-45%.[64] Testis-specific protein on the Y chromosome (*TSPY*) is required for germ cell tumor risk.[90] The most common tumor is a gonadoblastoma, which may arise in a streak gonad or a dysgenetic testis, is frequently bilateral, and occurs from the first year of life up to the fourth decade. Although pure gonadoblastomas do not metastasize, they are frequently associated with dysgerminomas or other malignant germ cell tumors. The risk for a tumor is the greatest for poorly differentiated gonadal tissue and an intra-abdominal or inguinal position; only rarely is there tumor formation in a scrotal testis. Unexpected testosterone or estrogen formation may signal tumor development. Total gonadectomy is recommended for those reared as females and considered for undescended gonadal tissue for those reared as males.

Mutation and Deletion of WT1: Denys-Drash, Fraser, and WAGR Syndromes. The Wilms tumor suppressor gene (*WT1*), which is on chromosome 11p13, encodes a transcription factor that is expressed in the urogenital embryonic tissues that develop into the kidney and gonad. A mutation or deletion of *WT1* causes abnormal gonadal development, as seen in Denys-Drash syndrome (nephropathy, genital abnormalities, Wilms tumor), WAGR syndrome (*W*ilms tumor, *a*niridia, *g*enitourinary malformations, mental *r*etardation), and Fraser syndrome (gonadal dysgenesis and chronic renal failure). Therefore, *WT1* is to be required for the early commitment and maintenance of renal and gonadal tissue and to exert its effects upstream from the *SRY* gene (see Fig. 89.1 and Table 89.1). Both 46,XY and 46,XX individuals may be affected. Although many patients present at birth with ambiguous genitalia ranging from clitoromegaly with labial fusion to hypospadias with undescended testes, others have external genitalia that are phenotypically normal male or female but may be inappropriate for the karyotype.[60] Their underlying DSD defect is in the development of the gonads, which anatomically show wide variation, ranging from streak gonads (complete gonadal dysgenesis) to dysgenetic or rudimentary testes or ovaries to ovotestes; gonadoblastomas have developed in some of the dysgenetic gonads. The internal genital ducts usually reflect the gonadal makeup; Müllerian duct structures are usually present.

Mutation of *SOX9* (SRY-Like HMG Box-Related Gene 9). *SOX9* mutation is a cause of campomelic dysplasia and XY gonadal dysgenesis. In the presence of *SRY*, *SOX9* expression is repressed in the female gonad but is upregulated in the developing testis and is crucial in the pathway for testis development. *SOX9* is also responsible for synthesis of collagen type II, and mutations of *SOX9* result in campomelic dysplasia. Campomelic dysplasia is a cartilage and skeletal malformation syndrome with congenital angulation and bowing of long bones that is associated with 46,XY complete gonadal dysgenesis in about three-fourths of XY cases. Testicular development in XY patients ranges from streak gonads to dysgenetic testes to normal testes; the external genitalia show a gradation of defects, from the female phenotype in those with complete gonadal dysgenesis to ambiguous genitalia to a normal male phenotype.[7] The internal genital ducts reflect the gonadal makeup. Patients who have more severe skeletal dysplasia die in the first months of life from respiratory failure, but less severely affected patients may live into adulthood. The mode of inheritance is autosomal dominant, with haploinsufficiency for *SOX9* on chromosome 17 as the cause of both campomelic dysplasia and gonadal or testicular dysgenesis.

Duplication of Dosage-Sensitive Sex Reversal. Duplication of the dosage-sensitive sex reversal, adrenal hypoplasia congenita critical region, on the X chromosome, gene 1 (*DAX1*), located on the short arm of the X chromosome, overrides the *SRY* gene and impairs or prevents testicular development, resulting in partial or complete XY gonadal dysgenesis. Affected patients have either ambiguous genitalia or a female phenotype and may also exhibit adrenal insufficiency and hypogonadotropic hypogonadism.[37] Familial cases have been reported.

Steroidogenic Factor-1. The *NR5A1* gene codes for steroidogenic factor-1 (*SF1*), a nuclear hormone receptor, and regulates the expression of genes involved in gonadal and adrenal development. Mutations in *SF1* can be associated with 46,XY DSD with genital ambiguity and normal adrenal function or adrenal insufficiency and lead to impaired Leydig cell function and androgen biosynthesis.[105] Mutations are most commonly associated with partial gonadal dysgenesis.[29]

46,XY Ovotesticular Disorder of Sex Development

See the section Ovotesticular Disorder of Sex Development in this chapter.

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Gonadal Regression

Early Regression With Genital Ambiguity (XY Gonadal Agenesis). This rare condition is characterized by the complete absence of testes, including the absence of gonadal streaks, and associated with the almost complete absence of both Müllerian and wolffian duct derivatives and female or partially masculinized genitalia (clitoromegaly and posterior labial fusion).[89] The gonadal and genital features may be explained by very early regression of the developing fetal testes between about 8 and 10 weeks. Testicular failure must have occurred after the initial production of AMH by Sertoli cells but before the Leydig cells could produce sufficient testosterone for a reasonable time. It has been suggested that testicular regression is part of the clinical spectrum of 46,XY gonadal dysgenesis.

Other XY individuals have testes with quite well-developed wolffian structures but incomplete masculinization of the external genitalia. Testicular regression presumably occurred slightly later than it did in those patients with the absence of internal genital ducts. Affected siblings have been reported, raising the possibility of autosomal recessive inheritance. In another family, there were subjects from two generations affected, with X-linked or autosomal dominant, sex-limited inheritance suggested. The differential diagnosis includes Leydig cell hypoplasia.

Late Regression: Congenital Anorchia (Vanishing Testes Syndrome). Many cases have been reported of cryptorchid 46,XY males who on exploration were found to have bilateral anorchia but with normal wolffian structures, the absence of Müllerian structures, and normal male external genitalia. The vas deferens ends blindly, often without an epididymis, in either the inguinal canal or upper scrotum (sometimes palpable as a small knot of tissue), which is retroperitoneally near the usual location of the internal inguinal ring or in the iliac fossa. Neonates and infants with congenital anorchia fail to show any rise in testosterone during either endogenous LH or exogenous hCG stimulation, and they lack AMH. In the 46,XY individual with a male phenotype, these findings are usually but not always diagnostic. If uncertainty exists, laparoscopy or surgical exploration may be necessary. The cause of congenital anorchia is not established, but infections, teratogens, immune mechanisms, or hereditary factors may play a role. Some of those with congenital anorchia also have micropenis.[89] The possibility that bilateral congenital anorchia is part of a continuum with early testicular regression has been suggested.[89]

Disorders of Androgen Synthesis or Action

In these disorders, there is abnormal differentiation of either the internal genital ducts or the external genitalia in a 46,XY individual who has bilateral testes with intact tubular elements (seminiferous tubules with Sertoli and germinal cells). Disordered synthesis or action of testosterone is the underlying cause of the observed abnormalities. Some cases of dysgenetic testes and rudimentary testes overlap phenotypically with this category, but their underlying cause is testicular dysgenesis and not a primary disorder of the testicular hormone synthesis. In patients with 46,XY DSD who are severely undermasculinized, a blind, distal vaginal pouch is present. It appears when a lack of androgen stimulation permits the urovaginal septum to persist.

Androgen Biosynthesis Defect

Five enzymatic steps are involved in the synthesis of testosterone from cholesterol (see Fig. 89.5).[75] A defect in any one results in decreased to absent androgen synthesis and 46,XY DSD (Table 89.7). Three of these enzymes are also necessary for the adrenal biosynthesis of cortisol: cholesterol

TABLE 89.7 Clinical and Hormonal Data for Forms of Congenital Adrenal Hyperplasia (CAH) in Male and Female Newborns

Enzyme Deficiency (Classical Forms)	External Genital Abnormalities		Symptoms		Plasma Steroid Hormones and Renin Levels						
	XX	XY	SW	HTN	17-OHP	Δ^4	T	DHEA	DOC	Aldo	Renin
21-OH: SW	+	–	+	–	H	H	H	H	L/U	L/U	H
21-OH: SV	+	–	–	–	H	H	H	H	N	N	N/H
11β-OH	+	–	–	+	H	H	H	H	H	L	L/U
3β-HSD	±	+	±	–	L/U	L/U	L/U	H	L/U	L/U	H
17α-OH and 17,20-Lyase	–	+	–	+	H/L/U	L/U	L/U	L/U	H	H	L/U
P450scc/StAR	–	+	+	–	U	U	U	U	U	U	H
POR	±	±	±	±	Variable; depends on extent and severity of involved enzyme deficiencies (21-OH, 17α-OH, and 17,20-lyase)						

Aldo, Aldosterone; Δ^4, androstenedione; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; H, high; 3β-HSD, 3β hydroxysteroid; HTN, hypertension; L, low; N, normal; 17-OHP, 17-hydroxyprogesterone; 17α-OH, 17α-hydroxylase; 21-OH, 21 α-hydroxylase; 11β-OH, 11β-hydroxylase; P450scc, cholesterol side chain cleavage; POR, P450-oxidoreductase; StAR, steroidogenic acute regulatory protein; SV, simple virilizing; SW, salt wasting; T, testosterone; U, undetectable.

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side-chain cleavage enzyme (P450scc), 17α-hydroxylase, and 3β-hydroxysteroid dehydrogenase. Their defects result in accompanying cortisol deficiency with or without aldosterone deficiency (see the section Congenital Adrenal Hyperplasia in this chapter). The remaining two testosterone biosynthetic enzymes, 17,20-desmolase and 17β-hydroxysteroid dehydrogenase, are not needed for cortisol synthesis. Their deficiencies primarily cause impaired testosterone synthesis that leads to abnormal male sexual differentiation. In addition, 5α-reductase deficiency is included under this category. Clinical diagnoses are made by finding biochemical evidence of disorders along the testosterone biosynthetic pathway, often accentuated by hCG stimulation testing.

Congenital Lipoid Adrenal Hyperplasia (StAR [Steroidogenic Acute Regulatory] Protein/P450scc Deficiencies). The first step in steroid hormone biosynthesis is the transport of cholesterol into the mitochondria mediated by the steroidogenic acute regulatory (*StAR*) protein followed by conversions of cholesterol to pregnenolone by the cholesterol side chain cleavage enzyme (P450scc).[70]

Congenital lipoid adrenal hyperplasia, rare in most countries, is the second most common form of CAH in Japan and Korea.[70] The underlying defect in lipoid CAH is inability to convert cholesterol to pregnenolone. Lipoid CAH is caused by either mutations in StAR protein or CYP11A1 (P450scc enzyme gene), resulting in deficiency of all adrenal and gonadal hormones (see Fig. 89.5). Patients present usually with salt-losing crisis during the first days of life but in milder cases may not be diagnosed until several months.[49] Male infants with this disorder have either undervirilization or complete female external genital phenotype, often with a blind vaginal pouch, and the testes may be descended. Hyperpigmentation and respiratory problems may occur.

Biochemically, there is decreased to absent production of all adrenal and gonadal steroids, depending on the severity of the defect (see Fig. 89.5). The adrenal glands are enlarged, with a characteristically enormous accumulation of lipid, thus the name *congenital lipoid adrenal hyperplasia*.

P450 Oxidoreductase Deficiency. The P450oxidoreductase (POR) enzyme acts as a cofactor for normal activity of key steroidogenic enzymes, including 17α-hydroxylase/17,20-lyase, 21-hydroxylase, and aromatase (see Fig. 89.5).[93]

P450 oxidoreductase deficiency is a rare form of CAH that manifests with variable phenotypes based on the extent of the involved enzyme deficiencies. Abnormal genital development can be seen in both sexes; males can be undervirilized, and females can be virilized.

The unique aspect in this form of CAH is the frequent association with skeletal malformations, termed *Antley-Bixler syndrome*. Antley-Bixler syndrome is a syndrome that includes craniosynostosis, midface hypoplasia, choanal atresia or stenosis, radiohumeral or radioulnar synostosis, femoral bowing, and joint contractures.[55] Maternal virilization and low maternal estriol and estrone levels during pregnancy may be seen. In infants, the risk for upper airway obstruction caused by skeletal abnormalities, including choanal obstruction, should be assessed. Because some hepatic P450 enzymes are dependent on POR, effects on drug metabolism owing to POR deficiency are possible. Insufficient information is currently available to describe the clinical implications.

Biochemically, affected patients may have elevated 17-OHP and low androgen levels; cortisol may be normal but is poorly responsive to adrenocorticotropic hormone. Both autosomal recessive inheritance and an autosomal dominant mutation in fibroblast growth factor receptor-2 (*FGFR2*) gene have been proposed as a cause of Antley-Bixler syndrome. Molecular diagnosis of POR can be made by mutation analysis.

Management includes hydrocortisone replacement if cortisol deficiency is confirmed by ACTH stimulation test. Salt-wasting secondary to mineralocorticoid deficiency is possible but rare and needs replacement with fludrocortisone and salt.

17α-Hydroxylase and 17,20-Lyase Deficiency. This form of enzyme deficiency accounts for 1% of CAH cases worldwide except in Brazil, where it represents the second most common form of CAH, accounting for 5%-7% of all cases. Combined 17α-hydroxylase and 17,20-lyase deficiency results in impaired production of cortisol and sex steroids, although mineralocorticoid production is intact. Although cortisol secretion is subnormal, patients can produce large amounts of corticosterone, which binds the glucocorticoid receptor with low affinity. Male 46,XY patients present with a mild form of glucocorticoid deficiency, high ratio of 17-OH progesterone to androstenedione, low DHEAS, and low renin hypertension caused by abnormally high 11-deoxycorticosterone (DOC).[6] Deficiency of 17,20-lyase impairs the production of androgen. Affected 46,XY neonates show incomplete masculinization ranging from mild undervirilization of external genitalia to completely female-appearing genitalia, depending on the severity of the defect. The inheritance is autosomal recessive. Hydrocortisone replacement in low doses is needed if adrenal insufficiency is present, which will suppress excessive mineralocorticoid production and normalize the blood pressure. Sex hormone therapy is required for puberty induction and subsequent maintenance replacement. If a 46,XY is assigned a female gender, concern for germ cell tumor formation in the testes exists but is not well quantified.[90]

3β-Hydroxysteroid Dehydrogenase Deficiency. 3βHSD deficiency is a rare autosomal recessive form of CAH characterized by marked clinical heterogeneity. The severity of the defect also varies, with some patients having no genital abnormality at birth but presenting with adrenal insufficiency and some having undervirilization. In severe 3βHSD deficiency, salt wasting, adrenal insufficiency, and abnormal development of male external genitalia are seen.[10] Sodium wasting varies, ranging from severe to mild to none. The characteristic biochemical finding is a marked elevation of ACTH-stimulated 17-OH pregnenolone and 17-OH pregnenolone to 17-OH progesterone ratio.[83] Aldosterone levels

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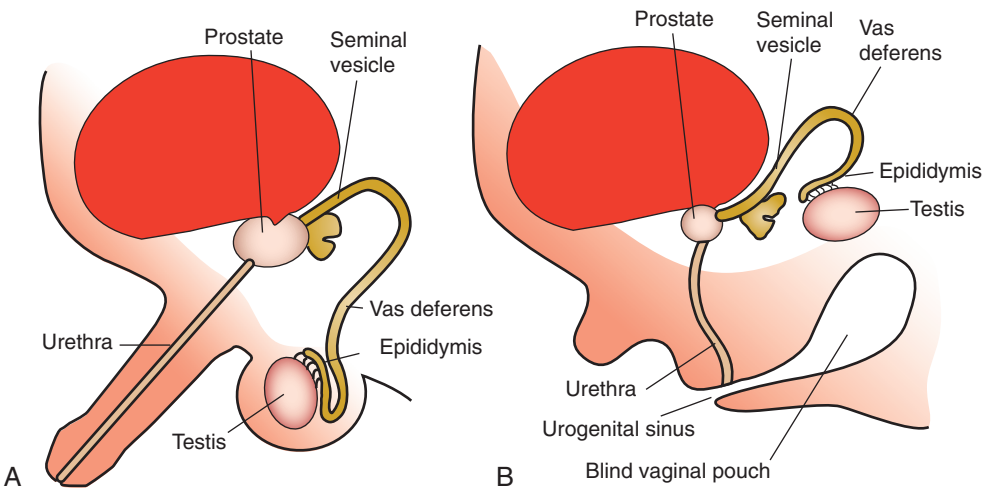
are low, and plasma renin activity is increased. Multiple gene defects in the *HSD3B2* gene have been described.[96] As with other forms of CAH, hydrocortisone replacement will correct cortisol deficiency and abnormal steroid secretion. If mineralocorticoid deficiency exists, fludrocortisone and salt replacements must be also administered.

17β-Hydroxysteroid Dehydrogenase Deficiency. 17β-hydroxysteroid dehydrogenase catalyzes the only reversible step involved in testosterone and estradiol synthesis, the interconversion of androstenedione and testosterone and of estrone and estradiol (see Fig. 89.5). It is present in both gonadal and peripheral tissues but only minimally so in adrenocortical tissue. Its deficiency is associated primarily with diminished testosterone synthesis with a decreased plasma testosterone-to-androstenedione ratio. This results in failure of male differentiation in utero. Affected 46,XY patients have slightly masculinized genitalia (clitoromegaly, posterior labioscrotal fusion); a few have more masculinization.[66] The epididymis and vas deferens are well developed, and in many patients, the testes are descended in the inguinal canal or labioscrotal folds. Because the degree of undervirilization of the external genitalia can be severe, the diagnosis may not be possible in infancy.

Untreated 46,XY patients undergo significant masculinization at puberty and may have an accompanying change in gender identity from female to male (a similar change in gender identity is seen in patients with untreated 5α-reductase deficiency). The inheritance of 17-ketosteroid reductase deficiency is autosomal recessive. It has a high prevalence in the Arab population in the Gaza Strip, Lebanon, Syria, and Turkey.

5α-Reductase Deficiency. 5α-Reductase is located peripherally in the tissues of the urogenital sinus, external genitalia, liver, prostate, hair follicles, and sebaceous glands, where it catalyzes the conversion of testosterone to its 5α-reduced product, dihydrotestosterone (DHT). Its deficiency in the 46,XY fetus results in failure of the external genitalia to undergo male differentiation. Affected males have normally developed testes that may be descended, absent Müllerian duct structures, and male internal ducts (stimulated by testosterone) but phenotypically female or ambiguous external genitalia.[65] Most patients are potentially recognizable at birth, with apparent clitoromegaly, a single perineal orifice that is a urogenital sinus, and posterior labial fusion (Fig. 89.14). A few patients have hypospadias or a micropenis. Most are reared as females; however, in some cultures in which the disorder is widely known and recognized, individuals may be recognized as a third gender. At puberty, 46,XY individuals who have not undergone gonadectomy show striking virilization because of the increase in testosterone, and about 50% change from female to male as adults.[65] DHT-dependent secondary sexual characteristics such as acne, body and facial hair, and prostatic enlargement develop minimally or not at all. The inheritance of primary 5α-reductase deficiency is autosomal recessive.

Leydig Cell Hypoplasia. Patients with testicular unresponsiveness to hCG and LH fail to undergo male genital differentiation. It is caused by an autosomal recessive inactivating mutation in the LH receptor. This results in agenesis or hypoplasia of the Leydig cells. In the complete absence of hCG binding, a female phenotype with a blind vaginal pouch, but no wolffian ducts, is seen. Other patients have shown clitoromegaly, posterior labial fusion, or perineal hypospadias with good development of the epididymis and vas deferens, suggesting an incomplete defect. Anti-Müllerian hormone is produced, so Müllerian structures



• **Fig. 89.14** **A,** Male differentiation of the external genitalia and urogenital sinus structures is stimulated by dihydrotestosterone (DHT) (*pink areas*), whereas wolffian duct differentiation is stimulated by testosterone (*tan area*). **B,** 5α-Reductase deficiency results in impaired male differentiation of DHT-responsive tissues (*pink area*). The external genitalia appear female, and the vesicovaginal septum develops to create a distal, blind vaginal pouch opening into a urogenital sinus. The wolffian duct differentiation is normal (*tan area*). (From Imperato-McGinley J, et al. Male pseudohermaphroditism: the complexities of male phenotypic development. *Am J Med.* 1976;61:251.)

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are absent. The testes are usually cryptorchid and small postpubertally, although possibly of normal size in infancy. The characteristic findings are a low basal level of testosterone and its precursors, high level of LH, the failure of testosterone response to hCG stimulation, and a marked paucity or absence of Leydig cells on biopsy of the testes.[56] The seminiferous tubules and Sertoli cells are normal, but spermatogenic arrest or absence is seen.

Defect in Androgen Action

Androgen Insensitivity Syndromes. The androgen insensitivity syndromes are disorders in which peripheral tissues are partially to completely incapable of responding to stimulation by any androgen because of an androgen receptor or postreceptor defect.[71] Many mutations in the X-linked androgen receptor gene have been described, leading to variable phenotypes in this disorder.[71] Androgen-mediated events, such as masculine differentiation in utero or virilization during puberty, fail to occur or are impaired to a variable extent, depending on the completeness of the defect.

Complete Androgen Insensitivity Syndrome. Affected individuals have a 46,XY karyotype with bilateral testes but a failure in wolffian duct development and complete absence of any masculinization of the external genitalia. They have female-appearing external genitalia with a distal vaginal pouch. The Müllerian structures are absent, but microscopic remnants have been reported, possibly from the interference of high, unopposed levels of estrogen with the action of AMH. The testes are of normal size and may be descended into the inguinal canal or labia majora, and more than half of these individuals have an inguinal hernia, which may lead to their clinical recognition in infancy. At puberty, these individuals undergo female breast development and acquire a female habitus because of peripheral conversion of testosterone to estradiol; however, they have primary amenorrhea. No masculinization is seen, and gender identity remains female.

The occurrence of cAIS is familial in about 30% of cases, and a family history of infertile female relatives is sometimes found. Spontaneous mutations are thought to account for the sporadic cases. Screening for the syndrome in an at-risk fetus can be carried out in utero by ultrasound examination of the genitalia and determination of the karyotype. The diagnosis is inferred in the phenotypically female neonate by establishing the absence of a uterine cervix and the presence of a Y chromosome. Both plasma testosterone and LH have been shown to be low at 30 days of age, suggesting that the expected postnatal testosterone rise requires the hypothalamic–pituitary axis to be responsive to testosterone.[15]

The differential diagnosis includes other causes of 46,XY DSD; hCG stimulation testing may be needed to rule out these possibilities. The gender is almost always female. There is a 2% risk for germ cell malignancy in childhood, with rates of 20%-30% reported in those who have had gonadectomy in their 20s-30s, probably related to the intra-abdominal location of the testes. For this reason, gonadectomy is indicated; however, current recommendations suggest delaying until after puberty, as testosterone is converted to estradiol peripherally and allows for spontaneous development of secondary sexual characteristics[27,87] and virtually all malignant tumors have occurred postpubertally.



• **Fig. 89.15** This 46,XY infant with partial androgen insensitivity had ambiguous genitalia at birth noted by a phallus with stretched length of 1.8 cm and perineal hypospadias. Both gonads were palpable in the inguinal canals. The labioscrotal folds showed posterior fusion with pigmentation and rugation. Before final decision for a male sex of rearing, a 3-month trial of testosterone was undertaken with increase in the size of the phallus.

Partial Androgen Insensitivity Syndrome. Affected 46,XY individuals have bilateral testes and absent Müllerian ducts, but incomplete masculinization of their external genitalia, ranging from female-appearing genitalia with clitoromegaly or posterior labial fusion to phenotypically normal male-appearing genitalia. Many have perineal, penoscrotal, or penile hypospadias and others have a micropenis (Fig. 89.15). There also is wolffian duct development, but it is often incomplete, which may not correlate with the extent of external genital masculinization. At puberty, both masculinization and feminization are seen, the extent depending on the severity of the androgen insensitivity.[71]

The causes of pAIS are heterogeneous. Most individuals have qualitatively abnormal receptors with variable function.[71] Others have reduced numbers of normal receptors, and a few have postreceptor defects. There is an X-linked recessive inheritance of the receptor-related mutations. The phenotype in pAIS is variable and does not necessarily correlate with the genotype even within the same family.[28]

Except for very few individuals with a normal male phenotype, all individuals with pAIS are infertile. The risk for development of gonadal tumors is not known, but intratubular germ cell neoplasia (a precancerous lesion) frequently occurs in patients with pAIS at as early as 2 months of age. Monitoring for the development of a testicular tumor is needed if the testes are not removed.[90] The testes are typically removed in those reared as females.

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Other

Disorders of Anti-Müllerian Hormone and Anti-Müllerian Hormone Receptor (Persistent Müllerian Duct Syndrome)

Isolated AMH deficiency or AMH receptor abnormalities result in failure of the Müllerian ducts to regress. The clinical picture in the 46,XY individual is that of a phenotypic male with bilateral fallopian tubes, a uterus (occasionally hypoplastic or absent), wolffian duct development, and bilaterally normal testes.[88] Two clinical presentations are seen. The typical clinical presentation is in a male with bilateral cryptorchidism and inguinal hernias and normal male external genitalia. During surgery for hernia repair, a uterus and fallopian tubes are found in the inguinal canal. Alternatively, one testis is at least partially descended and accompanied by a fallopian tube and uterus that easily enter the inguinal canal. In addition, about one-third have transverse ectopia, the opposite testis being pulled to the side with the inguinal hernia, so that both testes are in the same inguinal canal. Such patients may have an inguinal mass or the appearance of an incarcerated hernia without evidence of intestinal obstruction. Less commonly, the uterus is fixed in the pelvis and the testes are in an ovarian position. The vas deferens and epididymis are typically enmeshed in the uterine wall and mesosalpinx, making it difficult to bring the testes down into the scrotum.

Persistent Müllerian duct syndrome is caused by a mutation in either the *AMH* gene or its receptor and is inherited according to an autosomal recessive pattern.[88] The gender assignment is male. Orchiopexy should be performed early in infancy to improve testicular outcome. Achieving testicular descent into the scrotum usually requires extensive dissection to free the spermatic cord. The Müllerian structures do not need to be removed, because they do not develop malignancy and there is a strong risk for damaging the vas deferens. Spermatogenesis is intact, but many patients are infertile, possibly because of abnormal epididymal development, cryptorchidism, or injury to the vas deferens. Intracytoplasmic sperm injection may produce fertility in some of these cases. There is no evidence of an increased risk for testicular tumors compared with other causes of cryptorchidism.

Common Male Genital Abnormalities in Small-for-Gestational-Age Newborns

Newborns with low birth weight and those who suffered from intrauterine growth restriction (IUGR) have higher incidence of cryptorchidism and hypospadias. Because fetal testosterone secretion is under the influence of placental hCG during the first 14 weeks, placental insufficiency might reduce fetal hCG levels and hence testosterone biosynthesis. Several studies have demonstrated that the earlier the placental compromise in IUGR, the more severe the genital abnormality.[97]

The estimated incidence of hypospadias in IUGR newborns in postnatal studies is variable, ranging from 3.83%-19% compared with an incidence of 0.3% in the general population. Severe proximal hypospadias occurred in up to 62% of all cases. A clinical correlation has been found between the severity of IUGR and that of hypospadias.[21] The strongest evidence of an association between IUGR and hypospadias comes from monozygotic twins. A study of 18 twin pairs in which one of the twins had hypospadias found that in 16/18 twin pairs the twin with hypospadias weighed on average 500 g less than the twin who had no hypospadias. Similarly, several studies have found that the risk of cryptorchidism increases two- to fourfold in boys with low birth weight. Population-based surveys confirmed that this increased risk persists during infancy, after correction for prematurity, and despite spontaneous postnatal descent in the majority of cases.[97]

Environmental Influences: Endocrine-Disrupting Chemicals

Over the past decade, several studies reported an increasing trend in male external genital malformations that has led to the suspicion that environmental chemicals, also called endocrine disrupting chemicals (EDCs), could influence the fetal sexual development. Animal studies have confirmed the influence of such chemicals on genitourinary development through exogenous manipulation of steroid levels or hormone receptors. Of the EDCs, there have been concerns about the effects of substances pertaining to the general population, including pesticides, phytoestrogen from vegetarian food sources, and occupational chemicals, including phthalates (commonly found in plastics and hair spray), alkyl phenols (used in detergents, fuel, and fragrance), and heavy metals.[8,38]

The most widely studied epidemiologic association is the role of EDCs in the development of male hypospadias. Studies showed mixed and inconclusive results on the effects of these factors in increasing the risk of hypospadias in the offspring of mothers and fathers who have occupations with high exposure to EDCs. Nevertheless, data from populations with high exposure rates because of industrial accidents or in utero exposure to diethylstilbestrol (DES) suggested that EDCs adversely affect genitourinary development. Given the multifactorial component of the genital malformation and the limitation of current epidemiologic studies, the cause–effect relationship can only be assumed and not proved. Further studies of these chemicals are needed to gain a better understanding of their role in human sexual development.[97]

46,XX Disorders of Sex Development

This group includes four main categories: disorders of gonadal development, androgen excess, syndromic defects, and structural defects.

Disorders of Gonadal (Ovarian) Development

Gonadal Dysgenesis

Patients with XX gonadal dysgenesis have bilateral streak gonads or hypoplastic ovaries with intact Müllerian duct

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structures and female external genitalia. They differ from patients with Turner syndrome in that they usually have normal stature, an absence of Turner stigmata, structurally intact X chromosomes, and a positive family history as familial cases occur frequently. An abnormality of an autosomal gene that regulates germ cell migration, formation of the bipotential gonad, or ovarian differentiation may be the cause. Key regulatory genes in ovarian development that have been implicated in 46,XX disorders of ovarian development include *FOXL2*, *WNT4*, *β-CATENIN*, and *NR5A1*.[5,80] Associated features are seen in some families, including sensorineural hearing loss (*Perrault* syndrome), neurologic abnormalities, and renal disease. Isolated instances of clitoromegaly have been described, resulting from testosterone production by either hilar cells or luteinized gonadal stromal cells in a streak gonad. The differential diagnosis includes defects in estradiol synthesis, Slotnick-Goldfarb syndrome (streak gonad plus a hypoplastic ovary that may present as a neonatal ovarian cyst), Malouf syndrome (ovarian dysgenesis, dilated cardiomyopathy, ptosis, broad nasal bridge), and Denys-Drash and Fraser syndromes.

46,XX Ovotesticular Disorder of Sex Development

See the section Ovotesticular Disorder of Sex Development in this chapter.

Testicular Disorder of Sex Development (46,XX Male)

Individuals with 46,XX male phenotype have bilateral testes but lack of a Y chromosome on karyotype analysis. The incidence is about 3.5-4.7 per 100,000 male births. The most common cause is an abnormal X to Y translocation, occurring during paternal meiosis and involving a crossover of variable amounts of adjacent Y sequences to the distal end of the paternal short arm of the X chromosome.[13] Most, if not all, XX males inherit one maternal and one paternal X chromosome. The majority of 46,XX males have normal male internal and external genitalia. Around 15% have ambiguous genitalia due to decreased fetal testosterone production.[13] Testes are of normal size but may be cryptorchid. As with Klinefelter syndrome, the detrimental influence of the second X chromosome results in the absence of spermatogonia, hyalinization of the tubules, and small testes in adults. The testicular histology is almost normal in the first year of life, but after 1 year of age the spermatogonia are lacking. Most *SRY*-positive individuals have a normal male phenotype and no disability except infertility. A few have lost more of the X chromosome sequence, resulting in short stature or cognitive disability. Others with a very small Y interchange have hypospadias or other manifestations of incomplete male genital development, which is thought to be caused by altered *SRY* gene expression. A few XX males have been found to have no *SRY* gene and no detectable Y sequences. Most of these *SRY*-negative and Y-negative individuals have ambiguous genitalia and account for the majority of genital ambiguity among 46,XX males. A *SOX9* duplication was found in a family that resulted in 46,XX male phenotype.[25] A gain-of-function mutation in *SOX3* was reported in a 46,XX phenotypically male newborn who presented with hypospadias and bifid scrotum.[22] In both reports, the described mutations resulted in upregulation of *SOX9*, which acts downstream of *SRY*. This allowed for *SRY*-independent testicular induction leading to phenotypically male sexual differentiation. A loss-of-function mutation in *WNT4* has been shown to underlie SERKAL syndrome, involving 46,XX testicular DSD in association with adrenal, renal, and pulmonary dysgenesis.[80]

Androgen Excess

The external genital ambiguity is almost always androgen induced. Most cases are caused by fetal CAH and a few result from a maternal androgen source. More rarely, a source of androgens is not found, and an error in morphogenesis is presumed to be the cause.

Androgen exposure between 8 and 14 weeks of fetal age results in variable male differentiation of the external genitalia, particularly labioscrotal fusion, regression of the urovaginal septum to form a urogenital sinus, ventral displacement of the urethral (urogenital) meatus toward or on the phallus, and male phallus differentiation (Fig. 89.16).



• **Fig. 89.16** A 4-week-old 46,XX neonate with salt-losing 21-hydroxylase deficiency with significant virilization of external genitalia. A normal uterus and ovaries were seen in the pelvis, whereas both adrenal glands were enlarged with "cerebriform appearance." **A,** Clitoromegaly (1.6 × 1 cm) and rugated, hyperpigmented, partially fused labial majora. **B,** A single orifice visualized at the base of the clitoris, representing a common urogenital sinus. **C,** Genitogram showing an intermediate length urogenital sinus.

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Androgen exposure occurring beyond 12 or 14 weeks produces growth but not differentiation of the external genitalia, namely, clitoral hypertrophy, defined in the neonate by a clitoral width of greater than 6 mm. Most 46,XX DSDs are identified at birth because of genital ambiguity, but the more severely affected neonates may be missed initially, being incorrectly identified as males with hypospadias or undescended testes. The major reason to identify 46,XX DSDs in the immediate neonatal period is to recognize underlying CAH that, if present, may be life threatening.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders in which there is an inherited defect in one of the enzymes required for the adrenocortical synthesis of cortisol from cholesterol. Each of the enzyme defects leads to impaired cortisol production, and the lack of negative feedback to the pituitary gland causes a secondary increase in adrenocorticotropic hormone (ACTH). The elevated ACTH stimulates adrenocortical steroidogenic activity in an attempt to normalize cortisol production. Clinical problems arise as a consequence of impaired synthesis of the steroid hormones (glucocorticoids, mineralocorticoids, or gonadal sex steroids) downstream of the enzymatic block and overproduction of the precursor steroids or their side products upstream of the block. Adrenal enzyme defects not involving cortisol synthesis are excluded from the CAH designation.

The five enzymes or enzymatic steps involved in the synthesis of cortisol from cholesterol are cholesterol side chain cleavage enzyme complex (P450scc), 3β-hydroxysteroid dehydrogenase (3βHSD), 17α-hydroxylase, 21-hydroxylase, and 11β-hydroxylase (see Fig. 89.5). All except 3βHSD are members of the cytochrome P450 group of oxygenases. Except for 17α-hydroxylase, these enzymes are also necessary for mineralocorticoid (aldosterone) biosynthesis. The first three enzymes are present in gonadal tissue, where they are necessary for synthesis of the sex steroids. A deficiency in one of these three enzymes in males results in inadequate testosterone formation and incomplete male sex differentiation. In females, it results in deficient estrogen synthesis, which will not be apparent in the neonatal period but becomes clinically significant at puberty.

The 21- and 11β-hydroxylases are found predominantly in the adrenal cortex and only minimally in gonadal tissue. They are not necessary for the synthesis of sex steroids. However, their deficiencies (and to a lesser extent the deficiency of 3βHSD) result in excess formation of precursor steroids, which yield an increased production of androgens that induce masculinization of affected female fetuses in utero (see Table 89.7). By this mechanism, 46,XX DSD occurs, and affected females should be identifiable at birth by their virilized genitalia. Affected males who have 21- or 11β-hydroxylase deficiency do not manifest recognizable penile enlargement or other virilization at birth but develop these symptoms postnatally if untreated. On the other hand, affected males with 3βHSD deficiency do have genital ambiguity at birth because of testosterone deficiency. Finally, all five enzyme deficiencies are clinically important because of the associated adrenal glucocorticoid deficiency (with or without mineralocorticoid deficiency). This condition is life threatening and must be recognized and managed early.

21-Hydroxylase Deficiency. 21-Hydroxylase enzyme deficiency is the most common cause of CAH, accounting for 95% of all cases. It is caused by a mutation in *CYP21A2*. Two classic forms are seen in neonates: a simple virilizing form caused by a partial enzyme deficiency and a salt-losing form caused by a more complete enzyme deficiency. A third form, late-onset or nonclassic 21-hydroxylase deficiency, represents a mild enzyme deficiency that does not have clinical manifestations in the fetus, neonate, or infant. Both of the classic forms are characterized by abnormal virilization of the female fetus. In simple virilizing CAH, salt wasting is mild and adrenal insufficiency does not tend to occur except in stressful circumstances. In salt-losing CAH, adrenal insufficiency is present at baseline and this tends to present in the neonatal period or soon thereafter as an adrenal crisis. Around 75% of all reported cases of CAH are salt wasting and 25% are not.[31] The incidence of the classic form estimated from data from 13 countries (United States, France, Italy, New Zealand, Japan, United Kingdom, Brazil, Switzerland, Sweden, Germany, Portugal, Canada, and Spain) is 1 in 15,000 live births, and the carrier frequency of classic CAH is about 1 in 60 individuals.[67] A deficiency of 21-hydroxylase results in an impairment of cortisol and aldosterone biosynthesis, which is compensated for by the increased secretion of ACTH and angiotensin. This process causes overproduction of the steroids before the enzyme block and a secondary increased secretion of adrenal androgens, which are converted to testosterone and DHT in peripheral tissues and cause abnormal virilization.

Affected fetuses produce increased amounts of androgens beginning in the first trimester. In the female fetus, this leads to varying degrees of virilization of the external genitalia and urogenital sinus. However, the internal genital ducts develop normally along female lines. At birth, the spectrum ranges from mild clitoromegaly, usually with some posterior labial fusion, to perineal or penile hypospadias, to occasionally complete male differentiation, with the urethra opening at the tip of a male-sized phallus; the latter phenotype may have a normal male appearance except for impalpable gonads that may be interpreted as bilateral cryptorchidism. The extent of virilization intends to reflect the severity of the enzyme defect. Females with simple virilizing CAH often display less extensive virilization than those with the salt-losing type. In males, the increased secretion of adrenal androgens is insignificant compared with the fetal production of testicular androgens. The external genitalia are usually normal at birth; some enlargement of the penis may occur, but it is rarely recognized as abnormal. Due to elevated circulating ACTH, female and male neonates may have increased pigmentation of the genitalia or areolae.

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Simple Virilizing Form. Simple virilizing CAH is caused by a partial deficiency in the 21-hydroxylase enzyme.

Patients with untreated, simple virilizing 21-hydroxylase deficiency continue to produce excess androgens postnatally, resulting in accelerated growth and skeletal maturation as well as the signs of adrenarche. Patients with mild CAH generally do not develop symptoms of adrenal insufficiency unless they are exposed to major stress or significant salt depletion (reduced salt intake, vomiting, excessive sweating). A few patients with either form have received medical attention because of recurrent hypoglycemic episodes or seizures, usually occurring during common infections.

Salt-Wasting Form. Salt-wasting CAH is caused by a severe deficiency of the 21-hydroxylase enzyme that results in significant impairment of cortisol and aldosterone synthesis that cannot be compensated for by the increased levels of ACTH and angiotensin. The development of cortisol and aldosterone deficiency, usually in the first weeks of life, results in acute adrenal insufficiency and sodium wasting. Females with salt-losing CAH may show more complete masculinization of the external genitalia, and some are incorrectly identified as males at birth (see Fig. 89.16). If not identified by a newborn screening program, males generally present to medical attention when they develop a salt-losing crisis caused by adrenal insufficiency. The symptoms or signs of adrenal insufficiency are not present at birth and rarely occur before 3-4 days of age. About half of the untreated patients with salt-losing CAH develop adrenal crisis between 6 and 14 days of age; by 1 month of age, more than 75% have developed adrenal crisis. Less severely affected individuals may present later, at several months of age, usually in association with a stressful condition causing decreased salt intake or increased salt losses, and a few escape crisis entirely. The early symptoms and signs of adrenal crisis are nonspecific and include lethargy, poor appetite, regurgitation of feeds, failure to thrive, and weight loss. Hyperkalemia, hyponatremia, and metabolic acidosis may be seen early. The regurgitation of feedings may progress to projectile vomiting. Severe symptoms and signs may occur within 1-2 days, including dehydration (with accompanying azotemia), hypotension, muscle weakness, obtundation, a gray or cyanotic appearance, cold and clammy skin, hyperkalemic cardiac conduction abnormalities, and hyponatremic or hypoglycemic seizures.

The development of acute adrenal crisis is partially caused by hypoaldosteronism, which results in renal sodium wasting with depletion of total-body sodium content and an impaired ability to secrete potassium and hydrogen ions at the distal tubule. The decreased total-body sodium results in hyponatremia, hypovolemia, and decreased tissue perfusion, which account for many of the early symptoms and, eventually, results in hypovolemic shock.

Hypocortisolemia represents the other major component of adrenal insufficiency leading to impairment of cardiovascular, metabolic, and other systemic functions. The cardiovascular manifestations of glucocorticoid deficiency include decreased stroke volume and cardiac output and decreased peripheral vascular tone, resulting in decreased blood pressure. Depletion of the renin substrate occurs in the presence of cortisol deficiency and impairs the renin–angiotensin axis, contributing to circulatory failure. Norepinephrine acts in a cortisol-dependent manner to increase peripheral blood pressure, demonstrating another mechanism to protect hemodynamic stability that is impaired in the setting of cortisol deficiency. Cortisol sensitizes the renal-collecting tubules to vasopressin and, consequently, hypovolemia is further exacerbated by the urine concentration defect that results from adrenal insufficiency.

Cortisol plays a role in several elements of glucose homeostasis. It stimulates hepatic glucose production by inducing the activity of gluconeogenic enzymes. Cortisol also stimulates mobilization of hepatic glycogen stores via its permissive effects on glucagon and epinephrine mediated glycogenolysis. As a result, cortisol deficiency can lead to hypoglycemia during times of prolonged fasting. In the setting of impaired glucose production and mobilization, fat becomes the primary energy source, which may lead to lipid depletion.

Hormonal Abnormalities. Serum cortisol is normal or low with an inadequate rise in response to ACTH administration. Adrenocorticotropic hormone levels in untreated patients with either form of CAH are elevated. Plasma renin activity is also elevated, especially in salt-losing CAH.

Of the steroids preceding the enzyme block, 17-OHP is the most strikingly elevated. Serum concentrations are increased 40-400 times above the upper limit of normal and occasionally higher. Androstenedione can be up to 40 times higher than the normal limit. About 15% of the androstenedione produced is metabolized in peripheral tissues to testosterone, with the adrenals synthesizing very little testosterone. Serum testosterone levels in affected children can be elevated by 20 times the normal range.

Diagnosis. The diagnosis of 21-hydroxylase deficiency in a neonate or infant should be considered in females with any masculinization of the external genitalia, in presumed males with impalpable gonads (including males with hypospadias), in females or males who develop symptoms or signs of adrenal insufficiency or crisis (females should be recognized by their genital abnormalities), and in those who have a family history of CAH or an unexplained death in infancy. For 21-hydroxylase deficiency, the most useful diagnostic test is the determination of an increased level of serum 17-OHP (>80 times higher than normal in a full-term infant). The diagnosis of the salt-losing form of CAH is based on obtaining clinical or biochemical evidence of sodium wasting. High urinary sodium concentrations in the presence of normal or low serum sodium concentrations may indicate a salt-wasting infant. The measurement of aldosterone in the untreated state is not diagnostically useful because of the overlap with levels seen in untreated patients with simple virilizing CAH.[53] Patients with mild, salt-losing CAH may show normal electrolytes and lack

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the clinical signs of hypovolemia. In this case, the diagnosis is made biochemically by finding an increased level of plasma renin activity during physiologic glucocorticoid replacement therapy, indicating that mineralocorticoid replacement is required. In response to administration of synthetic ACTH (Cortrosyn, 35 μg/kg to a maximum of 250 μg intravenously), pre- and post-17-OHP levels can be plotted on a nomogram to predict the genotype.[77] Confirmatory genetic testing can also be pursued. While plasma ACTH and serum cortisol are useful for demonstrating and investigating adrenal insufficiency, they do not contribute to defining the enzyme defect of CAH.[76]

Newborn Screening. Many jurisdictions have newborn screening programs that include the measurement of 17-OHP and allow for early identification of infants with 21-hydroxylase deficiency. The justification lies in the increased mortality that occurs in infants who are not recognized at birth and die of salt-losing crisis or sudden infant death as well as the increased morbidity that results from adrenal insufficiency, incorrect gender assignment, and premature virilization.[107] Caution is needed in interpreting 17-OHP values on newborn screening tests, as the levels in unaffected full-term neonates may be elevated in the first 12 hours of life before declining to the normal range after 24 hours of age. Levels in premature and sick neonates may overlap with those found in many affected infants in the first few days of life.[94] Many jurisdictions with newborn screening programs have cutoff values that are adjusted according to gestational age or weight, or both. False-positive results are usually associated with prematurity (presumably caused by decreased metabolic clearance of 17-OHP), low birth weight and, less often, serious illness (presumably due to increased 17-OHP production associated with stress). Age less than 24 hours (fetoplacental contribution of 17-OHP) or technical problems are additional reasons for false positive newborn screen results. Although antenatal exposure to corticosteroids has been shown to have variable effects on 17-OHP levels, infants treated with these agents should still undergo newborn screening, with repeat screening at several days of life.[107]

The overall incidence of 21-hydroxylase deficiency in screened neonates is about 1 in 15,000, ranging from 1 in 11,000 to 1 in 21,000 for most programs. As expected, the male-to-female ratio is about 1:1 with salt losers making up about 72% of confirmed cases. Although females identified by screening often have variable masculinization of the external genitalia, one-third to one-half were missed clinically, including some inappropriately assigned a male gender. Identification at 5-21 days of age has prevented adrenal crises in many affected but unrecognized neonates, particularly male infants in whom clinical signs may not be apparent at birth. However, a negative newborn screening result does not necessarily rule out the diagnosis of classical CAH. A false-negative rate of 22% on CAH newborn screening has been recently reported. The missed cases included both simple virilizing and salt-wasting types in male and female neonates. This report emphasizes that diagnostic testing for CAH should be pursued when clinically suspected, even in the context of a negative newborn screen result.[92]

Ultrasonography. An experienced pediatric radiologist reading an adrenal ultrasound can identify enlargement and lobulation of the adrenal glands with stippled echogenicity, findings consistent with CAH. Adrenal ultrasonography has been shown to have a sensitivity of 92% and a specificity of 100% for diagnosing CAH.[4]

Treatment. The goals of the treatment of CAH are to normalize ACTH secretion, thereby lowering ACTH-stimulated precursor steroids and their side products, and to provide replacement or correction of end-product (cortisol, aldosterone, gonadal sex steroid) deficiencies. Due to the interconnectedness of the synthetic pathways for glucocorticoids, mineralocorticoids, and sex steroids, these two goals are closely related. Insufficient replacement permits increased ACTH and sodium wasting while excessive replacement produces a cushingoid state, growth suppression, and hypertension.

In the simple virilizing form of 21-hydroxylase deficiency, normalization of ACTH requires only cortisol replacement. The adequacy of cortisol replacement is reflected by serum 17-OHP and androstenedione levels, with a goal of maintaining values mildly above the range for age. The addition of mineralocorticoid therapy may decrease the amount of cortisol that is needed. In the salt-losing form of 21-hydroxylase deficiency, normalization of ACTH requires the correction of sodium wasting and hypovolemia in addition to the replacement of cortisol. Increased levels indicate the presence of hypovolemia caused by sodium wasting and mineralocorticoid deficiency, while subnormal levels indicate sodium retention caused by excessive mineralocorticoid replacement.

Maintenance glucocorticoid requirements must take into consideration differences in potency, absorption, and duration of action among the available preparations. Hydrocortisone is the oral preparation of choice. Oral replacement dose in CAH usually ranges from 10-15 mg/m^2 per day, given in three divided doses.[108]

Increases in the dose of hydrocortisone (or other glucocorticoid) should be made during periods of stress, with doubling or tripling of the dose during moderate and severe illnesses. Major illnesses, surgery, or trauma should be covered by the intramuscular or intravenous administration of hydrocortisone at three to six times the maintenance dose to avoid adrenal crisis (Table 89.8).[108] For infants who require maintenance mineralocorticoid replacement therapy, 9α-fludrocortisone acetate (florinef acetate) at a dose of 0.05-0.2 mg daily is administered orally in one or two divided doses. A salt supplement such as sodium chloride oral solution at 0.5-5 mmol/kg per day divided in four to six doses is usually required during the first 6-12 months.[108] Measurements of blood pressure and the level of plasma renin activity are used to adjust the mineralocorticoid dosage and sodium supplementation. Unlike hydrocortisone or other glucocorticoids, the dose of florinef acetate does not change with increases in body size or during stress. As infancy progresses, mineralocorticoid requirements diminish; salt supplementation should be

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TABLE 89.8 Treatment Guidelines for Neonate With Salt-Wasting Congenital Adrenal Hyperplasia (CAH)

Glucocorticoids: hydrocortisone	Maintenance: 12-20 mg/m^2 per day PO divided three times a day Stress dosing: Acute illness with stable hemodynamics: 40 mg/m^2 per day PO/IV/IM divided q 6-8 h Severe stress, such as major surgery or sepsis, or if hemodynamically unstable: 100 mg/m^2 (or 25 mg) IV/IM STAT once, then 25 mg/m^2/dose q 6 h for 24-48 h. Assess the need for ongoing stress dosing as per clinical status General anesthesia (either for surgery or procedure): 50 mg/m^2 IV/IM once 30-60 minutes before anesthesia induction
Mineralocorticoids: fludrocortisone	0.05-0.2 mg/day PO once or twice daily
Sodium chloride	0.5-5 mmol/kg per day divided in 4-6 doses as tolerated

discontinued, and the dose of florinef acetate may need to be lowered.

In acute salt-losing adrenal crises, fluid replacement (beginning with 20 mL/kg of body weight of 0.9% saline), sodium replacement, continuous glucose infusion, glucocorticoid therapy at 50-100 mg/m^2 (initially given intravenously as the phosphate or succinate ester of hydrocortisone), and mineralocorticoid replacement (at maintenance doses) are needed. Acidosis, hypoglycemia, and hyperkalemia may be present and should be managed, and the patient should be monitored for signs and symptoms of severe hyperkalemia. In patients stable enough for diagnostic testing, glucocorticoid therapy may be withheld until the tests are completed. However, glucocorticoids should be administered if blood pressure or other functions are not correctable with fluid, saline, glucose, and mineralocorticoid replacement.

Gender Assignment. (See subsection Gender Assignment in Newborns for a full discussion.) Here we discuss gender assignment issues specific to CAH. Female gender assignment is usually recommended in 46,XX CAH individuals regardless of the extent of masculinization of their genitalia, apart from those with complete virilization where either sex of rearing is considered. This recommendation is based on the observation that these patients have normal ovaries and Müllerian structures and have the potential for fertility as females and typically have a female gender identity. Surgical correction and its timing in females with masculinized external genitalia are controversial. If done, it is usually performed when a reasonable body size has been achieved, commonly in the first 2-6 months, but may be deferred until the patient can participate in decisions about surgery. Gender identity in girls with CAH is not related to the degree of genital virilization or the age at which genital reconstructive surgery was done.[69] Females with CAH have been shown to have more cross-gender role behaviors, such as more masculine play preferences and styles.[73] Lower rates of heterosexual orientation, marriage, and fertility have been reported, and although most identify as female, girls with CAH have an increased cross-gender identity compared to girls without CAH.[69,85,86]

Genetics. 21-hydroxylase deficiency is inherited as an autosomal recessive disorder. Molecular genetic studies show that two 21-hydroxylase genes are present on each chromosome 6. The first gene is nonfunctional (a pseudogene) and only the second one is functional. These two genes are named *CYP21P* and *CYP21*, respectively.

Diverse mutational abnormalities of the *CYP21* gene have been described for 21-hydroxylase deficiency, including point mutations, gene conversions (transfer of an abnormal sequence from the pseudogene to the active gene), and deletions. Point mutations and small-gene conversions represent most *CYP21* mutations. They may have mild or severe consequences, affecting messenger RNA stability, structural conformation, and enzyme function. Gene deletions and large-gene conversions account for the remaining *CYP21* changes, which usually result in defective or absent messenger RNA. More recently, intronic mutations affecting splice sites have been identified.[24] Patients with salt wasting have the most deleterious mutations and almost no residual enzyme activity, although there is overlap among phenotype–genotype correlations.[35] Genotyping to identify the mutation is available.[112]

Prenatal Diagnosis and Treatment. Prenatal diagnosis is available for pregnancies at risk of having a 21-hydroxylase CAH affected baby. A gene-specific diagnosis in utero can be made on fetal cells obtained by chorionic villus sampling or amniotic fluid analysis.[47]

There is general consensus that prenatal dexamethasone is effective, with a success rate of 80%-85%, in preventing or minimizing the virilization seen in classical 21-hydroxylase CAH affected female infants. However, prenatal therapy with dexamethasone remains controversial. To reduce or eliminate the masculinization of female fetus external genitalia, dexamethasone needs to be administered at a sufficient dose to suppress fetal ACTH and hence androgen production. As the genetic diagnosis cannot be made until 10-12 weeks, which is after virilization has already begun, all pregnancies at risk for CAH are treated empirically with dexamethasone from the time pregnancy is confirmed and preferably before 9 weeks of gestation. Treatment is discontinued once the genetic results confirm either a male fetal karyotype and or unaffected female fetus. The mother of the affected female fetus continues with treatment until delivery. With this approach, seven out of eight fetuses (boys and unaffected girls) are treated unnecessarily. Recent genetic advances have allowed for the determination of fetal sex by quantitative polymerase chain reaction of fetal Y-chromosomal DNA obtained directly from maternal blood. Such an approach can improve the probability of treating affected female fetuses from 1 in 8 to 1 in 4 by

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eliminating the unnecessary treatment of male fetuses. Additionally, the presence of single nucleotide polymorphisms related to a disease-causing *CYP21* allele from a paternal carrier in a maternal serum sample has been used for prenatal genetic diagnosis. The use of targeted massive parallel sequencing of maternal cell-free fetal DNA has also been used to successfully determine the allelic composition of the fetal *CYP21* locus. At this point, these tests are not routinely available.[34,47,48]

There is accumulating evidence from animal studies and follow-up data on cohorts of children exposed to prenatal dexamethasone that have raised concern about potential neurocognitive adverse effects.[41] These findings indicate that long-term follow-up of this group of patients is of extreme importance.

Based on the limited data on the long-term neurocognitive outcomes in children exposed to dexamethasone prenatally, the Endocrine Society's task force concluded that such treatment should be considered experimental and that parents should be informed of potential risks and benefits of this treatment. If parents choose to pursue prenatal treatment, it should be done through a protocol approved by a research ethics review board at a designated center.[108]

11β-Hydroxylase Deficiency (Hypertensive Congenital Adrenal Hyperplasia). 11β-Hydroxylase (CYP11B) deficiency is the second most common form of CAH, accounting for about 0.2%-8% of all cases. The deficiency results in impaired synthesis of cortisol and aldosterone, virilization of the female fetus from increased androgens, and low-renin hypertension caused by overproduction of deoxycorticosterone (DOC), a moderately potent mineralocorticoid. The clinical presentation of this form of CAH is variable, and not all patients develop hypertension. Classically, females are born with virilization ranging from clitoral enlargement to extensive masculinization of the external genitalia, which may lead to incorrect gender assignment. There may be hyperpigmentation of the genitalia and the areolae. Sodium retention and volume-induced hypertension develop in 50%-80% of the classic cases. Severe hypertension may occur as early as the first 4 days of life, but more often blood pressure is normal in neonates. The relative severities of the hypertension, virilization, and biochemical findings do not always correlate. Serum sodium levels tend to be in the upper-normal range or minimally elevated, but hypokalemia is inconsistently present.

Unlike the classic presentations, some affected and untreated neonates present with salt wasting, which may lead to diagnostic confusion with 21-hydroxylase deficiency. The cause of their salt-losing conditions is unclear, but possibilities include a combination of physiologic renal immaturity of sodium reabsorption, more severe aldosterone deficiency and less potent DOC, and the presence of precursor steroids with mineralocorticoid antagonist properties from the fetal adrenal glands. Salt wasting often resolves spontaneously later in life and is rarely clinically significant.

The diagnosis 11β-hydroxylase deficiency is supported by the finding of increased levels of serum 11-deoxycortisol and DOC, demonstrating their suppressibility with glucocorticoid replacement, and ACTH stimulation testing showing elevation in 11-deoxycortisol. This is an autosomal recessive condition, and two 11β-hydroxylase genes have been identified. Both genes are located on the long arm of chromosome eight and are linked, showing greater than 90% sequence homology. The *CYP11B1* gene is responsible for 11β-hydroxylase deficiency, and the *CYP11B2* gene encodes for aldosterone synthase. Prenatal diagnosis by genotyping of the *CYP11B1* gene by chorionic villus sampling is available.[18]

Treatment with hydrocortisone corrects the excessive production of DOC and androgens. Decreased DOC formation leads to the correction of hypertension in most affected patients. Glucocorticoid therapy is adjusted based on the patient's growth, blood pressure, and levels of serum 11-deoxycortisol, DOC, androstenedione, and plasma renin activity. The gender is usually assigned in agreement with the gonadal sex, because normal sexual function and fertility can be attained. Glucocorticoid stress dosing is required, as in 21-hydroxylase CAH. Salt-wasting precipitated by stress dose glucocorticoids has been reported and is thought to be secondary to the suppressed ACTH leading to decreased production of DOC. Sodium supplementation and mineralocorticoid replacement may be required in these circumstances.[18]

3β-Hydroxysteroid Dehydrogenase Deficiency. Similar to the affected males, 3β-hydroxysteroid dehydrogenase deficiency in female infants results in defective production of cortisol, mineralocorticoid, and sex hormones with accumulation of DHEA. Besides salt wasting and adrenal insufficiency, female infants with this form of CAH may present with variable degrees of virilization at birth caused by conversion of DHEA to a more potent androgen by 3βHSD type 1, present in the liver, skin, and other tissues. Biochemical abnormalities, diagnosis, and treatment are similar to the 46,XY male with the same disorder. For details, please refer to the section Androgen Biosynthesis Defect, subsection 3β-Hydroxysteroid Dehydrogenase Deficiency.[83]

P450 Oxidoreductase Deficiency. P450 oxidoreductase (POR) enzyme deficiency was discussed earlier as part of androgen biosynthesis defect in 46,XY DSD. Depending on the type of the mutation and the extent of enzyme deficiencies, a 46,XX female fetus may present with a variable degree of salt wasting, adrenal insufficiency, and virilization. Treatment depends on the symptoms and hormone profile, with glucocorticoid being the mainstay of replacement therapy.[93]

Placental Aromatase (CYP19) Deficiency

Placental–fetal aromatase (*CYP19*) is a cytochrome P450 enzyme that is necessary for the conversion of fetal androgens to estrogen. Placental aromatase deficiency is a rare autosomal recessive disorder that can result in variable degree of maternal and female fetus virilization. There is wide phenotypic variation observed, owing to mutations in *CYP19*.[62]

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Maternally Derived Androgenic Substances

Masculinization of the female fetus occasionally occurs from exposure to androgens or certain other agents derived from the maternal circulation. The extent of masculinization is related to the compound, dosage, duration, and timing of exposure. Exposure at 8-14 weeks of gestation may result in midline fusion of the labioscrotal folds or opening of the vagina and urethra into a common urogenital sinus. Exposure beginning after 12-14 weeks results in only clitoromegaly and hypertrophy of the labia majora, but no midline fusion and no development of a urogenital sinus. Maternally derived androgens do not usually stimulate wolffian duct development, and the Müllerian duct structures and bilateral ovaries develop normally in the absence of AMH. A considerable number of female fetuses do not undergo masculinization because the placenta aromatizes most maternal androgens to estrogen before they cross over to the fetus. Additionally, high maternal levels of sex hormone binding globulin favors the concentration of these androgens on the maternal side.

Maternal androgens may be of ovarian, adrenal, or exogenous origin. The Krukenberg tumor and luteoma of pregnancy cause increased androgen production.[19,103] Maternal androgen-secreting tumors of the ovary rarely occur in pregnancy. Several cases of maternal adrenocortical tumor are reported; maternal virilization in some has been mild compared to the degree of virilization seen in the neonate.[74] Other cases of 46,XX DSD have been reported in association with maternal CAH and maternal polycystic ovarian disease. The measurement of maternal serum levels of testosterone and DHEA or its sulfate is diagnostically useful even in the absence of maternal virilization. Maternal ingestion of synthetic progestins and androgens may cause abnormal masculinization of the female fetus. In the male fetus, progestin exposure at 8-14 weeks of gestation may result in hypospadias. Because these medications are often used in only part of the pregnancy, the extent of clitoral enlargement, urethral displacement, and labioscrotal fusion are often discordant, contrasting with other causes of 46,XX DSD. Maternal androgenization is usually not apparent.

The masculinization of females that occurs with in utero exposure to androgen or other drugs does not progress postnatally. Biochemical studies of the neonate show normal levels of androgens or their metabolites and of 17-OHP. Mild clitoromegaly may not need to be corrected, because the clitoris will become less prominent as the body size increases.

Other

Dysgenesis of External Genital Primordia

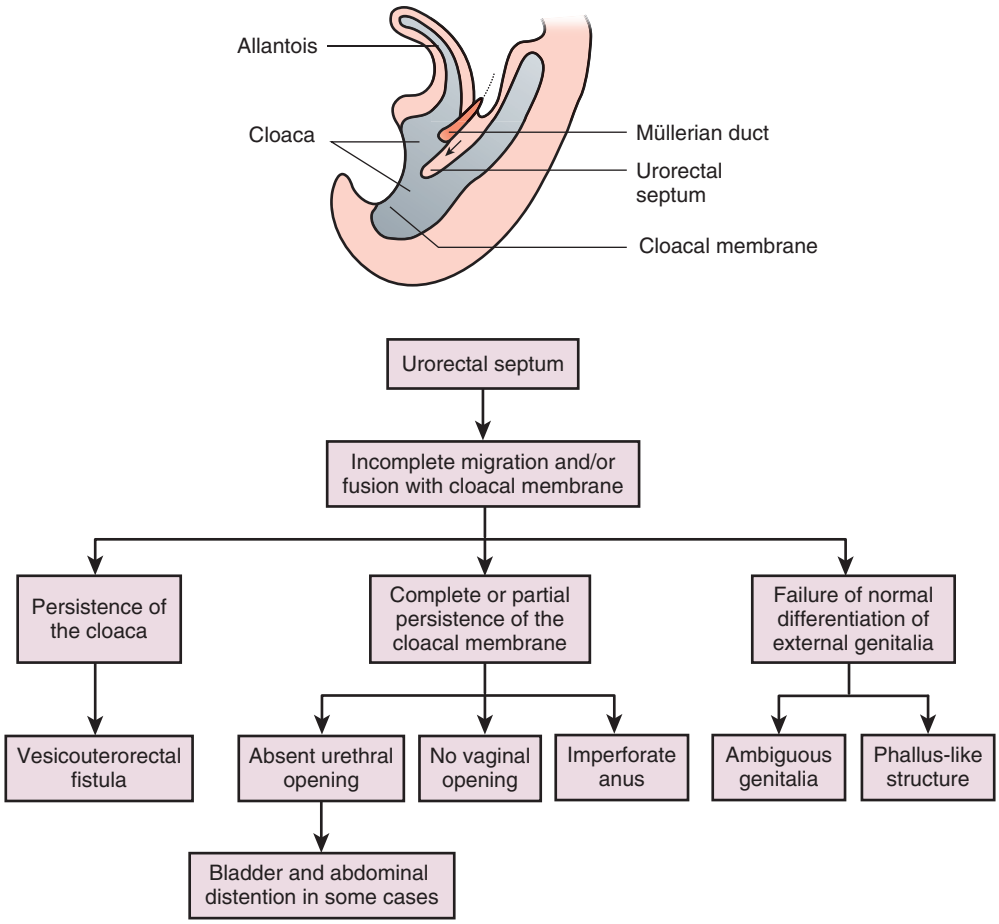
On rare occasions, the external genitalia of a 46,XX fetus may have a masculinized appearance because of an error in morphogenesis occurring at 4-7 weeks of fetal age rather than abnormal androgen exposure at 8-12 weeks. The formation of the urorectal septum and differentiation of the cloacal membrane into the urogenital and anal membranes, followed by their breakdown into the urogenital sinus and anus, are critical for the development of the indifferent external genitalia at 7 weeks as well as for the lower genital, urinary, and intestinal tracts. In cloacal dysgenesis (Fig. 89.17), a small phallus-like structure develops from the genital tubercle (there is variable formation of a phallic urethra and corpora tissue), and the labioscrotal swellings may or may not develop. The absence of a urogenital groove makes for a more male-appearing perineum. Associated abnormalities include an imperforate anus, the absence of urethral and vaginal outlets (unless a phallic urethra forms), and urinary tract and Müllerian (uterine and vaginal) anomalies, which are usually not found in traditional forms of 46,XX DSD. The ovaries are usually normal. These abnormalities may be seen in the VATER/VACTERL association (*v*ertebral abnormalities, *a*nal atresia, *t*racheoesophageal fistula with *e*sophageal atresia, *r*adial and renal dysplasia). Pulmonary hypoplasia is often an associated condition and obstructive uropathy may infrequently be associated with Eagle-Barrett (prune-belly) syndrome. Less severe clinical forms are reportedly associated with a small phallus, partial vaginal outlet obstruction, and other urinary and genital tract anomalies.

Müllerian and Vaginal Dysgenesis

There is a frequent association of abnormal to absent Müllerian duct structures with vaginal agenesis in 46,XX females with normal ovaries known as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. Mayer-Rokitansky-Küster-Hauser syndrome is further classified as either type 1/Rokitansky sequence (isolated) or type II/MURCS association (Müllerian duct aplasia, renal dysplasia, and cervical somite anomalies). It is sometimes also referred to as CAUV (congenital absence of the uterus and vagina), MA (Müllerian aplasia), or GRES (genital renal ear syndrome).[23] The underlying pathophysiology is likely related to a disturbance in mesodermal organization partially involving the formation of the caudal segments of the Müllerian ducts in the 4th and 5th weeks of embryogenesis. Possible etiologies include teratogens and pleiotropic genetic etiologies. The differential diagnosis includes cAIS. An examination to determine the presence or absence of a vaginal orifice (absent in this disorder), the occasional occurrence of hydrometra, and the presence of somatic abnormalities helps to identify affected neonates. About 70% of female patients with unilateral renal agenesis have ipsilateral Müllerian duct abnormalities.[23]

Mayer-Rokitansky-Küster-Hauser syndrome is caused by a heterozygous mutation in *WNT4*. The *WNT4* gene is important in the development and maintenance of Müllerian duct formation and ovarian steroidogenesis. A homozygous missense mutation in *WNT4* was described in SERKAL syndrome, in which some individuals with 46,XX testicular or ovotesticular DSD have been found to have male or undervirilized male genitalia, along with dysgenesis of the kidneys, adrenal glands, and lungs.[23,80]

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• **Fig. 89.17** Diagram showing proposed mechanism for urorectal septum malformation sequence. The resulting cloacal dysgenesis leads to malformation of the external genital primordia and other accompanying abnormalities. In the affected 46,XX fetus, the genital tubercle (between the cloaca and allantois) forms a small phallus-like structure. This development, coupled with the failure to form a urogenital groove, produces ambiguous or male-appearing external genitalia. (From Escobar LF, et al. Urorectal septum malformation sequence: report of six cases and embryological analysis. *Am J Dis Child.* 1987;141:1021.)

Common Presenting Problems

Hypospadias

Hypospadias is the second most common genital abnormality after cryptorchidism in male newborns. Estimated prevalence rates vary worldwide and range from 0.6-34.8 cases per 10,000 live births.[98] It results from incomplete fusion of urethral folds between the 7th and 14th week of gestation. Severity is graded based on the anatomic location of the meatus. In mild cases, the meatus opens on the ventral surface of the glans, corona, or upper penile shaft, and in severe cases, on the lower shaft, penoscrotal junction, or perineum (see Fig. 89.10). About 60% of cases are glandular or coronal, 20% penile, and 13% penoscrotal or perineal.[101]

Most cases of hypospadias are isolated with presumed multifactorial etiologies. A small percentage of severe hypospadias can be attributed to genetic syndromes or defects involving the androgen receptors. Hypospadias is equally transmitted from maternal and paternal sides of a family and has an overall heritability of 57%-77%. About 7% of cases have a family history, with a first-, second-, or third-degree relative having hypospadias. The sibling of an affected brother has an up to 17% chance of developing hypospadias.[101] A greater proportion of individuals with penoscrotal or perineal hypospadias have an affected relative compared to less severe forms. This familial tendency is thought to result from a polygenic mode of inheritance. *CXorf*, a gene on the X chromosome, has been identified as a causative gene for hypospadias.[36] Additional genes associated with hypospadias have been identified and studies investigating other candidate genes involved in male genital development are underway.[101] Mild hypospadias (glandular to penile) without other genital abnormalities or dysmorphic features is very unlikely to be associated with an identifiable endocrinopathy, disorder of sexual differentiation, or chromosomal abnormality. The risk of these conditions increases to about 15% in the setting of severe hypospadias (penoscrotal or perineal).

Newborns with hypospadias commonly have associated genital anomalies, including meatal stenosis, hydrocele, cryptorchidism (8%-10% of cases), and inguinal hernia

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(8% of cases). More severe forms of hypospadias are often associated with a shawl scrotum or incompletely translocated labioscrotal folds and with a prostatic utricle. Patients with severe hypospadias, urinary tract symptoms, a family history of ureteral reflux, or multiple congenital anomalies are also more likely to have significant abnormalities and should have uroradiographic evaluation.

Rare causes of hypospadias include a deficiency in the potent androgen DHT caused by impaired conversion of testosterone to DHT via 5α-reductase deficiency, decreased function of the androgen receptor protein (pAIS), and maternal exposure to progestins; these conditions occur between 8 and 14 weeks of gestation. However, androgen production defects are not identified as an underlying etiology of hypospadias.[42] The differential diagnosis of hypospadias includes female neonates with CAH, other DSDs, various syndromes (e.g., Smith-Lemli-Opitz, Beckwith-Wiedemann), and unknown causes. A virilized female with CAH must be considered when evaluating hypospadias, as a missed diagnosis can be life threatening (see Fig. 89.17).

The evaluation of hypospadias in the newborn includes a history of possible maternal progestin or estrogen exposure as well as a family history of hypospadias, endocrine disorders, or DSD. Physical examination should evaluate stretched phallus length, urethral meatus location, chordee, and scrotal folds. Ultrasound can be used to determine the presence of gonads and a uterus, identify any anatomic renal abnormalities, and look for additional somatic abnormalities. If hypospadias is not associated with other abnormalities, diagnostic studies are usually not needed.

Micropenis

For a description of how to examine and interpret penis size please see the subsection Penis Size under Physical Examination. A micropenis is caused by a deficiency in the factors needed for normal penile growth to occur after 14 weeks of gestation, when formation of the urethra is complete. Important mediators of penile growth that have been implicated in micropenis are testosterone, DHT, and growth hormone. The major causes include hypopituitarism (LH deficiency with or without GH deficiency, 30%), primary hypogonadism (25%), pAIS (2%), and idiopathic or undiagnosed causes (43%). The association of a micropenis with early neonatal hypoglycemia (GH and ACTH-cortisol deficiencies), cryptorchidism (LH deficiency–see Fig. 89.8), persistent neonatal jaundice (hypothyroidism, ACTH-cortisol deficiency), or cleft palate should immediately raise the possibility of congenital hypopituitarism. Other congenital malformations (e.g., septo-optic dysplasia) and chromosomal abnormalities are occasionally seen along with hypospadias. Complete absence of the penis may rarely occur. The diagnostic evaluation of a micropenis includes the assessment of GH, testosterone, LH, and FSH status and consideration of testing for hypopituitarism. Karyotype may be considered if there is associated cryptorchidism or additional concerns with the appearance of the genitalia. An hCG stimulation test may be performed if testosterone levels are low to assess biosynthetic defects. A course of testosterone therapy to assess penile responsiveness may be administered to exclude significant androgen insensitivity. Testosterone therapy should be planned to normalize penis size and consequently promote a positive body image in childhood.

Cryptorchidism

Cryptorchidism, or testicular maldescent, is present when one or both testes have failed to descend completely into the scrotum, reaching a final position 4 cm or more below the pubic crest in full-term males weighing more than 2.5 kg. As this process occurs between 7 months gestation and several months postnatal age, most affected newborns are found to be normal when they are reevaluated. The incidence of cryptorchidism at birth is about 3.7% in full-term males and 21% in premature males, approaching 100% in the very premature. However, the postnatal completion of testicular descent is seen by 6 weeks in 50% and by 3 months of age in 67% of full-term cryptorchid males. 73% of premature cryptorchid males will have completed testicular descent by 3 months. A few additional individuals attain full descent by 6-9 months of age. The net result is that about 75% of full-term and 90% of premature cryptorchid newborns have full testicular descent by the age of 9 months without therapeutic intervention. Spontaneous testicular descent is very rare after 9 months of age. The incidence of cryptorchidism is about 1% at 1 year of age. In addition to prematurity and low birth weight, other factors associated with an increased incidence of cryptorchidism are birth by cesarean delivery and maternal obesity.

Testicular descent is a complex process involving hormonal, mechanical, and genetic factors.[16] Factors thought to affect descent include the gubernaculum, attachment of the epididymis to the testis, rising abdominal pressure, AMH, testosterone or DHT, the genitofemoral nerve, and possibly LH and FSH. Cryptorchidism frequently occurs with disorders of the hypothalamic-pituitary-testicular hormone axis, dysgenetic testes, and with anatomic defects of the epididymis and the abdominal wall. Cryptorchidism is seen with a higher incidence in patients with umbilical hernia (6%), gastroschisis (15%), omphalocele (33%), and Eagle-Barrett (prune-belly) syndrome (100%), in which intra-abdominal pressure may be important. It is also seen in individuals with meningomyelocele (25%), particularly when the defect is above L2, and in those with cerebral palsy (41%). True cryptorchidism is associated with lower LH and testosterone levels during the pituitary–testicular hormonal surge (mini puberty of infancy) that occurs between 1 and 3 months it is also seen frequently in association with hypopituitarism or hypogonadotropism, Prader-Willi syndrome, primary hypogonadism, and

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androgen insensitivity. Cryptorchidism has been associated with persistent Müllerian duct syndrome, suggesting a role for AMH in this process.[32] An association is also seen with trisomies 13 and 18 and with Aarskog, Noonan, Robinow, Smith-Lemli-Opitz, and other syndromes. Familial cases are reported and cryptorchidism is found in 6.2% of the brothers and 1.5%-4% of the fathers of affected patients. The relative risk of developing cryptorchidism increases by 4-6 for the sons or brothers of individuals with cryptorchidism.[16]

Associated anomalies include an inguinal hernia in many patients, abnormal epididymal formation in 36%-66%, and hypospadias in about 3%. There are major upper urinary tract anomalies in about 3% of patients, but routine invasive diagnostic studies are not warranted. Complications of cryptorchidism include progressive histologic deterioration, with changes beginning after 6 months of age, impaired spermatogenesis, with a decrease in the number of germ cells after the first year of life (and later reduced fertility potential), a 4- to 10-fold risk of cancer in both the undescended and contralateral testis (in unilateral cases), trauma to the testis that is relatively fixed in position, testicular torsion, symptomatic inguinal hernia, and psychological concerns related to altered body image. An associated inguinal hernia may require repair in early infancy if it is large enough to permit the abdominal contents to enter or if it causes symptoms.

If both testes are impalpable, the differential diagnosis includes an XX female with CAH or other severe virilizing disorder, anorchia, which occurs in 1% of bilaterally cryptorchid patients, and intra-abdominal testes, which are either normal (as in persistent Müllerian duct syndrome) or dysgenetic (as in mixed gonadal dysgenesis or testicular dysgenesis). The evaluation of the infant with impalpable testes includes the determination sex chromosomes and 17-OHP. Hormone studies, including basal hormones levels (LH, FSH, and testosterone between 2 weeks and 3 months of age) and the response of testosterone to hCG, may provide information about Leydig cell function. The measurement of AMH, ultrasound, magnetic resonance imaging, and laparoscopy have been useful in locating intra-abdominal testes, but laparotomy with exploration to the ends of the spermatic blood vessels is definitive in cases that are not otherwise resolved. The presence of wolffian structures suggests that torsion, vascular accident, or other late in utero degeneration has occurred. Alternatively, a dysgenetic testis may be present. Parental counseling should be undertaken in anticipation of this likelihood.

Because of the early appearance of histologic changes in the cryptorchid testis and findings that early treatment improves the histologic outcome, the correction of cryptorchidism is recommended between 6 and 12 months of age or as soon as possible after diagnosis, if that occurs later.[99] Because spontaneous descent may occur up to 6-9 months of age, treatment before that time is not indicated unless the testis is ectopic or has other associated abnormalities. Orchidopexy is optimally performed by an experienced surgeon, because the risk for subsequent loss of the testis is high. Hormonal treatment with gonadotropin-releasing hormone is no longer recommended because of its poor efficacy and potentially serious side effects.[16]

• BOX 89.4 Causes of Clitoromegaly in the Neonate

Corpora Cavernosa of Normal Size

- Normal variation such as prominent clitoral hood or infant who is small for gestational age
- Swelling, edema, or both caused by bruising (e.g., breech presentation)

Corpora Cavernosa Enlarged Because of Androgen Stimulation

- 46,XX DSD, particularly 21-hydroxylase deficiency
- 46,XY DSD
- Gonadal dysgenesis, dysgenetic testes
- Ovotesticular disorder of sex development
- Tumor infiltration of clitoris (neurofibromatosis, lymphoma)

Clitoromegaly

For a description of how to examine clitoral size, see the subsection Clitoris Size under Physical Examination. Clitoromegaly is defined as the appearance of clitoral enlargement regardless of cause. The clitoris may be prominent (protruding from between the labia majora), swollen, widened, or elongated. The causes are listed in Box 89.4. The clitoris must be measured to determine whether the paired corpora cavernosa are abnormally enlarged and to rule out the extremely rare finding of a tumor. More commonly, the corpora cavernosa are of normal size and have no evidence of a tumor, making clitoromegaly a benign finding. No further diagnostic evaluation is necessary, and the parents should be reassured that their newborn girl is normal. If the corpora cavernosa are enlarged, a DSD is more likely, and an evaluation should be performed. Assessment should include other signs of androgenization or incomplete masculinization (posterior labial fusion, ventral placement of the urethra, or hypospadias), determination of whether the gonads are palpable, identification of internal genitalia (uterus), and measurement of androgens and 17-OH progesterone levels. A karyotype may also be warranted.

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Key Points

- There are four major components of sexual differentiation: chromosomes, gonads, internal genitalia, and external genitalia.
- Normal male differentiation requires (1) the actions of many genes that support testicular development, (2) normal local secretion of testosterone and AMH to ensure normal internal genital formation and (3) conversion of testosterone to dihydrotestosterone and normal androgen action for external genital formation.
- Normal female internal and external genital development occurs in the absence of androgen and AMH, but normal ovarian development requires actions of a number of genes.
- A careful physical exam can provide significant clues into the diagnosis of a child with a suspected disorder of sex development.
- First line investigations include karyotype and pelvic/abdominal ultrasound. Further investigations are guided by the karyotype and ultrasound results.
- Infants with significant genital ambiguity should be referred to a center with a DSD team that includes endocrinology, genetics, urology, and expert psychosocial support.

Resources for Families

AboutKidsHealth: Sex Development, http://www.aboutkidshealth.ca/En/HowTheBodyWorks/SexDevelopmentAnOverview/Pages/default.aspx. Accessed April 2, 2018.

Accord Alliance: Handbook for Parents, http://www.accordalliance.org/resource-guide/. Accessed April 2, 2018.

CARES Foundation: Congenital Adrenal Hyperplasia Research, Education and Support, http://www.caresfoundation.org. Accessed April 2, 2018.

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Inborn Errors of Metabolism

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The main problems facing the physician caring for a sick newborn infant are to know when to consider the possibility of a metabolic disorder, what to do to determine quickly and efficiently whether a child has a metabolic disease, and how to treat the patient until a diagnosis is established.[16,60] A listing of strategic clinical and laboratory findings characteristic of inborn errors of metabolism are presented. The differential diagnosis for these findings, and recommendations for further diagnostic testing to reach a tentative diagnosis, is provided. After a tentative diagnosis is reached, several reference sources can provide appropriate information about specific diseases.[2,102,103]

Two ongoing, complementary approaches to providing medical care for neonates with inborn errors of metabolism are (1) prospective care of the healthy newborn infant, and (2) reactive care of the clinically abnormal newborn infant. Prospective care seeks to identify neonates who have a specific metabolic disorder before clinical manifestations of that disorder develop. The aim of the prospective approach is to prevent the morbidity or mortality that often occurs in the period before recognition, diagnosis, and initiation of therapy for what might be a preventable or treatable disease. The reactive approach aims to arrest or minimize the sequelae of the disease state after the affected child shows recognizable symptoms or signs or becomes ill.

This chapter outlines several common misconceptions about inborn errors of metabolism, addresses prospective recognition of inborn errors, including newborn screening programs, and discusses reactive recognition and care of the abnormal newborn infant. In 1983, the US Orphan Drug Act was passed and has generated new therapies for inborn errors of metabolism.[122]

Common Misconceptions

Metabolic diseases of infancy are a difficult subject for many physicians and other medical professionals caring for newborns. Several misconceptions contribute to this difficulty. Eight of these misconceptions are stated in the following. These misconceptions are expressed in an exaggerated, tongue-in-cheek way to emphasize that, on reflection, most physicians would not acknowledge that these ideas are true. Nevertheless, experience suggests that in the intense atmosphere generated in response to the sick neonate, these misconceptions often influence the care of the child with an inborn error of metabolism.

Misconception 1

Inherited metabolic diseases are rarely a cause of disease in the neonate and should, therefore, be considered diagnostically as a last resort.

Although individual metabolic diseases are relatively rare, inherited metabolic diseases collectively represent a more common cause of disease in the neonatal period. The estimated incidence in the general population of inherited metabolic diseases varies by more than an order of magnitude, ranging from 1 case per 10,000 live births for phenylketonuria (PKU) to 1 case per 200,000 for homocystinuria. About 100 inherited metabolic disorders are identifiable in the neonatal period.

Assuming that most of these disorders have an incidence closer to the lowest incidence rather than the highest, the overall incidence of metabolic disease is about 1 case per 2000 persons. Newborn screening programs have found an incidence of approximately 1 in 4000 for a subset of these diseases. There is good reason to believe that this estimate of the incidence of metabolic disease in neonates is an underestimate, because many metabolic diseases are underdiagnosed and many diseases are yet to be identified.

Misconception 2

The possibility of a genetic metabolic disease should be considered only when there is a family history of the disease.

Most neonates with an inborn error of metabolism do not have a similarly affected sibling or relative.

The reasons for this pattern follow from the rules of Mendelian inheritance. Most inborn errors of metabolism are inherited as autosomal recessive traits, for which the odds are 3:1 in each pregnancy that two heterozygous parents will have an unaffected child. Small family sizes in developed countries make it unlikely to see two affected offspring in a sibship. In a family of two siblings, the odds are about 6% that both siblings will have the disease. In a family of three children, the odds are about 14% that two

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Abstract

This chapter provides an overview of inborn errors of metabolism that manifest in the neonatal period. It discusses the principles, techniques, and disorders identified by newborn screening programs, along with recommendations for follow-up of patients with an abnormal screening result. This discussion is followed by a presentation of the abnormal clinical features and laboratory features, which suggest that a newborn might have, and should be evaluated for, a possible inborn error of metabolism. The abnormal clinical features that are discussed include encephalopathy and/or seizures, cardiomyopathy, eye abnormalities, hepatic dysfunction and/or hepatomegaly, hair and skin abnormalities, hematologic abnormalities, sepsis, unusual odor, and dysmorphism. A differential diagnosis for each of these abnormal clinical features is provided, followed by recommendations for further laboratory evaluation. The laboratory evaluation should begin with routine tests that have a rapid turn-around time and provide results that guide the choice of more specialized laboratory testing. The principles and interpretation of selected biochemical tests that are used in this evaluation are provided. Diagnostic algorithms for evaluating four key laboratory phenotypes—metabolic acidosis, lactic acidemia, hypoglycemia, and hyperammonemia—are presented in detail. The chapter closes with an overview of the treatment strategies available for inborn errors of metabolism.

Keywords

inborn errors of metabolism
metabolic disease of the newborn
neonatal metabolic disease
newborn screening

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of the three siblings will be affected and about 2% that all three siblings will be affected.

There often is no forewarning of the birth of a sick male with an X-linked disorder, because he may have one or more healthy older sisters; heterozygous females do not express most X-linked disorders. Many X-linked disorders are the result of new mutations, and the birth of a sick newborn would not be anticipated. Similarly, because many autosomal dominant disorders are also the result of new mutations, a positive family history would not be expected.

Misconception 3

It is difficult to know when to suspect that a sick newborn infant may have a metabolic disorder, because presentation of such disorders often mimics that of sepsis in the newborn infant.

Three responses to this point may be made. First, the clinical manifestations of many metabolic diseases are similar to the presentation of many neonatal infections, but this does not mean that the physician should not investigate the possibility of a metabolic disorder. The "sepsis work-up" is a broadly focused approach to identifying a putative infection. The metabolic evaluation should be considered for most infants as part of the evaluation for suspected sepsis. Second, a neonate with a metabolic disease may be at greater risk of sepsis than other newborn infants, and the presence of documented sepsis does not exclude the possibility of an underlying metabolic disorder. Galactosemia is a well-documented example of a metabolic disease that predisposes an infant to serious infection. Third, many metabolic diseases do not have sepsis-like features.

Misconception 4

Many metabolic diseases are detectable in the neonatal period, and it is difficult to remember the presentation of each one.

Many metabolic diseases occur in the neonatal period, and it is impossible to remember the pattern of presentation of each; however, the great redundancy in clinical presentations simplifies evaluation. Relatively few algorithms are required to evaluate diseases that have overlapping phenotypes. Algorithms that have clear and multiple branch points are available to facilitate the clinical and laboratory evaluation of patients in whom a metabolic disease is suspected.

Misconception 5

The biochemical pathways and nomenclature of inborn errors of metabolism are impossible to remember.

The biochemical pathways and nomenclature of inborn errors of metabolism are often overwhelming for the expert in metabolic disorders as well as for the practitioner, but detailed knowledge of the pathways and nomenclature is not the important part of the metabolic evaluation. The important aspect of the metabolic evaluation is the development of general approaches to different clinical or laboratory findings that can rapidly reveal whether a metabolic problem exists and, if so, help direct the patient's care.

Misconception 6

It is difficult to diagnose a metabolic disease.

The examination of patients with suspected metabolic disease must be staged, progressing from broad screening tests, which should be available in all settings in which care is given to sick neonates, to highly specialized tests, which may be available in only a handful of centers. The idea of a staged evaluation is perhaps best illustrated by the congenital hyperammonemias. The ability to diagnose hyperammonemia should be available in most settings by measuring an ammonia level. However, the subsequent delineation of a specific cause of hyperammonemia and care of the patient are probably best reserved to a few specialized centers. The job of the physician faced with a sick newborn infant is to think of the possibility of hyperammonemia, to measure the blood ammonia level before the patient is irreversibly damaged by the effects of a disease, and to provide or refer them for appropriate treatment (this may require referral to a more specialized center with experts in metabolic diseases).

Misconception 7

Metabolic test results take forever to return.

There is often a sense of frustration on the part of physicians, especially house officers, who believe that they order many metabolic studies but rarely learn the results of these studies or find an answer. Some metabolic tests do take a long time to perform. It is important to stage the evaluation. It is generally best to begin with relatively broad-based screening tests that come back quickly and can then be followed by more specific diagnostic studies that usually take longer to perform. The aim is to use the screening studies to obtain preliminary indications on which to base further evaluation and care.

Misconception 8

Relatively few metabolic diseases can be treated, so why spend a great deal of effort looking for something that you cannot fix?

A number of metabolic disorders can be treated, often successfully. The approach to the differential diagnosis should give greater consideration to detecting potentially treatable entities. The initial screening studies should permit identification of classes of disease for which there are therapies. For example, the congenital hyperammonemias are a group of disorders for which generic therapy is available; therapy can be modified after a more specific diagnosis is made. It is also important to establish a diagnosis for the sake of the parents, who almost always seek to understand why they have a sick baby, and for the purpose of formal genetic counseling.

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Prospective Approaches

There are two types of prospective care. The first type is the screening of a high-risk segment of the population—the siblings or other at-risk relatives of patients known to have a particular metabolic disorder. The second type is screening of the entire population or specific subset of newborn infants. The former is of much more limited scope than the latter.

The Newborn Infant at High Risk for a Particular Metabolic Disorder

Neonates at high risk for metabolic disorders are the siblings or other at-risk relatives of patients with a known metabolic disorder. These infants include those at risk for diseases for which there is no prenatal diagnosis and those who are at risk for diseases for which prenatal diagnosis is available but whose parents did not wish to have such testing performed. Also included are patients for whom prenatal testing was performed and who require postnatal confirmation of the prenatal test result. Postnatal confirmation is required for a positive or a negative prenatal test result. Postnatal confirmation is especially important for avoiding the unlikely situation of a false-negative prenatal test result that could lead to failure to treat an affected patient. Finally, siblings of an infant with an inborn error of metabolism that may have a variable age of onset might also be at risk for developing disease and should undergo evaluation and testing.

Management of pregnancies and neonates at high risk requires a coordinated effort among the obstetrician, biochemical geneticist, neonatologist, and/or pediatrician. The first decision is to determine where the at-risk baby will be delivered. If the baby will not be delivered at a center at which a metabolic expert is available, the indications for transfer after birth must be developed before birth. Regardless of where the baby is delivered, a detailed plan must be prepared and made available to all personnel caring for the newborn. The plan should include specific details of what tests will be needed to identify the disease, how the tests will be performed, where the samples for testing are to be sent after they are obtained, and who will follow up on the test results and inform the family.

Newborn Screening Programs

Newborn screening is an important issue for all physicians caring for neonates, because it combines a number of significant medical and legal issues. These issues will become progressively more complex and diverse as an increasing number of inborn errors of metabolism become amenable to newborn screening and as the role of physicians in the administration and follow-up of such testing becomes greater.[65,70,119]

Although there is ongoing discussion and some debate about which medical conditions should be screened and how they are to be screened, there is a consensus about the goals of mass newborn screening. The medical requirements of an acceptable mass screening program for a particular disease include the following:

- The availability of a reliable screening test with a low false-negative rate
- A test that is simple and inexpensive, because many tests will be performed for each case identified
- A rapid screening test that can provide results quickly enough to permit effective intervention
- A definitive follow-up test that is available for unambiguous identification of true-positive results and elimination of false-positive results
- A disorder of a sufficiently deleterious nature that, if untreated, would result in significant morbidity or death
- An effective therapy that significantly alters the natural history of the disease

Relatively few metabolic disorders satisfy all these requirements. These criteria have probably been demonstrated, in a strict sense, only for biotinidase deficiency and phenylketonuria (PKU). On the other hand, neonates with classic galactosemia or maple syrup urine disease (MSUD), for example, might become very sick within the first few days of life before the results of newborn screening tests are available, thereby compromising the benefit of the screening program. Ascertainment and diagnosis of these disorders depend on specific biochemical testing of a sick infant (see Specialized Biochemical Testing).

Principles of Screening Programs

A few principles apply to all screening programs. First, all screening tests are subject to false-positive results because of normal biologic variation, genetic heterogeneity, and human error. Accordingly, all positive screening results must be confirmed by definitive analysis. It is important that all patients who require therapy receive it and, conversely, that patients who do not require therapy not be treated.

Second, all positive results must be considered medical emergencies. Many positive results turn out to be falsely positive, but the concept underlying newborn screening is that identification of the few affected patients is crucial. In addition to the potential tragedy of a missed diagnosis of the individual neonate, lack of attention that permits delayed care of a single affected patient can seriously jeopardize the public's confidence in and the cost-benefit structure of an entire statewide screening program and can compromise the continuation of such programs.

Third, the disorders that are part of newborn screening may exhibit variable clinical expression even within families. Thus, the siblings of a patient identified by a screening program should be biochemically evaluated for the same disorder, because they could be affected, although they appear free of symptoms.

Fourth, all patients should be referred to an experienced specialist for definitive diagnosis, because these disorders are characterized by clinical and genetic heterogeneity, which can significantly affect care of the patient and genetic counseling for the family.

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There is considerable variation in the screening programs of different states in the United States and in various nations. All states and US territories screen for PKU. Until relatively recently, most states performed newborn screening for three to six metabolic disorders (including PKU, homocystinuria, MSUD, and galactosemia), one endocrine disorder (congenital hypothyroidism), and the hemoglobinopathies. The requirements and procedures for the screening programs for congenital hypothyroidism and the hemoglobinopathies are discussed in Chapters 88 and 79, respectively.

Screening Techniques

Most state screening programs originally focused primarily on the classic inborn errors of metabolism. The testing programs employed separate tests for each disease of interest, which limited the scope of screening.[34,65,70] These assays could not be easily adapted to screen for other groups of disorders, such as disorders of organic acid metabolism and fatty acid oxidation. The other limitation in expanding newborn screening was that the standard methods being used to diagnose the organic acidemias and fatty acid oxidation disorders—gas chromatography, or combined gas chromatography and mass spectrometry (GC/MS)—could not be upgraded to large-scale newborn screening programs, because they require tedious sample preparation and long analysis times.

Since the 1990s, intensive efforts have been made to expand the scope of newborn screening using tandem mass spectrometry (MS/MS), which circumvents the limitations of the bacterial inhibition assay, gas chromatography, and GC/MS methods.[65,70,119] In brief, MS/MS permits analysis of a broad range of metabolites in hundreds of blood samples per day. Most states have adopted the MS/MS approach to newborn screening as part of their program. The process of expanding the scope of newborn screening programs is still continuing.[119]

Newborn screening by MS/MS starts, as did the traditional screening programs, by collecting by heel stick a small blood sample and applying it to a standardized paper card. The period for appropriate postpartum collection is 24-72 hours in the state of Ohio and is similar in other states. Samples collected from either premature infants or sick newborns are potentially more difficult to interpret and are subject to greater false-positive and false-negative rates. The blood samples are shipped to a centralized laboratory where a standardized amount of the specimen card is punched out, following which the metabolites of interest are extracted from the punch, subjected to specific chemical modifications to make them compatible for subsequent MS/MS analysis, and automatically introduced into and analyzed by the MS/MS system.

As opposed to traditional screening protocols that required different analytic approaches for each disorder, the current MS/MS techniques permit analysis of a large number of metabolites belonging to a particular category of disease—hence, many disorders—in each sample. Hundreds of samples can be prepared for analysis, analyzed, and interpreted each day. The analysis is performed by state-of-the-art mass spectrometers that permit highly sensitive, accurate, and concurrent identification of multiple metabolites. Computer software permits pattern recognition using several related metabolites, thereby improving the reliability of the testing. In summary, the MS/MS technology is ideally suited for newborn screening of many samples for many possible disorders.

As with traditional newborn screening programs, the current MS/MS screening programs must determine the normal range for the different metabolites they analyze in their system. More importantly, the programs must set cutoffs above or below, which they identify a case as at-risk. This is a difficult, ongoing task. Programs that set their cutoffs too high have an unacceptable false-negative rate, and programs that set their cutoffs too low have an unacceptable false-positive rate.

Experience has now demonstrated that MS/MS programs can detect PKU, MSUD, and homocystinuria as well as or better than the traditional screening approaches.[65,119] Nevertheless, the practitioner must still be aware that the MS/MS-based screening programs have similar problems with false-positive and false-negative results as their older counterparts, although they appear to have lower false-positive rates. The practitioner must still determine whether a particular result is truly positive or falsely positive as expeditiously as possible. The expanded newborn screening programs have found that approximately 1 in 4000 newborns have an identifiable inborn error of metabolism.

Screening for Disorders

Most states in the United States have adopted MS/MS screening to analyze disorders of amino acid metabolism (including several urea cycle disorders), organic acid metabolism, and fatty acid oxidation while still screening for several other disorders using test-specific methods (e.g., biotinidase deficiency or galactosemia).[119] The amino acid disorders and urea cycle disorders are detected by analyzing for increased blood concentrations of specific amino acids or combinations of amino acids. Most programs do not screen for disorders that are associated with reduced concentrations of specific amino acids, such as using a low serine concentration to screen for serine biosynthesis disorders. Similarly, the organic acidemias and fatty acid oxidation disorders are detected by analyzing for increased blood concentrations of specific acylcarnitines, which are the esters formed between carnitine and the acid(s) that characteristically accumulate in the various organic acidemias and fatty acid oxidation disorders. Many programs evaluate samples for combinations of particular acylcarnitines to increase the reliability of their results. Screening for the plasma membrane carnitine uptake defect (also known as carnitine uptake deficiency) is an exception to the rule of looking for increased concentrations of characteristic metabolites, because it is based on identification of a reduced (rather than increased) concentration of free carnitine.

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More recently, significant progress has been achieved in developing and introducing newborn screening for two additional categories of inborn errors of metabolism: lysosomal storage disorders and peroxisomal disorders. Two lysosomal disorders, Hurler syndrome (aka mucopolysaccharidosis type I)[67] and Pompe disease (aka glycogen storage disease type II),[11] and one peroxisomal disorder, X-linked adrenoleukodystrophy (X-ALD),[54] have been added to the federally recommended newborn screening panel.[119] Screening for each of these disorders is currently available or approved for implementation in several states. The infantile form of Hurler disease typically manifests in the first year of life, whereas Pompe disease typically manifests in the first 6 months of life. Effective treatment is now available for Hurler syndrome (hematopoietic stem cell transplantation, HSCT)[12] and Pompe disease (enzyme replacement therapy)[17,59] if it is started prior to the onset of irreversible clinical manifestations. Similarly, hematopoietic stem cell transplantation significantly improves the prognosis for X-ALD, a peroxisomal disorder that does not manifest clinically until 2 years or older. Here too, follow-up studies have shown that the outcome for patients who have received HSCT are best when it is performed prior to onset of subclinical evidence of neurologic damage.[132] The screening protocol for X-ALD also identifies patients who have Zellweger syndrome, a generalized defect in peroxisomal assembly and function, or one of several single-gene defects in peroxisomal very long-chain fatty acid oxidation. Unfortunately, there is no effective therapy for these peroxisomal disorders.

It should be noted that there is ongoing concern regarding screening for these lysosomal and peroxisomal disorders, since it is possible to detect later-onset forms of these diseases with the screening tests, for which there are limitations in our ability to predict if, or when, the patient will develop significant clinical manifestations. For example, in the case of X-linked adrenoleukodystrophy, some patients identified by newborn screening and then found to have an *ABCD1* mutation might not develop clinically significant disease but might nevertheless undergo HSCT transplantation because of the requirement to initiate treatment for the childhood form of the disease as early as possible. This concern may also apply to other disorders detected by newborn screening, but the concern for the lysosomal storage disorders and peroxisomal disorders is heightened by the fact that the recommended treatment for these disorders is more invasive (and expensive) than that required for most other disorders detected by newborn screening. It is anticipated that newborn screening for the lysosomal storage disorders and peroxisomal disorders will become available in more states in the near future. Similarly, it is expected that additional inborn errors of metabolism will be incorporated into newborn screening programs as screening technology improves, more therapeutic options are developed and assessed, and better genotype/phenotype correlations are established.

Table 90.1 lists abnormal laboratory findings, along with the disorders associated with those findings and the additional testing recommended to evaluate the significance of the findings, for the currently recommended newborn screening panel. In many cases, a particular abnormal laboratory finding can be associated with more than one disorder, because different enzymatic defects can lead to excessive accumulation of that metabolite. For example, acylcarnitine analysis can yield ambiguity in identifying several of the acylcarnitines evaluated in the newborn screening program, such as C4-acylcarnitine. C4-acylcarnitine is composed of an acid group with four carbons and carnitine; the acid group can be either butyrylcarnitine (wherein the four carbons are arranged in a linear pattern) or isobutyrylcarnitine (wherein the four carbons are arranged in a branched pattern). The diseases associated with these two

TABLE 90.1 Differential Diagnosis and Follow-Up for Abnormal Laboratory Findings Commonly Reported by Newborn Screening Programs

Abnormal Laboratory Finding*	Associated Disorders	Follow-Up Studies†
Amino Acids		
Leucine (and valine)	Maple syrup urine disease (MSUD)	Plasma amino acids Urine organic acids
Methionine	Homocystinuria	Plasma amino acids Plasma total homocysteine Plasma methylmalonic acid
Phenylalanine	Phenylketonuria (PKU)	Plasma amino acids
Tyrosine (and succinylacetone)	Tyrosinemia type I Tyrosinemia type II Tyrosinemia type III	If succinylacetone ↑: • Plasma amino acids • Serum AFP and LFT • Urine organic acids If succinylacetone normal: • Plasma amino acids

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TABLE 90.1 Differential Diagnosis and Follow-Up for Abnormal Laboratory Findings Commonly Reported by Newborn Screening Programs—cont'd

Abnormal Laboratory Finding*	Associated Disorders	Follow-Up Studies†
Urea Cycle Defect		
Arginine	Arginase deficiency	Plasma amino acids
Citrulline	Argininosuccinate synthetase deficiency Argininosuccinate lyase deficiency Citrin deficiency	Plasma amino acids Urine amino acids Serum LFT
Acylcarnitines‡		
C0 (↓)	Carnitine transporter deficiency Maternal carnitine transporter deficiency	Plasma carnitine analysis Urine carnitine analysis Maternal plasma carnitine analysis Maternal urine carnitine analysis
C3	Methylmalonic acidemia (MMA) Defect of cobalamin metabolism or vitamin B12 deficiency Multiple carboxylase deficiency (MCD) Propionic acidemia (PA) Succinyl-CoA synthetase (SUCLA2) deficiency	Plasma carnitine analysis with acylcarnitine profile Plasma total homocysteine Urine organic acids
C4	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency Ethylmalonic encephalopathy Isobutyryl-CoA dehydrogenase deficiency Multiple acyl-CoA dehydrogenase deficiency (Glutaric aciduria type II)	Plasma carnitine analysis with acylcarnitine profile Urine acylglycines Urine carnitine analysis Urine organic acids
C5	Isovaleric acidemia (IVA) 2-Methylbutyryl-CoA dehydrogenase deficiency (aka: short/branched chain acyl-CoA dehydrogenase deficiency)	Plasma carnitine analysis with acylcarnitine profile Urine acylglycines Urine organic acids
C5-OH	Biotinidase deficiency 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency 3-Ketothiolase deficiency 2-Methyl-3-hydroxyglutaryl-CoA dehydrogenase deficiency 3-Methylcrotonyl-CoA carboxylase (3-MCC) deficiency Multiple carboxylase deficiency	Plasma carnitine analysis with acylcarnitine profile Urine organic acids Biotinidase enzyme analysis If above tests normal, consider maternal 3-MCC deficiency and perform: • Maternal plasma carnitine analysis with acylcarnitine profile • Maternal urine organic acids
C5-DC	Glutaric aciduria type I (GAI)	Plasma carnitine analysis with acylcarnitine analysis Urine carnitine analysis with acylcarnitine profile Urine organic acids
C8	Medium-chain acyl-CoA dehydrogenase (MCAD)	Plasma carnitine analysis with acylcarnitine profile Urine organic acids Urine acylglycines
C14:1	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	Plasma carnitine analysis with acylcarnitine profile
C16	Carnitine-acylcarnitine translocase (CACT) deficiency Carnitine palmitoyltransferase II (CPT II) deficiency Glutaric acidemia type II	Plasma carnitine analysis with acylcarnitine profile Urine organic acids
C16-OH	Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency Trifunctional protein (TFP) deficiency	Plasma carnitine analysis with acylcarnitine profile Urine organic acids

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TABLE 90.1 Differential Diagnosis and Follow-Up for Abnormal Laboratory Findings Commonly Reported by Newborn Screening Programs—cont'd

Abnormal Laboratory Finding*	Associated Disorders	Follow-Up Studies†
Galactosemias		
Screening program based on galactose-1-phosphate uridyltransferase (*GALT*) activity: *GALT* activity (↓) OR	*GALT* deficiency	*GALT* activity, blood If *GALT* activity ↓: • Galactose-1-phosphate, RBC • *GALT* gene analysis (common mutation panel)
Screening program based on galactose and/or galactose-1-phosphate concentration: Galactose (↑) and/or galactose-1-phosphate (↑)	*GALT* deficiency Galactokinase (GALK) deficiency UDP-galactose-4-epimerase (GALE) deficiency	Measure *GALT* activity, blood If *GALT* activity normal: • Galactose, blood • Galactose-1-phosphate, RBC If galactose (↑), but galactose-1-phosphate normal: • *GALK* gene analysis If galactose (↑) and galactose-1-phosphate (↑): • *GALE* gene analysis
Other		
Biotinidase activity (↓)	Biotinidase deficiency	Serum biotinidase activity
Lysosomal Storage Disorders:		
α-Iduronidase activity (↓)	Hurler syndrome (MPS I)	α-Iduronidase activity, blood Urinary mucopolysaccharide analysis Sequence analysis of *IDUA* gene
α-Glucosidase activity (↓)	Pompe disease (GSD II)	α-Glucosidase enzyme, blood Urine hexose tetrasaccharide analysis (Hex4) Sequence analysis of *GAA* gene Clinical evaluation including chest X-ray and echocardiogram
Peroxisomal Disorders:		
C26:0 and/or C26:0-LPC (↑)	X-linked adrenoleukodystrophy (XALD) Other peroxisomal disorders (Zellweger spectrum disorder, acyl CoA oxidase deficiency, or D-bifunctional protein deficiency)	Plasma very long-chain fatty acids (VLCFA) Genetic testing of *ABCD1* gene If sequence analysis confirms diagnosis of *XALD*, no further testing If sequence analysis does not confirm XALD, obtain testing for other peroxisomal disorders: • Plasma plasmalogens • Plasma phytanic acid • Plasma pristanic acid

↓, Decreased; ↑, increased.

*All abnormal findings reflect increased blood concentrations except where otherwise indicated. The abnormal findings selected for this table are those used in the state of Ohio. Other states may select a different group of findings.

†The studies listed are those that should be done at the first encounter following receipt of the abnormal newborn screening result. Additional, more specific, confirmatory studies such as enzyme analysis or in vitro cell studies using blood cells, cultured skin fibroblasts, organ biopsies, or genetic studies are generally obtained after the results of the initial confirmatory tests are available.

‡The acylcarnitines associated with these disorders are designated by a capital C followed by the number of carbons contained within the fatty acyl group attached to the carnitine; for example, C8 refers to octanoylcarnitine. A colon followed by an Arabic numeral indicates one or more unsaturated carbons in the fatty acylcarnitine ester; for example, C10:1 refers to a monounsaturated C10 acylcarnitine. An OH in the designation indicates a hydroxylated acylcarnitine; for example, C5-OH refers to a monohydroxylated 5-carbon acylcarnitine. DC following the carbon number indicates a dicarboxylic acylcarnitine; for example, C5-DC refers to a dicarboxylic 5-carbon acyl group.

ABCD1, The gene that is involved in patients with X-linked adrenoleukodystrophy; AFP, alpha-fetoprotein; C26:0-LPC, a saturated, very long-chain fatty acid (26 carbon length) attached to lysophosphatidylcholine; GSD, glycogen storage disorder; LFT, liver function tests; MPS, mucopolysaccharidosis; RBC, red blood cells; WBC, white blood cells.

acylcarnitines are quite different, and further studies are required to determine which metabolite, or which disorder, is present.

The confirmatory studies listed in Table 90.1 are readily available or orderable in most clinical settings and are discussed in detail later (see Specialized Biochemical Testing). The confirmatory studies cited include tests that have a relatively rapid turnaround time, generally 1-2 weeks, hopefully leading to rapid confirmation or elimination of a possible diagnosis. Additional, more refined studies,

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including specific enzyme analysis, whole cell studies, or genetic mutational analysis, are often required to definitively establish a specific diagnosis, but these generally have a longer turnaround time.

The abnormal laboratory findings listed in Table 90.1 permit the diagnosis of more than 30 genetic disorders, including amino acid disorders, fatty acid oxidation disorders, organic acidemias, urea cycle disorders, and several unrelated enzymatic defects. The list of metabolites provided in Table 90.1 is not comprehensive. Many other metabolites have been identified or can theoretically be identified, but they are not listed because of the rarity or uncertain clinical phenotype of the associated disorder. Not all states test for this particular list of metabolites; some test for fewer and others for more. Practitioners should be familiar with the scope of their local newborn screening program. In any event, the laboratory findings listed in Table 90.1 should provide all practitioners with a foundation for interacting with their local program.

Table 90.2 provides basic information about the disorders cited in Table 90.1, including the name of each disorder along with its common abbreviation (if one is available), the underlying enzymatic defect, the clinical features and natural history, the general approach to treatment, and the prognosis. The frequency of these disorders ranges between approximately 1 in 10,000 for PKU to 1 in 200,000 for MSUD. However, several disorders have been reported in only a small number of patients. In addition to their rarity, most of these disorders are characterized by a high degree of clinical variability, making it difficult to provide a succinct but accurate summary. Hopefully, the information will provide the practitioner with a reasonable place to start when confronted with a patient who has an abnormal newborn screening result, following which he or she can turn to other resources after a diagnosis is established.

Handling Test Results

The first obligation of the practitioner who receives an abnormal newborn screening report is to inform the parents of the result. The practitioner should explain that the results are provisional and that confirmation is required. The physician must aim for an appropriate balance between his or her own natural desire to reassure the parents that the result might be falsely positive and the desire to instill a sense of appropriate concern in the parents so that they can carry through with appropriate follow-up evaluation. The practitioner's burden is generally more straightforward when the abnormal metabolite is associated with only a single disorder, but the principles of reassurance and follow-up are the same for metabolites that can be found in more than one disorder (see Table 90.1). The physician should then assess the newborn's clinical status and arrange to see the family as expeditiously as possible.

The primary physician should either see the patient or refer the patient to a metabolic disorders specialist for further evaluation and care. It is often best that the primary physician see the patient as soon as possible to assess the patient's status, discuss the newborn screening results with the family, and then work with the metabolic disorders specialist to develop an expeditious plan for evaluation. Confirmatory testing should be initiated as soon as possible.

The decisions about when to initiate treatment and how to treat are based on the nature of the laboratory abnormality found, the quantitative degree of the abnormality, the program's prior experience with false-positives for that metabolite, and the patient's clinical status. In general, starting a treatment immediately after the initial confirmatory studies are initiated is both safe and unlikely to compromise the ability to establish a diagnosis. However, this option is predicated on the ability of the physician to make certain that the diagnostic samples are collected properly, sent to the appropriate laboratory, and received in satisfactory condition by the laboratory. Failure to do this before starting treatment might significantly delay the time required to establish a diagnosis and initiate appropriate treatment.

Many of the disorders identified are treated, at least in part, by some form of dietary restriction. A family's desire to continue breastfeeding while the diagnostic studies are in progress should be carefully considered in all cases. However, depending on the disorder under consideration and the patient's clinical status, the default position should be in favor of pausing breastfeeding until a provisional diagnosis has been established. During that time, the mother can continue to express breastmilk via a breast pump and store it for later use. It is generally a matter of days to a week before the results of the initial confirmatory studies are available, when a more definitive decision can be made about the advisability of breastfeeding. Similar reasoning should be exercised about starting vitamin or cofactor supplementation.

Effect of Screening Programs

The impact of the expanded newborn screening programs is still being determined. There have clearly been many instances when the programs have led to the early recognition of an as-yet-unaffected newborn, followed by the introduction of appropriate treatment. In some cases, this has meant that a newborn with one of the organic acidemias or urea cycle defects that can manifest with an acute neurologic intoxication syndrome in the first few days of life does not suffer an insult that produces severe, irreversible neurologic damage. In other cases, the newborn screening result becomes available after a newborn is already ill, but the result provides a rapid diagnosis for the illness and leads to earlier introduction of appropriate therapy, thereby improving the patient's outcome.

However, it is not yet clear whether early recognition and institution of appropriate treatment changes the long-term prognosis for many of these diseases, such as recurrent hyperammonemic crises in the urea cycle defects or renal failure in methylmalonic acidemia. There may also be

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TABLE 90.2 Inborn Errors of Metabolism That Can Be Ascertained by Newborn Screening Programs*

Disorder	Defect	Clinical Features and Natural History	Treatment	Prognosis With Treatment
Amino Acid Disorders				
Homocystinuria	Cystathionine β-synthetase deficiency	Generally asymptomatic at birth Developmental delay, dislocated lens, skeletal deformities, and thromboembolic episodes	Dietary protein restriction Selective amino acid restriction (methionine) Vitamin B_6 supplementation, plus betaine, folate, and vitamin B_{12} for vitamin B6–nonresponsive patients	Patients with vitamin B_6–responsive form of disease have fewer complications and later age of onset of complications than do patients with vitamin B_6–nonresponsive form
Maple syrup urine disease (MSUD)	Branched-chain α-keto acid dehydrogenase deficiency	Patients might present before newborn screening results are available Difficulty feeding, vomiting, lethargy progressing to coma, opisthotonic posturing, and possibly death Ketoacidosis	Emergency treatment is indicated for symptomatic neonates* Chronic care includes: • Dietary protein restriction • Selective branched-chain amino acid restriction (leucine, isoleucine, valine) • Thiamine supplementation for thiamine-responsive patients	Improved intellectual outcome can be expected if treatment is initiated before first crisis, but developmental delay in severe cases Recurrent episodes of ketoacidosis, especially when ill or fasting
Phenylketonuria (PKU)	Phenylalanine hydroxylase deficiency OR Tetrahydrobiopterin (BH_4) biosynthesis or recycling defects	Generally asymptomatic at birth After a few months, microcephaly, seizures, and pale pigmentation develop, followed in later years by abnormal posturing, mental retardation, and behavioral or psychiatric disturbances Patients with BH_4 defects have additional neurologic problems secondary to dopamine and serotonin deficiency	• Dietary protein restriction • Selective amino acid restriction (phenylalanine) • Sapropterin dihydrochloride (a synthetic BH_4 analogue) for responsive patients • Depending on specific disorder, may require sapropterin dihydrochloride plus dopa/carbidopa, 5-hydroxytryptophan, and/or other medications	Normal development can be expected (although a mild decrease in IQ and behavioral difficulties relative to unaffected sibs might be seen) if diet is instituted early Patients with biopterin defects are at increased risk for neurologic problems, e.g., seizures, dystonia
Tyrosinemia type I	Fumarylacetoacetate hydrolase deficiency	Patients might present before newborn screening results are available Severe liver failure associated with jaundice, ascites, and bleeding diathesis Peripheral neuropathy and seizures can develop Renal Fanconi syndrome leading to rickets Survivors develop chronic liver disease with increased risk of hepatocellular carcinoma	Emergency treatment is indicated for symptomatic neonates* Chronic care includes: • Dietary protein restriction • Selective amino acid restriction (phenylalanine and tyrosine) • Administration of an NTBC, a selective enzyme inhibitor of the tyrosine degradative pathway • Liver transplantation indicated when hepatocellular carcinoma suspected	Liver disease could progress despite dietary treatment NTBC treatment improves liver, kidney, neurologic function, and reduces risk for hepatocellular carcinoma Liver transplantation might still be required

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Tyrosinemia type II	Tyrosine aminotransferase	Corneal lesions and hyperkeratosis of the soles and palms, and intellectual impairment in some cases	Selective amino acid restriction (phenylalanine and tyrosine)	Eye and skin lesions resolve with treatment, and intellectual outcome improves
Tyrosinemia type III	4-Hydroxy-phenylpyruvate dioxygenase	May include intellectual impairment	Low-phenylalanine, low-tyrosine diet	Improved intellectual outcome
Urea Cycle Disorders				
Argininemia	Arginase deficiency	Rarely symptomatic in neonatal period Progressive spastic diplegia or tetraplegia, opisthotonus, seizures Low risk of symptomatic hyperammonemia	Dietary protein restriction Alternative pathway drugs for removing ammonia (sodium benzoate and phenylbutyrate)*	Improved neurologic outcome
Argininosuccinic acidemia	Argininosuccinate acid lyase deficiency	Patients might present before newborn screening results are available: • Anorexia • Vomiting • Lethargy leading to coma • Seizures • Hyperammonemia	Emergency treatment might be indicated for symptomatic neonates Chronic care includes: • Dietary protein restriction • Essential amino acid supplementation • Arginine supplementation • Alternative pathway drugs for removing ammonia (sodium benzoate and phenylbutyrate)* • Liver transplantation	Improved intellectual outcome if treatment is initiated early, but developmental delay in severe cases. Recurrent hyperammonemic episodes
Citrullinemia type I	Argininosuccinate synthetase deficiency	Patients might present before newborn screening results are available Anorexia, vomiting, lethargy, seizures, and coma, possibly leading to death Hyperammonemia	Emergency treatment is indicated for symptomatic neonates Chronic care includes: • Dietary protein restriction • Essential amino acid supplementation • Arginine supplementation • Alternative pathway drugs for removing ammonia (sodium benzoate and phenylbutyrate)	Improved intellectual outcome can be expected if treatment is initiated early, but there is developmental delay in the severe cases Recurrent hyperammonemic episodes

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TABLE 90.2 Inborn Errors of Metabolism That Can Be Ascertained by Newborn Screening Programs*—cont'd

Disorder	Defect	Clinical Features and Natural History	Treatment	Prognosis With Treatment
Citrullinemia type II	Citrin deficiency	Neonatal-onset form: • Failure to thrive • Hepato(spleno)megaly • Abnormal liver function • Hypoglycemia and abnormal amino acid profile • Mild-to-moderately (↑) plasma ammonia concentration Early childhood-onset form: • Patients display a dietary preference for protein-rich and/or lipid-rich foods and an aversion to carbohydrate-rich foods • Failure to thrive • Dyslipidemia • Pancreatitis • Normal–slightly elevated plasma ammonia concentration Adult-onset form: • Recurring episodes of hyperammonemia and neuropsychiatric problems • Fatty liver	• Lactose-free diet • MCT and fat-soluble vitamin supplementation Early childhood-onset form: • Same diet as above • MCT and fat-soluble vitamin supplementation • Sodium pyruvate supplementation Adult-onset form: • Low-calorie/low-carbohydrate/high-protein diet • MCT, arginine, and sodium pyruvate supplementation • Liver transplantation	Generally associated with transient neonatal cholestasis and variable hepatic dysfunction, but some affected patients develop cirrhosis and have a poor prognosis Early childhood-onset form • Variable Adult-onset form: • Poor prognosis, improved with liver transplantation
Organic Acidemias				
Glutaric acidemia type I (GAI)	Glutaryl-CoA dehydrogenase deficiency	Rarely symptomatic in neonatal period, although macrocephaly may be present: • Progressive macrocephaly • Ataxia • Dystonia and choreoathetosis • Developmental regression • Seizures • Strokelike episodes	Emergency treatment is indicated for symptomatic neonates Chronic care includes: • Dietary protein restriction • Selective amino acid restriction with lysine and tryptophan • Selective amino acid supplementation with arginine • Riboflavin and carnitine supplementation	Improved intellectual outcome if treatment is initiated early, but poor neurologic outcome if treatment is started after acute neurologic injury occurs Treatment might slow neurologic deterioration

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Glutaric acidemia type II (GAII)	Electron transfer flavoprotein (ETF) deficiency ETF dehydrogenase deficiency	Commonly manifests in neonatal period: • Hypotonia • Hepatomegaly • Abnormal odor • (±) Congenital anomalies including facial dysmorphism and cystic kidney disease • Metabolic acidosis • Hypoglycemia • Hyperammonemia • Generally lethal Late-onset forms variable, rarely have structural birth defects	Emergency treatment is indicated for symptomatic neonates Chronic care includes: • Dietary low-fat/low-protein diet • Carnitine supplementation • Riboflavin supplementation for responsive cases Modification of above	Treatment for neonatal-onset forms is of limited benefit Treatment might be helpful for patients with late-onset disease
3-Hydroxy-3-methylglutaric aciduria	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	Generally does not manifest in neonatal period: • Episodic hypoglycemia may contribute to developmental delay	• Frequent feedings • Low-fat/low-protein (leucine-restricted) diet • Carnitine supplementation	Improved intellectual outcome may be expected if treatment is initiated early, but developmental delay in severe cases Recurrent hypoglycemic episodes decrease in frequency and severity with age
Isobutyric acidemia	Isobutyryl-CoA dehydrogenase deficiency	• Uncertain because number of cases is small; may be benign • Case reports of cardiomyopathy associated with carnitine deficiency	Carnitine supplementation if deficiency present	Unknown
Isovaleric acidemia (IVA)	Isovaleryl-CoA dehydrogenase deficiency	Patients might present before newborn screening results are available • Vomiting, lethargy and coma, possibly death • Abnormal odor (“sweaty socks”) • Thrombocytopenia, leukopenia, anemia • Ketoacidosis • Hyperammonemia	Emergency treatment is indicated for symptomatic neonates Chronic care includes: • Dietary protein restriction • Selective amino acid restriction (leucine) • Carnitine supplementation	Improved intellectual outcome if diagnosed and treated early If treated appropriately, most have normal development Recurrent metabolic episodes

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TABLE 90.2 Inborn Errors of Metabolism That Can Be Ascertained by Newborn Screening Programs*—cont'd

Disorder	Defect	Clinical Features and Natural History	Treatment	Prognosis With Treatment
3-Ketothiolase deficiency	Mitochondrial acetoacetyl-CoA thiolase deficiency	Patients might present before newborn screening results are available • Vomiting, lethargy and coma, possibly death • Abnormal odor • Thrombocytopenia, leukopenia, anemia • Possible basal ganglia damage • Ketoacidosis • Hyperammonemia	Emergency treatment is indicated for symptomatic neonates Chronic care includes: • Dietary protein restriction • Selected amino acid restriction (isoleucine) • Avoidance of fasting • Bicarbonate therapy and intravenous glucose in acute crises • Carnitine supplementation	Highly variable clinical course Improved intellectual outcome if diagnosed and treated early If recognized and treated appropriately, some patients have normal development Recurrent metabolic episodes
2-Methylbutyrylglycinuria	2-Methylbutyryl-CoA dehydrogenase deficiency (aka: short/branched chain acyl-CoA dehydrogenase deficiency	Most patients ascertained by newborn screening are clinically asymptomatic and remain so, although several patients have been described with a variety of problems	The need for treatment with a low-protein diet has not been established	Generally good
3-Methylcrotonylglycinuria	3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC) Maternal 3-MCC deficiency	• Highly variable phenotype • Hypoglycemia and metabolic acidosis • Many patients asymptomatic • Transplacental transport of 3-methylcrotonylglycine from mother to fetus • Newborn is unaffected • Mothers have variable neurologic phenotype	• Dietary protein restriction • Selected amino acid (leucine) restriction • Carnitine supplementation • Mother might benefit from carnitine supplementation if she has carnitine insufficiency	Generally good Mother generally improves with treatment
2-Methyl-3-hydroxybutyric acidemia	2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (aka:17-beta-hydroxysteroid dehydrogenase X deficiency)	Clinical variability has been observed in this X-linked disorder: • In severe cases, neurodegenerative disease, associated with mental retardation, rigidity, choreoathetosis, seizures, and cerebral atrophy, is often present • In milder cases, some males may have normal neurologic development. Affected females have less severe disease	Dietary protein restriction improves the metabolic markers but does not alter clinical outcome	Poor for severe affected patients but better for mildly affected patients

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Methylmalonic acidemia (MMA)	Methylmalonyl-CoA mutase deficiency Defect affecting vitamin B12 (adenosylcobalamin) metabolism	Neonatal presentation: • Vomiting, lethargy and coma, possibly death • Thrombocytopenia, leukopenia, anemia • Ketoacidosis • Hyperammonemia • Seizures and risk of basal ganglia infarcts • Long-term sequelae include psychomotor retardation, seizures, pyramidal and extrapyramidal movement disorder, basal ganglia strokes, interstitial renal disease, cardiomyopathy, and pancreatitis Variable, depending on specific disorder	Emergency treatment is indicated for symptomatic neonates Chronic care includes: • Dietary protein restriction • Selective amino acid restriction (isoleucine, methionine, threonine, and valine) • Daily hydroxycobalamin IM injection if patient responsive • Oral carnitine supplementation • Antibiotic suppression of gut flora (metronidazole or neomycin) • Liver and/or kidney transplantation might be required Same as above, plus: • Daily intramuscular injection of hydroxocobalamin • Daily oral betaine supplementation, if methylcobalamin also involved	Improved outcome if diagnosed and treated early However, recurrent metabolic episodes and long-term sequela may still occur Renal failure often develops despite appropriate therapy Variable, depending on specific disorder
Propionic acidemia (PA)	Propionyl-CoA carboxylase deficiency	Patients might present before newborn screening results are available • Vomiting, lethargy and coma, possibly death • Seizures and risk of basal ganglia infarcts • Thrombocytopenia, leukopenia, anemia • Ketoacidosis • Hyperammonemia • Long-term sequelae include cardiomyopathy and pancreatitis	Emergency treatment is indicated for symptomatic neonates Chronic care includes: • Dietary protein restriction • Selective amino acid restriction (isoleucine, methionine, threonine, and valine) • Carnitine supplementation • Antibiotic suppression of gut flora (metronidazole or neomycin) • Liver transplantation might be considered	Improved outcome if diagnosed and treated early Recurrent metabolic episodes

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TABLE 90.2 Inborn Errors of Metabolism That Can Be Ascertained by Newborn Screening Programs*—cont'd

Disorder	Defect	Clinical Features and Natural History	Treatment	Prognosis With Treatment
Multiple carboxylase deficiency	Holocarboxylase synthetase deficiency	May present in the newborn period: • Lethargy, hypotonia, seizures, and coma, possibly leading to death • Metabolic ketoacidosis • Hyperammonemia • Long-range, skin rash, impaired T-cell immunity, seizures, and developmental delay may develop	Biotin supplementation	Most patients respond to biotin supplementation, but those who have poor or no response to biotin supplementation may have significant residual neurologic impairment
Fatty Acid Oxidation				
Carnitine uptake defect	Carnitine uptake defect	Does not generally manifest in neonatal period • Cardiomyopathy • Skeletal myopathy • Inability to tolerate prolonged fasting (hypoketotic hypoglycemia)	Carnitine supplementation (high-dose, high-frequency)	Good response to treatment, prevents and/or reverses cardiomyopathy, skeletal myopathy, and impaired ketogenesis
Carnitine/acylcarnitine translocase (CACT) deficiency	Carnitine/acylcarnitine translocase deficiency	Commonly manifests in neonatal period • Lethargy leading to coma • Hepatomegaly/hepatic dysfunction • Cardiomyopathy with ventricular arrhythmia • Skeletal myopathy • Hypoketotic hypoglycemia ± hyperammonemia	Avoid fasting, continuous enteral feeding in severe cases High-carbohydrate, low-fat diet Carnitine supplementation	Severe neonatal cases generally have poor outcome and early death Patients with later onset might respond to treatment, but they often succumb to chronic skeletal-muscle weakness or cardiac arrhythmias
Carnitine palmitoyltransferase type II (CPT II) deficiency	CPT II deficiency	"Severe" form of disease manifests in neonatal period: • Lethargy leading to coma • Cardiomyopathy with ventricular arrhythmias • Hepatic dysfunction • Skeletal myopathy • Congenital malformation (brain and cystic renal disease) • Hypoketotic hypoglycemia "Intermediate" form of disease: • Presents in infancy with similar (but milder) features than the "severe" form, absent the congenital brain and kidney malformations "Mild, late-onset" form of disease: • Presents in childhood/adulthood and is characterized by weakness and exercise-induced rhabdomyolysis	"Severe" form: • Avoid fasting, may require continuous enteral feeding • High-carbohydrate, low-fat diet, including MCT oil • Carnitine supplementation "Intermediate" form: • Treated with an attenuated regimen of the above "Late-onset" form: • Treated with an attenuated regimen of the above	Severe neonatal cases generally have poor outcome and early death Patients with intermediate form of disease have milder problems than those with neonatal-onset form Patients with late-onset disease generally do well

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Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency OR Trifunctional protein (TFP) deficiency	LCHAD deficiency/TFP deficiency	"Severe" form of disease: • Manifests in neonatal period with cardiomyopathy with arrhythmia, hypotonia, hepatic dysfunction, hypoketotic hypoglycemia, and sudden death "Infantile/childhood" form: • Patients have milder form of "severe" disease and later develop rhabdomyolysis, peripheral neuropathy, and pigmentary retinopathy. Maternal disease: • Heterozygous pregnant women are at risk for acute fatty liver of pregnancy if they are carrying an affected (homozygous or compound heterozygous) fetus	"Severe" form: • Avoid fasting • High-carbohydrate, low-fat diet with MCT oil supplementation • Carnitine supplementation • Docosahexanoic acid supplementation "Infantile/childhood" form: • Treat with an attenuated regimen of the above, plus supplementation with docosahexanoic acid Maternal rx: • Early delivery • Carnitine supplementation if deficient	Prognosis for "severe" form is guarded despite therapy Early dx and rx generally improves outcome for patients with "infantile/childhood" form of disease, but risk of peripheral neuropathy and visual impairment persists Prognosis guarded for pregnant woman
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	MCAD deficiency	Generally does not manifest in neonatal period: • Recurrent episodes of lethargy, vomiting, coma, seizures, and possibly sudden death associated with prolonged fasting, especially when associated with infection • Cardiomyopathy not generally seen • Hypoketotic hypoglycemia	• Avoid fasting • "Heart healthy" diet (fat: 30% or less) • Nightly cornstarch supplementation (optional) • Carnitine supplementation	Excellent intellectual and physical outcome generally seen if treatment is initiated before irreversible neurologic damage occurs Fasting tolerance improves with age
Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	SCAD deficiency	Generally does not manifest in neonatal period: • Hypoglycemia uncommon • Most patients detected by newborn screening program are asymptomatic	Normal diet Carnitine supplementation, if testing demonstrates deficiency	The need for and efficacy of treatment is unknown

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TABLE 90.2 Inborn Errors of Metabolism That Can Be Ascertained by Newborn Screening Programs*—cont'd

Disorder	Defect	Clinical Features and Natural History	Treatment	Prognosis With Treatment
Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	VLCAD deficiency	"Severe" form of disease manifests in neonatal period: • Lethargy progressing to coma • Cardiomyopathy and ventricular arrhythmias • Hepatic dysfunction • Skeletal myopathy • Hypoketotic hypoglycemia "Intermediate" form of disease: • Presents in infancy with similar (but milder) features than "severe" form "Late-onset" form: • Manifests in childhood or adulthood with weakness and exercise-induced rhabdomyolysis	"Severe" form: • Avoid fasting, consider continuous enteral feeding • High-carbohydrate, low-fat diet supplemented with MCT oil • Carnitine supplementation "Intermediate" form: • Treated with an attenuated regimen of the above "Late-onset" form: • Treated with an attenuated regimen of the above	Severe neonatal cases generally have poor outcome and early death Patients generally do well Patients generally do well
Galactosemias				
Galactose-1-phosphate uridyltransferase (*GALT*) deficiency	Galactose-1-phosphate uridyltransferase deficiency	Patients may present in the neonatal period: • Lethargy and poor feeding • Jaundice with hepatic dysfunction • Possible sepsis (especially with *Escherichia coli*) Chronic problems include: • Growth failure • Cirrhosis • Cataracts • Seizures • Intellectual disabilities • In females, ovarian failure	Strict dietary galactose restriction must be started immediately	Improved intellectual outcome, but may have milder problems such as speech delay, if diagnosed and treated early Ovarian failure develops in most female patients despite appropriate therapy Recurrent metabolic episodes may occur
Galactokinase (GALK) deficiency	Galactokinase (GALK) deficiency	Cataracts, with no other medical problems	Milk restriction only. Rapid initiation of milk restriction may resolve cataracts that were already present	Good

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UDP-galactose-4-epimerase (GALE) deficiency (aka: epimerase deficiency galactosemia)	UDP-galactose-4-epimerase deficiency	Neonates with generalized epimerase deficiency galactosemia: • Poor feeding, vomiting, weight loss, • Jaundice, liver dysfunction, hepatomegaly • Hypotonia • Cataracts • Generalized aminoaciduria Neonates with the peripheral or intermediate form of epimerase deficiency: • Generally remain clinically well • May tolerate a normal diet	Similar to *GALT* deficiency, i.e., a lactose/ galactose-restricted diet is required Galactose-restricted diet is not generally required for peripheral form but may be required for intermediate form	Similar to *GALT* deficiency, with no evidence of ovarian failure if maintained on proper diet Good
Other				
Biotinidase deficiency	Biotinidase deficiency	Generally does not manifest in neonatal period but may manifest with lethargy, hypotonia, seizures, and apnea in early infancy	Biotinidase deficiency	Biotinidase deficiency
Lysosomal Storage Disorders				
Hurler syndrome (MPS I)	α-Iduronidase deficiency	"Severe" form has onset within 1st year of life and is progressive over time: • Short stature • Coarse facial features, corneal clouding, and hearing loss • Cardiomyopathy/ valvular disease • Hepatosplenomegaly • Dysostosis multiplex and stiff joints • Hirsutism • Hydrocephalus & spinal cord compression • Intellectual disabilities • Death by cardiorespiratory failure usually occurs by age 10 years "Mild" form has normal intellectual development and moderate somatic manifestations at age 2 years, with variable disease progression	"Severe" form: • Initiate enzyme replacement therapy following diagnosis • Hematopoietic stem cell transplant (HSCT) if patient is <2 years of age; careful consideration of risk vs. benefit advised if patient >2 years of age "Mild" form: • HSCT not recommended for mild form because of treatment complications	"Severe" form: • Early initiation of enzyme replacement therapy followed by HSCT improves outcome, except for skeletal changes. • Comprehensive symptomatic treatment "Mild" form: • Symptomatic therapy alone

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TABLE 90.2 Inborn Errors of Metabolism That Can Be Ascertained by Newborn Screening Programs*—cont'd

Disorder	Defect	Clinical Features and Natural History	Treatment	Prognosis With Treatment
Pompe disease (GSD II)	α-Glucosidase deficiency	Clinical features of early infantile form generally present within the first 6 months of life and are progressive: • Hypotonia • Macroglossia • Cardiomegaly/cardiomyopathy • Hepatomegaly • Progressive weakness • Elevated creatine kinase activity • Death in the first 2 years of life Later-onset form (generally >12 months): • Proximal muscle weakness • Respiratory insufficiency • Cardiac involvement uncommon • Other features described for infantile-onset form of disease	Clinical evaluation including for cardiomyopathy Start enzyme replacement therapy as soon as possible CRIM-negative patients should receive immune tolerance induction before initiating therapy Patients who develop enzyme neutralizing antibodies after starting ERT should receive immunomodulation therapy Later-onset form: • Enzyme replacement therapy	Rapid initiation of enzyme replacement therapy (ERT) improves outcome. Later-onset form: • Variable depending on age of onset and age of initiation of therapy
Peroxisomal Disorders				
X-linked adrenoleukodystrophy	Impaired peroxisomal metabolism of very long-chain fatty acids	Childhood-onset form: • Typically presents between 4-8 years of age • More likely to affect males than females (X-linked recessive disorder) • Adrenal insufficiency • Intracerebral inflammatory response leads to demyelination • Regression of cognition, behavior, vision, • Hearing and motor function follow the initial symptoms, often leading to total disability • Death generally by 2 years Later-onset forms: • More likely to affect males than females, with females more mildly affected • Adrenomyeloneuropathy beginning in late 20s (paraparesis, sphincter and sexual dysfunction, and adrenal insufficiency) • Adrenal insufficiency precedes and dominates neurologic abnormalities	Childhood-onset form: • Immediate HSCT (if neurologic involvement is not yet present) Later-onset forms: • HSCT • Corticosteroid replacement therapy	Childhood-onset form: • May improve neurologic outcome (further follow-up studies are underway) Later-onset forms: • Limited benefits of HSCT for neurologic problems after onset of symptoms

ABCD1, The gene mutated in patients with X-linked adrenoleukodystrophy; CRIM, cross-reactive immunologic material; CSF, cerebrospinal fluid; GSD, glycogen storage disease; HSCT, hematopoietic stem cell transplantation; MCT, medium-chain triglycerides; NTBC, 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione; VLCFA, very long-chain fatty acids.

*This table does not provide a complete listing of all the inborn errors that have been identified or might be identified by tandem mass spectrometry. It is important to note that all these disorders are characterized by considerable clinical variability and that treatment must be individualized for each patient.

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negative consequences to these new programs. For example, the screening programs could produce undesirable effects on the family of a child with a false-positive result, including increased hospitalization of the child, parental stress, and parent–child dysfunction.[133] Carefully organized multicenter studies are needed to determine the long-term benefits of the expanded newborn programs.

In addition to the current MS/MS newborn screening programs for amino acid and acylcarnitine analysis, new methods for evaluating other groups of inborn errors of metabolism, including the lysosomal storage disorders, are being utilized in several states and are under development in others. It seems reasonable to anticipate that many of these methods will be introduced over the next several years, further expanding the responsibility and role of the pediatrician and neonatologist in caring for children with metabolic disorders.

Separate summaries of several disorders that were part of the traditional screening programs and that are now evaluated by MS/MS programs (e.g., homocystinuria, MSUD, PKU) are provided next because they are useful paradigms for understanding the benefit of the newborn screening programs and how they work.[138] A summary is also provided for MCAD deficiency, because it is the most common of the fatty acid oxidation disorders that are now evaluated by MS/MS programs, and it is one of the paradigms for this group of disorders. Summaries are also provided for biotinidase deficiency and galactosemia, which are disorders that are primarily evaluated by methodologies other than MS/MS. Other disorders that are now part of expanded newborn screening programs are discussed elsewhere in this chapter, including fatty acid β-oxidation disorders (see Hypoglycemia), nonketotic hyperglycinemia (see Metabolic Seizures), organic acidemias (see Metabolic Acidosis), tyrosinemia type I (see Hepatic Dysfunction), urea cycle defects (see Hyperammonemia), and most recently, certain lysosomal disorders and peroxisomal disorders.

Screening for Specific Disorders

Biotinidase Deficiency

Biotinidase is an enzyme necessary for recycling biotin, a vitamin cofactor required for four critical intracellular carboxylation reactions: acetyl-coenzyme A (acetyl-CoA) carboxylase, 3-methylcrotonyl-CoA carboxylase, propionyl-CoA carboxylase, and pyruvate carboxylase. Hence biotinidase deficiency is one cause of multiple carboxylase deficiency (the other cause is holocarboxylase synthetase deficiency).[138,139] These carboxylase reactions are involved in fatty acid biosynthesis, branched-chain amino acid metabolism, and gluconeogenesis.

Biotinidase deficiency is characterized by a variable clinical presentation but can lead to severe metabolic decompensation in the newborn period; features include ketoacidosis, hypotonia, seizures, and coma. Some infants also have significant dermatologic findings (including rash and alopecia) and immunodeficiency. If untreated, older children could have visual problems, hearing loss, and developmental delay. This disorder can be treated successfully with biotin supplementation (5-10 mg/day PO). Some residual neurologic deficits could persist if treatment does not begin before the onset of symptoms. Newborn screening allows for early diagnosis and initiation of treatment, which may reduce morbidity.

Serum biotinidase enzyme activity is the gold standard for newborn screening of biotinidase deficiency.[138,139] The disorder can also be detected using MS/MS to measure the blood concentration of C5-OH (3-hydroxyisovalerylcarnitine), the acylcarnitine that is formed due to the secondary deficiency of 3-methylcrotonyl-CoA carboxylase. However, the sensitivity of the MS/MS approach is unknown, and it might not provide a reliable method for newborn screening. A positive screening result should be confirmed by quantitative serum biotinidase analysis and by performing plasma carnitine analysis and urine organic acid analysis, looking for the characteristic plasma acylcarnitine pattern and organic aciduria that is present in a small percentage of affected patients.

Care must be exercised in collecting and processing the serum specimen used for biotinidase enzyme analysis. It is best to obtain a concurrent control from an unrelated individual to establish that the sample has been processed properly (i.e., eliminate the chance of a false-positive result) and was not exposed to environmental factors during transport that could affect the results (such as excess heat or cold).

Galactosemia

Classic galactosemia is the consequence of galactose-1-phosphate uridyltransferase (*GALT*) deficiency. Classic galactosemia can manifest in the newborn period with lethargy, poor feeding, jaundice, cataracts, and in some cases, *Escherichia coli* sepsis.[10,138] If unrecognized, this disorder can lead to early death or a chronic course characterized by cirrhosis, cataracts, seizures, and mental retardation. The mainstay of therapy for classic galactosemia is strict dietary galactose restriction.[10,138] Diet therapy is difficult to sustain because lactose (a disaccharide formed from galactose and glucose) is a ubiquitous food additive. Dietary galactose restriction should be started as early as possible (preferably within the first few days after birth) to have the best chance of precluding the development of the severe illness described above as well as long-term speech and learning problems. However, even children treated early often have mild growth failure, learning disabilities, and verbal dyspraxia. Affected girls almost invariably develop premature ovarian failure (~80%).[10,47] This observation serves as a caution to those caring for children with galactosemia that long-term follow-up is mandatory and further improvements in treatment are required over time as new recommendations and information becomes available.

There are two other forms of galactosemia: uridine diphosphate galactose-4′-epimerase deficiency and galactokinase deficiency. In most cases, epimerase deficiency is a

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benign condition that does not require treatment. The rarer, systemic form of epimerase deficiency produces a clinical picture similar to classic galactosemia. Galactokinase deficiency is also rare and produces nuclear cataracts but none of the other manifestations of classic galactosemia. Early recognition and treatment of this disorder via dietary galactose restriction is generally successful.

One approach to newborn screening for galactosemia measures *GALT* enzyme activity in red blood cells. This assay can detect *GALT* deficiency without regard to prior dietary intake of galactose. It does not evaluate for either epimerase activity or galactokinase activity. Therefore, newborns with either epimerase deficiency or galactokinase deficiency are not ascertained by this approach to newborn screening. Another approach to newborn screening for galactosemia is to measure galactose and galactose-1-phosphate (the substrate for *GALT*), which evaluates for all three enzyme deficiencies. However, recent galactose intake (in the form of breastmilk or formula) may affect these results; patients not receiving a lactose-containing diet may have false-negative results.[16] Because of the rapid onset of symptoms in classic galactosemia and the presence of galactose in breast milk and many cow milk–based formulas, screening programs for galactosemia must provide rapid results. However, the screening results are not always available before the affected neonate becomes ill; initial evaluation of a sick newborn should, therefore, include testing for the presence of urinary-reducing substances (see Specialized Biochemical Testing). A newborn identified by newborn screen as possibly having classic galactosemia should have definitive biochemical testing by measuring whole blood or erythrocyte *GALT* activity and erythrocyte galactose-1-phosphate. In addition, genetic analysis for the common *GALT* mutations is often helpful in interpreting the results of the *GALT* activity measurements and making treatment decisions. Following initiation of these studies, galactose should be withdrawn from the diet, pending results of the laboratory investigations, by replacing breastmilk or cow's milk–based formula with a soy-based formula).

Widespread neonatal testing of erythrocyte *GALT* activity in various populations has revealed considerable genetic heterogeneity of this enzyme deficiency.[10] Some individuals have a partial enzyme deficiency that does not result in significant impairment of galactose metabolism or any discernible clinical disorder; there is no evidence of a need for dietary treatment of these cases. In other cases with partial enzyme activity, erythrocyte galactose-1-phosphate concentrations are increased, and minimal symptoms can develop. These cases can be managed with less severe restriction of dietary galactose intake.

Homocystinuria

Several inborn errors of metabolism produce homocystinuria.[77,97,138] The most common of these disorders is caused by cystathionine β-synthase deficiency, an autosomal recessive disorder. Cystathionine β-synthase is a pyridoxine (vitamin B_6)-dependent enzyme. Rare disorders that also lead to homocystinuria include defects in folate or cobalamin metabolism. Screening programs for homocystinuria are based on detection of elevated blood levels of methionine, a precursor of cystathionine. Hypermethioninemia is characteristic of cystathionine β-synthase deficiency but may not be associated with other causes of homocystinuria. In fact, patients who have homocystinuria due to a defect in cobalamin metabolism may actually have low methionine levels. Therefore, only some cobalamin disorders are detected by newborn screening for hypermethioninemia, while others are detected by their abnormal acylcarnitine profile. For example, cobalamin C disease will exhibit both methylmalonic acidemia and homocystinuria. These patients are ascertained by an elevated propionylcarnitine (C3), which is related to the methylmalonic acidemia associated with their disease. In the case of a related disorder, patients with cobalamin E disease exhibit homocystinuria/homocystinemia, megaloblastic anemia, and low methionine but are missed by newborn screening.

Other false-positive and false-negative results occur in screening programs for homocystinuria.[97,138] False-positive results are generally the consequence of artifacts (e.g., poor quality of sample), but they may also result from nongenetic causes of hypermethioninemia, such as parenteral administration of amino acids, generalized liver disease, hepatic immaturity, or rarely, from a genetic cause such as hereditary tyrosinemia, galactosemia, or citrin deficiency (see Hepatic Dysfunction). False-negative results are produced by the milder variants of cystathionine β-synthase deficiency, especially the pyridoxine-responsive form, which might not exhibit hypermethioninemia in the neonatal period.

The diagnosis of homocystinuria should be confirmed in patients with a positive newborn screening test by measuring total plasma homocysteine, plasma amino acids, and plasma methylmalonic acid. The diagnosis of cystathionine β-synthase deficiency can be confirmed by measuring the enzyme activity in cultured skin fibroblasts or by genetic testing.

Cystathionine β-synthase deficiency rarely manifests in the neonatal period, but it can cause lethargy, poor feeding, and thromboembolic phenomena when it does.[77,97,138] If untreated, the disorder can lead to musculoskeletal anomalies suggestive of a marfanoid habitus, ectopia lentis, thromboembolic vascular disease, behavioral or psychiatric problems, and mental retardation. Patients with pyridoxine-responsive defects tend to have milder disease than do patients with pyridoxine-nonresponsive defects. All patients should undergo a pyridoxine challenge test to determine whether they are pyridoxine responsive.

Patients with pyridoxine-responsive forms of homocystinuria might require only daily vitamin B_6 supplementation and mild methionine restriction, whereas nonresponders may require a stricter, low-methionine diet with cysteine supplementation (cysteine is the product of the cystathionine β-synthase reaction, and may, therefore, be deficient in patients with classic homocystinuria). Patients might also

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benefit from folate, vitamin B_{12}, and betaine supplementation, which augment the remethylation of homocysteine to methionine, thereby reducing the toxic effects of excessive homocysteine. The outcome for vitamin B_6–responsive patients appears to be good, but the outcome for nonresponders has often been less satisfactory because of the irreversible damage caused by the presenting episode, the therapeutic inadequacy of the present dietary management, or both.

Medium-Chain Acyl-CoA Dehydrogenase Deficiency

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common inherited disorder of fatty acid oxidation, with an incidence of approximately 1 in 15,000.[49,68] It has a highly variable clinical presentation, even within families. Patients are rarely symptomatic in the newborn period. Most patients present between 3 and 24 months of age, but others remain asymptomatic until they are much older, even into adulthood. The initial retrospective studies on MCAD deficiency found that in almost one-fourth of patients, the diagnosis followed sudden, unexplained death.

The typical presentation is that of an infant who has unexplained progressive vomiting, hepatomegaly, lethargy leading to coma, and seizures associated with an infectious illness or a period of prolonged fasting. The characteristic laboratory finding is nonketotic or hypoketotic hypoglycemia; signs of liver dysfunction may also be present. Older patients could have a more indolent course that is associated with failure to thrive, developmental delay, or chronic muscle weakness. A significant proportion of patients are asymptomatic. MCAD deficiency may be diagnosed in an "unaffected" older sibling after his or her younger sibling comes to medical attention for an acute metabolic crisis or a positive newborn screening result for MCAD deficiency.

The diagnosis of MCAD deficiency is confirmed by plasma carnitine analysis with an acylcarnitine profile, urine organic acid analysis, and urine acylglycine analysis.[68,138] The plasma total and free carnitine concentration can vary with the phase of the illness. The plasma acylcarnitine profile typically shows increased amounts of C6, C8, and C10 acylcarnitines. However, patients with secondary carnitine deficiency could have a relative increase, but not an absolute increase, in these acylcarnitines. Urine organic acid analysis generally shows a typical medium-chain dicarboxylic aciduria (C6-C10) in symptomatic patients, but it could be normal in asymptomatic patients. Urinary acylglycine analysis can be useful in detecting the characteristic metabolite (suberylglycine) in asymptomatic patients.

Genetic testing is useful for confirming the diagnosis. It used to be thought that at least 90% of patients carried at least one copy of the same abnormal allele, the A985G mutation, but the frequency of this particular allele is lower in patients identified by newborn screening programs compared with those who present symptomatically.

Patients with MCAD deficiency should receive frequent feedings and avoid fasting. Infants younger than 6 months require feeding every 3-4 hours. The older infant or child may be allowed to fast for progressively longer periods of time as they get older but not for more than 12 hours.[68] The potential metabolic stress of nocturnal fasting might be reduced for toddlers by providing them with uncooked cornstarch as a source of slow-release glucose immediately before going to bed for the night. Dietary fat restriction is no longer recommended, but oral carnitine supplementation may be indicated for patients with secondary carnitine deficiency. Carnitine supplementation should be monitored with periodic plasma carnitine analysis. Patients should be evaluated and admission to the hospital considered for patients with anorexia or vomiting associated with an acute infectious illness or other potential metabolic stressor. Acute metabolic crises should be treated with intravenous glucose and carnitine. The prognosis for patients who are identified and treated before the onset of irreversible neurologic damage due to severe or recurrent hypoglycemia and its sequelae is generally excellent.

Phenylketonuria

Several genetic disorders produce hyperphenylalaninemia. Classic PKU and non-PKU hyperphenylalaninemia are caused by defects in phenylalanine hydroxylase, and variant PKU is caused by one of several defects in tetrahydrobiopterin (BH_4) metabolism.[92,138] Several nongenetic factors also produce hyperphenylalaninemia in the newborn, but this hyperphenylalaninemia disappears in the first year of life. The most common causes of transient hyperphenylalaninemia are prematurity and high protein intake just prior to the blood draw. Newborn screening programs identify infants with genetic and nongenetic hyperphenylalaninemia. It is imperative that patients identified by the screening program receive a rapid, accurate, and definitive diagnosis, because the clinical implications and therapies for the various forms of hyperphenylalaninemia are different and early initiation of appropriate treatment minimizes morbidity.

All genetic forms of hyperphenylalaninemia are caused by defects that directly or indirectly affect the activity of the enzyme phenylalanine hydroxylase. This enzyme catalyzes the conversion of phenylalanine to tyrosine and requires BH_4 as a cofactor. Classic PKU and non-PKU hyperphenylalaninemia are caused by allelic defects of phenylalanine hydroxylase itself, whereas variant PKU is caused by defects of BH_4 biosynthesis or reutilization. BH_4 is also a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are enzymes involved in neurotransmitter biosynthesis. Approximately 98% of patients with hyperphenyl have a defect in phenylalanine hydroxylase, whereas 2% have a defect in BH_4 metabolism.

Patients with milder deficiencies of phenylalanine hydroxylase (i.e., patients with transient hyperphenylalaninemia or non-PKU hyperphenylalaninemia) usually do not require dietary treatment. However, patients with more

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severe deficiencies, that is, patients with classic PKU, require lifelong phenylalanine restriction. Treatment should start within the first month of life to avoid irreversible neurologic damage. Early treatment is generally effective in preventing the long-term neurologic sequelae of this disease. However, standard treatment may not prevent subtle intellectual and behavioral disabilities in some individuals.[92,138] Dietary restriction of phenylalanine should be lifelong. Women with PKU who fail to maintain the appropriate diet are at risk for having neurologically impaired offspring (maternal PKU syndrome; see Maternal Diseases Affecting the Fetus).

In recent years, clinical trials have demonstrated that some patients with milder forms of classic PKU respond to oral supplementation with a synthetic form of BH_4 known as sapropterin. They appear to tolerate a higher dietary protein intake while maintaining acceptable serum phenylalanine concentrations. However, most patients still require some degree of dietary phenylalanine restriction with or without a specialized metabolic formula. The drug is now available for clinical use.

Defects of BH_4 metabolism cause defective neurotransmitter synthesis as well as hyperphenylalaninemia and lead to a more generalized neurologic syndrome known as *variant PKU,* characterized by convulsions, abnormal tone and posture, abnormal movements (i.e., dystonia), hyperthermia, hypersalivation and swallowing difficulties, drowsiness, irritability, and developmental delay. Standard dietary management corrects the hyperphenylalaninemia that these patients have but does not improve the neurologic problems related to their neurotransmitter deficiencies. Only a small percentage of patients with hyperphenylalaninemia have BH_4-related defects, and these patients must be identified early to initiate appropriate therapy. A variety of approaches are being used to treat these patients with some success, depending on the specific biopterin defect present.[92,138]

Newborn screening for hyperphenylalaninemia is based on measuring the concentration of phenylalanine in the blood while the newborn infant is receiving breast milk or a standard formula (i.e., a phenylalanine-containing diet).[70,138] Blood samples are generally obtained for newborn screening between 24 and 48 hours of age. The results for samples collected before 24 hours of age may not be reliable, and a follow-up sample should be obtained for screening.

The rate of false-negative results is less a problem with MS/MS screening than the traditional approaches, partly because it is possible to measure the concentrations of phenylalanine and tyrosine (the product of the phenylalanine hydroxylase reaction) concurrently. Those who have a positive screening result require prompt attention, including plasma amino acid analysis. If the plasma phenylalanine concentration and the plasma phenylalanine-to-tyrosine ratio are increased, the patient should be placed on a low-phenylalanine diet. Therefore, breastfeeding should be stopped. In all cases of confirmed hyperphenylalaninemia, the patient should be evaluated by a metabolic disorders specialist to rule out a defect in BH_4 metabolism.

The Abnormal Newborn Infant: Clinical Phenotypes

On the whole, newborn infants with inborn errors of metabolism have relatively few types of presentation. The most common clinical presentations are listed in Table 90.3, along with a differential diagnosis of the categories of metabolic disorders that may be associated with each presentation. A more detailed discussion of each presentation follows.

Prenatal Onset

Several inborn errors of metabolism can manifest prenatally, affecting the pregnant mother and/or the developing fetus. These inborn errors can be grouped into three categories: maternal diseases affecting the fetus; fetal diseases affecting the mother; and fetal diseases affecting the fetus. The obstetrician and/or pediatrician should be aware of these metabolic disorders.[24,134]

Maternal Diseases Affecting the Fetus

The prototype of a maternal disease affecting the fetus is maternal PKU.[95] A pregnant woman who has poorly controlled PKU is at increased risk for spontaneous abortion. She also has an increased risk of having a child with major birth anomalies, including intrauterine growth restriction, microcephaly, mental retardation, and a congenital heart defect, as well as a broad range of minor anomalies. The risk of birth defects is proportional to the mother's serum phenylalanine concentration. There is no safe level below which the fetus is not at risk. Women with PKU should be placed on a strict low-phenylalanine diet before conception. This has proved difficult to do in practice, however, and maternal PKU syndrome remains a significant problem for women with PKU.

Fetal Diseases Affecting the Mother

As a rule, inborn errors of metabolism of the fetus do not affect the pregnant mother. However, reports began to appear in the 1990s describing mothers who had experienced acute fatty liver of pregnancy (AFLP) while carrying a fetus who subsequently manifested evidence of a long-chain fatty acid oxidation defect after birth. Acute fatty liver of pregnancy is the most extreme end of a clinical spectrum of maternal complications of pregnancy that includes HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count) and AFLP. The HELLP syndrome and AFLP are potentially serious complications of pregnancy (see Chapter 17).

Clinical, biochemical, and histologic evidence of hepatic dysfunction mark both disorders. Patients with HELLP syndrome commonly develop epigastric pain, nausea, vomiting, headache, proteinuria, low platelets, elevated serum liver enzymes, and occasionally disseminated intravascular coagulation. Acute fatty liver of pregnancy is less common than HELLP syndrome and shows a greater degree of

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TABLE 90.3 Clinical Findings Helpful in the Differential Diagnosis of Suspected Metabolic Disease in Neonates

Diagnostic Finding	Considerations
Prenatal Onset	
Maternal diseases affecting fetus	Phenylketonuria
Fetal diseases affecting mother	Fatty acid oxidation disorders
Fetal diseases affecting fetus	See Dysmorphic Syndromes
CNS	
Encephalopathy	Amino acid disorders Mitochondrial disorders Organic acidemias Respiratory chain defects Urea cycle disorders
Metabolic seizures	Neurotransmitter disorders and related disorders
Cardiomyopathy (see Table 90.4)	Congenital disorders of glycosylation Fatty acid oxidation disorders Glycogen storage diseases Lysosomal storage disorders Mitochondrial disorders
Eye Anomalies	
Cataracts	Carbohydrate disorders Lysosomal storage disorders Mitochondrial disorders Peroxisomal disorders
Corneal clouding	Lysosomal storage disorders
Retinal anomalies	Congenital disorders of glycosylation Lysosomal storage disorders Peroxisomal disorders
Gastrointestinal Abnormalities	
Hepatic dysfunction (see Table 90.5)	Amino acid disorders Bile acid biosynthetic disorders Carbohydrate disorders Congenital disorders of glycosylation Fatty acid oxidation disorders Lysosomal storage disorders Mitochondrial disorders Peroxisomal disorders
Hepatomegaly/ splenomegaly	Congenital disorders of glycosylation Fatty acid oxidation disorders Glycogen storage diseases Lysosomal storage disorders
Hair or Skin Abnormalities	Amino acid disorders Menkes disease Organic acidemias
Hematologic Abnormalities	Mitochondrial disorders Organic acidemias
Sepsis	Galactosemia Disorders of biotin metabolism
Unusual Odor (see Table 90.7)	Amino acid disorders Organic acidemias
Dysmorphic Syndromes (see Table 90.8)	Cholesterol biosynthesis disorders Congenital disorders of glycosylation Lysosomal storage disorders Organic acidurias Peroxisomal disorders Others

hepatic dysfunction. It often produces a severe coagulopathy, hypoglycemia, and fulminant hepatic failure. Microvesicular fatty deposits in the liver characterize both disorders. Both disorders can have life-threatening consequences for the fetus and mother. Women with either of these disorders improve remarkably after delivery, suggesting that the fetus is causing a toxic effect on the mother that resembles that seen in patients with inborn errors of fatty acid oxidation.

There is convincing evidence that a specific defect of fatty acid oxidation, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency in the fetus, is associated with the HELLP syndrome and AFLP spectrum in the mother.[9,91] Long-chain 3-hydroxyacyl-CoA dehydrogenase is part of a trifunctional multimeric enzyme complex that performs the three terminal steps in the long-chain fatty acid β-oxidation: long-chain 2,3-enoyl-CoA hydratase, LCHAD, and long-chain 3-ketoacyl-CoA thiolase. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency can be seen as an isolated deficiency or as part of trifunctional protein deficiency that affects all three enzyme activities. Both disorders are inherited as autosomal recessive traits.

Isolated LCHAD deficiency is marked by relative genetic homogeneity. More than 50% of the mutant alleles found in patients who have this disease carry the same mutation: a G1528C change in the gene that encodes for the α-subunit of LCHAD. Other mutations in the same gene that predispose a heterozygous mother to AFLP have also been identified. A relatively large number of at-risk pregnancies have now been identified and reviewed after the birth of a child with LCHAD deficiency.[9,91] These studies show that a woman who is heterozygous for LCHAD deficiency is at risk for developing HELLP syndrome or AFLP during a pregnancy in which she is carrying a fetus who is homozygous for the same deficiency. Thus, a heterozygous mother is only at risk if her fetus inherits a second LCHAD mutation from the father. The fetus, in turn, is at risk for significant postnatal problems associated with its enzyme deficiency. The diagnosis and care of a child with LCHAD deficiency is discussed later under Hypoglycemia. Rarely,

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other inborn errors of long-chain fatty acid β-oxidation can also produce AFLP.

The current recommendation is to evaluate all pregnant women who develop AFLP for LCHAD deficiency and related fatty acid oxidation disorders by biochemical and genetic testing. This recommendation should also be considered for women who develop recurrent and/or severe HELLP syndrome.

Fetal Diseases Affecting the Fetus

The fetus does not generally suffer prenatal consequences of its own inborn error of metabolism, because the abnormal metabolites that it produces are removed by the maternal circulation, or conversely, metabolic deficiencies produced by the inborn error are replenished by the maternal circulation. There are, however, several groups of disorders that include significant exceptions: amino acid disorders, congenital disorders of glycosylation, fatty acid β-oxidation disorders, lysosomal storage disorders, mitochondrial disorders, and peroxisomal disorders (see Dysmorphic Syndromes).

Although most of the clinical disorders that affect the developing fetus are discussed later, the disorders that can lead to congenital ascites or hydrops fetalis are discussed here. A major group of inborn errors of metabolism that lead to hydrops fetalis are the lysosomal storage disorders, including β-glucuronidase deficiency and Morquio syndrome (which are mucopolysaccharidoses); Farber disease and GM1-gangliosidosis (which are spingolipidoses); galactosialidosis and sialidosis (which are oligosaccharidoses); and free sialic storage disease (a lysosomal transport defect).[24,113] Other disorders that can also lead to hydrops fetalis are congenital disorders of glycosylation (specifically type Ia), glycogen storage diseases (specifically type IV), Niemann-Pick disease type C, and transaldolase deficiency,[24,134] as well as several inborn errors of red cell glycolytic enzymes (see Chapter 23).

Central Nervous System Disease

Newborn infants have a limited number of responses to an illness such as an inborn error of metabolism.[16,60] These responses generally include cardiorespiratory, feeding, and neurologic difficulties. The neurologic difficulties, such as altered consciousness (encephalopathy), altered tone, or seizures, are discussed elsewhere in this book (see Chapters 52, 54, and 55). As noted in these chapters, these neurologic difficulties are most commonly caused by infection, brain malformations, or hypoxemic-ischemic encephalopathy, and less commonly by inborn errors of metabolism. Although it is important to evaluate a patient for these common problems, it is also important to remember that inborn errors of metabolism can also produce brain malformations and can mimic the clinical picture of hypoxic-ischemic encephalopathy.[29]

This section discusses inborn errors of metabolism that cause two different clinical phenotypes: (1) metabolic encephalopathies—inborn errors of metabolism that produce a clinical picture in which encephalopathy predominates; and (2) metabolic seizures—inborn errors in which seizures predominate. The distinction between these two groups is somewhat arbitrary, because patients with a disorder that produces metabolic encephalopathy often have seizures, and conversely, patients with a disorder that produces metabolic seizures often have encephalopathy. Nevertheless, the distinction is useful, because patients generally fall more easily into one group than the other. In addition, many of the disorders that produce neonatal seizures yield negative results on the standard metabolic evaluation for metabolic encephalopathy and require additional specialized testing, including biochemical analysis of numerous metabolites in the cerebrospinal fluid (CSF).

Metabolic Encephalopathy

The inborn errors of metabolism that can produce metabolic encephalopathy in the neonatal period or early infancy are associated with what appears to be a cascade of biochemical effects. A number of specific metabolites are overproduced as a result of a particular enzyme deficiency. In excess, these metabolites serve as endogenous toxins that impair other metabolic or physiologic processes. Disruption of these processes leads, in turn, to production of additional metabolites, which further impair cellular processes. Early interruption of the cascade through such relatively simple measures as fluid and caloric support might abort episodes of metabolic decompensation. Physicians who care for children who present with a metabolic disorder in late infancy, childhood, or even adulthood often receive a retrospective history of "sepsis" in the neonatal period that was never confirmed by culture and that resolved spontaneously; these episodes might have represented an interrupted metabolic intoxication syndrome. Early nonspecific supportive treatment may abort the pathologic cascade or delay the onset of a more fulminant course until a provisional metabolic diagnosis and specific treatment become available.

The symptoms and signs of neonates who develop metabolic encephalopathy generally do not appear on the first day of life but usually begin later in the first week. The initial symptoms are often poor feeding associated with a poor suck and irritability. Muscle tone is decreased, sometimes marked by a fluctuating pattern of decreased and increased tone. Reflexes are sometimes abnormal, and seizures can develop. The poor feeding is sometimes accompanied by vomiting. Diarrhea is uncommon. Disorders accompanied by a metabolic acidosis (e.g., the lactic acidemias or organic acidemias) can lead to a compensatory increase in respiratory rate. In the case of urea cycle defects, hyperammonemia increases the respiratory drive, leading to hyperpnea. The neonate shows lethargy, which can progress to coma and death. These symptoms often progress rapidly, sometimes within a matter of hours, but more often during the course of a few days. It is important to suspect a metabolic disorder as early as possible in its course to interrupt the progression of symptoms because many of these disorders are life threatening.

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The diagnostic evaluation of a newborn suspected of having a metabolic encephalopathy should include testing for disorders of amino acid metabolism, organic acid metabolism, the mitochondrial respiratory chain, and the urea cycle (see Table 90.3). The differential diagnosis for these patients can often be narrowed by the presence of other clinical or routine laboratory findings, such as acidosis, hyperammonemia, hypoglycemia, ketosis, or lactic acidemia. The diagnosis will be narrowed further by performing more specialized laboratory testing, including plasma amino acid analysis, urine organic analysis, plasma carnitine analysis with acylcarnitine profile, and urine carnitine analysis with acylcarnitine profile. Effort should be made to perform a prompt and vigorous laboratory evaluation of the patient suspected of having a metabolic encephalopathy, because many of them are potentially treatable. The disorders that produce metabolic encephalopathy are discussed later in this chapter (see The Abnormal Newborn Infant: Laboratory Phenotypes).

Metabolic Seizures

There are an ever-growing number of inborn errors of metabolism that have been recognized as a cause of seizures in the neonatal period or early infancy.[32,88,129] These disorders produce a variety of seizure types, including partial, tonic, and myoclonic seizures, and EEG patterns, including burst-suppression (see Chapter 55). The seizure type and EEG pattern may evolve over time. As in the case of patients who present with a metabolic encephalopathy, many of the disorders that produce neonatal seizures are potentially treatable. The approach to laboratory testing of these patients should include the same laboratory testing noted in the preceding for the evaluation of patients with suspected metabolic encephalopathy. In addition, the patient with a suspected metabolic seizure disorder should undergo additional, specialized testing for both potentially treatable and untreatable disorders, with emphasis directed toward identification of potentially treatable disorders. As a rule, different specialized testing must be obtained for each disorder.[32,88,129] The physician caring for these patients should strongly consider starting therapy after the samples for laboratory testing have been obtained rather than awaiting the receipt of test results.

The clinical features, biochemical basis, diagnostic testing, treatment, and prognosis for several of the disorders that produce metabolic seizures are presented in three groups: treatable disorders, potentially treatable disorders, and untreatable disorders, to allow the attending physician to prioritize the diagnostic evaluation. The listing of disorders is by no means complete.

Treatable Disorders

The treatable disorders include folinic acid-responsive seizures, glucose transporter type I deficiency, pyridoxine-dependent epilepsy, and pyridoxal 5′-phosphate–dependent epilepsy.

Folinic Acid–Responsive Seizures. Folinic acid–responsive seizures are defined operationally as isolated neonatal seizures (and associated EEG abnormalities) that respond rapidly to treatment with folinic acid (3-5 mg/kg per day) with response expected within 2-3 days. Recognition of this and related disorders of neurotransmitter metabolism has increased with the clinical availability of biochemical analysis of neurotransmitters in CSF.[48,89] Studies have shown that most cases of folinic acid–responsive seizures are variants of pyridoxine-dependent epilepsy (see Pyridoxine-Dependent Epilepsy). More specifically, patients with both disorders share the same biochemical abnormalities (i.e., increased concentrations of α-aminoadipic semialdehyde and related metabolites) and genetic defects (e.g., *ALDH7A1* mutations). Patients who are identified as having folinic acid–responsive seizures based on clinical responsiveness to folinic acid and then shown to have the biochemical and genetic evidence of pyridoxine-dependent epilepsy should be treated with a combination of folinic acid (3-5 mg/kg per day) and pyridoxine (15-30 mg/kg per day).

Other forms of folinic acid–responsive seizures that have no relationship to pyridoxine-dependent epilepsy have been described. The biochemical hallmark of these seizure disorders is cerebral folate deficiency.[89] More specifically, these disorders are characterized by a decreased concentration of 5-methyltetrahydrofolate in the CSF, without evidence of systemic 5-methyltetrahydrofolate deficiency (i.e., normal serum and red cell 5-methyltetrahydrofolate concentrations, normal serum homocysteine, and normal hematologic findings). Two disorders can be associated with this phenotype: (1) the presence of autoantibodies to the folate receptor that transports 5-methyltetrahydrofolate across the choroid plexus (FRα)[90]; and (2) mutations in the gene that encodes for this folate receptor (*FOLR1*).[115] These two disorders are characterized by psychomotor retardation, cerebellar ataxia, pyramidal tract signs, dyskinesias, and seizures starting at 4-6 months of age or later in infancy. Neither disorder has been reported to produce seizures during the neonatal period. Nevertheless, it is prudent to investigate the patient who has electroencephalographic evidence of folinic acid–responsive seizures without evidence of the biochemical or genetic markers of pyridoxine-responsive seizures for antibodies to the FRα and mutations in the *FOLR1* gene, because confirmation of either diagnosis would improve evaluation and treatment of the patient and of at-risk, presymptomatic family members.

Glucose Transporter Type 1 Deficiency. The glucose transporter type 1 (GLUT1) is the primary protein that facilitates glucose transport across the blood–brain barrier and into astrocytes. Glucose transporter type 1 deficiency is (in almost all cases) an autosomal dominant disorder that reduces glucose transport by approximately 50%, leading to impaired energy production by the brain and a range of neurologic abnormalities.[56,137] Patients with GLUT1 deficiency syndrome typically develop seizures between 1 and 6 months of age. They can have a variety of seizure types,

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including partial, generalized, or myoclonic seizures. The seizures are refractory to standard anticonvulsants and may be exacerbated by phenobarbital and diazepam, which inhibit GLUT1 function. Many affected infants also develop episodic eye movements, ataxia, oculomotor apraxia, developmental delay, microcephaly, and "stroke-like events with reversible hemiplegia" as they get older.[56,137] There are less common variants of GLUT1 deficiency that do not manifest problems until later in life.

Once considered, the diagnosis can be readily established by concurrently measuring glucose and lactate in the plasma and CSF. The characteristic findings are a low CSF glucose concentration (<60 mg/dL in all cases, and almost always <40 mg/dL) and a decreased CSF glucose/plasma glucose ratio (<0.40; normal, 0.60). The plasma lactate concentration is normal in patients with GLUT1 deficiency, whereas the CSF lactate concentration is either normal or less than normal. The diagnosis can be confirmed by measuring erythrocyte uptake of 3-methylglucose (a nonmetabolizable glucose homologue) or by mutational analysis of the *SLC2A1* gene.

Glucose transporter type 1 deficiency can be treated successfully with a low-carbohydrate, high-fat diet (ketogenic diet), which provides ketones as an alternative fuel source for the brain (as opposed to glucose). Treatment also includes oral supplementation with carnitine and several vitamins that are missing from the ketogenic diet, and the avoidance of barbiturates (including phenobarbital), valproic acid (which inhibits fatty acid oxidation), and methylxanthines (including caffeine). It is important that the diagnosis be made as early as possible to initiate treatment before irreversible neurologic damage occurs.

Pyridoxine-Dependent Epilepsy. Another disorder that should be considered in the evaluation of a newborn infant with unexplained seizures accompanied by negative findings on a standard metabolic evaluation is pyridoxine (vitamin B_6)-dependent epilepsy.[35] This disorder typically begins in the neonatal period, although in some cases the seizures begin in utero.

Studies have demonstrated that the metabolic basis of pyridoxine-dependent epilepsy is complicated. It now appears that pyridoxine-dependent epilepsy is caused by genetic defects in the *ALDH7A1* gene. This gene encodes for a protein called antiquitin, which functions as an α-aminoadipic semialdehyde dehydrogenase in the lysine catabolic pathway. Antiquitin deficiency leads to accumulation of α-aminoadipic semialdehyde, pipecolic acid, and Δ^1-piperideine 6-carboxylic acid. Δ^1-Piperideine 6-carboxylic acid reacts with and inactivates the active form of pyridoxine (i.e., pyridoxal 5–phosphate). Thus, patients with pyridoxine-dependent epilepsy have an autosomal recessive disorder in lysine metabolism that inactivates pyridoxal 5′–phosphate, which is required for GABA synthesis and other vitamin B_6–dependent enzyme reactions. GABA is a critical inhibitory neurotransmitter. The CSF concentration of GABA is decreased in patients with pyridoxine-dependent epilepsy. Pyridoxine supplementation compensates for the increased loss of pyridoxal 5′–phosphate, as does direct supplementation with pyridoxal 5′–phosphate itself.

The disorder can be diagnosed most quickly by demonstrating clinical and electroencephalographic responses to a pharmacologic challenge dose of pyridoxine (initial dose is 30 mg/kg per day, followed by 15-30 mg/kg per day for 3 days). The response to parenteral pyridoxine (50-100 mg) is often dramatic, with normalization of the electroencephalographic pattern within minutes. This pyridoxine challenge test must, however, be done with caution, because patients can experience apnea, hypotonia, and hypotension. The test should be done in an intensive care setting with electroencephalographic monitoring. Once the diagnosis is established, daily oral pyridoxine supplementation (5-10 mg/kg per day) is continued. The diagnosis should be confirmed by biochemical analysis of lysine metabolites (α-aminoadipic semialdehyde, pipecolic acid, and/or Δ^1-piperideine 6-carboxylic acid) in the blood, urine, and/or CSF. It has been shown that α-aminoadipic semialdehyde may also be increased in patients with sulfite oxidase deficiency or molybdenum cofactor deficiency, so these disorders must be ruled out before concluding that the patient has pyridoxine-dependent epilepsy based on measurement of α-aminoadipic semialdehyde alone. It is also possible to confirm the diagnosis of pyridoxine-dependent epilepsy by genetic analysis of the *ALDH7A1* gene. The prognosis for this disorder, if recognized early and treated, is improved.

Pyridoxal 5′-Phosphate–Dependent Epilepsy. A variant of pyridoxine-dependent epilepsy has been recognized in which the patient does not respond (or responds partially) to parenteral or oral pyridoxine but responds to oral pyridoxal 5′–phosphate (pyridoxal phosphate).[109] Pyridoxal 5′–phosphate is the "active" form of vitamin B_6; that is, it serves as the cofactor for the enzymes involved in neurotransmitter biosynthesis. The patients who respond to pyridoxal 5′–phosphate have a clinical presentation similar to that of patients with pyridoxine-dependent epilepsy. However, they have a number of unique biochemical findings: decreased CSF concentrations of homovanillic acid (an L-dopa metabolite) and 5-hydroxyindoleacetic acid (a serotonin metabolite), increased CSF concentrations of two other L-dopa metabolites (3-O-methyldopa and vanillactic acid), and increased CSF concentrations of two amino acids (glycine and threonine). These changes are thought to be secondary to a generalized dysfunction of three vitamin B_6–dependent enzymes, aromatic L-amino acid decarboxylase, glycine cleavage enzyme, and threonine dehydratase. The underlying genetic defect is a deficiency of pyridox(am)ine 5′–phosphate oxidase (*PNPO*), which is required for the conversion of dietary pyridoxine and pyridoxamine phosphate to pyridoxal 5′–phosphate.

A patient suspected of having this disorder can be evaluated biochemically for the CSF abnormalities enumerated in the preceding or, more simply, by using pyridoxal 5′–phosphate in place of pyridoxine in an oral challenge test (pyridoxal 5′–phosphate is not available in a parenteral

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form). The patient should receive 50 mg of pyridoxal 5′–phosphate by nasogastric tube while in an intensive care unit with EEG monitoring because of the risk of apnea, hypotonia, and hypotension. In some cases, the EEG response was relatively rapid (within an hour), but the patient remained unresponsive for several days following administration of pyridoxal 5′–phosphate. If the challenge test is positive, the patient should continue to receive pyridoxal 5′–phosphate (10 mg/kg every 6 hours), and the diagnosis should be confirmed by genetic testing of the *PNPO* gene. See Chapter 55 for further details on evaluating and managing patients with this disorder.

Potentially Treatable Disorders

There are also several disorders for which treatment may be available for a subset of patients. Further study is required to determine which patients may benefit from the currently available therapies. These disorders include congenital glutamine synthetase deficiency, Menkes disease, nonketotic hyperglycinemia, serine biosynthesis defects, and sulfite oxidase deficiency/molybdenum cofactor deficiency.

Congenital Glutamine Synthetase Deficiency. A new disorder of glutamine metabolism has been described in recent years; the disorder affects systemic glutamine metabolism and produces cerebral malformations and intractable seizures. Glutamine synthetase catalyzes the conversion glutamate and ammonia to glutamine, thereby detoxifying ammonia. In the brain, glutamine is the source of glutamate (an excitatory neurotransmitter) and GABA (an inhibitory neurotransmitter). The two patients who were initially described with congenital glutamate synthetase deficiency presented in the neonatal period with severe neurologic compromise (with severe hypotonia and/or seizures); very low plasma, urine, and CSF concentrations of glutamine (but normal glutamate); hyperintensity of white matter, enlarged ventricles, and severe lissencephaly on cranial MRI; and a small brain with no visceral malformations on autopsy. Both infants died within the first days or weeks of life.[39] A third patient with a milder course survived until 3 years of age, with severe seizures and chronic hyperammonemia. This patient was treated with progressively increased doses of enteral or parenteral glutamine supplementation, monitored biochemically, electrophysiologically, and by brain MRI and MRS.[40] The patient's plasma glutamine concentration normalized, while the CSF glutamine concentration increased but remained lower than normal. The plasma ammonia concentration did not increase from the pretreatment baseline. The EEG showed improvement, and the MRS showed increased concentrations of glutamine and glutamate in the brain. Overall, the patient showed biochemical improvement and mild clinical improvement, suggesting that early intervention with glutamine supplementation might provide beneficial therapy for patients with congenital glutamine synthetase deficiency.

Menkes Disease. Abnormalities of the skin and hair are characteristic of several inborn errors of metabolism. Menkes disease is an X-linked disorder that is caused by a defect in intracellular copper metabolism and generally presents soon after the neonatal period with hypotonia, failure to thrive, and seizures.[51] Characteristic hair changes are either already present or manifest soon thereafter. The scalp and eyebrow hair is sparse, short, brittle, and may be lightly pigmented (hence the eponymic term kinky-hair disease). The hair is morphologically abnormal (e.g., pili torti). Other clinical features that develop later include facial dysmorphism (sagging cheeks), skin laxity, umbilical or inguinal hernias, skin hypopigmentation, hypotonia, and neurodevelopmental delays. The pathogenetic bases of these clinical features are presumably related to the deficiency of multiple copper-dependent enzymes. For example, seizures may be the consequence of cytochrome c oxidase (also known as complex IV of the respiratory chain) deficiency, which impairs energy metabolism in the brain, and/or dopamine-β-hydroxylase deficiency, which impairs neurotransmitter (catecholamine) production in the brain.

The biochemical hallmarks of this disorder are decreased serum copper and ceruloplasmin concentrations.[51] However, the normal concentrations of these markers are low and can be difficult to interpret. Definitive diagnosis requires CSF catecholamine analysis to measure the absolute and relative amounts of catecholamines, which depend on the activity of the copper-dependent enzyme dopamine-β-hydroxylase. The diagnosis can also be confirmed by genetic testing of the *ATP7A* gene, the only gene known to be associated with Menkes disease. In classic Menkes disease, treatment with subcutaneous injections of copper histidine or copper chloride before 10 days of age normalizes developmental outcome in some individuals, improves the neurologic outcome in others, and is of no benefit in the remainder.[51,52] Clearly, there is a brief window available for the initiation of beneficial therapy, which would only be available for newborns already known to be at risk for Menkes disease by virtue of a positive family history or those identified prenatally. The option for effective treatment for older patients is more guarded.

Nonketotic Hyperglycinemia. Nonketotic hyperglycinemia (also known as glycine encephalopathy) is an autosomal recessive disorder caused by a defect in the glycine cleavage enzyme that leads to increased concentrations of glycine in the blood, urine, and CSF.[45,128] Prenatal onset of hiccups and seizures has been observed. Patients typically present in the first days of life with profound hypotonia, poor feeding, hiccups, severe (generally myoclonic) seizures, apnea, and lethargy, often leading to coma. The disorder often leads to death in the neonatal period. Electroencephalogram analysis in typical cases initially shows a burst-suppression pattern, which evolves with time into hypsarrhythmia. Patients who survive this initial period generally have intractable seizures and profound intellectual impairment. A small minority of patients with neonatal-onset disease have a better prognosis. There is no way of predicting outcome for the severely affected neonate.

The biochemical hallmarks of nonketotic hyperglycinemia are increased CSF glycine and plasma glycine

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concentrations, with an increased CSF/plasma glycine ratio. Standard laboratory analysis of plasma amino acids might not suffice to establish the diagnosis, because the plasma glycine concentration varies over the course of the day and may be normal or only be minimally elevated at certain times. The diagnosis of this disorder requires amino acid analysis on concurrently collected plasma and CSF samples to demonstrate an elevated CSF/plasma glycine ratio (>0.08; normal: <0.04). In addition, patients who are suspected of having nonketotic hyperglycinemia should undergo urine organic acid analysis to confirm that the patient does not have one of the organic acidurias associated with ketotic hyperglycemia (see Specialized Biochemical Testing).

Treatment for nonketotic hyperglycinemia is limited. The plasma glycine concentration can be reduced by oral administration of sodium benzoate, and dextromethorphan can be administered to reduce the activity of glycinergic *N*-methyl-D-aspartate receptors. These medications appear to be beneficial for some patients, especially those with milder forms of disease. Valproate should not be used to control seizures, because it inhibits the glycine cleavage enzyme.

Serine Biosynthesis Defects. Whereas most inborn errors of amino acid metabolism are the consequence of enzyme deficiencies that impair the catabolism of one or more particular amino acids, the serine biosynthetic defects represent a class of disorders that affect de novo anabolism of a particular amino acid, namely, serine. Three enzymes are required for the biosynthesis of serine in the central nervous system: (1) 3-phosphoglycerate dehydrogenase (3-PGDH); (2) 3-phosphoserine aminotransferase (3-PSAT); and (3) 3-phosphoserine phosphatase (3-PSPH). The clinical phenotypes have been well described for patients with 3-PGDH deficiency and PSAT deficiency but not for 3-PSPH deficiency.[41,120]

Patients with 3-phosphoglycerate dehydrogenase deficiency or phosphoserine aminotransferase deficiency typically present with congenital microcephaly, severe psychomotor retardation, and intractable seizures; hence, these disorders may have prenatal onset. The seizure type is variable and may include infantile spasms, multifocal clonic seizures, and myoclonic seizures. The seizure pattern often changes over time. Some patients may also develop spastic quadriparesis, adducted thumbs, nystagmus, cataracts, hypogonadism, and megaloblastic anemia. The characteristic finding on cranial MRI is severe hypomyelination with cortical and subcortical atrophy. The pathogenesis is, at least in part, the consequence of the underlying serine deficiency that leads to impaired sphingomyelin and cerebroside production, which are required for the synthesis of myelin.

Biochemical studies show decreased concentrations of serine in CSF and, to a lesser extent, in blood. Glycine, the transamination product of serine, is also decreased in CSF and blood but to a relatively milder degree than serine. The diagnosis can be confirmed by enzyme analysis in cultured skin fibroblasts or by genetic testing. Effective treatment is available using oral supplementation with serine (500-600 mg/kg per day) and glycine (200-300 mg/kg per day), using four to six doses per day and careful biochemical monitoring of serine and glycine concentrations in the CSF and blood. This treatment leads to improved seizure control and increased myelination of the brain, especially when it is started early. Treatment for an affected fetus identified prenatally is available by maternal serine and glycine supplementation during pregnancy.

Sulfite Oxidase Deficiency/Molybdenum Cofactor Deficiency. Sulfite oxidase deficiency exists in two forms: (1) an isolated genetic deficiency of sulfite oxidase and (2) a genetic defect affecting synthesis of the molybdenum cofactor, which is required for the function of sulfite oxidase, xanthine oxidase, and aldehyde oxidase.[7,123] Sulfite oxidase is involved in the degradation of three sulfur-containing amino acids, methionine, homocysteine, and cysteine, to sulfate. Xanthine dehydrogenase and aldehyde oxidase are involved in the purine degradation pathway leading to production of uric acid. The clinical role of aldehyde oxidase deficiency is uncertain. Both sulfite oxidase deficiency and molybdenum cofactor deficiency are characterized clinically by early onset, refractory seizures, hypotonia evolving to hypertonia, and if the patients survive long enough, microcephaly, lens dislocation, and severe psychomotor delay. Many affected infants die in the first year of life.

The key biochemical findings of sulfite oxidase deficiency, either in cases of isolated deficiency or in cases of molybdenum cofactor deficiency, are increased excretion of urinary sulfite and thiosulfate, increased plasma and urinary S-sulfocysteine, and decreased plasma cystine. In addition, the plasma homocysteine concentration is very low in these patients and provides a biochemical marker that can be obtained rapidly. Patients with molybdenum cofactor deficiency produce the same set of metabolites as patients with the isolated deficiency, plus they excrete increased amounts of xanthine and hypoxanthine and decreased amounts of uric acid. As in the case of homocysteine, the serum uric acid is sometimes very low in patients with molybdenum cofactor deficiency and provides an easily measured marker for this form of the disease.

Isolated sulfite oxidase deficiency and molybdenum cofactor deficiency are both autosomal recessive disorders. The sulfite oxidase enzyme is encoded by the *SUOX* gene. The molybdenum cofactor is synthesized from guanosine triphosphate (GTP) in three steps: (1) the conversion of GTP to cyclic pyranopterin monophophate (cPMP); (2) the conversion of cPMP to molybdopterin; and (3) the conversion of molybdopterin to molybdenum cofactor. Molybdenum cofactor deficiency type A, type B, and type C are associated with genetic defects impairing step 1 (the *MOCS1* gene), step 2 (the *MOCS2* and *MOCS3* genes), and step 3 (the *GPHN* gene), respectively. Approximately two-thirds of patients with molybdenum cofactor deficiency have type A disease.

There is no proven treatment for either isolated sulfite deficiency or molybdenum cofactor deficiency. Efforts to treat patients with either disorder with a low-methionine,

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low-cysteine diet have been tried and may have been beneficial in a few patients with mild disease but not for those with severe disease. However, one patient with molybdenum cofactor deficiency who had a defect in the *MOCS1* gene was treated intravenously with purified cPMP and showed clinical and metabolic improvement. This was reported in 2012.[130] Since then, other patients have been treated with encouraging results. This treatment remains experimental but is available for compassionate use. However, this approach will not benefit patients with isolated sulfite oxidase deficiency or with the other genetic forms of molybdenum cofactor deficiency (i.e., patients with defects in the *MOCS2*, *MOCS3*, or *GPHN* genes).

Untreatable Disorders

In addition to evaluating the patient for treatable or potentially treatable inborn errors of metabolism, the physician will want to consider other inborn errors of metabolism that are not treatable at this time. A partial listing of currently untreatable inborn errors of metabolism that can cause neonatal seizures is provided in the following.

Adenosylsuccinate Lyase Deficiency. Two disorders of purine biosynthesis may present in the neonatal period, adenosylsuccinate lyase deficiency and AICA-ribosiduria. Both disorders are rare, but AICA-ribosiduria has been described in only a single patient and is not discussed further here. Adenosylsuccinate lyase catalyzes two distal steps in the purine synthetic pathway: (1) the conversion of SAICAR (succinylaminoimidazole caboxamide riboside) to AICAR (5-phosphoribosyl-5-amino-4-succinoimidazolecarboxamide) in the de novo purine synthesis pathway and (2) the conversion of adenosylsuccinate to adenylic acid for recycling and synthesis of nucleic acids. Adenosylsuccinate lyase deficiency can present in the neonatal period with intrauterine growth restriction, microcephaly, fetal and neonatal hypokinesia, lack of fetal heart rate variability, severe hypotonia, severe seizures, and early death.[76] The biochemical hallmarks of adenosylsuccinate lyase deficiency are increased urinary concentrations of 5-phosphoribosyl-5-aminoimidazole-4-(N-succino)caboxamide and adenosylsuccinate. Clinical analysis for these purine precursors is clinically available. The diagnosis can be confirmed by enzyme analysis or genetic testing.

Congenital Disorders of Glycosylation. The congenital disorders of glycosylation are an increasingly recognized group of disorders that present with an extraordinarily diverse range of phenotypes.[50,64] These disorders are discussed in sections provided elsewhere in this chapter (see the subsection on Hepatic Dysfunction and the subsection on Dysmorphic Syndromes in the section discussing The Abnormal Newborn Infant: Clinical Phenotypes). One group of disorders that is discussed in the Dysmorphic Syndromes section is called the dystroglycanopathies, which produce a form of congenital muscular dystrophy that is associated with skeletal muscle and brain abnormalities.[111] The dystroglycanopathies are caused by defects in O-glycosylation (i.e., glycosylation of the protein is via the hydroxyl group of serine or threonine) rather than a defect in N-glycosylation (i.e., glycosylation of the protein is via the amide group of asparagine). Two of these disorders in O-glycosylation are called Walker-Warburg syndrome and muscle-eye-brain disease, both of which are characterized by severe muscle weakness, psychomotor retardation, ocular abnormalities (including unilateral or bilateral microcornea, microphthalmia, hypoplastic or absent optic nerves, retinal coloboma, cataracts, iris hypoplasia, and abnormal anterior chamber angle leading to glaucoma), and epilepsy. Some patients may have cardiac involvement. Laboratory evaluation often reveals increased serum creatine kinase activity, whereas cranial MRI shows brain malformations including structural abnormalities (e.g., hydrocephalus, brainstem hypoplasia, cerebellar hypoplasia or cysts) or neuronal migration abnormalities (e.g., cobblestone lissencephaly or polymicrogyria). Diagnosis of these disorders can be made by morphologic examination of a skeletal muscle biopsy or by genetic testing. Mutations of several different genes can produce Walker-Warburg syndrome, including *POMT1*, *POMT2*, *FKTN*, *FKRP*, *LARGE*, or *ISPD*, whereas muscle-eye-brain disease is associated with mutations in the *POMGnT1* gene. Additional disorders within this category of disease are still being described.

Congenital Neuronal Ceroid Lipofuscinosis. The congenital form of neuronal ceroid lipofuscinosis (NCL) is caused by deficiency of a lysosomal enzyme called cathepsin D.[88] This disorder may present prenatally or neonatally, distinguishing it from the other forms of NCL, which present later than 6 months of age. The diagnosis can be established by microscopic examination of a skin biopsy, by enzymatic testing (measurement of tripeptidyl peptidase 1 [TPP1] and palmitoyl-protein thioesterase 1 [PPT1] in leukocytes), or by genetic testing.

Dihydropyrimidine Dehydrogenase Deficiency. Dihydropyrimidine dehydrogenase is an enzyme involved in the catabolism of pyrimidine metabolism, more specifically the catabolism of thymine and uracil. Patients with deficiency of this enzyme generally present in the first year of life with growth delay and seizures and subsequently manifest microcephaly with craniofacial dysmorphism, growth restriction, and autistic features. A minority of patients present earlier with neonatal seizures. The biochemical hallmark of the disease is increased urinary excretion of thymine and uracil. The diagnosis can be confirmed by enzyme analysis or genetic testing. No therapy is available.

There is also an adult form of this disease in which patients present with severe, potentially life-threatening toxicity after receiving chemotherapy with 5-flourouracil, a pyrimidine analogue. The neonatal or infantile form of this disease is inherited as an autosomal recessive disorder, whereas the adult form may affect heterozygous or homozygous individuals. Thus, first-degree relatives of infants identified with this disorder should also be tested and counseled regarding their risk of adverse reactions to 5-fluorouracil therapy.

Gamma-Aminobutyric Acid Disorders. Gamma-aminobutyric acid (GABA) is an essential neurotransmitter.

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There are two rare disorders of GABA metabolism that can produce isolated neonatal seizures: GABA transferase deficiency and succinic semialdehyde dehydrogenase (SSADH) deficiency.[88] Gamma-aminobutyric acid transferase deficiency presents with poor feeding, psychomotor delay, hypotonia, hyperreflexia, and intractable seizures. Cranial diffusion-weighted MRI demonstrates increased signal in the internal and external capsules and the subcortical white matter. The biochemical findings include increased concentrations of GABA, β-alanine, and homocarnosine in the CSF. There is no effective treatment for this disease. Succinic semialdehyde dehydrogenase deficiency generally produces a nonspecific encephalopathy that evolves into a neurobehavioral disorder associated with global developmental delays, most notably including severe speech delay, and seizures that may develop in infancy. Cranial T_1-weighted MRI demonstrates increased signal in the basal ganglia. The biochemical hallmark is an increased GABA concentration in the blood, urine, and CSF. The diagnosis can be confirmed by enzyme analysis of white cells or genetic testing. Currently available treatment for this disorder is poor.

Mitochondrial Glutamate Transporter. Glutamate is a strategic excitatory neurotransmitter in the brain. The mitochondrial glutamate transporter is involved in intracellular trafficking of glutamate between the mitochondrion and cytosolic compartments and is expressed ubiquitously and both pre- and postnatally. For reasons that remain unclear, deficiency of this receptor causes an exclusively neurologic picture characterized by neonatal onset of microcephaly, myoclonic seizures with a burst-suppression EEG pattern, low-amplitude visual evoked potential, and MRI findings of cerebellar hypoplasia and abnormal corpus callosum.[73] Standard biochemical testing reveal normal plasma amino acids, plasma carnitine and acylcarnitines, and urinary organic acids. The biochemical hallmark of the defect is impaired mitochondrial glutamate oxidation, as demonstrated by polarographic analysis of cultured skin fibroblasts (see the subsection Specialized Biochemical Testing under The Abnormal Newborn Infant: Laboratory Phenotypes). Alternatively, the diagnosis can be established by genetic testing of the *SLC25A22* gene, which encodes for the mitochondrial glutamate transporter. No effective treatment is available.

Peroxisomal Disorders. The peroxisomal disorders can be divided into two groups: (1) defects of peroxisomal biogenesis that affect synthesis and assembly of the peroxisomal organelle that affect most or all of the peroxisomal enzymes and (2) defects in single enzymes that function within the assembled peroxisome (see The Abnormal Newborn Infant: Clinical Phenotypes, Dysmorphic Syndromes).[114,135] Zellweger syndrome is the paradigm of the peroxisomal biogenesis disorders. It is an autosomal recessive disorder characterized by craniofacial dysmorphism, failure to thrive, renal cortical cysts, epiphyseal stippling, profound hypotonia and severe psychomotor retardation, seizures, and early death. Epiphyseal stippling is an unusual radiographic finding of ectopic calcification found most characteristically in the ankle, patella, vertebrae, hips, and trachea. Other peroxisomal assembly disorders may also present with seizures. In addition, single enzyme defects of the peroxisomal fatty acid β-oxidation pathway (which is genetically and functionally different from the mitochondrial fatty acid β-oxidation pathway) can mimic the physical and neurologic features of Zellweger syndrome. The biochemical hallmarks and diagnosis of these disorders are discussed elsewhere in this chapter (see the subsection Specialized Biochemical Testing in The Abnormal Newborn Infant: Laboratory Phenotypes and the subsection Dysmorphic Syndromes in The Abnormal Newborn Infant: Clinical Phenotypes). The diagnosis can be confirmed by genetic testing.

Cardiomyopathy

See Chapter 76. Inborn errors of metabolism that can produce cardiomyopathy and associated arrhythmias in the neonatal period can be divided into five major diagnostic categories: (1) congenital disorders of glycosylation; (2) fatty acid β-oxidation disorders; (3) glycogen storage disorders; (4) lysosomal storage disorders; and (5) respiratory chain defects (Table 90.4).[55,127]

Another group of disorders that can cause cardiomyopathy in children, the lysosomal storage disorders, does not generally produce cardiomyopathy in early infancy.

The different groups of inborn errors of metabolism that can lead to cardiomyopathy do so via different pathophysiologic mechanisms. The glycogen storage disorders lead to impaired gluconeogenesis, depriving the heart of an essential energy source during fasting. The glycogen storage disorders may also lead to an infiltrative process, resulting from the accumulation of partial breakdown products of glycogen in the myocardium. Fatty acid β-oxidation disorders also lead to an energy-deficient state after glucose and glycogen stores have been depleted. The mitochondrial disorders also compromise energy production in the heart and/or lead to production of toxic metabolites.[33,43,101]

Congenital Disorders of Glycosylation

An inborn error that may be associated with cardiomyopathy in early infancy is congenital disorder of glycosylation type Ia (CDG-Ia). The CDG-Ia syndrome is a highly pleiotropic disorder that can produce pericardial effusions, cardiomyopathy, or both, in addition to a broad range of other abnormalities, including neurologic abnormalities, hepatic dysfunction and, in some cases, a characteristic pattern of malformation (see Dysmorphic Syndromes).[50,64] Other, less common forms of CDG may also produce cardiomyopathy.

Fatty Acid β-Oxidation Disorders

The myocardium derives a significant fraction of its energy from the mitochondrial oxidative metabolism of fatty acids, especially long-chain fatty acids.[43,58] The oxidation of these fatty acids requires a carnitine-mediated system to transport long-chain fatty acids into the mitochondrion, a

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TABLE 90.4 Disorders Associated With Cardiomyopathy

Category of Disorder	Disorder
Congenital disorders of glycosylation	CDG-Ia and others
Fatty acid oxidation disorders	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase II deficiency Carnitine transporter deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/trifunctional protein deficiency Multiple acyl-CoA dehydrogenase deficiency Very-long-chain acyl-CoA dehydrogenase deficiency
Glycogen storage disorders	GSD type II (Pompe disease) GSD type IX (phosphorylase kinase deficiency)
Lysosomal storage disorders	Glycolipidoses Mucopolysaccharidoses Oligosaccharidoses
Mitochondrial disorders	mtDNA disorders Genes involved in protein synthesis of RC complexes Complex I and IV ($tRNA^{Leu}$) Genes that encode for RC complexes Complex III (cytochrome b subunit) Complex V (*ATP6* and *ATP8*) nDNA Genes that encode for RC complexes Complex I (*NDUFS2*, *NDUFV2*) Complex II (*SDHA*) Genes that encode for assembly or stabilization of RC complexes Complex IV (*SCO2*, *COX10*, *COX15*) Complex V (*TMEM70*) Genes that encodes for other necessary components of the RC complexes Coenzyme Q_{10} biosynthesis (9 genes) Mitochondrial phosphate carrier (*SLC25A3*) Genes involved in maintaining mitochondrial milieu Barth syndrome (*TAZ*) Mitochondrial DNA depletion syndrome 13 (*FBXL4*)

ATP6, Gene that encodes for structural subunit 6 of complex V; *ATP8,* gene that encodes for structural subunit 8 of complex V; CDG, congenital disorder of glycosylation; *COX10,* gene that encodes assembly protein for complex IV; *COX15,* gene that encodes assembly protein for complex IV; *FBXL4*, F-box/LRR-repeat protein 4, which involved in maintenance of mtDNA; GSD, glycogen storage disease; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; *NDUFS2*, gene that encodes for subunit 1 of complex I; *NDUFV2*, gene that encodes for subunit 1 of complex I; *RC*, respiratory chain; *SCO2*, gene that encodes assembly protein for complex IV; *SDHA*, gene that encodes subunit A of complex II; *SLC25A*, gene that encodes for the mitochondrial phosphate carrier; t^{Ile}, transfer RNA for isoleucine; t^{Leu}, transfer RNA for leucine; *TAZ*, gene that encodes for taffazin; *TMEM70*, gene that encodes for protein required for assembly of complex V.

β-oxidation pathway to break down the fatty acids in the mitochondrion, and the mitochondrial respiratory chain to derive energy from the breakdown products. Cardiomyopathy would be expected to develop in the context of a defect in carnitine-mediated transport of long-chain fatty acids into the mitochondrion, defects of the fatty acid β-oxidation pathway, and defects of the respiratory chain itself. Studies have demonstrated that defects of long-chain fatty acid β-oxidation are a significant cause of cardiac disease in the neonatal period, whereas defects affecting primarily medium- or short-chain fatty acid β-oxidation are less so.

Several defects of long-chain fatty acid transport across the mitochondrial membranes and β-oxidation pathway can cause hypertrophic cardiomyopathy in the neonatal period, including carnitine-acylcarnitine translocase (CACT) deficiency, carnitine palmitoyltransferase II (CPT II) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency/trifunctional protein (TFP) deficiency, and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (see Approaches to Specific Abnormal Laboratory Findings, Hypoglycemia).[104,105] Multiple acyl-CoA dehydrogenase deficiency (also known as glutaric aciduria type II), a defect in the transfer of reducing equivalents from the enzymes of the β-oxidation pathway to the respiratory chain, can also produce cardiomyopathy (see Dysmorphic Syndromes). Two other defects associated with long-chain fatty acid β-oxidation, plasma membrane carnitine transporter deficiency (also known as carnitine uptake defect or systemic primary carnitine deficiency) and carnitine palmitoyltransferase I (CPT I) deficiency, do not generally cause cardiomyopathy in the neonatal period. The plasma membrane carnitine transporter deficiency does, however, lead to dilated cardiomyopathy in later infancy and childhood.

The clinical features, diagnosis, treatment, and prognosis of these disorders are discussed further in later sections of this chapter (see the subsection Hypoglycemia in The Abnormal Newborn Infant: Laboratory Phenotypes).

Glycogen Storage Disorders

The glycogen storage disorder that most commonly causes hypertrophic cardiomyopathy in early infancy is Pompe disease, also known as α-glucosidase deficiency, acid maltase deficiency, or glycogen storage disease type II. α-Glucosidase is the only enzyme involved in glycogen metabolism that is located within the lysosome. Pompe

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disease can also be considered a lysosomal storage disorder, and it is probably helpful to consider its pathogenesis from this perspective. Acid maltase is a key enzyme responsible for degrading glycogen; it cleaves the α-1,4-glucoside linkages of the glycogen polymer, converting glycogen to glucose.

Generalized hypotonia, failure to thrive, and cardiomyopathy characterize the neonatal form of Pompe disease.[24] Hepatomegaly does not develop in patients with Pompe disease (except as a consequence to heart failure), as it does in patients with some other glycogen storage disorders (most notably types I and III). The diagnosis is supported by an increased serum creatine kinase activity and increased urinary excretion of a specific glucose tetrasaccharide and then confirmed by enzyme analysis using skeletal muscle, cardiac muscle, or cultured skin fibroblasts, or by genetic testing. Enzyme replacement therapy for the infantile form of Pompe disease appears promising.[17,59,152]

Cardiomyopathy is not generally seen in the neonatal period in association with the other glycogen storage disorders, except in rare cases of cardiac-specific phosphorylase b kinase deficiency. Studies have shown that most, if not all, cases of cardiac-specific phosphorylase kinase deficiency (glycogen storage disease type IX) are really caused by mutations in the γ_2-subunit of adenosine monophosphate (AMP)–activated protein kinase (*PRKAG2*).[24]

Lysosomal Storage Disorders

Many of the lysosomal storage disorders produce cardiomegaly, valvular disease, and/or cardiomyopathy (dilated or hypertrophic).[33,113] Lysosomal storage disorders should be considered in the differential diagnosis of the newborn infant with cardiac disease who has other physical findings suggestive of a lysosomal storage disorder, such as craniofacial dysmorphism, corneal clouding or retinal abnormalities, hepatosplenomegaly, or skeletal anomalies (see Dysmorphic Syndromes). Examples of lysosomal storage disorders that may, on rare occasion, present with cardiomyopathy in the newborn period include those with multiple enzyme defects (multiple sulfatase deficiency, galactosialidosis), sphingolipidoses (e.g., GM1-gangliosidosis, Sandhoff disease), and transport/trafficking disorders (e.g., infantile free sialic acid storage disorder and sialidosis).[113]

Mitochondrial Disorders

Several mitochondrial defects are associated with cardiomyopathy in the neonatal period.[44,101,108,117] These disorders may be classified according to whether they are the consequence of an error in a mitochondrial-encoded (mtDNA) component or in a nuclear-encoded (nDNA) component of the respiratory chain (see Table 90.4).

Several mtDNA defects can cause cardiomyopathy. One group of defects involves the mitochondrial-encoded tRNAs required for protein mitochondrial protein synthesis; for example, the C3303T point mutation in the $tRNA^{Leu(UUR)}$ affects the synthesis of complexes I and IV.[14] This mutation causes Leigh syndrome, which produces a variable clinical pattern that can include hypotonia, optic atrophy, nystagmus, developmental delay, hepatic dysfunction, myopathy, and cardiomyopathy. A second group of defects involves the genes that encode for the mitochondrial-encoded protein subunits of the respiratory chain. For example, the G15498A point mutation in the gene that encodes for the cytochrome b subunit of complex III causes neonatal cardiomyopathy, whereas another mutation affects the ATP6 and ATP8 subunits of complex V.

The classification of nDNA defects that cause neonatal cardiomyopathy includes three groups of disorders: (1) defects affecting individual subunits of the respiratory chain complexes; (2) defects affecting proteins required for assembly or stabilization of the respiratory chain complexes; and (3) defects affecting the mitochondrial milieu, including substrates for the respiratory chain and oxidative phosphorylation.[24,27,108] Examples of the first group of disorders include mutations affecting the mitochondrial-encoded subunits of complex I (i.e., *NDUFS2* and *NDUFV2*), complex II (*SDHA*), and coenzyme Q_{10} biosynthesis. Group 2 includes mutations of the *SCO2*, *COX10*, and *COX15* genes, which are required for assembly of respiratory complex IV (also known as cytochrome c oxidase), and *TMEM70*, which is required for assembly of complex V (ATP synthase).[26,62,83] Group 3 involves genes associated with the mtDNA depletion syndrome. This includes mitochondrial DNA depletion syndrome 13, which is inherited in an autosomal recessive manner and is caused by mutations in the *FBXL4* gene. These mutations lead to an impairment of phosphorylation-dependent ubiquitination, which is involved in protein degradation affecting multiple mitochondrial pathways. Clinically, patients with this disorder present with encephalomyopathy, failure to thrive, developmental delay, seizures, movement disorders, cerebral atrophy, hepatic dysfunction, arrhythmias, and occasionally hypertrophic cardiomyopathy. Finally, group 3 includes Barth syndrome, an X-linked disorder that impairs production of the lipid membrane required for normal mitochondrial function. This disorder is characterized by cardiomyopathy, cataracts, deafness, and neutropenia.[21] Group 3 also includes defects in the gene that encodes for the mitochondrial phosphate carrier (*SLC25A3*).

Eye Anomalies

Many inborn errors of metabolism manifest with unusual ophthalmologic findings (see Table 90.3). A careful ophthalmologic examination is a crucial part of the clinical evaluation for a suspected inborn error of metabolism; conversely, patients with unusual ophthalmologic findings might require a metabolic evaluation (see Chapter 95).

Inborn errors of metabolism can affect any of the structural components of the eye.[85] Cataracts are classically associated with carbohydrate disorders (e.g., galactosemia), Lowe syndrome (oculocerebrorenal syndrome), and certain forms of other groups of disorders, including lysosomal disorders (e.g., galactosialidosis), mitochondrial disorders

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(e.g., Barth syndrome), and peroxisomal disorders (e.g., Zellweger syndrome). Corneal clouding may be seen in early infancy in patients with several lysosomal storage diseases, such as GM1-gangliosidosis, β-glucuronidase deficiency, I-cell disease, and sialidosis. Lens dislocation does not generally occur during the neonatal period in patients with homocystinuria or sulfite oxidase deficiency but may occur in older patients with these disorders.

Several inborn errors of metabolism affect retinal development.[85] The so-called cherry-red spot is found in several of the lysosomal storage disorders (e.g., Farber disease, galactosialidosis, GM1-gangliosidosis, Tay-Sachs disease, Sandhoff disease, infantile free sialic acid storage disorder, and sialidosis). Abnormal deposits in the retinal pigment epithelial layer leading to retinitis pigmentosa may develop in older patients who have congenital disorder of glycosylation type Ia (CDG-Ia), fatty acid oxidation disorders (LCHAD deficiency), peroxisomal disorders (Zellweger syndrome and its variants), and mitochondrial disorders.

Gastrointestinal Abnormalities

Newborn infants with inborn errors of metabolism might have various gastrointestinal abnormalities. Common clinical findings include poor feeding, jaundice, hepatomegaly, and splenomegaly, while abnormal liver function studies are a common laboratory finding (see Hepatic Dysfunction and Hepatomegaly and Splenomegaly). Many of the organic acidurias and urea cycle disorders are associated with vomiting. Several patients with an organic acidemia have undergone surgery for and been found to have pathologically confirmed pyloric stenosis. Researchers hypothesize that the organic acidemias produce toxic metabolites that affect pyloric sphincter tone. Similarly, pancreatitis is a well-documented problem in patients with several organic acidemias, fatty acid β-oxidation disorders, and mitochondrial disorders.[63]

Diarrhea is a relatively uncommon finding, but it can occur in patients who have defects of bile acid synthesis (see Hepatic Dysfunction), CDG-Ia and CDG-Ib (see Dysmorphic Syndromes), CDG-Ib, congenital chloride diarrhea (see Chapter 83), intestinal disaccharidase and monosaccharide transport deficiencies, lysosomal storage disorders (e.g., Wolman disease) (see Hepatomegaly and Splenomegaly), and mitochondrial disorders (see Hematologic Abnormalities). Lastly, several lysosomal storage disorders can produce congenital ascites and hydrops fetalis (see Prenatal Onset). Inborn errors are associated with hepatic dysfunction, and hepatomegaly/splenomegaly are discussed in the next two sections.

Hepatic Dysfunction

A number of inborn errors of metabolism are associated with hepatic disease. Excluding disorders that are associated primarily with defects in bilirubin metabolism (see Chapter 91), several groups of disorders lead to hepatic dysfunction and some degree of hepatomegaly. One approach to categorizing these disorders is to divide them into those that impair one or more aspects of hepatic function to a more significant degree than they produce liver enlargement and those for which the reverse is true. The former group of disorders is discussed in this section; the latter group, composed primarily of storage disorders, is discussed under Hepatomegaly and Splenomegaly.

The inborn errors of metabolism that can cause hepatic dysfunction can be categorized further according to the function or functions that they impair: defects that cause hypoglycemia, defects that cause hepatocellular damage leading to liver failure and cirrhosis, and defects that cause cholestatic disease. Although this approach is useful from a physiologic perspective, many inborn errors affect more than one of these hepatic functions, and an alternative scheme based on biochemical classification may be applied more practically. The biochemically based approach has been adopted in organizing this section. It is recommended that defects of the following biochemical categories be considered in evaluating patients with hepatic dysfunction: amino acid metabolism, bile acid metabolism, carbohydrate metabolism, congenital disorders of glycosylation, fatty acid β-oxidation, peroxisomal disorders, respiratory chain defects, and a miscellaneous group of disorders (Table 90.5).[22] The clinical aspects of these disorders are presented in greater detail in Chapter 91.

Amino Acid Defects

Tyrosinemia Type I. Tyrosinemia type I, also known as hepatorenal tyrosinemia, is the classic aminoacidopathy that can produce a fulminant disorder characterized by progressive hepatocellular damage leading to cirrhosis, proximal renal tubular dysfunction, and peripheral neuropathy.[110] The biochemical basis of this disorder is a defect in fumarylacetoacetate hydratase, an enzyme acting late in the tyrosine catabolic pathway. Fumarylacetoacetate accumulates secondary to this enzyme deficiency and is nonenzymatically converted to succinylacetone, which is the characteristic urinary metabolite identified in patients with this disorder. Succinylacetone can be identified by urine organic acid analysis or liquid chromatography/tandem mass spectrometry.

Until recently, the only treatment for this disorder that appeared to be effective was liver transplantation. However, a new treatment based on pharmacologic inhibition of 4-hydroxyphenylpyruvate dioxygenase (an enzyme upstream of the hydratase in the tyrosine catabolic pathway) with Nitisone (Orfadin) [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC)] has been introduced and is effective in preventing liver disease, especially when therapy is begun before the onset of acute liver failure and is combined with a tyrosine-restricted diet.

Citrin Deficiency. Urea cycle defects are generally associated with mild hepatocellular dysfunction during their acute presentation, but the neurologic manifestations of these disorders are the predominant signs (see Hyperammonemia). The degree of hepatocellular disease can become

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TABLE 90.5 Disorders Associated With Hepatic Dysfunction

Category of Disorder	Defect
Amino acid metabolism	Tyrosinemia type I Citrin deficiency
Bile acid biosynthesis	*See text for specific disorders*
Carbohydrate metabolism	Galactosemia Hereditary fructose intolerance Glycogen storage disease type IV
Congenital disorders of glycosylation	CDG-Ib and other forms
Fatty acid oxidation	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase Ia deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/ trifunctional protein deficiency Multiple acyl-CoA dehydrogenase deficiency Very-long-chain acyl-CoA dehydrogenase deficiency
Lysosomal storage disorders	Gaucher disease type 2 Niemann-Pick disease type C
Mitochondrial disorders	mtDNA disorders Genes involved in protein synthesis of RC complexes • Multiple complexes ($tRNA^{Glu}$) Large-scale deletions (Pearson syndrome) nDNA Genes that encode for assembly or stabilization of RC complexes • Complex III (*BCS1L*) • Complex IV (*SCO1*) • Complex V (*TMEM70*) Genes involved in intergenomic communication • mtDNA depletion syndromes (*DGUOK*, *FBXL4*, *MPV17*, *POLG*, *SUCLG1*)
Peroxisomal disorders	Single enzyme disorders Biogenesis disorder

BCS1L, Gene required for assembly of complex III; CDG, Congenital disorder of glycosylation; *DGUOK*, gene that encodes for deoxyguanosine kinase; *FBXL4*, gene associated with regulation of protein degradation; *MPV17*, gene associated with mitochondrial DNA depletion syndrome 6; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; *POLG*, gene that encodes for polymerase γ; RC, respiratory chain; *SCO1*, gene required for insertion of copper into Complex IV; *SUCLG1*, gene that encodes for subunit 1 of succinyl-CoA ligase; $tRNA^{Glu}$, transfer RNA for glutamic acid; *TMEM70*, gene required for assembly of complex V (ATP synthase).

more significant later in the course of these diseases, especially in argininosuccinic aciduria. There is, however, a urea cycle–related disorder called *citrin deficiency* that may produce neonatal intrahepatic cholestasis.[79,98]

Citrin deficiency is a genetic disorder caused by a defect in the mitochondrial aspartate-glutamate carrier, which plays a strategic role in the urea cycle, gluconeogenesis, and the malate shuttle (which moves NADH between intracellular compartments). Impaired citrin function would limit the conversion of citrulline and aspartate to argininosuccinic acid, a strategic component of the urea cycle. Absent aspartate, citrulline accumulates and urea production is impaired. Hence, citrin deficiency is also known as citrullinemia type II, whereas citrullinemia type I (or more simply, citrullinemia) is a urea cycle disorder caused by argininosuccinic acid synthetase deficiency (see Hyperammonemia).

Citrin deficiency was originally identified as a self-limited disorder associated with hepatic dysfunction that resolves by 1 year of age and can be treated successfully with a low-lactose diet and support for the hepatic dysfunction. However, more severe, progressive cases have been identified subsequently that produced severe neonatal intrahepatic cholestasis.[79,98] Patients with this form of citrin deficiency have increased serum concentrations of citrulline, methionine, and phenylalanine, as well as galactose. It does not lead to hyperammonemia. These patients are often ascertained by newborn screening that identified the increased amino acid concentrations and by programs that measure serum galactose as their screen for galactosemia (but not by programs that measure *GALT* activity) (see Newborn Screening). It is a treatable disease. Citrin deficiency can also present as a mild, adult-onset form of hyperammonemia (hence its other name, citrullinemia type II).

Bile Acid Biosynthesis Defects

Heritable defects in bile acid biosynthesis can cause severe hepatobiliary disease (cholestatic jaundice and intestinal malabsorption) in the newborn infant.[23,36] These defects are probably underdiagnosed, because they are not ascertained by the standard methods of metabolic screening of the sick neonate. However, once considered, they can be diagnosed with relative ease. Recognition of these disorders is especially important because effective treatment exists for some of these defects.

In simple terms, bile acid biosynthesis involves conversion of cholesterol to two bile acids, cholic acid and chenodeoxycholic acid. The first steps in this conversion involve transformation of the cholesterol nucleus, and the last few steps involve transformation of the cholesterol side chains. Several defects in conversion of the cholesterol nucleus to bile acids have been described, including 3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase deficiency and 3-oxo-Δ^4-steroid-5β-reductase deficiency.[23,36] Both of these disorders can result in severe cholestatic disease in the newborn period and can lead in later months to steatorrhea, clinically significant malabsorption of fat-soluble vitamins D and K, failure to thrive, and chronic hepatitis. The patients

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generally have no or relatively mild hepatomegaly, mildly elevated hepatic aminotransferase values, and nonspecific findings on liver biopsy. If untreated, many patients progress to irreversible liver disease and die in early childhood. Early recognition is crucial, because it permits institution of bile acid replacement therapy using a combination of cholic and chenodeoxycholic acids, which is effective in reversing the hepatotoxic manifestations of these enzyme deficiencies.

Several of the peroxisomal disorders also impair bile acid biosynthesis, because they affect enzymes required for the final steps of cholesterol side-chain oxidation.[23,36,135] These enzymes (i.e., the bifunctional enzyme and the thiolase) are also involved in peroxisomal oxidation of very-long-chain fatty acids, and their deficiency leads to a highly pleiotropic dysmorphic syndrome associated with severe neurologic consequences. Bile acid replacement therapy does not ameliorate the neurologic consequences of these disorders. The peroxisomal disorders, including those that produce cholestatic disease, are discussed further under Dysmorphic Syndromes.

Carbohydrate Disorders

Two disorders of monosaccharide metabolism, galactosemia (see Newborn Screening) and hereditary fructose intolerance, are associated with hepatocellular disease.[104] These disorders manifest only when the newborn's diet contains the monosaccharide to which the newborn is intolerant, such as galactose in the case of galactosemia and fructose in the case of hereditary fructose intolerance. Similarly, these disorders are detectable by urinary screening tests only when the affected newborn is receiving a diet containing the offending monosaccharide. Because fructose is not a component of breast milk and is a component of only the infant formulas that contain sucrose, hereditary fructose intolerance usually does not manifest in the neonatal period. Both disorders can be detected by the presence of reducing substances other than glucose in urine (see Specialized Biochemical Testing). The diagnosis of galactosemia or hereditary fructose intolerance must be confirmed by specific biochemical analysis or genetic testing.

Treatment of these disorders consists of dietary restriction of the hepatotoxic monosaccharide. Such restriction is not easily managed because of the nearly ubiquitous presence of galactose (as a component of lactose) and fructose (as a component of sucrose) in many processed foods. Nevertheless, dietary restriction can be successful and is associated with improved long-term outcomes.

Several other disorders of carbohydrate metabolism can also cause hepatic dysfunction, including the glycogen storage disease types I and III, fructose-1,6-bisphosphatase deficiency, and pyruvate carboxylase deficiency. However, these disorders affect gluconeogenesis and, in contrast to galactosemia and hereditary fructose intolerance, result primarily in hypoglycemia and hepatomegaly rather than generalized hepatocellular dysfunction (see Hypoglycemia). In contrast to these disorders, glycogen storage disease type IV (branching enzyme deficiency) causes severe hepatic dysfunction.

Congenital Disorders of Glycosylation

Congenital disorder of glycosylation type Ib (CDG-Ib) is discussed herein because it manifests exclusively with hepatic and intestinal problems including vomiting, hypoglycemia, protein-losing enteropathy, failure to thrive, diarrhea, hepatomegaly and hepatic dysfunction associated with congenital hepatic fibrosis, and thrombosis or an increased bleeding tendency.[50] Congenital disorders of glycosylation type Ib are caused by phosphomannose isomerase deficiency, an enzyme involved in N-glycosylation of numerous glycoproteins. Patients with CDG-Ib can be identified by transferrin isoelectric focusing or mass spectrometry (see Dysmorphic Syndromes and Specialized Biochemical Testing), and the diagnosis then confirmed by enzyme analysis or genetic testing. Unlike the situation for other forms of CDG, effective treatment exists for patients with CDG-Ib. The clinical problems of several patients with CDG-Ib have been reversed with oral mannose supplementation.

Fatty Acid Oxidation Defects

In general, the disorders of long-chain fatty acid β-oxidation cause hepatic dysfunction to a greater degree than do the disorders of medium- or short-chain fatty acid β-oxidation. The disorders of long-chain fatty acid β-oxidation include carnitine palmitoyltransferase type Ia (CPT Ia) deficiency, carnitine-acylcarnitine translocase (CACT) deficiency, carnitine palmitoyltransferase type II (CPT II) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, and trifunctional protein (TFP) deficiency.

A related disorder of fatty acid β-oxidation that is associated with hepatic dysfunction is multiple acyl-CoA dehydrogenase deficiency. This deficiency is a genetically heterogeneous disorder caused by defects in either electron transfer protein (ETF) or ETF dehydrogenase, which function as intermediates between several acyl-CoA dehydrogenases that are involved in fatty acid β-oxidation or amino acid catabolism, and the mitochondrial respiratory chain. This disorder can also be classified as an organic aciduria and is also called glutaric aciduria type II because glutaric acid is a major metabolite observed on urinary organic acid analysis (see Specialized Biochemical Testing). More severe forms of this disorder are associated with dysmorphic features (see Dysmorphic Syndromes).

All of these long-chain fatty acid β-oxidation disorders produce several forms of disease, ranging from a severe neonatal/early infantile form to a relatively benign adult-onset form. The severe neonatal form is usually associated with hepatic dysfunction, presumably due to the impaired mitochondrial energy production from long-chain fatty acids and/or hepatotoxic metabolites that might accumulate secondary to the impaired fatty acid oxidation. The diagnosis and treatment of these disorders is discussed elsewhere in this chapter (see Hypoglycemia).

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Lysosomal Storage Disorders

Two lysosomal storage disorders may cause hepatic dysfunction in the newborn period: Gaucher disease type 2 and Niemann-Pick disease type C. Gaucher disease type 2 is a lysosomal storage disease involving sphingolipid metabolism that presents with neonatal cholestasis, thrombocytopenia, and hepatosplenomegaly, as well as severe neurologic dysfunction (including bulbar signs, opisthotonus, and nystagmus). Niemann-Pick disease type C is a lysosomal disorder of intracellular cholesterol trafficking that may cause neonatal liver disease with prolonged jaundice and pulmonary infiltrates or progressive neurologic disease in childhood or later in life.[113]

Mitochondrial Disorders

Multiple mitochondrial disorders are associated with hepatic dysfunction in the neonatal period.[31,44] These disorders can be classified according to whether they are the consequence of an error in a mitochondrial-encoded (mtDNA) component or in a nuclear-encoded (nDNA) component of the respiratory chain and the function of the affected gene (see Table 90.5).

Several mtDNA defects can cause hepatic dysfunction. One group of defects involves a large-scale deletion in the mtDNA, affecting many transfer RNA genes and protein coding genes. Pearson syndrome (also known as Pearson marrow-pancreas syndrome) is the prototype of this group of diseases.[121] It manifests in the newborn period with a variable pancytopenia (characterized by severe macrocytic anemia) and ring sideroblasts in the bone marrow; exocrine pancreatic dysfunction leading to fat malabsorption and diarrhea; hepatic dysfunction (steatosis and cirrhosis, potentially leading to liver failure and death); renal tubular dysfunction; and skeletal muscle weakness. 3-Methylglutaconic aciduria is a biochemical marker for this disorder, and it can be detected by urine organic acid analysis. A second group of mtDNA defects involves genes that encode for the mitochondrial tRNAs required for mitochondrial protein synthesis. For example, defects of the $tRNA^{Glu}$ gene lead to hepatic dysfunction and myopathy.

The classification of nDNA defects that cause neonatal hepatic dysfunction includes two groups of disorders: (1) defects affecting proteins required for assembly or stabilization of the respiratory chain complexes and (2) defects involved in intergenomic communication.[19,31] Examples of the first group of disorders include: mutations in the *BCS1L* gene, which encodes for a protein required for assembly of complex III; mutations of the *SCO1* gene, which encodes for a protein required for assembly of complex IV; and mutations of the *TMEM70* gene, which is required for assembly of complex V (ATP synthase).[26,62,83] Mutations of the *BCS1L* gene lead to GRACILE syndrome, an eponymic association of *g*rowth *r*estriction, *a*mino aciduria due to a Fanconi-like tubulopathy, *c*holestasis, *i*ron overload, *l*actic acidosis, and *e*arly death. *SCO1* mutations produce an encephalohepatopathy. The diagnosis of *BCS1L* and *SCO1* deficiencies can be facilitated by detailed biochemical studies that identify the impaired respiratory chain complex. However, definitive diagnosis requires genetic testing. There is no effective therapy for either disorder.

The second group of nDNA defects affects intergenomic communication (i.e., the defects impair the nDNA-encoded factors that regulate mtDNA replication, producing the mtDNA depletion syndromes).[31,74,75] This is a group of autosomal recessive disorders characterized by reduced mtDNA copy number. Several nuclear genes have been identified as a cause of mtDNA depletion syndromes: (1) the *DGUOK* gene encodes for an enzyme (deoxyguanosine kinase) involved in the mitochondrial nucleotide salvage pathway; (2) the *FBXL4* gene is involved in phosphorylation-dependent ubiquitination that is involved in protein degradation in several key mitochondrial pathways; (3) the *MPV17* gene encodes for an inner mitochondrial membrane protein; (4) the *POLG* gene encodes for polymerase γ, which performs mtDNA replication; and (5) the *SUCLG1* gene encodes for a subunit of succinyl-CoA ligase, a Krebs cycle enzyme. Mutations of these genes have been identified as a cause of neonatal liver disease. *DGUOK* mutations produce a hepatorenal syndrome characterized by hepatic failure, failure to thrive, abnormal eye movements, lactic acidosis, hypoglycemia, and elevated α-fetoprotein. *FBXL4* mutations produce a disorder characterized by encephalomyopathy, failure to thrive, developmental delay, seizures, movement disorders, cerebral atrophy, hepatic dysfunction, arrhythmias, and occasionally hypertrophic cardiomyopathy. *MPV17* mutations produce progressive hepatic failure with hepatomegaly. *POLG* and *SUCLG1* mutations produce hepatocerebral syndromes with lactic acidosis; *SUCLG1* mutations are also associated with mild elevations in urinary methylmalonic acid that can be detected by urine organic acid analysis. These disorders can be identified by a combination of classical biochemical studies followed by genetic testing (see Lactic Acidemia).

Peroxisomal Disorders

Several of the peroxisomal disorders cause significant hepatocellular disease in the neonatal period. Many of these disorders also produce dysmorphic manifestations and are discussed later (see Dysmorphic Syndromes).

Hepatomegaly and Splenomegaly

Several inborn errors of metabolism are associated with hepatomegaly in the newborn period. In many of these disorders (e.g., congenital disorders of glycosylation, organic acidemias, peroxisomal disorders, urea cycle disorders), liver enlargement develops as a result of primary hepatocellular disease; these disorders are not discussed further in this section. Fatty acid oxidation disorders produce hepatomegaly through excessive storage of fat and are discussed elsewhere in this chapter. Another group of disorders, the lysosomal storage disorders, results in hepatomegaly because of excessive storage of incompletely metabolized macromolecules in the liver.

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TABLE 90.6 Lysosomal Storage Disorders in Neonates

Category of Disorder	Substrate	Disorders
Glycogenoses	Glycogen	GSD type II (Pompe disease)
Lipidoses	Glycolipids or other complex lipids	Farber disease GM1-gangliosidosis Gaucher disease Krabbe disease Niemann-Pick disease type A Wolman disease
Mucopolysaccharidoses	Mucopolysaccharides	β-Glucuronidase deficiency
Oligosaccharidoses	Glycoproteins Glycolipids	Free sialic acid storage disease Fucosidosis Galactosialidosis I-cell disease Sialidosis

GSD, Glycogen storage disease.

Lysosomes contain a large number of enzymes involved in degrading macromolecules. In the absence of one or more of these enzymes, the macromolecules are only partially degraded. Depending on the origin and nature of the macromolecules, the partially degraded products accumulate in one or more tissues or organs and produce a range of clinical phenotypes. The lysosomal storage disorders can be classified according to the types of macromolecules that accumulate in the lysosome: glycogen, glycolipids or other complex lipids, mucopolysaccharides, or oligosaccharides (Table 90.6). Another group of lysosomal storage diseases is associated with defects of lysosomal transport (e.g., cystinosis, which does not manifest clinically in the neonatal period).

Several lysosomal storage disorders manifest in the neonatal period and should be considered in the differential diagnosis of patients who present with hepatomegaly, with or without other signs of storage disease (see Table 90.6).[16,113] Type II glycogen storage disease (Pompe disease) is the only glycogen storage disease caused by a defect in a lysosomal enzyme, but it generally is associated with hypotonia or cardiomyopathy rather than severe hepatomegaly (see Cardiomyopathy). Other glycogenoses, such as glycogen storage disease types I, III, IV, and VI, may be associated with hepatomegaly and, especially in the case of type I and type III, with hypoglycemia. However, these disorders do not generally present in the neonatal period. Similarly, defects of gluconeogenesis can present with hepatomegaly, but they will also be discussed elsewhere (see Hypoglycemia).

Several glycolipidoses or related disorders of complex lipid catabolism can manifest with hepatomegaly or splenomegaly in the newborn period.[16,113] Farber disease is an untreatable autosomal recessive defect of acid ceramidase. There are different clinical forms of this disorder, and patients can have joint swelling and pain, hoarseness, disturbance in swallowing, macular cherry-red spots, or central nervous system (CNS) dysfunction. Gaucher disease type 2, the acute neuronopathic form of Gaucher disease, results in hepatosplenomegaly during the first months of life (see earlier, Hepatic Dysfunction section under the Other Disorders subheading). This autosomal recessive disorder is caused by a deficiency of glucosylceramidase. Niemann-Pick disease type A (i.e., sphingomyelinase deficiency) usually begins in early infancy with hepatosplenomegaly and progresses with failure to thrive, psychomotor retardation, pulmonary infiltrates, macular cherry-red spots, and early death. One of the most striking of these disorders associated with hepatomegaly is Wolman disease, which is characterized by massive hepatomegaly and splenomegaly, abdominal distention, vomiting, diarrhea, anemia, failure to thrive, and adrenal calcifications. The prognosis for this disorder, caused by lysosomal acid lipase deficiency, has improved with the introduction of HSCT and, more recently, enzyme replacement therapy.

β-Glucuronidase deficiency (also known as mucopolysaccharidosis type VII) occasionally manifests in the neonatal period, although it usually begins later. It presents rarely with hydrops fetalis rather than the more common signs of a mucopolysaccharidosis, such as hepatosplenomegaly, inguinal or umbilical hernias, skeletal dysplasia, corneal clouding, and coarse facial features.

I-cell disease, also known as mucolipidosis type II, is caused by a processing defect that leads to multiple lysosomal enzyme deficiencies and is characterized by coarse facies and disproportionate craniofacial features, limitation of joint movement, hepatosplenomegaly, corneal clouding, and gingival hypertrophy. Severe forms of fucosidosis, galactosialidosis, infantile free sialic acid storage disease, and sialidosis may have similar manifestations. Patients with defects of mucopolysaccharide or oligosaccharide catabolism may also present with hydrops fetalis.

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Two other lysosomal storage disorders can manifest in the neonatal period, but neither is associated with hepatomegaly in the first month of life. Patients with the infantile form of GM1-gangliosidosis (i.e., β-galactosidase deficiency) have psychomotor delay and coarse facial features but do not develop hepatomegaly until later in the first year of life. These patients might also have cherry-red spots.[85] Rarely, Krabbe disease (i.e., galactosylceramidase deficiency) begins in the neonatal period with progressive psychomotor retardation, but hepatomegaly does not develop in affected patients.

Preliminary clinical assessment of a patient with a suspected lysosomal storage disease should include a careful eye examination to detect corneal clouding, cataracts, or abnormal retinal pigment changes; a cardiac evaluation, including an electrocardiogram and echocardiogram; a peripheral blood smear to detect leukocyte inclusions; and a radiologic study of the skeleton for identification of dysostosis multiplex. Leukocyte inclusions are characteristic of the oligosaccharidoses (i.e., fucosidosis, α-mannosidosis, sialidosis) and mucolipidoses (I-cell disease), are the exception in the glycolipidoses (they can be associated with Niemann-Pick type C disease), and are not found in glycogen storage disease type II. Laboratory evaluation of patients with suspected lysosomal storage disorders is presented in Specialized Biochemical Testing.

Enzyme replacement therapy is now available for several lysosomal storage diseases, including Fabry disease, Gaucher disease, Hunter disease, Hurler disease, Maroteaux-Lamy syndrome, Morquio syndrome type A, lysosomal acid lipase deficiency, and Pompe disease, with therapy for other disorders under development. Hematopoietic stem cell transplantation has also been shown to be effective for many disorders and may arrest or even reverse some of the somatic disease and neurologic degeneration associated with some of these disorders.[12,81,113,152]

Hair and Skin Abnormalities

See Chapter 94. Abnormalities of the skin and hair are characteristic of several inborn errors of metabolism. Menkes disease, an X-linked disorder involving intracellular copper transport, leads to defects in several copper-dependent enzymes.[51] Menkes disease is a highly pleiotropic disorder characterized by sparse and kinky scalp hair (hence the name kinky-hair disease), hypopigmentation, hypotonia, hypothermia, intractable seizures, profound developmental delay, and early death. The disorder may be associated with lactic acidosis and seizures caused by impaired activity of cytochrome c oxidase, a copper-dependent enzyme. The hair is brittle and coarse in the childhood-onset form of argininosuccinic aciduria, a urea cycle defect, but this is not typically seen in neonates with this disease (see Hyperammonemia).

A number of disorders include abnormalities of skin pigmentation. Phenylketonuria may be associated with fair hair and skin in affected Caucasian neonates. Similarly, newborn infants with cystinosis have fairer hair and skin than their unaffected siblings. However, cystinosis, an autosomal recessive defect affecting lysosomal transport of cystine, a sulfur-containing amino acid, does not produce symptoms until several months of age, when it results in renal Fanconi syndrome and, ultimately, renal failure caused by cystine crystal deposits in the kidney.[28]

An eczema-like rash and partial alopecia may be associated with multiple carboxylase deficiency, an organic aciduria caused by two defects in biotin metabolism: holocarboxylase synthetase deficiency and biotinidase deficiency (see Newborn Screening and Abnormal Laboratory Findings).[139] Both defects can produce severe ketoacidosis, feeding difficulties, apnea, lethargy, hypotonia, and coma in the newborn period. Holocarboxylase synthetase and, in some cases, biotinidase deficiency can be detected by urinary organic acid analysis. Both conditions respond to biotin therapy.

Hematologic Abnormalities

Several organic acidemias, including isovaleric acidemia, propionic acidemia, and methylmalonic acidemia, are characterized by neutropenia, thrombocytopenia, anemia, or pancytopenia.[124] The thrombocytopenia may be severe enough to lead to clinically significant bleeding and bruising. The precise pathophysiologic basis of these findings is not well understood but is thought to be caused by direct bone marrow suppression by the abnormally elevated metabolites (organic acids) associated with these disorders.

Hematologic abnormalities may be associated with certain mitochondrial disorders, including Barth syndrome[21] and Pearson syndrome.[121] Barth syndrome is characterized by neutropenia and cardiomyopathy, whereas Pearson syndrome is characterized by sideroblastic anemia, pancreatic exocrine insufficiency, and lactic acidosis. Pearson syndrome is the consequence of a heteroplasmic mutation (large deletion) of the mtDNA (see Lactic Acidemia). Neutropenia is a characteristic feature of glycogen storage disease type Ib, and this diagnosis should be considered in the patient who presents with hypoglycemia, hepatomegaly, hypertriglyceridemia, neutropenia, inflammatory bowel disease-like symptoms (i.e., diarrhea), and recurrent infections (see Hypoglycemia).[131] Last, inborn errors of cobalamin metabolism, folate metabolism, and pyrimidine metabolism (e.g., hereditary orotic aciduria) can produce macrocytic anemia.

Sepsis

A newborn infant with a metabolic disease may be at greater risk for sepsis than other neonates, and the presence of documented sepsis does not exclude the possibility of an underlying metabolic disorder. Several inborn errors of metabolism predispose the newborn infant to infections. The best-documented of these associations is the risk of *E. coli* infection in patients with galactosemia. Infections with other bacteria can also develop, but an *E. coli* infection is

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relatively specific. The diagnosis of galactosemia should be suspected in all neonates with *E. coli* sepsis, and these infants might need a galactose-free formula until the diagnosis has been excluded.

Disorders of biotin metabolism, including biotinidase deficiency and holocarboxylase synthetase deficiency, are associated with impaired B- and T-cell function, predisposing patients to mucocutaneous candidiasis and other immunologic problems. Recurrent mucocutaneous candidiasis may also develop in patients with maple syrup urine disease.

Unusual Odor

Several inborn errors of metabolism are characterized by unusual odors (Table 90.7). In many of these disorders, the odor is an inconsistent finding and can be detected only during episodes of acute metabolic decompensation. In some cases, the odor is difficult to appreciate during a bedside examination and can more easily be detected by smelling a urine specimen that has been kept at room temperature for several hours. Cerumen is another secretion that may contain increased concentrations of abnormal metabolites and allow the early detection of an inborn error of metabolism, such as maple syrup urine disease.

Dysmorphic Syndromes

In most cases, newborn infants with inborn errors of metabolism do not have physical abnormalities identifiable by physical examination; that is, they do not have a characteristic pattern of dysmorphism or identifiable congenital malformations. The pragmatic corollary to this observation is that metabolic evaluations of dysmorphic patients are not likely to be fruitful (see Chapter 30). However, there has been a growing appreciation of the fact that many inborn errors of metabolism do cause dysmorphic syndromes, and a steadily increasing number of such inborn errors have been identified. These inborn errors can be classified into several groups depending on the metabolic pathway(s) involved and the pathogenetic mechanism(s) by which they produce physical abnormalities.

Several groups of disorders will be considered in this section, including: (1) defects in cholesterol biosynthesis; (2) congenital disorders of glycosylation; (3) lysosomal storage disorders; (4) mitochondrial disorders; (5) peroxisomal disorders; and (6) miscellaneous pathways of small molecule metabolism (Table 90.8). Disorders associated with isolated malformations that are not detectable by physical examination will not be discussed in detail.

Cholesterol Biosynthesis

Several defects of cholesterol biosynthesis manifest in infancy. Inborn errors of cholesterol biosynthesis include defects in the early steps of the pathway and defects in the late steps. For example, mevalonic aciduria is caused by a defect in an early step in cholesterol biosynthesis (i.e., mevalonate kinase deficiency) and is discussed later (see Organic Acidurias).

Smith-Lemli-Opitz (SLO) syndrome is the prototypic example of a recognizable malformation disorder that is

TABLE 90.7 Characteristic Odors of Several Neonatal Inborn Errors of Metabolism

Disorder	Nature of Odor
Isovaleric acidemia	Sweaty feet
Maple syrup urine disease	Maple syrup
β-Methylcrotonyl-CoA carboxylase deficiency	Male cat urine
Multiple acyl-CoA dehydrogenase deficiency (aka: glutaric aciduria type II)	Sweaty feet
Multiple carboxylase deficiency (aka: holocarboxylase deficiency)	Male cat urine
Phenylketonuria	Musty

TABLE 90.8 Inborn Errors of Metabolism That Cause Dysmorphic Syndromes

Category of Disorder	Syndrome
Cholesterol biosynthesis	Smith-Lemli-Opitz syndrome Others
Congenital disorders of glycosylation	N-Glycosylation disorders CDG-Ia Others O-Glycosylation disorders Walker-Warburg syndrome and related disorders
Lysosomal storage disorders	Glycolipidoses Mucopolysaccharidoses Oligosaccharidoses
Organic acidurias	Mevalonic aciduria* Multiple acyl-CoA dehydrogenase deficiency (aka: glutaric aciduria type II)
Peroxisomal Disorders	
Biogenesis disorders	Chondrodysplasia punctata, rhizomelic type Zellweger syndrome and its variants
Single-enzyme disorders	Acyl-CoA oxidase deficiency Bifunctional enzyme deficiency Thiolase deficiency
Other	Vitamin K metabolism

*Mevalonic aciduria has been classified as an organic acidemia on the basis of the method used for its diagnosis, but it can also be classified as a peroxisomal single-enzyme disorder or as a defect in cholesterol biosynthesis because of its intracellular location and function, respectively.
CDG, Congenital disorders of glycosylation.

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caused by a defect in a late step in cholesterol biosynthesis.[42,86,126] Smith-Lemli-Opitz syndrome was recognized in the 1970s as a highly variable malformation syndrome. The mild form of this disorder is characterized by prenatal and postnatal growth restriction, microcephaly, characteristic craniofacial dysmorphism (including ptosis, low-set ears, epicanthal folds, and micrognathia), strabismus, syndactyly of the second and third toes, hypospadias, hypotonia, and intellectual disability. In its most severe form, patients also exhibit postaxial polydactyly, cleft palate, eye malformations, holoprosencephaly, cardiac defects, and, in boys, pseudohermaphroditism ranging from hypospadias to sex reversal. At autopsy, a range of severe malformations of the brain, heart, and kidneys can be identified.

In 1994, the genetic basis of SLO syndrome was shown to be a heritable defect in cholesterol biosynthesis.[126] Patients were found to have an abnormally low plasma cholesterol concentration and a markedly increased concentration of 7-dehydrocholesterol and, to a lesser degree, 8-dehydrocholesterol in plasma and cultured skin fibroblasts. Further work established the enzymatic basis of this syndrome as an autosomal recessive defect affecting 7-dehydrocholesterol reductase. After recognition of the underlying defect causing the SLO syndrome and development of specific methods for diagnosis, SLO syndrome has been recognized as a relatively common inborn error of metabolism, with a frequency of approximately 1 case in 20,000 persons.

The diagnosis of SLO syndrome should be investigated in patients with suggestive clinical phenotypes. Because the clinical phenotype is so variable and may be difficult to recognize in female patients without obvious genital anomalies, the diagnosis should also be pursued in patients with low plasma cholesterol concentrations. The diagnosis should also be pursued in patients who have a suggestive clinical phenotype but normal plasma cholesterol concentrations, because many of the methods in standard clinical use for measuring the plasma cholesterol concentration could yield false-negative results for patients with SLO syndrome. SLO syndrome can be diagnosed more specifically by measuring 7-dehydrocholesterol in plasma or cultured skin fibroblasts using gas chromatography or combined gas chromatography/mass spectrometry, followed by enzymatic analysis or genetic testing.

Efforts to treat SLO patients with supplemental cholesterol began immediately after recognition of the biochemical basis of the disease. Cholesterol supplementation could improve some aspects of the outcome, including the behavioral aspects of the disease, especially when treatment is begun very early in infancy.[42] The outcome appears to be better for patients with milder forms of the disease than for those with the severe forms (patients with significant defects in prenatal morphogenesis). However, the long-term intellectual outcome of this form of treatment remains poor.

Other defects of cholesterol biosynthesis have been identified subsequent to the discovery of the genetic basis of SLO syndrome, including Conradi-Hunermann syndrome, the rhizomelic form of chondrodysplasia punctata, lathosterolosis, desmosterolosis, Greenberg skeletal dysplasia, and CHILD (congenital hemidysplasia, ichthyosiform erythroderma, and limb defects) syndrome.[42,86]

Patients with Conradi-Hunermann syndrome have chondrodysplasia punctata and rhizomelic skeletal dysplasia. Chondrodysplasia punctata is a distinctive radiologic finding that refers to the abnormal pattern of punctate calcification of epiphysial cartilage and related tissues. This finding can be seen in some of the neonatal forms of peroxisomal disease (e.g., Zellweger syndrome) as well as SLO syndrome.

Rhizomelic dysplasia is a pattern of proximal limb shortening that is found in several malformation syndromes. Using the same analytic methods required to diagnose and evaluate patients with SLO syndrome, a previously unrecognized defect in sterol biosynthesis was identified in a fraction of patients with the rhizomelic form of chondrodysplasia punctata and in patients with Conradi-Hunermann syndrome.

Desmosterolosis has an osteosclerotic form of skeletal dysplasia and malformations similar to SLO syndrome. It appears that defects of sterol biosynthesis will prove to be responsible for a family of recognizable malformation syndromes, including many characterized by unusual skeletal dysplasia.

Congenital Disorders of Glycosylation

The congenital disorders of glycosylation (CDG) are a large group of clinically diverse inborn errors of metabolism caused by genetic deficiencies in the pathways of glycoconjugate biosynthesis. Glycoconjugates are defined as molecules in which carbohydrates are covalently linked with proteins (forming glycoproteins) or lipids (forming glycolipids). From a pathogenetic perspective, the CDG represent the reverse of the lysosomal storage disorders. The CDG are the consequence of enzyme deficiencies in the endoplasmic reticulum or Golgi that impair the biosynthesis of glycoconjugates, whereas the lysosomal storage disorders are primarily the consequence of enzyme deficiencies in the lysosome that impair the biodegradation of glycoconjugates.

The most common group of CDG impairs the synthesis of N-linked glycoproteins (i.e., the carbohydrates are attached to the protein through the amide group of asparagine). The prototypic form of this group of disorders is CDG type Ia (CDG-Ia), which has a characteristic pattern of dysmorphism plus multisystem disease.[50,64] The nomenclature for the CDG has been changed recently to reflect more directly the underlying enzyme deficiency. Thus, CDG-Ia is now referred to as *PMM2-CDG* (PMM2 refers to phosphomannomutase 2, the enzyme deficiency responsible for this disease). The older nomenclature is used in the chapter because it is more commonly used in the existing clinical literature.

Most patients with CDG-Ia come to medical attention in the neonatal period or in early infancy with neurologic

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abnormalities, including strabismus or other eye movement abnormalities, cardiac problems (cardiomyopathy and/or pericardial effusion), failure to thrive (usually attributed to poor feeding, vomiting, or diarrhea), hepatic dysfunction (mild elevations in liver enzyme values, hypoalbuminemia, and a characteristic coagulopathy), proteinuria, skeletal anomalies, recurrent infections (especially of the pulmonary tree), hypotonia, ataxia, and developmental delay. The patients typically have a characteristic pattern of dysmorphism that can be recognized in the neonatal period, which includes an abnormal pattern of fat distribution, with an especially prominent fat pad in the suprapubic area and buttocks, doughy skin texture, and inverted nipples.

Cranial imaging demonstrates cerebellar or olivopontocerebellar hypoplasia and a milder degree of cerebral hypoplasia. Microscopic examination of liver biopsy specimens reveals a characteristic form of fibrosis, whereas ultrastructural studies demonstrate a characteristic pattern of lysosomal inclusions and changes in the endoplasmic reticulum.

About 20% of patients with neonatal onset of the disease die in the first year of life as a result of cardiac failure, liver failure, or infection. Those who survive the first year of life manifest ataxia, peripheral neuropathy, retinal pigmentary degeneration, multiple endocrinopathies, skeletal dysplasia, strokelike episodes, and intellectual disabilities.

The characteristic biochemical marker of this disease is a generalized abnormality of glycosylation of circulating and cell membrane glycoproteins. The diagnosis of CDG-Ia is made by isoelectric focusing of transferrin, a circulating glycoprotein that contains two carbohydrate side-chains attached by N-glycosidic linkage to the protein backbone. Patients with CDG-Ia show an immunoisoelectric focusing pattern consistent with underglycosylation. The diagnosis is now being made by a modification of this method that uses mass spectrometry (see Specialized Biochemical Testing). The underlying cause of this syndrome is an autosomal recessive deficiency of phosphomannomutase 2 (PMM2), the major isozyme of phosphomannmutase. The diagnosis of CDG-Ia can be confirmed by measuring PMM2 activity in leukocytes or cultured skin fibroblasts or genetic analysis of the *PMM2* gene. There is no effective treatment for CDG-Ia disease.

Approximately three dozen forms of CDG have been described since type Ia was identified and the transferrin immunoisoelectric-focusing analysis was developed.[50,64] The immunoisoelectric-focusing test has provided a useful method for identifying additional forms of CDG with a remarkable range of clinical phenotypes. For example, CDG-Ib (also known as MPI-CDG; MPI denotes mannose-6-phosphate isomerase) is one of the most distinctive of these variants, because it manifests with hepatic dysfunction (abnormal liver function tests and coagulopathy) and protein-losing enteropathy rather than neurologic problems and is treatable (see Hepatic Dysfunction). The other CDG associated with impaired N-glycosylation are primarily neurologic disorders associated with severe developmental delay and mental retardation, but several of them also have distinguishing dysmorphic features.[64]

In addition to the forms of CDG that affect N-linked glycoproteins, several defects in the biosynthesis of O-linked glycoproteins (i.e., the oligosaccharide side-chains are attached to the protein through the hydroxyl group of serine or threonine) have been identified. Patients with these defects cannot be ascertained by the transferrin isoelectric-focusing test, because it only detects abnormalities of N-linked glycoconjugates. Several defects in O-linked glycoconjugation have been identified, including Walker-Warburg syndrome and muscle-eye-brain disease (a neuronal migration abnormality associated with malformations of the brain and eye, as well as congenital muscular dystrophy) (see Metabolic Seizures).[111] There is every reason to expect that additional disorders of N-linked and O-linked glycosylation will be identified in the future, particularly with the increased utilization of whole exome and whole genome sequencing.[50]

Lysosomal Storage Diseases

Most lysosomal storage disorders do not present in the neonatal period. However, several of these disorders do so, and they do so with a relatively limited spectrum of clinical features. The clinical manifestations of lysosomal storage disorders are the consequence of the disruption caused by storage of incomplete catabolism glycoconjugates. The particular set of clinical features associated with each disorder is determined by the chemical nature of the storage material, the quantity of material that accumulates, and the site(s) of storage.

The most extreme clinical feature is nonimmune hydrops fetalis or congenital ascites (see Prenatal Onset). Other clinical presentations may include dysmorphic (e.g., flattened nasal bridge, macroglossia, hypertrophic gums, coarse facies), ocular (cataracts, corneal clouding, glaucoma, cherry-red spot), cardiovascular (cardiomegaly, cardiomyopathy, arrhythmias, congenital heart failure), respiratory (hoarseness, recurrent respiratory infections), gastrointestinal (hepatomegaly, splenomegaly, cholestasis), skeletal (joint contractures, dysostosis multiplex, vertebral beaking, broad tubular bones), dermatologic (congenital ichthyosis, collodion infant), hematologic (anemia, thrombocytopenia), and endocrinologic (osteopenia, hyperparathyroidism) features. A differential diagnosis for the underlying storage disorder can be developed based on the pattern of features that is identified.

A sequence of laboratory studies, beginning with screening tests and progressing to more specialized testing (enzyme analyses and/or genetic testing), is required to diagnose the lysosomal storage disorders (see Biochemical Testing under the section The Abnormal Newborn Infant: Laboratory Phenotypes). An accurate and specific diagnosis is mandatory for developing a treatment plan. Effective treatment is now available for many of the lysosomal storage disorders, with options for enzyme replacement therapy, bone marrow transplantation, and stem cell transplantation.

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Unfortunately, effective treatment is not available for all of the lysosomal storage disorders.

Organic Acidurias

Two inborn errors of organic acid metabolism are associated with dysmorphic syndromes: mevalonate kinase deficiency (mevalonic aciduria) and multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II).

Mevalonate Kinase Deficiency

Mevalonic aciduria is caused by a rare defect, mevalonate kinase deficiency, which catalyzes an early step in cholesterol biosynthesis.[37] The disorder is classified herein as an organic aciduria, because it is diagnosed by urine organic acid analysis. It can also be classified as a peroxisomal single enzyme disorder, because mevalonate kinase is located within the peroxisome (see Peroxisomal Disorders).

The pathogenesis of this disorder is complex, because mevalonic acid has a role in several strategic pathways. In addition to its role as a precursor of cholesterol, mevalonic acid is a precursor of dolichol, which is required for glycoprotein biosynthesis; heme, which plays a key role in oxygen transport; and ubiquinone, a component of the respiratory chain (see Lactic Acidemia).

Mevalonate kinase deficiency is a highly pleiotropic disorder associated in the newborn period with dysmorphic features (e.g., nonspecific craniofacial anomalies, cataracts), hepatosplenomegaly, lymphadenopathy, diarrhea, hypotonia, and anemia. In severe cases, it leads to profound failure to thrive, developmental delay, and early death. Although the defect would be expected to lead to lactic acidosis because of decreased synthesis of ubiquinone and malfunctioning of the respiratory chain, lactic acidosis is not a common feature of the disorder. The hypocholesterolemia seen in these patients is generally mild. Alternatively, mevalonate kinase deficiency can produce a very different clinical phenotype, hyper IgD syndrome, which is one of the periodic fever disorders. Mevalonic aciduria and hyper IgD syndrome appear to be allelic forms of mevalonate kinase deficiency.

The characteristic diagnostic feature is mevalonic aciduria, which can be documented by urinary organic acid analysis. No effective treatment exists for this disorder, although corticosteroids might be of some benefit.

Multiple Acyl-CoA Dehydrogenase Deficiency

Multiple acyl-CoA dehydrogenase deficiency is also known as glutaric aciduria type II because of the very large urinary excretion of glutaric acid, a product of amino acid catabolism (lysine, hydroxylysine, and tryptophan) (see Newborn Screening).[105] The organic acid pattern also shows many other metabolites, and the disorder came to be called multiple acyl-CoA dehydrogenase deficiency when it was recognized that the pattern reflected secondary impairment of several flavin-dependent acyl-CoA dehydrogenases required for amino acid catabolism, choline metabolism, and fatty acid β-oxidation. The biochemical defect affects one of two proteins (electron-transfer flavoprotein dehydrogenase [ETFDH] or ETF ubiquinone oxidoreductase [ETFQO]) involved in transferring electrons generated by flavin-dependent acyl-CoA dehydrogenases to the respiratory chain.

Multiple acyl-CoA dehydrogenase deficiency is a clinically heterogeneous disorder. The severe neonatal form of this disease is associated with metabolic abnormalities (e.g., acidosis, hypoglycemia, ketosis, hyperammonemia) and in some cases dysmorphic features (e.g., craniofacial dysmorphism, polycystic kidneys, cerebral cortical dysplasia, intrahepatic biliary hypoplasia). The patients often die in early infancy from cardiomyopathy. Less severe later-onset forms can present at any age thereafter and do not have congenital malformations. The dysmorphic form of the disease is found more commonly in patients with ETFQO deficiency. It is unclear how ETFQO deficiency leads to dysmorphism.

The diagnosis is initially made by urine organic acid analysis and then confirmed by in vitro cell studies using cultured skin fibroblasts or genetic testing. There is no effective treatment for the severe neonatal form of the disease, but more mildly affected patients may improve with riboflavin supplementation.

Peroxisomal Disorders

Many peroxisomal disorders produce dysmorphic syndromes. The peroxisomal disorders are a highly diverse group of disorders, reflecting the metabolic diversity of the enzymes contained within this organelle.[114,135] In contrast to the lysosome, which primarily contains a large number of degradative enzymes, the peroxisome contains biosynthetic and catabolic enzymes. Many of these enzymes are involved in unusual oxidation reactions; the name of this organelle was derived from one such reaction involving hydrogen peroxide.

The peroxisomal disorders can be classified into two groups: defects of peroxisome biogenesis and defects affecting a single enzyme (see Table 90.8).[114,135]

Biogenesis Disorders

The first group consists of disorders associated with absent or severely reduced numbers of peroxisomes and multiple enzyme deficiencies. These disorders are caused by defects in peroxisomal biogenesis, which lead to impaired import of proteins and enzymes into the peroxisome.[114] The paradigm of this group of disorders is Zellweger syndrome, an autosomal recessive trait characterized by craniofacial dysmorphism, optic atrophy, renal cortical cysts, epiphyseal stippling, failure to thrive, polymicrogyria, severe psychomotor retardation, and early death. Epiphyseal stippling is an unusual radiographic finding of ectopic calcification found most characteristically in the ankle, patella, vertebrae, hips, and trachea (see Cholesterol Biosynthesis). Other peroxisomal assembly disorders include neonatal adrenoleukodystrophy, infantile Refsum disease, and rhizomelic chondrodysplasia punctata.

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Genetic studies have identified approximately 20 different genetic loci associated with peroxisomal biogenesis defects. Genetic complementation studies have shown that Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease represent allelic variants at many of these loci. Zellweger syndrome is the most severe variant, and infantile Refsum disease is the least severe variant. There is no cure or effective treatment for this group of disorders, although bile acid supplementation may be effective treatment for the gastrointestinal manifestations of this disorder.

Rhizomelic chondrodysplasia punctata is the consequence of mutations at one of the other loci involved in peroxisomal biogenesis. Peroxisomal deficiencies have been found only in the rhizomelic form of chondrodysplasia punctata, which is an autosomal recessive disorder characterized by severe shortening of the proximal extremities (hence the term *rhizomelic*), craniofacial dysmorphism, congenital cataracts, joint contractures, and severe psychomotor retardation. The skeletal abnormalities of this form of dwarfism are evident in the neonatal period. There is no treatment for this disorder.

Single-Enzyme Defects

The second group of peroxisomal disorders includes defects associated with a normal number of peroxisomes and a single enzyme deficiency. The best known disorder in this group is X-linked adrenoleukodystrophy, which does not produce dysmorphism and does not manifest in the neonatal period and, therefore, is not discussed further. However, several other peroxisomal monoenzymopathies with onset in the neonatal period have been recognized.[135] Several of these disorders have been identified in patients who appear to have the physical stigmata of Zellweger syndrome or its variants but have normal numbers of peroxisomes. The best characterized of these disorders are acyl-CoA oxidase deficiency, bifunctional enzyme deficiency, and thiolase deficiency. These three enzymes share a common biochemical role in peroxisomal (rather than mitochondrial) fatty acid oxidation and bile acid biosynthesis. Many of the dysmorphic and laboratory abnormalities associated with Zellweger syndrome and its variants, therefore, can be attributed to abnormal fatty acid metabolism or abnormal bile acid metabolism. Similarly, defects affecting the enzymes that catalyze plasmalogen biosynthesis produce a clinical phenotype that resembles rhizomelic chondrodysplasia punctata.

Several other single-enzyme deficiencies have been described that do not involve the peroxisomal pathways of fatty acid oxidation or plasmalogen biosynthesis. One of these disorders, mevalonic aciduria, is a defect in cholesterol biosynthesis and is described under the section Organic Acidurias.

Other Disorders

Vitamin K Metabolism

Vitamin K epoxide reductase deficiency is an autosomal recessive disorder that produces a phenocopy of the fetal warfarin embryopathy syndrome.[84] The enzyme deficiency is characterized by persistent coagulopathy, stippled epiphyses, nasal hypoplasia, brachydactyly with distal digital hypoplasia, and conductive hearing loss. Vitamin K epoxide reductase is the site of warfarin's pharmacologic action. The various dysmorphic features of fetal warfarin syndrome and vitamin K epoxide reductase deficiency are consequences of impaired activity of the vitamin K–mediated carboxylation reactions, which include proteins of the bone matrix and circulating coagulation factors. Vitamin K supplementation is an effective therapy for the coagulopathy associated with this disorder but might not be effective for the other manifestations because of their prenatal onset.

The Abnormal Newborn Infant: Laboratory Phenotypes

Biochemical Testing

The laboratory evaluation plays a strategic role in the differential diagnosis of the metabolic disorders of infancy. The laboratory investigation of these patients should be staged. It should begin with broadly focused screening tests, which are then followed by more specialized examinations. Laboratory findings helpful in the differential diagnosis of suspected metabolic disease are listed in Table 90.9. Further discussion of each of the findings in Table 90.9 is provided below and in the text accompanying other tables and figures provided elsewhere in this chapter.

Screening Studies

The precise composition of the metabolic screen varies from one institution to another. However, there should be a core of tests available at all institutions that care for sick neonates.[4,16] A suggested list of tests is presented in Table 90.10. These laboratory tests are chosen because they provide a relatively rapid, inexpensive evaluation for a wide range of disorders. It is strongly recommended that the specific details of collection and handling of all samples be clearly understood before samples are obtained and that there be collaboration with laboratory personnel throughout the process.

Blood Studies

A number of blood studies are indicated, many of which are routinely performed during the care of sick neonates.[4,16] The complete blood cell count should include examination of cell morphology and a differential cell count. Neutropenia and thrombocytopenia may be associated with a number of the organic acidemias, including isovaleric acidemia, methylmalonic acidemia, and propionic acidemia (see Hematologic Abnormalities).[124] Neutropenia may be found with glycogen storage disease type Ib, an uncommon variant of glucose-6-phosphatase deficiency.[131] This variant is caused by a defect of the glucose-6-phosphate translocase associated with the phosphatase rather than the phosphatase itself (see Hypoglycemia). Barth syndrome can also be a cause of neonatal neutropenia,[21] while Pearson syndrome

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TABLE 90.9 Laboratory Findings Helpful in the Differential Diagnosis of Suspected Metabolic Disease in Neonates

Finding	Diagnostic Considerations
Acidosis (see Figs. 90.1 and 90.2)	Fatty acid oxidation disorders Gluconeogenesis disorders Glycogen storage diseases Ketogenesis disorders Ketolytic disorders Krebs cycle disorders Mitochondrial disorders Organic acidemias
Alkalosis: respiratory	Urea cycle disorders
Alkalosis: metabolic	Steroid biosynthetic disorders
Hepatic dysfunction (see Table 90.5)	Amino acid disorders Bile acid biosynthesis disorders Carbohydrate disorders Fatty acid oxidation disorders Mitochondrial disorders Peroxisomal disorders Other
Hyperammonemia (see Box 90.2 and Fig. 90.5)	Fatty acid oxidation disorders Gluconeogenesis disorders Mitochondrial disorders Organic acidemias Urea cycle disorders
Hypoglycemia (see Table 90.17 and Fig. 90.3)	Fatty acid oxidation disorders Gluconeogenesis disorders Glycogen storage disease Ketogenesis disorders Organic acidemias
Ketosis/ketonuria (see Fig. 90.1 and Fig. 90.2)	Gluconeogenesis disorders Glycogen storage diseases Ketolytic disorders Mitochondrial disorders Organic acidemias
Pancytopenia	Organic acidemias Mitochondrial disorders
Proximal renal tubular dysfunction (see Table 90.14)	Amino acid disorders Carbohydrate disorders Mitochondrial disorders Organic acidurias

TABLE 90.10 Initial Laboratory Screening of Neonates With Suspected Metabolic Disease

Body Fluid	Laboratory Studies
Blood	Complete blood count Electrolytes Blood gases Lactate Glucose Ketones (α-hydroxybutyrate and acetoacetate) Ammonia Uric acid
Urine	Smell* Reducing substances pH Ketones 2,4-Dinitrophenylhydrazine (DNPH) (α-ketoacids)** Ferric chloride Sulfitest
Cerebrospinal fluid	Glucose Amino acid analysis*** Lactate (and pyruvate)*** Neurotransmitter analysis***

*A urine sample should be evaluated for an abnormal odor, which might be characteristic for a specific disorder and direct provisional treatment and further diagnostic studies.
**A qualitative screening test that might direct provisional treatment and further diagnostic studies.
***Additional metabolic studies may be indicated depending on the clinical circumstances, e.g., amino acid analysis and neurotransmitters in a patient with seizures.

is a mitochondrial DNA disorder that causes pancytopenia and/or sideroblastic anemia[121] (see Lactic Acidemia for further discussion of these disorders). Megaloblastosis may be found in disorders of purine biosynthesis, such as some rare forms of homocystinuria or orotic aciduria.

Electrolytes and blood gases are required to determine whether acidosis or alkalosis exists and, if so, whether the abnormality is associated with an increased anion gap. Lactate and pyruvate analysis should be measured to identify the nature of any excess anions (see Lactate and Pyruvate Analysis). Lactic acidemia may be present without frank acidosis.

Hypoglycemia is a frequent finding in sick neonates, especially premature infants, but is also a critical finding in some metabolic disorders. Hypoglycemia should be investigated further when it is severe, when accompanied by other signs of metabolic disease, or when it proves refractory to conventional therapy.

Ketones (i.e., β-hydroxybutyrate and acetoacetate) are useful in developing a differential diagnosis for newborns with hypoglycemia. In particular, nonketotic or hypoketotic hypoglycemia is the hallmark of defects of fatty acid oxidation.

The blood ammonia concentration should be determined in all neonates with evidence of unexplained lethargy and neurologic intoxication. Early recognition of the congenital hyperammonemias is crucial, because they are a rapidly progressive group of disorders that can quickly lead to irreversible damage after hours rather than days. Effective treatment is available for many of these disorders, but it must be instituted early in the course of the disease.

A blood uric acid test is a convenient screen for the few inborn errors of metabolism that are associated with hypouricemia or hyperuricemia. Type I glycogen storage disease is probably the most common inherited disorder associated with hyperuricemia (see Hypoglycemia), whereas xanthine

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TABLE 90.11 Characteristic Urinary Findings in Inborn Errors of Metabolism

Test	Disorder
Reducing substances	Galactosemia Hereditary fructose intolerance Tyrosinemia type I
DNPH*	Maple syrup urine disease Phenylketonuria Tyrosinemia type I
Ferric chloride	Phenylketonuria Tyrosinemia type I
Ketonuria	Organic acidemias
Ferric chloride	Phenylketonuria Tyrosinemia type I
Sulfitest	Sulfite oxidase deficiency

*DNPH= 2,4-dinitrophenylhydrazone.

oxidase deficiency associated with molybdenum cofactor deficiency causes hypouricemia (see Metabolic Seizures).

Urine Studies

A urine sample should be sent for metabolic screening using simple colorimetric agents or strips, if such testing is still available at one's institution (Table 90.10 and Table 90.11).[4,16] However, this approach to testing has been abandoned or replaced by more specialized forms of testing in most institutions and may no longer be possible to obtain. In this event, a urine specimen should be sent directly for the more specialized testing. In either case, an aliquot of urine should be collected, covered, and set aside by the infant's incubator when possible. After a few hours at room temperature, the specimen should be smelled for evidence of an unusual odor. Several inborn errors of metabolism, especially the organic acidurias, are associated with characteristic odors (see Table 90.7).

Urine specimens should be tested for reducing substances, which include principally the monosaccharides (i.e., simple sugar molecules). The Clinitest reaction detects excess excretion of galactose and glucose but not fructose. False-positive reactions are found with ampicillin and related penicillin derivatives and with some other drugs that are excreted as their glucuronide conjugates. A specimen that shows a positive reaction with the Clinitest reaction should be investigated further by means of the Clinistix reaction (i.e., glucose oxidase), which is specific for the monosaccharide glucose. A specimen with positive Clinitest and negative Clinistix results should be analyzed specifically for galactose. It is important to note that in the United States the Clinitest and Clinistix testing methods have not been available in recent years, following cessation of production of these tests. We include this testing in this chapter as it may still be available in other countries worldwide and may again become available in this country.

The urine pH should be determined to characterize the renal response to an alteration in blood pH. In the face of a significant acidemia, the kidneys should produce an acidic urine (pH <5). A renal acidification disorder should be considered in the absence of an appropriate urine pH.

Spot tests may be used to detect excessive urinary excretion of ketones, α-ketoacids, or other metabolites. Ketonuria should be investigated, especially in patients with hypoglycemia. The Acetest or Ketostix reactions are used to detect acetone and acetoacetate (β-ketoacid), whereas the 2,4-dinitrophenylhydrazone (DNPH) test and the ferric chloride test are complementary methods used to detect α-ketoacids. The Sulfitest detects excessive sulfite excretion and can be useful for screening patients with a hypoxic-ischemic encephalopathy–like picture who are suspected of having sulfite oxidase deficiency or molybdenum cofactor deficiency. The Sulfitest should be performed on freshly obtained urine specimens, because it otherwise has a significant false-negative rate.

Cerebrospinal Fluid Studies

Many sick infants undergo lumbar puncture for CSF analysis as part of a sepsis evaluation. In addition to obtaining the standard samples for CSF glucose and protein analysis, additional samples for more specialized testing, such as amino acid analysis, lactate (and pyruvate) analysis, and neurotransmitter analysis should also be obtained if clinically indicated for encephalopathy or seizures.[48] In certain cases, blood samples should be collected at the same time as the lumbar puncture is performed to permit comparison of blood and CSF concentrations. For example, concurrent plasma and CSF amino acid measurements (specifically including glycine) are required for the diagnosis of nonketotic hyperglycinemia, whereas concurrent plasma and CSF glucose measurements are required for the diagnosis of GLUT1 deficiency (see Metabolic Seizures).

Specialized Biochemical Testing

Screening studies help determine whether further metabolic testing is indicated and, if so, what testing should be done next (Table 90.12). In general, the more specialized tests require relatively sophisticated equipment and personnel to perform and interpret, take longer to perform (sometimes days to weeks), are more expensive, and are usually available in only a few centers. All physicians who might care for a sick neonate with a suspected inborn error of metabolism should develop their own referral system for patients with various metabolic abnormalities. It is a good idea to set up a referral system in advance of a specific emergency so that appropriate referral can be obtained more easily when the time comes.

Because not all patients require transfer or tolerate transfer to a tertiary care center, plans should also be on hand for collecting samples for various specialized tests. It is truly unfortunate when the often extraordinary and well-intentioned efforts of those caring for a sick newborn infant are subverted by improper collection or handling of samples.

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TABLE 90.12 Specialized Laboratory Tests That May Be Required for the Care of Neonates With Suspected Metabolic Disease

Body Fluid or Tissue	Laboratory Tests
Blood	Acetoacetate and β-hydroxybutyrate * α-Aminoadipic semialdehyde (also known as Δ^1-piperideine-6-carboxylate) Amino acids* Carnitine (total, free, and acylcarnitine profile)* Creatine and guanidinoacetate 7-Dehydrocholesterol Galactose-1-phosphate Homocysteine, total Lactate and pyruvate* Methylmalonic acid Tests for congenital disorders of glycosylation* • Carbohydrate deficient transferrin analysis • N-Glycan profile Tests for peroxisomal disorders* • Very long-chain fatty acids • Phytanic acid Uric Acid
Urine	Acylglycines Amino acids* α-Aminoadipic semialdehyde (also known as piperideine-6-carboxylate) Carnitine (total, free, and acylcarnitine profile)* Creatine and guanidinoacetate Methylmalonic acid Organic acids* Orotic acid Pyrimidine panel Purine panel S-sulfocysteine Succinylacetone Tests for lysosomal storage disorders* • Mucopolysaccharides • Oligosaccharides (including free sialic acid)
Cerebrospinal fluid	Amino acids* Lactate and pyruvate* Neurotransmitters Tetrahydrobiopterin and related metabolites Tetrahydrofolate
Other	
Cultured skin fibroblasts	Metabolite analysis Enzyme analysis Genetic analysis
White blood cells	Metabolite analysis Enzyme analysis Genetic analysis
Other tissues (e.g., liver)	Metabolite analysis Enzyme analysis Genetic analysis

*These analyses are discussed in the subsection Specialized Biochemical Testing under the section The Abnormal Newborn Infant: Laboratory Phenotypes. The unmarked laboratory tests are discussed with their associated disorders elsewhere in this chapter.

Detailed requirements for collection and handling of samples for various metabolic analyses should be available in the nursery, and they should be kept in a place where they can be found in an emergency.

The distinction between a screening study and a specialized follow-up test is not always clear. In some circumstances, the physician would proceed directly to performing a specialized study. For example, a urinary organic acid analysis should be performed as soon as a neonate is thought to have a metabolic acidosis or has an unusual odor typical of one of the neonatal organic acid disorders. Similarly, it is generally best to perform some of the specialized studies during an episode of acute metabolic decompensation, such as hypoglycemia, when they are most likely to be informative rather than waiting until the results of the screening tests become available. As a rule, the sequence of ordering tests should be compressed in an acutely ill patient.

Amino Acid Analysis

The most commonly performed of the specialized studies is probably quantitative plasma and urinary amino acid analysis.[4,15,16] Some laboratories provide a qualitative amino acid screening study performed by paper or thin-layer chromatography as part of their screening protocol. Although this study may be useful, it does not substitute for a quantitative determination when the clinical findings suggest a disorder that is reflected in an abnormal amino acid pattern (Table 90.13). In most cases, a complete quantitative analysis is required, whereas in other situations, specific amino acids should be the focus of attention.

For example, when evaluating a patient with hyperammonemia, it is important to inform the laboratory personnel so that they will look for argininosuccinic acid and its anhydrides; otherwise, these metabolites could be overlooked or misinterpreted. This recommendation to inform the laboratory of the clinical context of the investigation applies equally to the other specialized studies discussed here.

Quantitative amino acid analysis of CSF is not usually indicated, but it should be performed when appropriate, such as in the context of a hypotonic newborn infant who has seizures and an elevated plasma glycine level that is not accompanied by acidosis or ketosis. These findings suggest the diagnosis of nonketotic hyperglycinemia. The plasma

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TABLE 90.13 Neonatal-Onset Inborn Errors of Metabolism Characterized by Abnormal Plasma Amino Acid Patterns

Disorder	Finding
Amino Acid Disorders	
Glutamine synthetase deficiency	↓ Glutamine (Note: Plasma glutamine may be normal; CSF glutamine consistently ↓)
Maple syrup urine disease	↑ Isoleucine, leucine, valine, and allo-isoleucine
Nonketotic hyperglycinemia*	↑ Glycine (Note: Plasma CSF glycine may be normal, but CSF glycine/plasma glycine ratio consistently ↑)
Phenylketonuria	↑ Phenylalanine
Serine biosynthesis disorders	↓ Serine (↓ glycine) (Note: These abnormalities may be missed in blood samples but are more prominent in CSF samples)
Sulfite oxidase deficiency / molybdenum cofactor deficiency	↑ S-Sulfocysteine (Note: This abnormality is more prominent in urine and CSF than blood)
Tyrosinemia type I	↑ Tyrosine, methionine
Lactic Acid Disorders	
Mitochondrial disorders	↑ Alanine (± ↑ proline)
Pyruvate carboxylase deficiency	↑ Alanine, citrulline, lysine
Pyruvate dehydrogenase deficiency	↑ Alanine
Organic Acidemias	
Propionic acidemia	↑ Glycine
Isovaleric acidemia	↑ Glycine
Methylmalonic acidemia	↑ Glycine
Urea Cycle Disorders	
Urea cycle disorders	↑ Glutamine (±) plus …
Arginase deficiency	↑ Glutamine (±) plus ↑↑ Arginine
Argininosuccinic aciduria†	↑ Glutamine (±) plus ↑ ASA, ↑ citrulline
Carbamoylphosphate synthetase deficiency	↑ Glutamine (±) plus ↓ Citrulline, ↓ arginine
Citrullinemia type I	↑ Glutamine (±) plus ↑↑ Citrulline, ↓ arginine
Ornithine transcarbamylase deficiency	↑ Glutamine (±) plus ↓ Citrulline, ↓ arginine
N-Acetylglutamine synthetase deficiency	↑ Glutamine (±) plus ↓ Citrulline, ↓ arginine
Urea Cycle–Associated Amino Acid Transport Disorders	
Citrin deficiency (aka: citrullinemia type II)	↑↑ Citrulline, arginine, threonine (and threonine-to-serine ratio)
Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome	↑↑ Ornithine and ↓ citrulline; ↑ urine homocitrulline

ASA, Argininosuccinic acid (including its two anhydrides); CPS, carbamyl phosphate synthetase; OTC, ornithine transcarbamylase; PC, pyruvate carboxylase; ↑, increased; ↑↑ very increased; ↓, decreased; ±, with or without.
*Glycine concentrations are elevated in plasma and, to an even greater extent, in the cerebrospinal fluid.
†ASA is present in very large amounts in urine but is only marginally increased in plasma because of efficient renal clearance.

glycine level may be only minimally elevated in some patients with nonketotic hyperglycinemia. The biochemical hallmark of this disorder is an elevated ratio of CSF glycine to plasma glycine.

Carnitine Analysis

Plasma and urinary carnitine analysis is indicated for patients who show evidence of unexplained acidosis, hyperammonemia, hypoglycemia, or ketonuria when there might be a disorder accompanied by an abnormal organic aciduria, defect in fatty acid oxidation, or respiratory chain defect. In these settings, carnitine insufficiency or frank carnitine deficiency can develop.

Many of the organic acidurias or fatty acid oxidation defects are associated with overproduction of specific acyl-CoAs (e.g., CoA esters of an acid molecule). As they accumulate, these acyl-CoAs are transesterified with free carnitine to form acylcarnitines and free CoA. Many of these acylcarnitines then leave the cell, circulate in the bloodstream, and are ultimately excreted in the urine. If the production of a particular acyl-CoA is very large, comparably large amounts of the corresponding acylcarnitines are excreted in the urine, resulting initially in intracellular carnitine insufficiency and ultimately in carnitine deficiency (e.g., secondary carnitine deficiency). Abnormal acylcarnitines can also inhibit renal reabsorption of carnitine. Carnitine analysis should be performed whenever possible on samples of plasma and urine obtained concurrently.

Carnitine analysis should include measurement of total carnitine, free carnitine, and total acylcarnitines, as well as the individual acylcarnitine profile. Measurement of total carnitine, free carnitine, and total acylcarnitines will help

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determine whether the patient has carnitine insufficiency or deficiency, whereas a quantitative acylcarnitine profile will help identify which, if any, acyl-CoA are accumulating and hence identify the locus of the patient's metabolic defect.

Lactate and Pyruvate Analysis

Blood lactate analysis is indicated when acidosis or an increased anion gap is found, and it is used to investigate the possibility of a defect in carbohydrate metabolism, fatty acid oxidation, organic acid metabolism, or the respiratory chain (see Lactic Acidemia).[4,16] Lactate should also be measured in patients who have skeletal myopathy, cardiomyopathy, encephalopathy, retinal pigmentary deposits, neutropenia, or thrombocytopenia and in patients with hypoglycemia or ketosis, even if they do not have frank acidosis. Many inborn errors of metabolism result in lactic acidemia without lactic acidosis.

When possible, the concentration of lactate and pyruvate should both be determined. These metabolites should be measured concurrently in blood and CSF, when a lumbar puncture is being performed for other reasons or the patient's presentation suggests the possibility of a CNS-specific defect. Measuring CSF lactate and pyruvate concentrations does not generally add useful information when the blood lactate and pyruvate concentrations have already been found to be elevated. Lactic acid is the reduction product of pyruvic acid. The lactate-to-pyruvate (L:P) ratio is a useful measure of the intracellular redox potential and is useful in approaching the differential diagnosis of the lactic acidemias (see Lactic Acidemia). Lactic acidemia and pyruvic acidemia are often accompanied by lactic aciduria and pyruvic aciduria, which can be detected, but poorly quantitated, by urinary organic acid analysis.

The significance of the finding of lactic acidemia can be investigated further by reviewing a quantitative plasma amino acid analysis for evidence of an increased alanine concentration, because alanine is the transamination product of pyruvate. Therefore, the evaluation for lactic acidemia should include measurement of lactate, pyruvate, and alanine.

Urine Organic Acid Analysis

Urinary organic acid analysis was originally used to document defects in amino acid metabolism distal to the removal of the amino group from the amino acid. As currently performed, urinary organic acid analysis detects and quantitates a large number of metabolites that represent intermediates of carbohydrate and fatty acid oxidation, as well as those of amino acid catabolism.[1,4,15,16,57] Accordingly, urinary organic acid analysis is a highly useful study and is performed in a wide variety of clinical contexts. Urinary organic acid analysis is indicated for patients who have unexplained acidosis, lactic acidemia, hyperammonemia, hypoglycemia, or ketonuria.

A partial list of the organic acidurias with onset in the neonatal period is presented in Box 90.1. The organic acid disorders are called *-emias* or *-urias* for historical reasons.

• BOX 90.1 Organic Acidurias With Onset in the Neonatal Period

- 3-Hydroxyisobutyric aciduria
- 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
- Isovaleric acidemia*
- 3-Ketothiolase deficiency
- Maple syrup urine disease
- 3-Methylcrotonyl-CoA carboxylase deficiency
- Methylmalonic aciduria*
- Mevalonic aciduria
- Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II)
- Multiple carboxylase deficiency (biotinidase deficiency; holocarboxylase synthetase deficiency)
- Propionic acidemia*
- Pyroglutamic acidemia
- Succinyl-CoA 3-ketoacid transferase deficiency

*Most commonly seen disorders.

In most cases, abnormal metabolites accumulate in blood and urine in these disorders, and the terms *organic acidemia* and *organic aciduria* are used interchangeably in this chapter. Isovaleric acidemia, methylmalonic acidemia, and propionic acidemia appear to be the most common of the organic acid disorders that appear in the newborn period. The incidence of the organic acidemias that are detected by MS/MS newborn screening differs from the incidence of disorders that appear in the newborn period. Urinary organic acid analysis is generally performed by gas–liquid chromatography or, with increasing incidence, by combined gas–liquid chromatography and mass spectrometry.

Tests for Congenital Disorders of Glycosylation

The possibility of a CDG syndrome should be suspected in a newborn infant with the characteristic dysmorphism of CDG-Ia (e.g., abnormal fat pads of the buttocks and inner thighs, orange peel skin, inverted nipples) or a child with pericardial effusion or cardiomyopathy, hepatomegaly, diarrhea, an increased bleeding tendency or thrombosis, or neurologic abnormalities (such as strabismus, hypotonia, and developmental delay). Several clinical forms of CDG syndrome have been described, each having a different genetic basis. Fortunately, most of the disorders described can be diagnosed using the transferrin immunoisoelectric-focusing assay or the mass spectrometric adaption of this method to identify patients with an abnormal pattern of glycosylation.[50,64] Patients found to have a positive test result will require further testing to determine their particular disorder, via either enzymatic analysis or molecular genetic testing.

Tests for Lysosomal Storage Disorders

Patients with coarse facial features, corneal clouding, cataracts, hepatomegaly, or dysostosis multiplex should be evaluated for a possible lysosomal storage disorder. Urine screening tests are available for quantitation of

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mucopolysaccharide excretion. The test results should be interpreted with caution, because many of the tests have significant false-positive and false-negative rates. If the quantitative mucopolysaccharide screening test result is positive, chromatographic separation and quantification of the individual mucopolysaccharides may be performed. Alternatively, selective analysis of the enzymes involved in mucopolysaccharide metabolism whose deficiency would be consistent with the patient's clinical phenotype can be performed as the next step. Finally, enzyme analyses can be performed using white blood cells or cultured skin fibroblasts, as well as genetic testing.

Patients with clinical features suggestive of an oligosaccharidosis can be evaluated using one of the available chromatographic systems for separating and quantitating various oligosaccharides. A positive result can be investigated by performing a selective battery of enzyme assays using white blood cells or cultured skin fibroblasts, depending on the particular disorder that is suspected, or by using genetic testing.

Tests for Peroxisomal Disorders

Peroxisomal disorders include defects of biogenesis (group 1) and defects of individual enzymes (group 2). Almost all of the disorders in group 1 (Zellweger syndrome and its milder variants) and many of the disorders in group 2 (defects of peroxisomal fatty acid oxidation: acyl-CoA oxidase deficiency, bifunctional enzyme deficiency, and thiolase deficiency) have impaired very-long-chain fatty acid oxidation and are characterized by increased plasma concentrations of very-long-chain fatty acids (chain length longer than 22 carbons). In most cases, measurement of individual plasma very-long-chain fatty acids is the most useful single measure of peroxisomal function and serves as a useful initial test for these disorders.[135] Very-long-chain fatty acids can also be measured in cultured fibroblasts, thereby permitting premortem or postmortem diagnosis from a skin biopsy specimen established in culture.

Other measurements are required to diagnose some forms of peroxisomal disease, such as rhizomelic chondrodysplasia punctata, and to distinguish between the various forms of peroxisomal disease. These additional tests include plasma phytanic acid analysis, erythrocyte plasmalogen analysis, and plasma dihydroxycholestanoic and trihydroxycholestanoic acid analysis. Mevalonic aciduria is diagnosed with urinary organic acid analysis. More definitive testing, including complementation analysis, assays of peroxisomal fatty acid β-oxidation, or genetic testing, is required to establish a specific diagnosis.[114,135]

Definitive Biochemical Diagnosis

Judicious application of the various biochemical tests described in the preceding will in many cases, but not all, allow the physician to establish a diagnosis. However, it is important to remember that the diagnosis must be confirmed by definitive testing, because the same metabolite pattern (i.e., biochemical phenotype) can be associated with more than one inborn error of metabolism, which might differ in their treatment, prognosis, and inheritance pattern. Definitive diagnosis is generally done by specific enzyme analysis or genetic testing. Relatively few laboratories perform the specific enzyme study that is required to confirm the diagnosis of a particular rare genetic disorder. As a rule, these enzyme analyses are time consuming, relatively difficult to perform, and expensive. Specific enzyme analysis can often be done using blood cells (most commonly, white blood cells) but often require cultured skin fibroblasts or other tissue specimens.

It is, therefore, not surprising that laboratories performing these studies prefer (or require) evidence that there is a significant likelihood that the test being performed will demonstrate an abnormality. It behooves the physician caring for a sick neonate to obtain the preliminary evidence suggesting that a specific defect is likely before proceeding to specific enzyme analysis. This is often best done in consultation with local experts in metabolic disease, but when such expertise is not available, the laboratories performing such assays usually are willing to give advice that will ultimately maximize the benefit of their efforts.

Genetic Testing

The discussion in this chapter focuses almost exclusively on the classic methods of biochemical genetics, which include analysis of metabolites, structural macromolecules, and enzymes. For the most part, little consideration is given to the role that recent advances of molecular genetics are playing in facilitating the diagnosis, improving our understanding of the pathogenesis, and expanding the possibilities for treatment of inborn errors of metabolism. This has been an intentional omission, because a discussion of the tools of molecular genetics is presented in Chapter 10, and molecular diagnosis is generally performed after a clinical diagnosis has been established biochemically or enzymatically. The reasons for this omission notwithstanding, there are five clinical circumstances in which molecular testing has traditionally come to the forefront, and the clinician should be aware of them.

First, diagnosis can be accomplished easily and rapidly by mutational analysis for diseases that are characterized by relative genetic homogeneity (i.e., a few mutations account for most cases of the disease). Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency provides an excellent example. Approximately 90% of the disease-causing alleles found in affected patients have the same mutation (e.g., an A to G change at nucleotide 985). Second, diagnosis can be provided by mutational analysis but not by conventional biochemical studies. This is the situation for many disorders caused by mutations of the mitochondrial DNA (mtDNA), which are not amenable to metabolic approaches, such as errors in the mitochondrial mRNA or tRNA genes. DNA-based mutation analysis can provide a specific diagnosis for disorders associated with mutations in these genes, whereas classic metabolite or enzymatic studies cannot. Third, mutation analysis can provide useful prognostic information. For

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example, in cases of galactosemia ascertained by newborn screening, mutation analysis can assist the clinician in determining the need to restrict the patient's dietary galactose intake. Fourth, mutation analysis of postmortem samples can be used to diagnose the condition in patients who have died without a diagnosis.[72,140] Fifth, knowledge of a patient's mutation can sometimes be used to direct therapy, as well as facilitate genetic counseling of other family members and prenatal testing.

In recent years, the scope and sensitivity of genetic testing has expanded remarkably with the development of new technologies (see Chapter 10). Classical sequence analysis and deletion/duplication analysis permitted analysis of only one gene at a time. This approach had two readily apparent limitations: (1) the patient in fact has a mutation in the gene tested, but the testing methods cannot not detect all mutations in a particular gene, and (2) the patient does not have a mutation in the gene tested but does have a mutation in another related gene. Ways of circumventing limitation 1 has been addressed further in Chapter 10. Limitation 2 has been addressed by developing more sophisticated methods of concurrent mutation analysis. The simplest approach was to initiate classical analysis for more than one gene. This approach worked well but was limited by its expense (the total cost was roughly equal to the cost of sequencing one gene times the total number of genes analyzed).

The next advance was the development of next generation sequencing (NGS), which performs parallel sequencing of a large number of genes. Large gene panels (usually including ten to several hundred genes) are commercially available to evaluate patients who have a particular symptom or sign. Large gene panels are currently available for a wide variety of disorders, including neonatal seizure, cardiomyopathy, cholestatic liver disease, hyperinsulinemic hypoglycemia, hyperammonemia, mitochondrial disorders, peroxisomal assembly disorders, and many more. The results of these panels are, in many cases, available within just a few weeks. These panels provide a diagnosis for many patients, but not all patients. The proportion of patients who receive a diagnosis from these panels depends on the particular panel but is generally greater than 50%.

In the case of a negative test result, further genetic testing should be considered, especially when the differential diagnosis for the patient's constellation of clinical features is broad. Further testing to be considered should include whole exome sequencing (WES) or whole genome sequencing, which both evaluate for approximately 25,000 genes. The diagnostic yield of whole exome sequencing of neonates is approximately 50%, depending on the patient's phenotype, the extent of prior metabolic and genetic testing, and whether the patient's parents were also analyzed (trio analysis). It is too early to provide an estimate for the yield for whole genome sequencing.

The various forms of gene and exome panels are often a more cost-effective approach to testing than sending successive rounds of individual gene tests, especially when a clear diagnosis is not identified by extensive biochemical testing. As discussed above for single gene testing, NGS of large gene panels may provide including a diagnosis early in the course of the disease to guide treatment, to allow physicians to better understand the expected disease course and prognosis, and to permit genetic counseling of other family members. These benefits have been demonstrated for patients in the neonatal intensive care environment.[72]

Postmortem Evaluation

Although the management of a very sick newborn who is at imminent risk of dying is a familiar issue in neonatal care, certain points must be considered in the case of a newborn infant with a suspected inborn error of metabolism.[13,30,94] Samples of blood, urine, and, if possible, CSF should be obtained before death. Serum and plasma samples should be obtained; a total of 10 mL should be collected, aliquoted, and saved for metabolite studies and for preparation and storage of DNA. As much urine as possible should be saved. All samples should be frozen to −20°C or below.

A thoughtful but direct discussion should be arranged before death with the parents, during which the reasons for a postmortem examination are presented. It should be explained that an autopsy performed for the purpose of investigating a suspected metabolic disorder may be different from autopsies performed for other purposes in that the autopsy examination must be performed within 4 hours of death, preferably within 2 hours. This urgency is dictated by the need to obtain tissue before postmortem changes compromise the integrity of enzyme systems and metabolite concentrations.

If the performance of a complete autopsy is not acceptable to the parents, the option of a limited autopsy should be discussed.[20,30,94] The selection of tissues or organs requested in a limited postmortem examination vary with the clinical situation but in general should include specimens of liver and skeletal muscle and/or at least a skin biopsy specimen for establishing a fibroblast cell culture. These specimens can be obtained with minimal disfigurement. Several small (1 cm^3) specimens of liver and skeletal muscle should be obtained. Similar specimens of heart tissue should be obtained from patients with cardiomyopathy. If permission for a limited postmortem examination is refused, permission for premortem percutaneous liver and open skeletal muscle biopsies should be sought; these procedures can be performed at the bedside. Once obtained, all tissue specimens should be stored at −70°C for future study.

Similar arrangements should also be made for neonates who die suddenly in the hospital or at home, because inborn errors have become a well-recognized cause of sudden death. Approximately 2% of sudden, unexpected deaths in the neonatal period are the consequence of a metabolic disorder.[25] It is understandably more difficult to make arrangements that comply with the recommendations for the sick infant, but experience has shown that a modified protocol can be successful.[94] These modifications are dictated in part

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by the logistics of arranging for a prompt autopsy after an unexpected death, but equally important are the requirements dictated by the differential diagnosis of inborn errors that cause sudden death of the neonate.

The diagnostic entities that have to be considered primarily include defects in energy metabolism: glycogen storage diseases, defects in fatty acid oxidation, and electron transport chain defects. The most common pathogenetic mechanism that leads to sudden death in these disorders is cardiomyopathy or cardiac arrhythmia, which is the consequence of myocardial energy deficiency or disruption of the electrical conduction system by toxic metabolites that accumulate in these disorders.

Practically, recommendations are that a full autopsy be done within 72 hours of death. The autopsy should include particular attention to examination of the heart, liver, and skeletal muscle for evidence of glycogen or lipid storage. The following specimens should be obtained and stored frozen: liver, urine from the bladder (no matter how small the sample size), and bile from the gallbladder.[13,20,94] A skin biopsy should be obtained for establishing a cell line of cultured fibroblasts.

The choice of metabolic studies to perform is dictated by the clinical history and the results of the standard pathologic evaluation. For example, findings consistent with a possible fatty acid oxidation defect should include measurement of glucose, free fatty acids, and total and free acylcarnitines in the liver specimen; organic acids and an acylcarnitine profile in urine; and an acylcarnitine profile in bile. The possibility of an inborn error of metabolism can also be investigated by genetic testing of blood cells, cultured skin fibroblasts, or frozen tissue specimens. For example, autopsies performed for patients who died of sudden unexpected death in the neonatal period or infancy were evaluated for a possible inborn error of fatty acid oxidation using standard biochemical methods plus next generation sequencing (NGS) of a panel of 13 genes known to cause fatty acid oxidation disorders.[140] Genetic testing confirmed the biochemical results and, in some cases, established the diagnosis for patients with indeterminate biochemical results. This approach of combining pathologic finding, biochemical studies, and current genetic technology to postmortem diagnosis is expandable to many other circumstances.

Approaches to Specific Abnormal Laboratory Findings

Most newborn infants with an inborn error of metabolism have one or more of only a handful of strategic laboratory findings: metabolic acidosis, lactic acidemia, hypoglycemia, and hyperammonemia. An approach to differential diagnosis of inborn errors with each of these findings is now presented. As with all attempts to develop a useful approach to differential diagnosis, it is important to remember that the algorithm never quite fits all patients. Such probably will be the case for these algorithms as well because of the range of diagnostic possibilities and the considerable genetic heterogeneity that characterizes all inborn errors of metabolism. Nevertheless, the approaches presented should serve as useful first approximations.

Disorders Characterized by the Absence of Metabolic Acidosis, Lactic Acidemia, Hypoglycemia, and Hyperammonemia

There are many inborn errors of metabolism that do not generally manifest with any of the strategic laboratory findings mentioned in the preceding (e.g., metabolic acidosis, lactic acidemia, hypoglycemia, hyperammonemia). Among the most important of these inborn errors is maple syrup urine disease (MSUD), which is a cause of severe metabolic encephalopathy, and the neurotransmitter defects and related disorders, which are important causes of neonatal seizures. The neurotransmitter defects and related disorders are discussed earlier in this chapter (see The Abnormal Newborn Infant: Clinical Phenotypes). Maple syrup urine disease was not discussed in detail previously and is presented in the following section.

Maple Syrup Urine Disease

Maple syrup urine disease is an inborn error of branched-chain amino acid metabolism caused by branched-chain α-ketoacid dehydrogenase deficiency, which impairs isoleucine, leucine, and valine metabolism.[116,138] The classical clinical variant of this disorder manifests in the neonatal period and can lead to serious consequences if it is not recognized and treated quickly (i.e., within the first week of life). Patients with the severe neonatal form of MSUD are generally normal for the first 2 or 3 days of life but then develop lethargy, hypertonia with extreme opisthotonic posturing (even when unconscious), seizures, and progressive encephalopathy, which may lead to death. The disease does not generally produce metabolic acidosis, lactic acidemia, hypoglycemia, hyperammonemia, ketosis, or abnormal acylcarnitines. If untreated, however, it may lead to hypoglycemia and ketoacidosis. If the patient recovers from this initial episode, the disorder can be characterized by growth failure, mental retardation, and recurrent episodes of metabolic decompensation.

Newborn screening programs for MSUD are based on the detection of hyperleucinemia. There are relatively few false-positive results for healthy full-term infants. The rate of false-positive and false-negative results has been reduced by the use of MS (mass spectrometry)/MS technology, which can concurrently measure the concentrations of isoleucine, leucine, and valine, thereby permitting the use of amino acid ratios to more reliably identify at-risk newborns. However, a positive newborn screening result might not be received until after the newborn has already become ill and is in the neonatal intensive care unit. In either case, response to a positive screening result must be rapid.

Bedside detection of the characteristic odor of maple syrup by an alert parent or nurse might be the first clue to the diagnosis of this disorder. Once suspected, the diagnosis may be provisionally confirmed by a rapid screening test,

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the dinitrophenylhydrazine (DNPH) test, which detects the α-ketoacids that are formed from the isoleucine, leucine, and valine (see Screening Studies under Biochemical Testing). The diagnosis should then be established by plasma amino acid analysis and urine organic acid analysis. The characteristic plasma amino acid findings are increased concentrations of leucine, isoleucine, valine, and allo-isoleucine (the presence of allo-isoleucine is pathognomonic for MSUD), and the characteristic urinary organic acid pattern (see Specialized Biochemical Testing). Maple syrup urine disease is not associated with abnormal carnitine metabolism. Definitive enzyme analysis can be performed with leukocytes or cultured skin fibroblasts, but treatment should not be delayed pending definitive diagnosis.[116,138]

Treatment of an acutely ill newborn should include hypercaloric nutritional support that contains high concentrations of glucose (>10 mg/kg per minute); an insulin infusion (0.05-0.10 units/kg per hour) to avoid hyperglycemia; and a leucine, isoleucine, and valine-free protein source (intravenous, if available, or enteral, using specially prepared formula). The rationale for this treatment is to suppress protein catabolism (which will increase production of leucine and the other toxic branched-chain amino acids) and induce an anabolic state (which will stimulate de novo protein synthesis and thereby decrease the concentration of the free branched-chain amino acids). The concentrations of isoleucine and/or valine may become too low on this regimen and limit the rate of new protein synthesis. The progress of treatment must, therefore, be monitored frequently to determine when the branched-chain amino acids (isoleucine, valine, and ultimately leucine) must be added back to the diet. The offending amino acids should be carefully reintroduced, either parenterally or orally. In extreme cases, this approach may not reduce the leucine concentration and correct the other metabolic abnormalities rapidly enough, and hemodialysis may be required (see Metabolic Acidosis).

Treatment has prolonged the life expectancy and the quality of life for patients with MSUD, but the prognosis for intellectual outcome remains guarded, because treatment is often not initiated until after onset of the first metabolic crisis and because most patients experience recurrent episodes of ketoacidosis.[116,138] The strategic factor that correlates with ultimate intellectual outcome is the age at initiation of therapy. Initiation of therapy after 10 days of age for a patient with the severe neonatal form of MSUD is rarely associated with normal intellectual outcome.

Metabolic Acidosis

Metabolic acidosis is a common laboratory finding in sick neonates. It is most often a consequence of shock or severe organ failure of the kidney or liver. In other cases, acidosis is a discrete finding suggesting that the patient has an inborn error affecting acid production or renal acid excretion. It is important to determine the cause of the acidosis, because many cellular functions rapidly deteriorate at reduced pH. The most common treatment of acidosis is to "correct" the acidosis with bicarbonate; however, the most effective treatment of acidosis is to correct the cause of the acidosis. It is often possible to correct the acidosis caused by an inborn error of metabolism by reducing endogenous overproduction of specific acids.

Differential Diagnosis

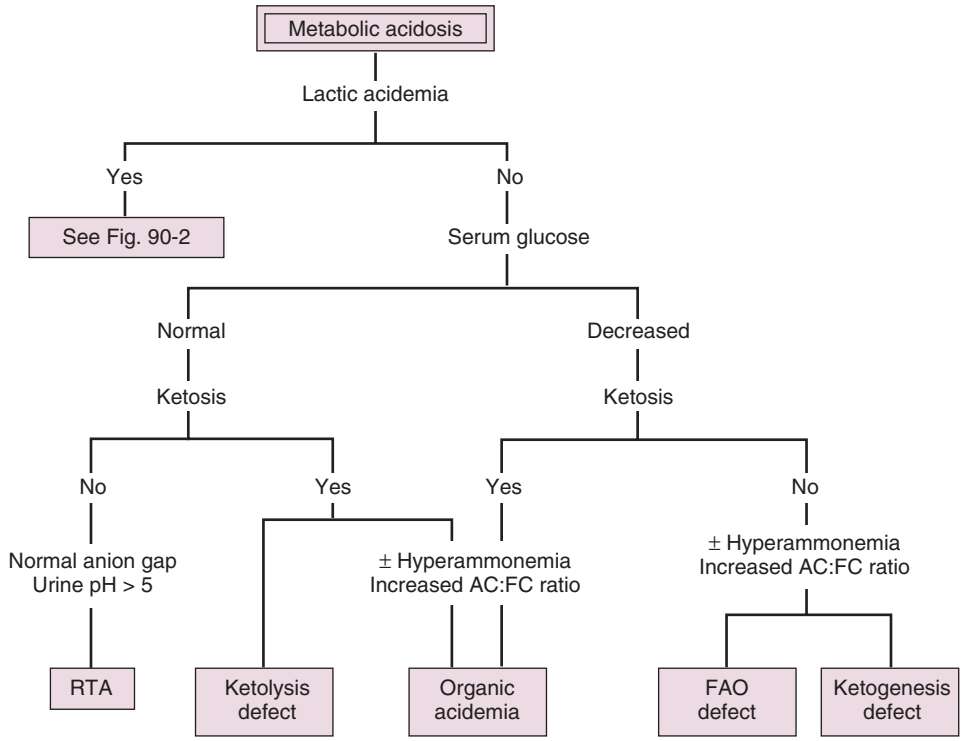
The evaluation of metabolic acidosis should begin with an investigation for systemic shock, renal failure, and generalized liver disease. In the case of shock, the patient should be re-evaluated for recurrent acidosis after restoration of normal cardiopulmonary function. Shock might have been the consequence of an inborn error of metabolism. Similarly, patients with severe liver disease should be evaluated for an underlying inborn error of metabolism as the cause of their liver disease (see Table 90.5).

After assessing the patient's cardiopulmonary, renal, and hepatic status, the physician should initiate a diagnostic study for a possible inborn error of metabolism by measuring serum electrolytes, blood gases, and urine pH. The anion gap should be calculated. Acidosis that is associated with a normal anion gap and an inappropriate renal response to systemic acidosis (urine pH >5) implicates a renal tubular defect. The presence of a normal kidney response to the systemic acidosis (urine pH <5) and an increased anion gap suggests that the excess acid load is systemic in origin rather than renal (see Chapter 92). However, an increased anion gap is not always present in disorders associated with excessive production of abnormal acidic metabolites, and additional studies should be performed before concluding that a patient with a normal anion-gap metabolic acidosis has a renal defect rather than another disorder.

Additional studies that should be performed include determinations of blood lactate and pyruvate, serum glucose, plasma amino acids, plasma and urinary ketones, blood ammonia, plasma and urinary carnitine, and urinary organic acids. The results of these studies can be used to develop the algorithm for the differential diagnosis of metabolic acidosis shown in Fig. 90.1. This algorithm uses the blood lactate concentration as the discriminant at its first branch point, thereby dividing the causes of metabolic acidosis into the lactic acidemias and other acidemias. The advantage to this approach is that a discrete algorithm can then be used to evaluate patients with lactic acidemia. One limitation of this approach is that many categories of disease (e.g., the organic acidemias) include a subset of disorders that produce lactic acidemia and a subset that does not; another disadvantage is that the same disease might produce lactic acidemia in some patients but not in others. Therefore, the presence of lactic acidemia can serve as a useful discriminant as long as one is mindful of its limitations. The disorders associated with lactic acidemia are discussed later under Lactic Acidemia.

The serum glucose concentration is then used in Fig. 90.1 to differentiate among the disorders that cause metabolic acidosis without lactic acidemia. Several groups of disorders are associated with a normal or increased serum glucose

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• **Fig. 90.1** Approach to neonatal metabolic acidosis. AC:FC, Ratio of acylcarnitine to free carnitine; FAO, fatty acid oxidation; RTA, renal tubular acidosis.

concentration at onset, whereas other groups of disorders are associated with hypoglycemia. These groups of disorders can be divided further into those that exhibit ketosis and those that do not. Ketosis is a relatively uncommon finding in the neonate. The possibility of ketosis should be searched for carefully in blood and urine in the sick newborn infant. If present, ketosis should be taken as strong evidence that the neonate has a metabolic disorder.[4,16] However, if ketosis is not present, especially in the premature newborn infant, the possibility of an underlying ketotic metabolic disorder should not be dismissed, because the pathways of ketone synthesis might not have developed sufficiently.

Other information from the initial screening studies should also be considered at this point. Serum electrolyte concentrations should be used to calculate the anion gap. The blood ammonia concentration should be assessed, because it has diagnostic and therapeutic implications. Plasma amino acid analysis and plasma and urine carnitine analyses should be reviewed, because they also might have diagnostic and therapeutic implications.

Patients who have a normal serum glucose concentration with ketosis might have an organic acidemia or a ketolytic defect. Approximately a dozen organic acidemias can have their onset in the neonatal period (see Box 90.1). Many of the organic acid disorders have a common set of features, including ketoacidosis, vomiting, seizures, coma, and in some disorders, an unusual smell (see Table 90.7). Because the main diagnostic test for the organic acid disorders—urinary organic acid analysis—can detect essentially all of these defects, the physician need only consider this diagnostic category and order the appropriate analysis.

In general, analysis of a urine sample collected early in the course of an acute episode of metabolic decompensation has the best chance of revealing the characteristic pattern of organic aciduria. In other cases, the sample obtained during an acute episode contains too many metabolites, and the primary defect is obscured. Accordingly, it is advisable to send at least two samples to the laboratory, one obtained during and the other after an acute episode, when an organic acid disorder is suspected.

In addition to an abnormal urinary organic acid pattern, patients with many of the relatively common organic acidemias generally have an increased serum anion gap, reflecting the accumulation of abnormal organic acids, and hyperammonemia. The degree of hyperammonemia may be so great (>200 μmol/L) that it generates concern and possibly confusion about whether the patient has a primary urea cycle defect rather than an organic acidemia (see Hyperammonemia).[3] However, the organic acidemias can generally be distinguished from the urea cycle defects. The organic acidemias are associated with a more significant metabolic acidosis than is seen in the urea cycle defects (especially early in the course of the illness, when the urea cycle defects are associated with a respiratory alkalosis); an abnormal organic acid pattern; and an increased acylcarnitine-to-free carnitine ratio, which is often accompanied by a pathognomonic acylcarnitine profile. The clinical features of individual organic acidurias are discussed later in this chapter.

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Renal Tubular Defects

The most likely diagnosis when metabolic acidosis is associated with a normal serum glucose concentration, the absence of ketosis, a normal blood ammonia concentration, a normal anion gap, and an inappropriate renal response to systemic acidosis (urine pH >5) is a renal tubular defect.

Isolated renal tubular acidosis (RTA) is not discussed here, because it is more appropriately discussed in Chapter 93. However, certain inborn errors of metabolism are associated with RTA. In general, there are two forms of RTA that reflect the anatomic and functional locus of the defect: proximal RTA and distal RTA. The inborn errors of metabolism that are discussed in this chapter are associated with defects causing proximal RTA but not distal RTA. Most inborn errors of metabolism that cause proximal RTA also affect other components of proximal renal tubular function, producing the renal Fanconi syndrome (i.e., generalized aminoaciduria, glucosuria, phosphaturia, and RTA). Inborn errors of metabolism that cause renal Fanconi syndrome include defects of amino acid and carbohydrate and organic acid metabolism, as well as mitochondrial disorders (Table 90.14). The diagnostic approach and general treatment of these disorders are discussed in the respective parts of this chapter.

Disorders of Ketone Metabolism

The next category to consider includes disorders associated with hypoglycemia and a disorder of ketone formation or catabolism. Patients who have hypoglycemia without ketosis (i.e., nonketotic or hypoketotic hypoglycemia) have a defect in ketogenesis or mitochondrial fatty acid β-oxidation unless another cause is found. Patients with defects of mitochondrial fatty acid β-oxidation are unable to generate acetyl-CoA for ketone body synthesis, whereas patients with defects in ketogenesis are unable to use acetyl-CoA for ketone body synthesis. These disorders can also be associated with hyperammonemia, an increased anion gap, and disordered carnitine homeostasis. Defects of ketogenesis are discussed in the next section, followed by a discussion of defects of ketolysis. Defects in mitochondrial fatty acid β-oxidation are discussed in more detail under Hypoglycemia.

TABLE 90.14 Disorders That Cause Renal Fanconi Syndrome

Category of Disorder	Disorder
Amino acid disorders	Tyrosinemia type I
Carbohydrate disorders	Fanconi-Bickel syndrome Galactosemia Glycogen storage disorder type I Hereditary fructose intolerance
Mitochondrial disorders	Coenzyme Q biosynthesis defect (*COQ2*)* Complex III assembly (*BCS1L*)** mtDNA depletion syndromes (*DGUOK, MPV17, RRM2B, TWNK*)** Pearson syndrome
Organic aciduria	Pyroglutamic aciduria
Others	Lowe syndrome Wilson disease

mtDNA, Mitochondrial DNA.
**COQ2*, gene encoding parahydroxybenzoate-polyprenyl transferase
***BCS1L, DGUOK, MPV17, RRM2B, TWNK*: also see "Disorders Associated with Hepatic Dysfunction, Mitochondrial Disorders (Table 90.5)" and Disorders Associated With Lactic Acidemia in Neonates (Table 90.15) for further discussion of these disorders.

Defects of Ketogenesis. 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (also known as 3-hydroxy-3-methylglutaric aciduria) is an autosomal recessive disorder of ketogenesis.[99] This deficiency affects ketone body formation from fatty acid β-oxidation and from leucine catabolism. This disorder can, therefore, be classified as an amino acid disorder and a fatty acid β-oxidation defect, which is characterized by an abnormal urine organic acid pattern. The defect interferes with the major pathways of ketone body formation and consequently is a cause of severe nonketotic hypoglycemia and acidosis in the newborn infant. Patients generally have vomiting, hypotonia, or lethargy at presentation, but others present with seizures caused by the profound hypoglycemia associated with this disorder. This disorder is treated with frequent feedings of a combined low-fat/low-protein/leucine-restricted diet and carnitine supplementation. Other treatment modalities described above for the organic acidurias may also be helpful.

Defects of Ketolysis. Disorders of ketolysis are defects in the degradation of ketone bodies once they are formed. Ketolytic defects constitute a subset of organic acidemias. They are identified by urinary organic acid analysis but are considered separately here, because their pathogenesis is unique. In normal individuals, ketone bodies are formed in the liver and then transported to peripheral tissues, where they are used as a glucose-sparing energy source.

Ketolytic defects are primarily defects in extrahepatic ketone use rather than ketone body synthesis by the liver. These defects are characterized by normoglycemia or even hyperglycemia. Ketolytic defects are relatively rare, especially in the neonate. Two ketolytic defects with onset in the newborn period are succinyl-CoA:3-ketoacid CoA-transferase deficiency and 3-ketothiolase deficiency.[1,57] Both result in lethargy, hypotonia, a normal or decreased serum glucose concentration, and marked ketosis during the fed state and the fasted state.

The diagnosis of succinyl-CoA:3-ketoacid CoA-transferase deficiency should be considered in a patient with negative findings on organic acid analysis except for markedly increased concentrations of β-hydroxybutyrate, acetoacetate, and β-hydroxyisovalerate. Confirmation of the diagnosis requires specific enzyme analysis or genetic testing.

3-Ketothiolase deficiency impairs ketone body use and isoleucine metabolism, because the enzyme is involved

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in both pathways. The urinary organic acid pattern seen in patients with this disorder shows increased amounts of 2-butanone, 2-methyl-3-hydroxybutyrate, and tiglylglycine, as well as increased excretion of acetoacetate and β-hydroxybutyrate. This disorder can be confused with diabetic ketoacidosis or salicylism when it occurs in the older child.

The treatment for both disorders is a low-protein diet and possibly a low-fat diet, especially during intercurrent illnesses. Carnitine supplementation might also be helpful.

Organic Acidemias

Patients who have hypoglycemia with ketosis should be evaluated for an organic acidemia. Methylmalonic acidemia and propionic acidemia, two of the most common organic acid disorders, are often associated with ketosis. This is also true of several other branched-chain organic acidemias. These common organic acidemias may be associated with hypoglycemia, an increased anion gap, hyperammonemia, hyperglycinemia, and an increased ratio of acylcarnitine to free carnitine with an abnormal pattern of specific acylcarnitines, but none of these findings is present invariably.[1,15,57] Definitive diagnosis can be accomplished by plasma amino acid analysis, urinary organic acid analysis, and plasma carnitine analysis with an acylcarnitine profile, followed by enzymatic or other specialized biochemical testing.

Defects in Branched-Chain Amino Acid Metabolism. The most common organic acidurias in the newborn period are isovaleric acidemia, methylmalonic acidemia, and propionic acidemia (see Box 90.1).[1,15,57] These three disorders share many of the same clinical and biochemical features. All three disorders are the consequence of defects in branched-chain amino acid metabolism, affecting the catabolism of isoleucine, leucine, or valine. Patients born with these disorders are generally healthy at birth and then become inexplicably ill on the second or third day of life. Standard supportive management might not halt the progression of the disease, and the neurologic status deteriorates until the patient develops a severe metabolic encephalopathy and in many cases dies (see Metabolic Encephalopathy).

Biochemically, these disorders are characterized by hypoglycemia plus a combination of many or all of the following features: severe ketoacidosis, hyperammonemia, lactic acidemia, hyperglycinemia, abnormal carnitine metabolism (i.e., relative carnitine insufficiency with an increased total acylcarnitine-to-free carnitine ratio and abnormal acylcarnitine profile), hypocalcemia, and neutropenia, thrombocytopenia, or pancytopenia. Occasionally, patients with an organic acidemia do not present with acidosis. The blood sugar level may be decreased, normal, or increased.

Other defects in branched-chain amino acid metabolism (such as 3-methylcrotonyl-CoA carboxylase deficiency) have similar clinical and biochemical phenotypes. Many patients with this disorder are ascertained by the alert nurse, physician, or parent who notices an abnormal odor emanating from the sick newborn infant's bed or diaper (see Table 90.7).

Multiple Carboxylase Deficiency. Several organic acidurias represent compound phenotypes, because the genetic defect affects the synthesis or functioning of several enzymes. The most common of these compound disorders is multiple carboxylase deficiency, which may be the consequence of either of two genetically distinct defects: biotinidase deficiency and holocarboxylase synthetase deficiency (see Newborn Screening Programs). Both enzyme deficiencies lead to functional deficiencies of four enzymes, all carboxylases: acetyl-CoA carboxylase, which is involved in fatty acid synthesis; 3-methylcrotonyl-CoA carboxylase deficiency, which is involved in branched-chain amino acid metabolism; propionyl-CoA carboxylase, which is also involved in branched-chain amino acid metabolism; and pyruvate carboxylase deficiency, which is involved in gluconeogenesis. Both forms of multiple carboxylase deficiency can cause lactic acidemia and a complex organic aciduria; both are also considered in the algorithm for lactic acidemia (see Lactic Acidemia).

Both forms of multiple carboxylase deficiency can lead to severe metabolic encephalopathy and/or neonatal seizures and require prompt diagnosis and treatment. The sick infant should be evaluated with plasma carnitine analysis, including an acylcarnitine profile, urine organic acid analysis, and serum biotinidase analysis. Treatment with oral biotin supplementation should be started at an initial dose of 20-40 mg/day.

Multiple Acyl-CoA Dehydrogenase Deficiency. Another disorder that represents a compound organic aciduria is multiple acyl-CoA dehydrogenase deficiency, or glutaric aciduria type II (see Dysmorphic Syndromes).[1,57] This disorder is the consequence of a defect in ETF dehydrogenase or ETF ubiquinone oxidoreductase, which are enzymatic components in the pathway that transfers reducing equivalents from the flavin-dependent dehydrogenases involved in mitochondrial fatty acid β-oxidation and the oxidation of several amino acids to the respiratory chain. This disorder is characterized by dysmorphogenesis of the brain, face, and kidneys, as well as the more expected clinical and biochemical phenotype of a combined amino acid and fatty acid β-oxidation defect. This disorder is also associated in many cases with lactic acidosis, especially during acute phases of the illness.

Other. Many of the other organic acidurias listed in Box 90.1 present in a different manner from the disorders listed in the preceding and need to be evaluated and treated differently once they are identified by urine organic acid analysis. For example, mevalonic aciduria is associated with hepatosplenomegaly, diarrhea, anemia, hypocholesterolemia, and craniofacial dysmorphism. The underlying defect in this disorder is deficiency of mevalonate kinase, which is a peroxisomal enzyme that catalyzes the first committed step in the biosynthesis of cholesterol and nonsterol isoprenoids (see Dysmorphic Syndromes).[37]

Similarly, pyroglutamic acidemia is caused by a defect in glutathione synthetase, an enzyme required for the biosynthesis of glutathione. Glutathione is a tripeptide involved in maintaining the redox status within the cell. This rare

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disorder produces acidosis but not ketosis or hypoglycemia in the newborn period. Clinically, it causes RTA type I (see Table 90.14), hemolysis, and hyperbilirubinemia in the newborn period. It leads to acidosis during intercurrent illnesses later in childhood and progressive neurologic abnormalities, including ataxia, spasticity, and mental retardation. The primary objective of treatment is to correct the acidosis and electrolyte imbalances associated with the disorder, especially during acute illnesses. In the neonatal period, it is also important to aggressively treat any anemia or hyperbilirubinemia that develops. Early treatment with vitamin E and vitamin C is recommended, because it may be of long-term benefit. Of note, patients with particular organic acidemias, such as methylmalonic acidemia and propionic acidemia, may develop secondary glutathione deficiency and may benefit from similar treatment.

Management. Management of a patient with an organic acidemia that can produce a neurologic intoxication syndrome and metabolic encephalopathy (e.g., defect in branched-chain amino acid metabolism or multiple carboxylase deficiency) should include supportive care (i.e., administration of bicarbonate, a high rate of glucose infusion [>10 mg/kg per minute], no protein-containing feedings, cofactor supplementation if a specific diagnosis is suspected, and mechanical ventilation, if needed). If the patient has a severe encephalopathy, hemodialysis should be considered.[1,46,57,96,107] Centers unable to provide hemodialysis to newborn infants should consider transferring such patients, because exchange transfusion, peritoneal dialysis, and hemofiltration are considerably less effective than hemodialysis for managing these disorders.

Treatment should be modified as soon as a provisional diagnosis is available. For example, branched-chain amino acid–free parenteral nutrition and specially designed enteral formulas are used to manage acutely ill patients with MSUD. Insulin can be used to augment the anabolic state, starting at 0.05-0.10 units/kg per hour.

Carnitine is used in many of these disorders to remove toxic metabolites during the acute phase. Carnitine can be given orally or intravenously. During an acute crisis, it is probably best to provide intravenous carnitine at 100-200 mg/kg per day (larger doses are sometimes given) as a continuous drip or in four divided doses. If parenteral carnitine is unavailable, carnitine should be given orally at comparable amounts in three or four divided doses. Glycine has been given for similar reasons to patients with isovaleric acidemia and related disorders.[1,57] Glycine should be given orally at a dosage of 250-500 mg/kg per day in three divided doses during the acute crisis. Intralipid can be started after carnitine supplementation has begun and when it is certain that the patient does not have a defect of fatty acid β-oxidation.

After the patient's condition is stabilized, oral feedings should be initiated. In the absence of a specific diagnosis, a high-carbohydrate formula that contains proportionately reduced amounts of protein and fat should be started. The diet should be modified after the neonate's diagnosis has been established. As a rule, it is necessary to limit protein intake or, more correctly, the intake of certain amino acids, but restriction of both protein and fat intake may be required for some disorders. A range of special formulas is commercially available for these patients, but specialized diets should always be designed with the assistance of a dietitian experienced in managing patients with inborn errors of metabolism.

Efforts to reduce the endogenous production of toxic metabolites could also include antibiotic suppression of gut flora that produce metabolites that enter the patient's bloodstream (e.g., long-term metronidazole in patients with methylmalonic and propionic acidemias).[46,125] Specific vitamins may be provided as cofactors for certain enzyme deficiencies, possibly including biotin (10-40 mg PO), hydroxycobalamin (1 mg/day IM), pyridoxine (10 mg/day PO), riboflavin (20 mg/day PO), or thiamine (10 mg/day PO). Carnitine (100 mg/kg per day) is also used during the maintenance phase of treatment.

The various approaches to the acute and long-term management of organic acidemias have led to improved survival and outcome. However, the prognosis for patients with these disorders still varies widely for different disorders and for patients with the same disorder.[1,57] Efforts to establish correlations of genotype and phenotype for these disorders are under way and may soon provide a rational basis for providing prognostic information.

Lactic Acidemia

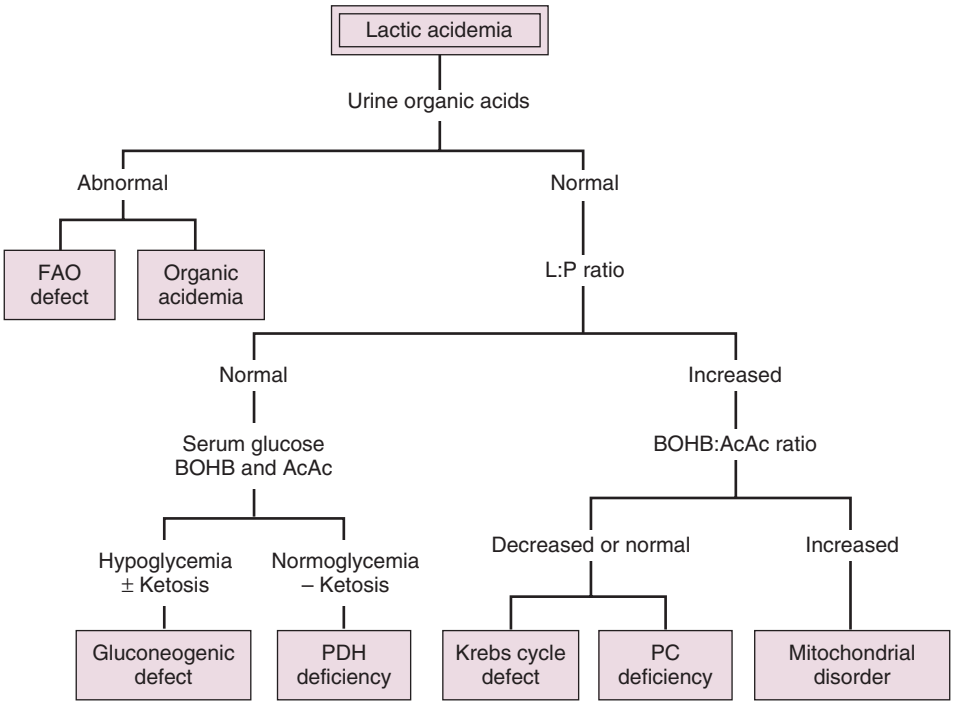
The lactic acidemias are a complex group of inborn errors of metabolism. The classification, diagnosis, and treatment of these disorders will almost certainly change as understanding of their pathogenesis improves. In particular, current understanding of the pathogenesis of defects of the respiratory or electron transport chain is evolving rapidly.

Lactic acidemia may be the consequence of overproduction of lactate, underuse of lactate, or both. A prerequisite for evaluating a patient with lactic acidemia is to assess the adequacy of tissue oxygenation. After it has been established that tissue oxygenation is adequate, several laboratory studies should be performed to determine the cause of the lactic acidemia, including measurement of blood lactate and pyruvate, blood gases and electrolytes, serum glucose, blood ammonia, plasma amino acids, plasma and urinary ketones, plasma and urinary carnitine, and urinary organic acids. If a lumbar puncture is planned to investigate the possibility of sepsis, a sample of CSF should be obtained for lactate and pyruvate analysis, along with samples for the more routine studies; a blood sample should be obtained concurrently for blood lactate and pyruvate analysis. The results of these studies can be used to generate an algorithm for establishing the diagnosis of a neonate with lactic acidemia (Fig. 90.2).

Differential Diagnosis

The differential diagnosis of the primary genetic lactic acidemias with onset in the neonatal period includes defects

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• **Fig. 90.2** Approach to neonatal lactic acidemia. AcAc, Acetoacetate; BOHB, β-hydroxybutyrate; *BOHB:AcAc,* β-hydroxybutyrate-to-acetoacetate ratio; FAO, fatty acid oxidation; L:P, lactate-to-pyruvate ratio; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase complex.

of gluconeogenesis, glycogenolysis, or pyruvate metabolism; defects of the Krebs (or tricarboxylic acid) cycle; and defects of the respiratory chain (Table 90.15). Many defects of fatty acid oxidation, organic acid metabolism, and the urea cycle are associated with lactic acidemia because of relationships among the various pathways of intermediary metabolism. These disorders are more properly considered secondary lactic acidemias and are discussed elsewhere in this chapter. Multiple carboxylase deficiency is an exception to this rule, because the underlying defect impairs biotin metabolism, which may produce pyruvate carboxylase deficiency and lactic acidemia.

The urinary organic acid pattern, along with the blood ammonia concentration and plasma and urine carnitine analyses, provides a practical means for discriminating between the primary and secondary lactic acidemias. The urinary organic acid pattern is by definition abnormal in patients with an organic acidemia and is abnormal in many of the disorders of fatty acid β-oxidation. Patients with fatty acid oxidation defects often excrete increased amounts of dicarboxylic acids, 3-hydroxydicarboxylic acids, or both. In contrast, the primary lactic acidemias are associated with a normal organic acid pattern or a nonspecific pattern of increased excretion of lactate and pyruvate, various Krebs cycle intermediates, dicarboxylic and 3-hydroxydicarboxylic acids, or 3-methylglutaconic acid. The dicarboxylic and 3-hydroxydicarboxylic acids are the consequence of secondarily impaired mitochondrial fatty acid β-oxidation.

Despite the potential overlap between the patterns of urinary organic acids produced by these disorders, urinary organic acid analysis generally provides a useful means of discriminating between the primary and secondary lactic acidemias, because qualitative and quantitative differences exist between the patterns seen in the two groups of disorders. The concentrations of urinary metabolites excreted in the primary lactic acidemias are generally less than those produced by the organic acidurias and fatty acid β-oxidation defects.

The plasma ammonia concentration and the plasma and urine carnitine analyses also provide useful information for distinguishing between the primary and secondary lactic acidemias. Patients with an organic aciduria or a fatty acid β-oxidation defect often have hyperammonemia and relative carnitine insufficiency, with an increased acylcarnitine-to-free carnitine ratio and specific acylcarnitine abnormalities.[78,93] In contrast, patients with one of the primary lactic acidemias generally have a normal plasma ammonia concentration and relatively mild and nonspecific changes in their plasma and urinary carnitine values.

The exception to this rule is the severe neonatal form of pyruvate carboxylase deficiency, because these patients can have hyperammonemia. Similarly, patients with a primary urea cycle defect could have lactic acidosis, but the degree of acidosis is relatively mild, especially early in the course of the disease, when respiratory alkalosis rather than metabolic acidosis is generally present (see Hyperammonemia).

Primary Lactic Acidemias

In practical terms, the first step in discriminating among the primary lactic acidemias is to examine the results of the lactate (L) and pyruvate (P) analyses in terms of the absolute and relative values of this pair of metabolites. The

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TABLE 90.15 Disorders Associated With Lactic Acidemia in Neonates

Category of Disorder	Disorder
Disorders of gluconeogenesis, glycogenolysis, or pyruvate metabolism	Fructose-1,6-bisphosphatase deficiency GSD type I (glucose-6-phosphatase deficiency) GSD type III (debrancher deficiency) GSD type IX (liver phosphorylase kinase deficiency) Phosphoenolpyruvate carboxykinase deficiency Pyruvate carboxylase deficiency Pyruvate dehydrogenase complex deficiency
Krebs cycle disorders	Dihydrolipoamide dehydrogenase deficiency Fumarase deficiency α-Ketoglutarate dehydrogenase deficiency Succinate dehydrogenase deficiency
Organic acidemias	See Box 90.1
Mitochondrial Disorders	
mtDNA Mutations	
Point Mutations	
mRNA	Maternally inherited Leigh syndrome (*ATPase6*)
rRNA	Aminoglycoside-induced nonsyndromic deafness
tRNA	Hepatic dysfunction ($tRNA^{Glu}$) Isolated cardiomyopathy ($tRNA^{Leu}$)
Large deletions/duplications	Pearson syndrome
nDNA Mutations	
Mutations that directly affect protein subunits of the RC complexes	Complex I, II, III, IV, and V, or combined deficiencies
Mutations that affect nuclear genes required for transport, assembly, or stabilization of the RC complexes	Complex III (*BCS1L*) Complex IV (*SURF*, *SCO1*, *SCO2*, *COX10*, *COX15*) Complex V (*TREM70*)
Mutations that affect nuclear genes required for replication or maintenance of the mitochondrial genome	Mitochondrial DNA depletion syndromes (*DGUOK*, *FBXL4*, *POLG*, *TK2*)
Mutations that affect genes involved in other mitochondrial processes required for normal mitochondrial function	Barth syndrome (*TAZ*)

ATPase 6, Subunit 6 of ATP synthase; COX, cytochrome oxidase; GSD, glycogen storage disorder; nDNA, nuclear DNA; mtDNA, mitochondrial DNA; RC, respiratory chain; $tRNA^{Leu}$, transfer RNA for leucine (UUR); $tRNAG^{Glu}$, transfer RNA for glutamic acid; TAZ, tafazzin.

L:P ratio is a reflection of the redox state of the cytoplasm. The L:P ratio is normally between 10:1 and 20:1. Defects of gluconeogenesis or the pyruvate dehydrogenase complex are generally associated with a normal L:P ratio, whereas defects of the mitochondrial respiratory chain are often associated with an increased L:P ratio. The possibility of a mitochondrial respiratory chain defect should not be ignored in patients with a normal blood lactate concentration or a normal L:P ratio when the patient's clinical picture otherwise suggests a respiratory chain disorder.

Further differentiation of the primary lactic acidemias can be made with the results of the plasma β-hydroxybutyrate (BOHB) and acetoacetate (AcAc) analysis and the serum glucose analysis. As discussed in regard to the results of the blood lactate and pyruvate analyses, the results of plasma BOHB and AcAc analyses should be evaluated in terms of the absolute and relative values of this pair of metabolites. Whereas the L:P ratio is a reflection of the redox state of the cytoplasm, the BOHB:AcAc ratio is a reflection of the redox state within the mitochondrion. Both ratios must be examined to appreciate the redox state within the cell.

The primary lactic acidemias associated with a normal L:P ratio include defects of gluconeogenesis and defects of the pyruvate dehydrogenase complex (see Fig. 90.2). These two groups of disorders can be distinguished from each other by the presence or absence of hypoglycemia and ketosis. Defects of gluconeogenesis are generally associated with hypoglycemia and ketosis, whereas patients with pyruvate dehydrogenase complex deficiency are generally normoglycemic and do not have ketosis (see Hypoglycemia).

Pyruvate Dehydrogenase Complex Deficiency

Patients with pyruvate dehydrogenase complex deficiency can present in the neonatal period with severe lactic acidosis and rapidly progressive deterioration. Less severe deficiencies are compatible with survival but lead to psychomotor retardation. Most patients with pyruvate dehydrogenase complex deficiency have an X-linked form of the

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disease, in which male patients are more severely affected than female patients. In many cases, patients with pyruvate dehydrogenase complex deficiency are born with structural CNS malformations, including agenesis of the corpus callosum and cystic lesions of cerebral cortex; in other patients, lesions of the basal ganglia and brainstem that are consistent with Leigh disease are present or develop later in infancy. However, the Leigh disease phenotype is not pathognomonic for pyruvate dehydrogenase deficiency, because Leigh disease is genetically heterogeneous; it can also be the consequence of PC deficiency[136] or defects of nuclear- or mitochondrial-encoded subunits of the mitochondrial respiratory chain.[19,27,44]

Efforts to treat patients with pyruvate dehydrogenase complex deficiency have included a high-fat, low-carbohydrate diet with thiamine and lipoic acid supplementation. The rationale for this therapy is that glucose is catabolized through the glycolytic pathway to pyruvate and then requires the action of the pyruvate dehydrogenase complex before it can enter the Krebs cycle, whereas fatty acids enter the Krebs cycle without passing through the pyruvate dehydrogenase complex. Thiamine and lipoic acid are cofactors for the first and second components of the pyruvate dehydrogenase complex, respectively. Some patients have been treated with dichloroacetate, a drug that maintains the pyruvate dehydrogenase complex in its activated state. These treatment efforts have met with mixed success.

As shown in Fig. 90.2, the primary lactic acidemias associated with an increased L:P ratio can be distinguished by considering the absolute and relative concentrations of BOHB and AcAc. Patients with PC deficiency, a Krebs cycle defect, or a mitochondrial respiratory chain defect all exhibit postprandial ketosis. However, for the reasons explained previously, severe PC deficiency and Krebs cycle defects may be accompanied by a decreased or a normal BOHB:AcAc ratio, whereas mitochondrial respiratory chain defects may be accompanied by an increased BOHB:AcAc ratio. PC deficiency is discussed elsewhere (see Hypoglycemia), whereas respiratory chain defects are discussed in this section.

Krebs Cycle Defects

Krebs cycle defects are rare. Four defects affecting the Krebs cycle have been described: α-ketoglutarate dehydrogenase complex deficiency, fumarase deficiency, succinate dehydrogenase deficiency, and dihydrolipoamide dehydrogenase deficiency. The clinical presentations of α-ketoglutarate dehydrogenase deficiency and fumarase deficiency are variable but always affect neurologic function. They can cause hypotonia, ataxia, and, in some cases, CNS malformations. Succinate dehydrogenase contains four subunits (SDHA, SDHB, SDHC, SDHD), as well as two assembly proteins (SDHAF1, SDHAF2). Succinate dehydrogenase deficiency associated with mutations in the *SDHA* gene produces clinical phenotypes consistent with a respiratory chain defect, such as Leigh syndrome or cardiomyopathy, which is not surprising because succinate dehydrogenase forms part of complex II of the respiratory chain. Defects of the other SDH subunits produce cancer predisposition syndromes for paraganglioma. Similarly, individuals who are carriers for fumarase deficiency have an increased disposition for leiomyomatosis and renal cell cancer. The connection between fumarase deficiency and SDH deficiency and hereditary cancer syndromes is not well understood and is an area of intense research.

Dihydrolipoamide dehydrogenase deficiency affects a protein that is a component of three different α-ketoacid dehydrogenase complexes: the α-ketoglutarate dehydrogenase complex (i.e., Krebs cycle component), the pyruvate dehydrogenase complex (i.e., the enzyme that converts pyruvate to acetyl-CoA and thereby permits its entry into the Krebs cycle), and the branched-chain α-ketoacid dehydrogenase complex (i.e., the enzyme that is deficient in MSUD). Dihydrolipoamide dehydrogenase deficiency is, therefore, a compound deficiency of these three α-ketoacid dehydrogenase complexes and is associated with severe ketoacidosis and a pathognomonic organic aciduria. The Krebs cycle defects can be detected by urinary organic acid analysis. Effective treatment does not exist for these Krebs cycle disorders.

Mitochondrial Disorders

Defects of the mitochondrial respiratory chain and oxidative phosphorylation (hereafter referred to as mitochondrial disorders) are a diverse group of disorders reflecting the large number of genes involved in this metabolic system.[19,27] The mitochondrial respiratory chain and oxidative phosphorylation system is composed of five multimeric protein units: complex I, II, III, IV, and V. The number of protein subunits in these complexes ranges from 4-43 proteins. An additional level of complexity is that some subunits are encoded by nuclear DNA (nDNA) and others are encoded by mitochondrial DNA (mtDNA). The nDNA encodes for approximately 85% of the subunits, whereas mtDNA encodes for approximately 15%. Complexes I, III, IV, and V contain subunits encoded by both genomes, whereas complex II contains only nuclear-encoded subunits. The common names, composition, and genetic origin of the subunits of the five respiratory chain complexes are listed in Table 90.16.

The mitochondrial genome differs in several strategic ways from the nuclear genome.[19,27] There are both structural and biologic differences between the two genomes. The structural differences include the following:

- mtDNA is much smaller than nDNA. It is a circular, double-stranded genome that contains about 16,500 base pairs (16.5 kb), which encode for 37 genes (compared with the 30,000 genes that are encoded by the nuclear genome). The mtDNA encodes for 13 mRNAs, two rRNAs, and 22 tRNAs. The mRNAs encode for the polypeptide subunits of the respiratory chain complexes. The two rRNAs and 22 tRNAs are necessary for translation of mtDNA.

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TABLE 90.16 Respiratory Chain Complexes

Complex	Name	Composition and Genetic Origin		
		nDNA	mtDNA	Total
I	NADH-CoQ reductase	37	7	44
II	Succinate-CoQ reductase	4	0	4
III	$CoQH_2$-cytochrome c reductase	10	1	11
IV	Cytochrome c oxidase	10	3	13
V	ATP synthase	12	2	14

CoQ, Coenzyme Q (ubiquinone); $CoQH_2$, reduced coenzyme Q (ubiquinol); nDNA, nuclear DNA-encoded subunits; mtDNA, mitochondrial DNA-encoded subunits; NADH, reduced nicotinamide adenine dinucleotide.

- The genetic codes of the mtDNA and nDNA differ in several key codons, such that the two genomes require their own translational apparatus.
- Almost all regions of mtDNA are part of coding sequence; that is, the mtDNA has few introns. This is very different from the situation for nDNA, which contains a high proportion of noncoding regions.
- The mutation rate for mtDNA is approximately 10-fold greater than that of nDNA, in part because it does not have histones and in part because it has a poor mutation repair apparatus.

Combining the high mtDNA mutation rate with the high proportion of coding sequence in mtDNA, mtDNA mutations are thought to account for a disproportionate percentage (based on their relative size) of human disease compared with the nuclear genome. Conversely, the number of nuclear genes involved in mitochondrial structure and function is far greater than the number of mitochondrial encoded genes, supporting the clinical observation that nuclear mutations are also a significant cause of mitochondrial disease, especially in children.

In addition to these structural differences, there are also several strategic biologic differences between the mitochondrial and nuclear genomes:

- mtDNA is inherited exclusively from the mother, leading to maternal or matrilineal inheritance of mitochondrial encoded disorders.
- Each mitochondrion contains multiple copies of mtDNA, varying between 2 and 10 copies per organelle. Each cell, in turn, contains a variable number of mitochondria, leading to hundreds to thousands of copies of mtDNA per cell. In contrast, each cell (except mature germ cells) contains two copies of nDNA.
- Each cell may contain only one form of mtDNA ("normal" or "abnormal") or more than one form of mtDNA ("normal" or "abnormal"). The presence of only one form of mtDNA is called *homoplasmy*; the presence of more than one form is called *heteroplasmy*. The cell can contain any proportion of abnormal mtDNA. The clinical consequences of abnormal mtDNA are proportional to the degree of heteroplasmy of that mutation. The phenomenon of mtDNA heteroplasmy differs sharply from that for nDNA, wherein an individual is either homozygous or heterozygous for a normal or abnormal allele.
- The proportion of normal and abnormal mtDNA in a cell can change over time, because mtDNA replication is not synchronous with nuclear division. A shift in the degree of heteroplasmy can occur prenatally or postnatally, lead to improvement or worsening of the clinical phenotype, or produce a change in the pattern of tissue and organ involvement.
- The clinical consequences of an mtDNA defect (homoplasmic or heteroplasmic) vary in different tissues and organs, depending on the mitochondrial (aerobic) energy requirements of each tissue or organ. This phenomenon has been termed the *threshold effect*.

The unique biologic properties of mtDNA provide a rationale for the unusual mode of inheritance, pattern of clinical involvement, and sometimes evolving clinical picture of some respiratory chain disorders.

An extraordinarily broad range of clinical phenotypes has been described among patients with mitochondrial disorders.[19,27,44] This is not surprising given the almost universal requirement that different cells, tissues, and organs have for mitochondrial energy production. The clinical abnormalities primarily observed in newborns with respiratory chain disorders involve the CNS (lethargy, apnea, hypotonia, near-miss episodes, and coma), skeletal muscle (decreased spontaneous movements, atrophy, hypertonia or hypotonia, recurrent myoglobinuria), heart (hypertrophic cardiomyopathy), liver (hepatomegaly, hepatic failure), kidney (proximal tubular dysfunction), exocrine pancreas, and hematopoietic system (sideroblastic anemia, neutropenia, and thrombocytopenia). In some cases, other clinical abnormalities can be identified (e.g., ocular abnormalities), which often provide a clue that facilitates further diagnostic evaluation. Thus, all patients suspected of having a mitochondrial disorder should undergo a comprehensive clinical evaluation to delineate the full pattern of organ involvement.

Similarly, all patients suspected of having a mitochondrial disorder should undergo a metabolic evaluation for

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lactic acidemia and related biochemical abnormalities, as discussed in the beginning of this section (see Lactic Acidemia). These studies should be done in both the fasting and fed state (1 hour postprandial). The metabolic evaluation should include measurement of blood lactate and pyruvate, plasma, and urine ketones (β-hydroxybutyrate and acetoacetate), plasma amino acids (focusing on alanine, the transamination product of pyruvate), plasma carnitine analysis (including total carnitine, free carnitine, and the acylcarnitine profile), plasma coenzyme Q10 (which is required for normal functioning of the mitochondrial respiratory chain), and urine organic acid analysis. In addition to measuring the blood lactate and pyruvate concentrations, these metabolites should also be measured in the CSF (especially in patients with CNS symptoms) if they are normal in blood. Magnetic resonance spectroscopy (MRS) of the brain may also be helpful in identifying increased lactate. It is important to remember that the absence of lactic acidemia, or any of the other aforementioned biochemical findings, does not exclude the diagnosis of a mitochondrial disorder.

More specialized diagnostic evaluation for a suspected mitochondrial disorder entails a combination of enzyme and morphologic analysis of tissues, polarographic analysis of intact mitochondria, and genetic analysis of mtDNA and nDNA-encoded genes.[27,38] Polarographic analysis measures oxygen consumption by intact mitochondria using a variety of substrates. It requires freshly isolated mitochondria and is available in only a few centers. Interpretation of the results of all these diagnostic studies is complicated by the fact that many defects are tissue specific. In particular, many defects are not expressed biochemically in blood cells or cultured skin fibroblasts, which mandates the need for invasive studies to obtain a skeletal muscle, cardiac, or liver biopsy. Similarly, the biochemical defect may not be expressed in all these tissues. Enzyme and polarographic analysis can implicate deficiency of one or more of the respiratory chain complexes, but they do not permit the clinician to determine whether the patient has a defect in a nuclear- or mitochondrial-encoded subunit. Genetic analysis of the mitochondrial genome is available, but many mtDNA defects are not detectable in all tissues because of heteroplasmy. In recent years, considerable progress has been made in identifying the nuclear genes that encode for the respiratory chain subunits and related mitochondrial processes, and genetic analysis is becoming increasingly available for many nuclear-encoded defects. Genetic analysis of nuclear defects is not limited by the tissue-specificity issue that plays a role in the genetic evaluation of mtDNA-encoded defects.

A general consensus seems to have developed about the diagnostic evaluation of patients with a suspected mitochondrial disorder.[19,27,38] As noted, the first step is to perform a comprehensive clinical evaluation and a noninvasive metabolic evaluation to establish whether the patient is likely to have a mitochondrial disorder. If the patient appears likely to have a mitochondrial disorder and the clinical phenotype is characteristic of a specific, well-defined mitochondrial disorder that can be confirmed by genetic testing of a blood sample, then proceeding with specific genetic testing for that disorder is indicated. If, however, it appears that the patient has a mitochondrial chain disorder that can be the consequence of a defect in one of many genes, molecular genetic testing may also be indicated using a blood sample for a relatively limited phenotype-specific panel of genes (i.e., 10-50 genes) or using the more comprehensive approach of whole exome or whole genome sequencing.

The key to learning the well-characterized clinical phenotypes that can be diagnosed by focused genetic testing using blood samples is to acquire an understanding of the current classification scheme for mitochondrial disorders. The traditional approach to classifying mitochondrial disorders was based on clinical phenotypes, pathologic findings, and biochemical findings. This approach is still useful. However, a clinically based classification system is limited by two well-established characteristics of mitochondrial respiratory chain disorders: a particular clinical phenotype can be caused by more than one genetic defect, and conversely, the same genetic defect can produce more than one clinical phenotype. Recognition of these limitations led to efforts to classify mitochondrial disorders according to their genetic bases. This approach to classification is also imperfect, but it is improving as current understanding of the genetic bases of these disorders becomes greater.

The genetic classification divides the mitochondrial disorders into two broad categories, mtDNA defects and nDNA defects (see Table 90.15). The mitochondrial encoded disorders can be classified into those caused by point mutations and those caused by large deletions or duplications that affect multiple genes of the mitochondrial genome. Mitochondrial point mutations can be subclassified into those that affect mRNA, rRNA, or tRNA. The nuclear-encoded disorders can be divided further into mutations that directly affect the genes that encode for subunits of the respiratory chain complexes; genes required for transport, assembly, or stabilization of the respiratory chain complexes; genes required for replication or maintenance of the mitochondrial genome; and genes involved in other mitochondrial processes required for normal mitochondrial respiratory chain function.

The differential diagnosis of several mitochondrial disorders that produce recognizable clinical syndromes in the newborn period are listed in Table 90.15. Most patients whose respiratory chain disorder manifests in the newborn period have an nDNA defect; when the disorder manifests later in childhood or adulthood, mtDNA defects predominate. Many of the most common and best characterized mitochondrial respiratory chain disorders that manifest in late childhood or adulthood do not generally appear in early infancy or manifest as much more severe, markedly different clinical phenotypes. The list of disorders is not comprehensive; rather, it includes disorders that are relatively well-characterized and illustrates the basic approaches to diagnosis of these disorders.

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Maternally inherited Leigh syndrome (MILS) is an example of a point mutation that affects an mtDNA structural gene (an mRNA) that encodes for a subunit of a mitochondrial respiratory chain complex (see Table 90.15). Maternally inherited Leigh syndrome is associated with a point mutation (generally T8993C, T8993G, or T9176C) in the gene that encodes for subunit 6 of complex V (*ATPase 6*). Leigh syndrome was originally defined as a subacute necrotizing encephalopathy that involves the thalamus, brainstem, and posterior columns of the spinal cord. Typically, it has a mean age of onset of 2 years of age and is characterized by psychomotor regression, tremor, dystonia, optic atrophy, ophthalmoplegia, and respiratory difficulty with apnea. Death usually occurs by 4 years of age. Some patients have a Leigh syndrome–like disorder that is associated with hypertrophic cardiomyopathy, skeletal myopathy, or renal proximal tubular dysfunction. The defects that produce Leigh syndrome or a Leigh syndrome–like disorder include (but are not limited to) nuclear-encoded subunits of complex I, II, or IV; nuclear-encoded assembly genes for complex I or complex IV; nuclear-encoded subunits of the pyruvate dehydrogenase complex; or mtDNA-encoded tRNAs.[19,27,118] Maternally inherited Leigh syndrome is an early-onset, severe form of Leigh syndrome that is caused by mutations in the mitochondrially encoded subunit 6 of complex V. Patients without the ATPase 6 mutations listed should be evaluated for the other causes of Leigh syndrome. Detailed biochemical studies might refine the diagnosis to a specific complex or protein and direct further genetic studies.

Aminoglycoside-induced nonsyndromic deafness is caused by the A1555G mutation in the mitochondrial rRNA gene that encodes for the 12S ribosomal complex component. The aminoglycoside-induced nonsyndromic deafness disorder is a pharmacogenetic disorder that physicians should be aware of when obtaining a family history of maternally inherited hearing loss thought to be attributable to aminoglycoside use. The use of aminoglycosides in neonates with this mutation may produce irreversible deafness and may cause cardiomyopathy. However, this mutation is not the cause of aminoglycoside-associated renal toxicity.

Isolated hypertrophic cardiomyopathy has been found in association with several tRNA mutations, principally involving a tRNA for leucine ($tRNA^{Leu}$). The $tRNA^{Leu}$ defects include the A3243G mutation and the C3305T mutation. The A3243G mutation is probably the most commonly identified mtDNA mutation and is the most common cause of MELAS (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes), which manifests rarely in the newborn period as a severe encephalopathy syndrome. The C3305T mutation generally produces an infantile-onset hypertrophic cardiomyopathy with or without skeletal myopathy (see Table 90.15).

Pearson syndrome is an example of a mitochondrial-encoded disorder associated with large deletions or duplications of mtDNA. Pearson syndrome is characterized clinically by refractory sideroblastic anemia, neutropenia, thrombocytopenia, exocrine pancreatic dysfunction, and lactic acidosis.[121] Patients with Pearson syndrome who survive the neonatal period can subsequently have gradual regression of the symptoms and signs of Pearson syndrome and subsequently develop Kearns-Sayre syndrome, which is an encephalomyopathy associated with progressive external ophthalmoplegia, hearing loss, cardiac arrhythmias, diabetes mellitus, and renal dysfunction.[27] Kearns-Sayre syndrome is an alternate expression of the same mtDNA mutation and is an example of how the phenotypes of mtDNA-encoded disorders can evolve dramatically with time.

Nuclear-encoded defects that produce recognizable clinical phenotypes in the newborn period are also listed in Table 90.15. The first group of such disorders involves genes that encode for a specific subunit of the respiratory chain complexes. These disorders are often characterized by severe ketoacidosis that is associated with seizures, apnea, severe hypotonia, hepatomegaly, and renal proximal tubular dysfunction. Detailed enzymatic and polarographic studies are required to identify the biochemically deficient respiratory chain complex or complexes. The specific deficiency can then be investigated by genetic analysis. For example, genetic testing is now available clinically for 7 of the 37 nuclear-encoded subunits of complex I.

The second group of nuclear disorders involves genes that encode for proteins that are required for transport, assembly, or stabilization of the respiratory chain complexes. For example, defects of several genes involved in assembly of complex IV (cytochrome oxidase, COX) have been identified. These defects appear to produce distinctive clinical phenotypes. *SURF1* mutations produce Leigh syndrome. As noted earlier, Leigh syndrome does not manifest until later in infancy, but Leigh syndrome–like disorders can manifest in the newborn period.[19,27,118] *SCO1* mutations can lead to encephalomyopathy and hepatic failure. *COX10* mutations also lead to a Leigh syndrome–like phenotype (or encephalopathy), which is sometimes accompanied by hypertrophic cardiomyopathy, renal proximal tubular dysfunction, or anemia. *SCO2* mutations and *COX15* mutations lead to encephalopathy or hypertrophic cardiomyopathy. Mutations of the assembly factors required for the other respiratory chain complexes have also been described. GRACILE syndrome, an eponymic association of growth restriction, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death, is the best described of these disorders; it is caused by mutations of the *BCS1L* gene, which is required for assembly of complex III.[19] The number of assembly and maintenance factors that are recognized continues to increase, providing new insights into the pathogenesis of many mitochondrial disorders and their diagnosis.[26]

The third group of nuclear-encoded disorders involves genes that are required for replication or maintenance of the mitochondrial genome. These disorders are characterized by a reduction in mtDNA copy number, a condition known as mitochondrial DNA depletion syndrome. This syndrome can result from a mutation of the mitochondrial DNA polymerase γ gene (*POLG*), which encodes for an enzyme

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required for mitochondrial replication. It can also be the consequence of deoxyguanosine kinase (DGOUK) deficiency or thymidine kinase 2 (TK2) deficiency. DGOUK and TK2 are enzymes that are encoded by the *DGOUK* gene and the *TK2* gene, respectively, which are required for synthesis or recycling of the deoxyribonucleotides necessary for DNA replication. In brief, mitochondrial DNA is wholly dependent on the nucleus for production of the enzymes and deoxyribonucleotides it requires for its own replication. Absent these materials, the mitochondrion cannot replicate and its numbers decline. POLG deficiency leads to isolated encephalopathy or seizures, or to liver failure, hepatoencephalopathy, or Alpers syndrome (hepatopathic poliodystrophy); DGOUK deficiency presents with encephalopathy and liver failure; and TK2 presents with encephalopathy and severe skeletal myopathy.[19]

The fourth group of nuclear-encoded disorders is caused by mutations in genes required for other mitochondrial processes that are necessary for normal respiratory chain function. Barth syndrome is an example of such a disorder.[21] Clinical features of Barth syndrome include hypertrophic cardiomyopathy, cyclic neutropenia, and cataracts. It is an X-linked recessive disorder caused by a mutation in the *tafazzin* gene (*TAZ*), which encodes for a protein required for synthesis of the lipid milieu of the mitochondrial membranes. Mutations in the *TAZ* gene can also produce an unusual form of cardiomyopathy known as left ventricle noncompaction.

Treatment of patients with a respiratory chain defect is largely supportive.[19,27,44,106] Therapy includes symptomatic management, such as treating acute or chronic acidosis with bicarbonate or citrate and treating cardiac, renal, and other systemic disease with standard methods. It also includes avoiding certain drugs, such as valproate and barbiturates, which may be mitochondrial toxins. There is no dietary therapy of proven benefit for patients with mitochondrial disorder, although vitamins or other nutritional supplements are generally tried using the rationale that they might stabilize or augment residual enzyme activity of the mitochondrial respiratory chain complexes or serve as artificial electron acceptors or antioxidants.[106] Coenzyme Q10 is administered because it is a structural homologue of ubiquinone, which accepts electrons from complex I and complex II and passes them on to complex III. Riboflavin is used based on the rationale that complexes I and II contain flavin. Vitamins C and K are used in combination based on the rationale that they can provide an electron transfer shuttle to bypass a complex III deficiency. Thiamine is a cofactor in the pyruvate dehydrogenase complex, which serves as the point of entry for glucose into the Krebs cycle. The daily dietary supplements in use for a neonate with a mitochondrial disorder include coenzyme Q10 (20 mg), vitamin B_1 (thiamine, 20 mg), vitamin B_2 (riboflavin, 25 mg), vitamin C (250 mg), and vitamin K_3 (menadione, 5 mg). Carnitine may also be used, especially in patients with secondary carnitine deficiency (50-100 mg/kg per day). The doses cited are at the lower end of the range of doses recommended by various physicians; some investigators have recommended doses up to 10 times greater than these. However, none of these recommendations are based on controlled studies.

Dichloroacetate has been tried in patients with mitochondrial defects. The rationale for using dichloroacetate (50 mg per day) is that it maintains the pyruvate dehydrogenase complex in its activated state. PDC catalyzes the conversion of pyruvate (the final product of the anaerobic metabolism of glucose) to acetyl-CoA, which is further metabolized by the Krebs cycle and the mitochondrial respiratory chain. Recent clinical studies have shown that dichloroacetate is of no clinical benefit to patients with a mitochondrial disorder, and it can cause peripheral neuropathy in some patients.

Finally, all patients should receive a thorough clinical evaluation to determine whether they have an organ-specific mitochondrial defect that might be amenable to organ transplantation. However, the primary caveat in performing and then interpreting this evaluation is that mitochondrial disorders can have highly variable clinical presentations—in the pattern of organ involvement and/or the time of onset of different organ involvement—among patients with the same gene disorder or the same mutation, even among members of the same family. There have been reports of successful transplantation, e.g., a heart transplantation was reportedly successful for a patient with cardiomyopathy caused by a tissue-specific mtDNA depletion syndrome.[100] On the other hand, a patient who presents in childhood with *MPV17*-related hepatic failure might be found to have no evidence of other systemic manifestations, receive a successful liver transplant that cures his hepatic failure, and then develops severe cardiomyopathy later in life.[80] The current recommendation is that patients with mitochondrial disease should undergo a comprehensive clinical evaluation and have a specific, genetically confirmed diagnosis established before the risks and benefits of organ transplantation are discussed with the patient/family and a decision made whether to proceed with transplantation.[31,80]

Hypoglycemia

See Chapter 86. Recognizing hypoglycemia in the newborn may be difficult, because the symptoms of hypoglycemia (i.e., lethargy, poor feeding, hypothermia, and seizures) are nonspecific. Frequent blood sugar determinations are often required to confirm the suspicion of hypoglycemia. Because inborn errors of metabolism are a relatively infrequent cause of neonatal hypoglycemia, other diagnostic possibilities should be investigated concurrently.[104]

The first possibility to consider is neonatal stress secondary to perinatal asphyxia, hypothermia, or intrauterine malnutrition (e.g., placental abnormalities, prematurity, or multiple gestations). The second consideration is the possibility of a hormonal abnormality affecting insulin regulation. The inborn errors of metabolism associated with insulin dysregulation include 3-hydroxacyl-CoA dehydrogenase (HADH) deficiency[53] and hyperammonemia/

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hyperinsulinism (HA/HI) syndrome,[82] both of which are diazoxide-responsive. The third possibility to consider is a malformation syndrome, specifically including those syndromes associated with hormonal dysregulation such as Beckwith-Wiedemann syndrome, which is discussed in Chapter 86. The fourth possibility is that the patient has a severe hepatocellular or cirrhotic liver disease that leads nonspecifically to fasting hypoglycemia. The inborn errors that can produce this degree of liver damage are presented in Table 90.5 (see Hepatic Dysfunction). Finally, the patient should be evaluated for inborn errors of metabolism not considered as part of the diagnostic possibilities listed above.

Differential Diagnosis

Hypoglycemia may be associated with five categories of inborn errors of metabolism: fatty acid oxidation defects, gluconeogenesis defects, glycogen storage diseases, ketogenesis defects, and organic acidemias (Table 90.17). The diagnostic approach to hypoglycemia, therefore, must give consideration to entities belonging to each of these categories. Usually, Krebs cycle defects and mitochondrial disorders do not produce hypoglycemia, but these defects should be considered when other evidence points in their direction. The diagnostic approach must quickly narrow the field of possible diagnoses so that specific treatment can be instituted.

The classic approaches to the differential diagnosis of hypoglycemic disorders in children are the fasting study and specialized challenge tests. These studies are, however, not feasible in newborn infants because of the significant risks and technical difficulties associated with performing such studies and because of the lack of control data derived from normal neonates. Alternatively, efforts to determine the cause of hypoglycemia in the newborn infant should include hormonal and biochemical studies before and after feeding and especially during an acute episode of hypoglycemia. Definitive diagnosis might have to be postponed several months until the child is old enough to tolerate a formal fasting study or specialized in vitro cell studies.

An algorithm (Fig. 90.3) for diagnosing the disorders that cause neonatal hypoglycemia can be generated from the results of the following studies: blood electrolytes and pH, plasma and urinary ketones, plasma free fatty acids, blood lactate and pyruvate, blood ammonia, liver function tests, plasma and urinary carnitine and acylcarnitine analysis, and urinary organic acids. A specific diagnosis might not be made by these studies, but they are necessary for providing a provisional diagnosis that can be confirmed by specific enzyme analysis.

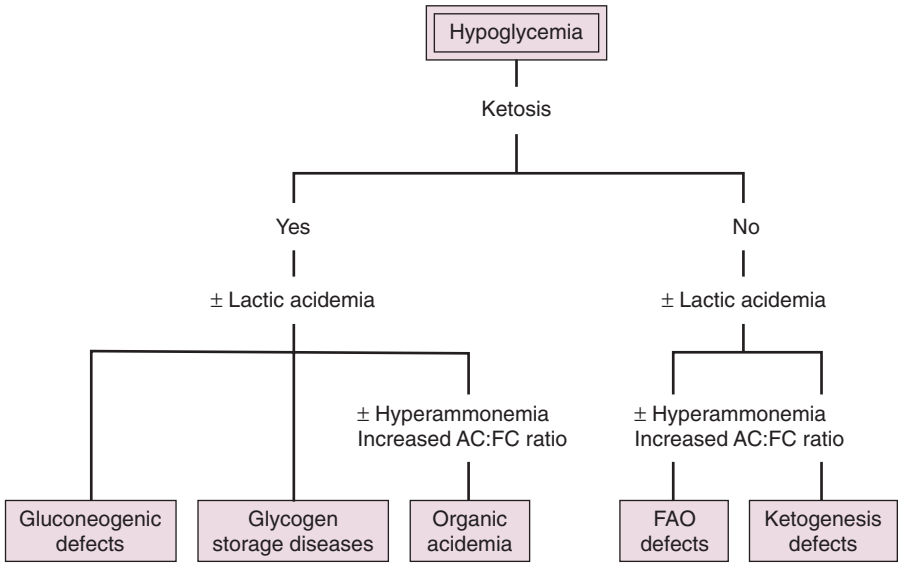
The first laboratory finding that is used to discriminate between the disorders that cause hypoglycemia is the presence or absence of ketosis (see Fig. 90.3), because the physiologic response to fasting or hypoglycemia should be increased lipolysis, fatty acid oxidation, and ketone body formation. Defects of gluconeogenesis, glycogenolysis, and organic acid metabolism (especially the common branched-chain disorders) are generally accompanied by ketosis, whereas defects in fatty acid β-oxidation and ketogenesis are accompanied by increased plasma free fatty acids without a concomitant increase in plasma β-hydroxybutyrate and acetoacetate concentrations.

TABLE 90.17 Metabolic Disorders Associated With Neonatal Hypoglycemia

Category of Disorders	Disorder
Fatty acid oxidation	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase Ia deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/ trifunctional protein deficiency Short-chain acyl-CoA dehydrogenase deficiency Very-long-chain acyl-CoA dehydrogenase deficiency
Gluconeogenesis	Fructose-1,6-diphosphatase deficiency Hereditary fructose intolerance Phosphoenolpyruvate carboxykinase deficiency Pyruvate carboxylase deficiency
Glycogen storage disease (GSD)	GSD type I (glucose-6-phosphatase deficiency) GSD type III (debrancher deficiency) GSD type IX (phosphorylase kinase deficiency)
Ketogenesis	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
Organic acidemias	Isovaleric acidemia Maple syrup urine disease Methylmalonic acidemia Multiple acyl-CoA dehydrogenase deficiency Multiple carboxylase deficiency Propionic acidemia

The second laboratory finding used to distinguish among the neonatal hypoglycemias is lactic acidemia (see Fig. 90.3). Although the simple presence or absence of lactic acidemia is not useful for discriminating among these disorders because they all can exhibit some degree of lactic acidemia depending on the physiologic circumstances, the relative degree of lactic acidemia and its relationship to feeding are important discriminating factors. For example, the magnitude of the lactic acidemia seen in the organic acidemias is generally less than that seen in the gluconeogenesis defects and glycogen storage diseases. The lactate concentration decreases in the fed state for patients with glycogen storage disease type I, whereas it increases for patients with glycogen storage disease type III. Similarly, lactic acidemia becomes more pronounced with fasting in patients with fatty acid oxidation defects and organic

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• **Fig. 90.3** Approach to neonatal hypoglycemia. AC:FC, Ratio of acylcarnitine to free carnitine; FAO, fatty acid oxidation.

acidemias but is greater in the fed state than in the fasted state for those with the glycogen storage disorders associated with hypoglycemia.

The third laboratory finding that may be useful is the plasma ammonia concentration. Hyperammonemia often accompanies hypoglycemia in patients with fatty acid oxidation defects, ketogenesis defects, and organic acidemias, but it is not seen in defects of gluconeogenesis (except severe PC deficiency) or the glycogen storage diseases. In addition, there is a disorder known as hyperammonemia/hyperinsulinism (HA/HI) syndrome, which is the consequence of a dominant activating mutation in the glutamate dehydrogenase gene (*GLUD1*).[82] Patients with this disorder have a consistent association of hypoglycemia and hyperammonemia. They typically have a relatively mild-moderate degree of hyperammonemia, and management is focused on insulin regulation rather than hyperammonemia. Hence, this disorder is discussed in more detail in Chapter 86.

Gluconeogenesis Defects

Gluconeogenesis is the pathway by which glucose is synthesized from non-carbohydrate metabolites. The principal gluconeogenic precursors are pyruvate and lactate, certain gluconeogenic amino acids, and glycerol, which is derived mainly from fat metabolism. Several inborn errors of gluconeogenesis cause hypoglycemia (see Table 90.17).

Fructose-1,6-bisphosphatase deficiency is an autosomal recessive disorder characterized by hyperventilation associated with severe ketoacidosis, hypoglycemia, seizures, and lethargy, sometimes leading to coma. Hepatomegaly and the degree of liver dysfunction are generally mild. The defect in gluconeogenesis leads to lactic acidosis. Diagnosis requires a liver, intestine, or kidney biopsy for specific enzyme analysis. Acute episodes are treated with glucose administration, which is generally successful in correcting the hypoglycemia and ketoacidosis. Long-term treatment requires avoidance of fasting and removal of most fructose from the diet. As discussed for the glycogen storage diseases, patients with fructose-1,6-bisphosphatase deficiency benefit from continuous nighttime feedings or the use of uncooked cornstarch.

Pyruvate carboxylase (PC) deficiency can manifest in the neonatal period with hepatomegaly, hyperammonemia, lactic acidosis, citrullinemia, hyperlysinemia, and structural CNS malformations.[136] Patients who present with the severe form of the disease in the newborn period might not survive beyond the first few months of life. Patients who have a less severe form of PC deficiency may do well when they avoid fasting, have nighttime feedings, and receive supplementation with citrate (which yields oxaloacetate, the product of the PC enzyme reaction).

Phosphoenolpyruvate carboxykinase (PEPCK) deficiency is a rare cause of neonatal hypoglycemia associated with lactic acidemia. There are two forms of this deficiency, corresponding to deficiency of the cytosolic form and the mitochondrial form of the enzyme, respectively. The clinical features of both forms are incompletely characterized owing to the rarity of these disorders. The diagnosis can be accomplished by enzyme analysis or genetic testing.

Glycogen Storage Disorders

Glycogen storage disease type I is the most common defect of gluconeogenesis or glycogenolysis.[6] This diagnosis should be considered if, in addition to increased plasma free fatty acid and ketone body concentrations, clinical examination demonstrates hepatomegaly and additional laboratory studies reveal lactic acidosis, hypertriglyceridemia, and hyperuricemia.

The most common form of glycogen storage disease (GSD) is GSD type Ia (commonly known as von Gierke disease), which is caused by glucose-6-phosphatase deficiency. Another form of this disorder is caused by deficiency of glucose-6-phosphate translocase and is known as GSD type Ib. In addition to the clinical features of type Ia disease,

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glycogen storage disease type Ib is also characterized by neutropenia and neutrophil dysfunction, which lead to a propensity for serious bacterial infections. The long-term complications of both forms of type I glycogen storage disease include intellectual delay as a result of unrecognized or untreated hypoglycemia, short stature, gout, renal disease, and hepatic adenoma.

Glycogen storage disease type III does not typically present in the neonatal period but may do so rarely. The hypoglycemia associated with GSD type III can be as severe as that seen with GSD type I, but GSD type III does not lead to increased concentrations of lactic acid and uric acid in blood. GSD type III may involve the skeletal muscle and heart, as well as liver, and be associated with increased serum CK activity.

Definitive diagnosis of GSD type I requires detailed enzymatic analysis of a liver biopsy specimen; the liver specimen must be fresh if studies for type Ib are to be done. GSD type III disease can be diagnosed by enzyme analysis of white blood cells, liver, or skeletal muscle. Alternatively, the diagnosis of GSD Ia, Ib, or III can be established by genetic testing.

The mainstay of treatment for these forms of glycogen storage disease is to avoid prolonged fasting. Older affected patients should be provided with frequent daytime feedings and continuous nasogastric infusion or uncooked cornstarch at night. These treatments appear to be successful in controlling the hypoglycemia and other metabolic consequences associated with these disorders, but they might not eliminate the long-term sequelae (e.g., development of hepatic adenoma in glycogen storage disease type Ia).[6]

Organic Acidemias

Several organic acidurias or acidemias cause neonatal hypoglycemia (see Table 90.17 and Metabolic Acidosis). These disorders should be suspected when there is a metabolic acidosis, an anion gap, ketosis, abnormal results on urine spot tests for α-ketoacids, or an abnormal smell. Urinary organic acid analysis is the strategic diagnostic study. Many patients with an organic acid disorder have significant hyperammonemia. Plasma and urinary carnitine measurements are useful in diagnosing and possibly managing these disorders. Many of the organic acidurias are characterized by an increased acylcarnitine-to-free carnitine ratio in plasma and urine and overproduction of a particular acylcarnitine.

Fatty Acid Oxidation Disorders

Two groups of disorders cause neonatal hypoglycemia without ketosis: defects of fatty acid oxidation and defects of ketogenesis. It should be pointed out that inborn errors of metabolism, which cause severe hepatocellular or cirrhotic liver disease, also produce nonketotic or hypoketotic hypoglycemia associated with lactic acidosis. The disorders of fatty acid oxidation are discussed further in this section, whereas the defects of ketogenesis (e.g., 3-hydroxy-3-methylglutaryl-CoA lyase deficiency) are discussed in the preceding section on metabolic acidosis.

The primary pathway of fatty acid oxidation takes place within the mitochondrion.[58,93] Most forms of dietary fat contain primarily long-chain fatty acids. For these long-chain fatty acids to be oxidized, they must be transported across the mitochondrial membranes into the mitochondrial matrix. The system for transporting these fatty acids across the mitochondrial membranes includes three components: carnitine palmitoyltransferase I (CPT I), carnitine-acylcarnitine translocase, and carnitine palmitoyltransferase II (CPT II). Medium- and short-chain fatty acids do not require this special system for transport across the mitochondrial membranes. Another transporter facilitates the uptake of free carnitine across the plasma membrane into the cytoplasm, making it available for transporting fatty acids into the mitochondrion.

Inside the mitochondrion, fatty acids exist as their acyl-CoA derivatives. These fatty acid acyl-CoAs are degraded by the mitochondrial fatty acid β-oxidation system to form acetyl-CoA. The acyl-CoAs are degraded sequentially by a series of four enzymes: acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and 3-ketothiolase. Different forms of these enzymes exist for fatty acid acyl-CoAs of different chain lengths. These enzymes sequentially degrade the acyl-CoAs two carbon groups per turn of the β-oxidation cycle, from long-chain acyl-CoAs, to medium-chain acyl-CoAs, and finally to short-chain acyl-CoAs. An intact mitochondrial respiratory chain is required for normal functioning of the fatty acid β-oxidation pathway, because it replenishes the oxidized forms of flavin adenine dinucleotide and nicotinamide adenine dinucleotide needed by the acyl-CoA dehydrogenases and the 3-hydroxyacyl-CoA dehydrogenases, respectively. Genetic deficiencies of each of these enzymes have been described.[58,93,105]

As a rule, defects of long-chain fatty acid oxidation are more likely to manifest in the neonatal period and cause serious problems than are defects of medium- or short-chain fatty acids.[93,105] Defects in long-chain fatty acid oxidation that may manifest in the neonatal period include CPT II deficiency (but generally not CPT I deficiency), carnitine-acylcarnitine translocase (CACT) deficiency, very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, and the related disorder, mitochondrial trifunctional protein (TFP) deficiency. Plasma membrane carnitine transporter deficiency (the cause of carnitine uptake deficiency) does not generally manifest in the neonatal period.

These disorders are a recognized cause of hypoglycemia, liver disease, cardiomyopathy, cardiac arrhythmias, and sudden death. The association of these defects with cardiomyopathy is consistent with the role of long-chain fatty acids as the chief energy source for the myocardium. The cause of the arrhythmias is less certain but may be a toxic effect of the long-chain acylcarnitines that accumulate in these disorders. Hyperammonemia may be seen in patients with the most severe forms of these deficiencies, for example, CACT deficiency and LCHAD deficiency.[78]

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Neonatal CPT II deficiency is also associated with renal microcysts and CNS malformations. LCHAD dehydrogenase deficiency and other defects of long-chain fatty acid oxidation have gained attention as a cause of acute fatty liver of pregnancy in pregnant women who are carrying a fetus that is homozygous for this deficiency (see Prenatal Onset).[9,91]

Defects of medium- or short-chain fatty acid β-oxidation include medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, short-chain acyl-CoA dehydrogenase (SCAD) deficiency, isobutyryl-CoA (IBD) deficiency, and short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency.[93,105] The clinical features of all these disorders differ significantly from those of the long-chain fatty acid β-oxidation disorders. MCAD deficiency is the most common of the fatty acid β-oxidation disorders when all age groups are considered, but it does not generally appear in the neonatal period (see Newborn Screening Programs).[68] Care should be taken, however, to promptly initiate diagnostic evaluation and treatment for a neonate who is at risk for MCAD deficiency by virtue of family history or identified by newborn screening (see Tables 90.1 and 90.2). In contrast, the clinical phenotype of SCAD deficiency and IBD deficiency are ill-defined. The original clinical reports on SCAD deficiency described patients with a variable pattern of medical problems, including developmental delay. However, few patients who were subsequently ascertained by newborn screening with SCAD deficiency have manifested any medical problems, suggesting that the originally described patients represented an ascertainment bias. A single patient with IBD deficiency was described with cardiomyopathy associated with carnitine deficiency. Carnitine deficiency has been observed subsequently in other patients with IBD deficiency, and patients identified by newborn screening may benefit from ongoing monitoring for carnitine deficiency. Last, SCHAD deficiency does not manifest as a classical disorder of fatty acid β-oxidation but rather manifests with hypoglycemia secondary to hyperinsulinism. The diagnosis and treatment of this disorder is discussed in Chapter 86.

Acute management of the newborn with a suspected fatty acid oxidation defect should begin with prompt infusion of high concentrations of glucose to correct the hypoglycemia and the underlying energy deficit. The patient should receive glucose at a rate of 10 mg/kg per minute or greater to maintain the serum glucose concentration greater than 100 mg/dL. A patient suspected of having a defect in short- or medium-chain fatty acid oxidation can continue to receive breast milk or formula. On the other hand, a patient suspected of having a defect in long-chain fatty acid oxidation should not receive breast milk or be on formula that contains long-chain fats (especially if symptomatic) until it is determined whether the patient has a defect of fatty acid oxidation. However, there is some debate regarding this approach among physicians who treat asymptomatic patients with VLCAD deficiency; some physicians restrict long-chain fats in the diet while others do not. The use of parenteral intralipids is advised against in patients with medium- and long-chain fatty acid oxidation disorders.

A related consideration is the use of carnitine in patients with a suspected or proven fatty acid oxidation disorder. Carnitine has been used in patients with these disorders, because they are often carnitine depleted. However, there is also concern about the use of carnitine supplementation in patients with long-chain fatty acid oxidation defects, because carnitine supplementation might increase the production of long-chain acylcarnitines, which can be arrhythmogenic.[58] The relative merits of using carnitine in the acute or chronic care of these patients with long-chain fatty acid β-oxidation defects are uncertain, but judicious use of a moderate carnitine dose (50 mg/kg per day) is often used until a diagnosis is established and then adjusted depending on the patient's diagnosis, clinical status, and plasma carnitine analysis.

When the initial hypoglycemic episodes are controlled, the patient should be started on a high-carbohydrate diet, while making certain to avoid fasting. Formulas enriched with medium-chain triglycerides (which are very commonly used in nurseries and in neonatal intensive care units) should not be started before the infant's diagnosis has been established, because they can be dangerous to patients with defects in medium-chain fatty acid oxidation. In contrast, patients suspected of having a defect in long-chain fatty acid oxidation might benefit from one of the long-chain fat–restricted, medium-chain fat–enriched formulas that are available. Once a diagnosis is established, a decision can be made regarding the infant's tolerance for fat and an appropriate diet started. Riboflavin supplementation (50 mg/day) should be tried and its benefit evaluated, especially for a patient suspected of having glutaric aciduria type II. Long-term carnitine supplementation may be of benefit in some patients.

Hyperammonemia

The neonate with a hyperammonemia syndrome generally does well for the first few days of life and then develops poor feeding, lethargy, vomiting, and tachypnea. If unrecognized and untreated, the illness may progress rapidly to coma, seizures, autonomic instability, and death. When hyperammonemia is suspected, the possibility should be investigated immediately, because these illnesses can produce irreversible neurologic sequelae and are life threatening.

Differential Diagnosis

Many inborn errors of metabolism can cause significant hyperammonemia in the newborn infant, and an attempt must be made to quickly reach a provisional diagnosis (Box 90.2). By convention, the primary hyperammonemias include deficiencies of the six enzymes that make up the urea cycle:

- N-acetylglutamine synthetase (NAGS);
- carbamoylphosphate synthetase I (CPS1), referred to simply as CPS elsewhere in the chapter;
- ornithine transcarbamylase (OTC);

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• BOX 90.2 Genetic Disorders Associated With Hyperammonemia in Neonates

Fatty Acid Oxidation Disorders

- Carnitine-acylcarnitine translocase deficiency
- Carnitine palmitoyltransferase II deficiency
- Long-chain acyl-CoA dehydrogenase deficiency
- Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

Lactic Acidemias

- Gluconeogenic disorders
  - Pyruvate carboxylase deficiency
- Mitochondrial disorders
  - Mitochondrial DNA depletion syndromes
  - *FBXL4*-associated deficiency
- Mitochondrial complex assembly
  - *TMEM70*-associated deficiency

Organic Acidurias

- 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
- Isovaleric acidemia
- 3-Ketothiolase deficiency
- Methylmalonic acidemia
- Multiple acyl-CoA dehydrogenase deficiency
- Propionic acidemia

Urea Cycle Disorders

- Argininemia
- Argininosuccinic acid lyase deficiency
- Argininosuccinic acid synthetase deficiency
- Carbamoyl phosphate synthetase deficiency
- Ornithine transcarbamylase deficiency
- N-Acetylglutamate synthetase deficiency
- Urea cycle-associated amino acid transport disorders
  - Citrin deficiency
  - Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

- argininosuccinic acid synthetase (ASS1), referred to simply as ASS elsewhere in the chapter;
- argininosuccinic acid lyase (ASL); and
- arginase (ARG1), referred to simply as ARG elsewhere in the chapter.

In addition, two amino acid transporters are required for normal functioning of the urea cycle:

- an ornithine transporter (ORNT1); and
- an aspartate transporter (citrin).

See Fig. 90.4 for an illustration of the urea cycle. The various steps in the urea cycle are described in the next section, Urea Cycle Disorders. The secondary hyperammonemias include genetic disorders that lead to overproduction of toxic metabolites that inhibit the urea cycle or depletion of substrates that are required for normal functioning of the urea cycle: fatty acid oxidation disorders, lactic acidemias, organic acidemias, and several other inborn errors.

A systematic approach to the differential diagnosis of these disorders is presented in Fig. 90.5. It is imperative that the possibility of a primary hyperammonemia syndrome (a urea cycle defect) be distinguished from a secondary hyperammonemia syndrome (e.g., an organic aciduria), because the best way of treating the hyperammonemia in the latter would be to treat the underlying disorder.

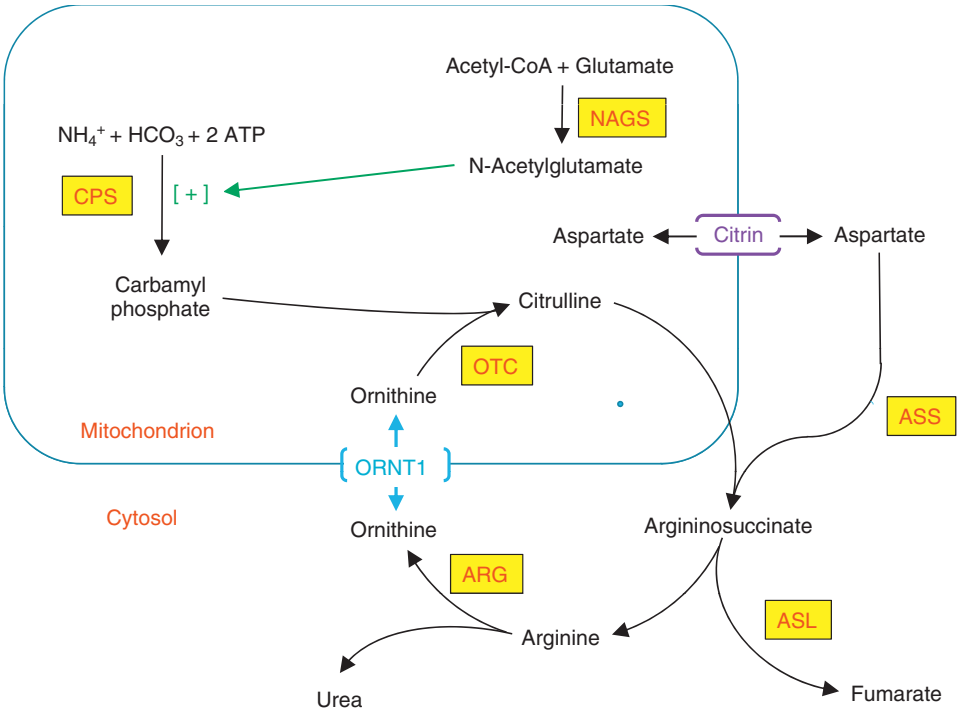
The first step in evaluating a patient with a suspected hyperammonemia is to obtain an accurate plasma ammonia concentration. The plasma sample for ammonia determination must be collected, transported on ice to the laboratory, and then rapidly analyzed. A plasma ammonia concentration greater than 150 μmol/L suggests the possibility that the patient has an inborn error of metabolism and should be evaluated further.

Most primary disorders of the urea cycle do not begin in the first 24 hours of life. Hyperammonemia that develops within the first 24 hours of life is generally associated with prematurity or a secondary hyperammonemia, usually a disorder of organic acid metabolism or fatty acid oxidation.[3,60] The severe hyperammonemia associated with prematurity has been designated transient hyperammonemia of the newborn. It is a mistake to believe that transient means that this disorder is benign. The degree of hyperammonemia found in this disorder can be as great as that found in many of the primary hyperammonemia syndromes, sometimes exceeding 1000 μmol/L. This disorder, therefore, requires the rapid and vigorous therapy, as do the other defects of the urea cycle.

Following confirmation that the patient has significant hyperammonemia, several laboratory studies should be obtained to determine whether the patient has a primary or secondary hyperammonemia: blood gas, electrolytes, glucose, and blood and urine ketones. It is generally advisable to obtain additional studies with the initial testing, or when the results of the initial studies are available, in order to establish a more specific diagnosis. The additional testing should include plasma amino acid analysis, plasma carnitine analysis with an acylcarnitine profile, urine amino acid analysis, urine organic acid analysis, and urine orotic acid analysis. Treatment should be started before the results of all these studies are available and modified as the nature of the underlying cause of the hyperammonemia is clarified.

The results of the initial testing provide information about several key laboratory features that can be used to distinguish between a primary and a secondary hyperammonemia syndrome: the presence or absence of acidosis, an increased anion gap, hypoglycemia, and/or ketosis (see Fig. 90.5). The urea cycle defects are generally associated with respiratory alkalosis during the initial phase of the illness in response to the increased ventilatory rate induced by the cerebral edema that often accompanies hyperammonemia. Later in the course of the illness, a component of acidosis can be superimposed on the initial respiratory alkalosis as the patient's clinical status deteriorates. As a result of the evolving acid–base balance associated with urea cycle defects, the presence or absence of acidosis is not a reliable finding to distinguish between patients with primary and secondary hyperammonemia and is not included in the algorithm provided in Fig. 90.5.

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• **Fig. 90.4** Urea cycle pathway. ARG, Arginase; ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase (associated with citrullinemia type I); CPS1, carbamoylphosphate synthetase 1; NAGS, N-acetylglutamate synthetase; ORNT1, ornithine transporter (associated with hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome); OTC, ornithine transcarbamylase. (Adapted from Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2017 Jun 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. GeneReviews® is a registered trademark of the University of Washington, Seattle. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1217.)

However, patients with a urea cycle disorder generally do not have an increased anion gap, hypoglycemia, or ketosis and can be distinguished from the secondary hyperammonemias using these laboratory findings. The organic acidemias are generally characterized by metabolic acidosis and an increased anion gap (see Fig. 90.1). Metabolic acidosis can also be seen with fatty acid oxidation defects and the severe neonatal form of pyruvate carboxylase (PC) deficiency, a gluconeogenic disorder that is associated with lactic acidemia, especially during fasting (see Fig. 90.2).

Hypoglycemia is not typically associated with urea cycle defects but is typically observed in fatty acid oxidation disorders and gluconeogenic disorders and can be observed in several organic acidemias and mitochondrial disorders (see Fig. 90.3).

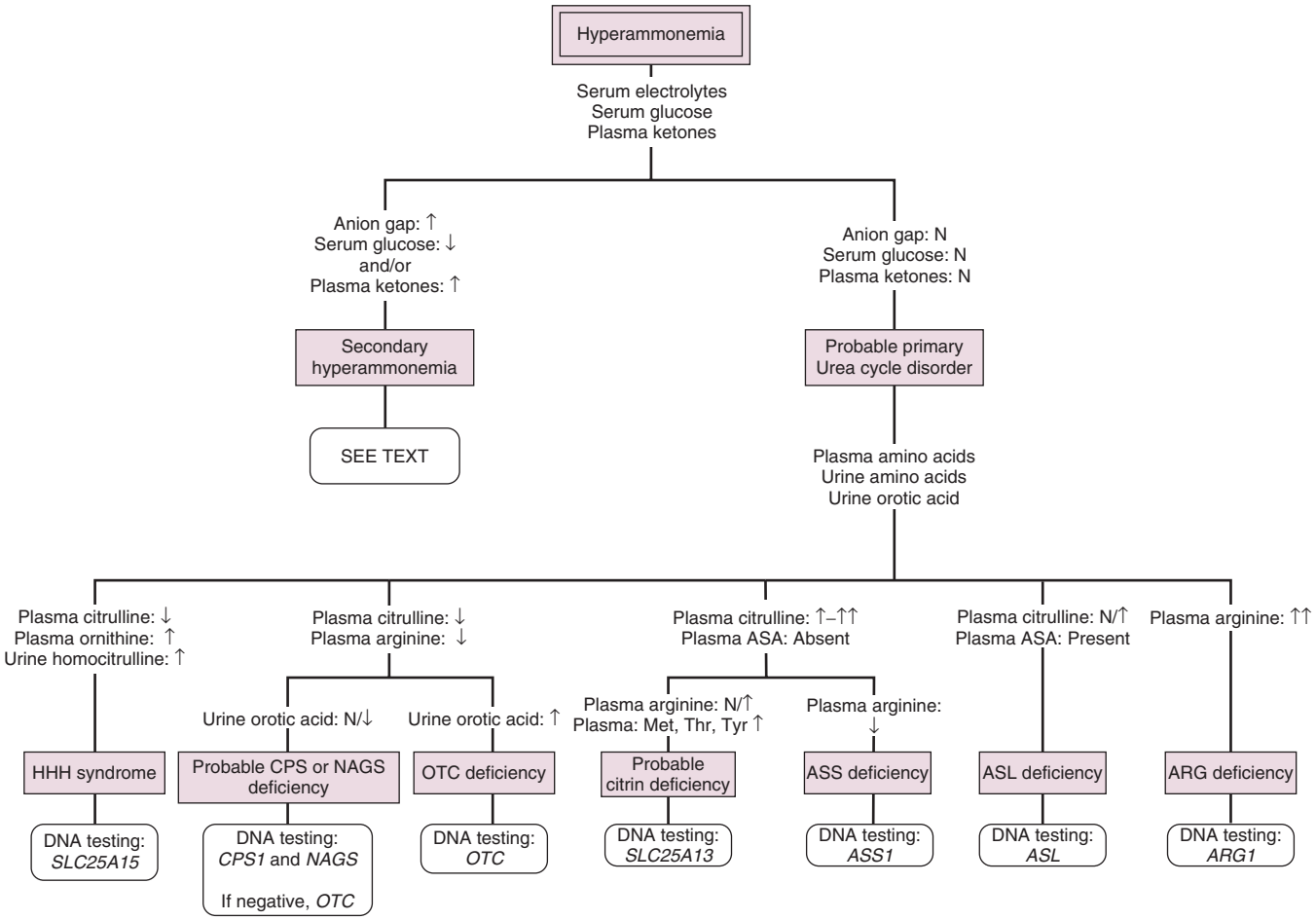
Ketosis is not a characteristic feature of urea cycle defects, but it is a hallmark of the several organic acidemias and PC deficiency and can be observed in mitochondrial disorders. In contrast, the distinguishing feature of the fatty acid oxidation disorders is nonketotic or hypoketotic hypoglycemia.

In summary, urea cycle disorders are characterized by a normal anion gap, a normal serum glucose concentration, and the absence of ketosis, whereas the secondary hyperammonemias are characterized by an increased anion gap (>20 mEq/L), hypoglycemia, and/or ketosis (see Fig. 90.5).[3] Further diagnostic evaluation and care of the patient with a suspected urea cycle disorder is presented in the following section, followed by a section dealing with the secondary hyperammonemias.

Urea Cycle Disorders

Patients with a urea cycle defect are generally well at birth but develop clinical signs of hyperammonemic encephalopathy at 48-72 hours of age. The initial clinical manifestations often include poor feeding, lethargy, hypothermia, hyperventilation, abnormal posturing, and seizures. The lethargy may progress to lethargy and coma, and ultimately death secondary to brain stem compression caused by cerebral edema. This course is typical of severe forms of N-acetylglutamate synthetase (NAGS) deficiency, carbamoyl phosphate synthetase 1 (CPS1) deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinic acid synthetase (ASS) deficiency (also known as citrullinemia type I), and argininosuccinic acid lyase (ASL) deficiency (see Fig. 90.4). This pattern is not typical of arginase (ARG1) deficiency, ORNT1 deficiency, hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, or citrin deficiency, which have different

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• **Fig. 90.5** Approach to neonatal hyperammonemia. ASA, Argininosuccinic acid; Met, methionine; N, normal; Thr, threonine; and Tyr, tyrosine. Abbreviations used for enzymes and transporters: ARG, arginase; ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase (associated with citrullinemia type I); CPS1, carbamoylphosphate synthetase 1; NAGS, N-acetylglutamate synthetase; ORNT1, ornithine translocase (associated with hyperornithinemia-hyperammonemia-homocitrullinuria [HHH] syndrome); OTC, ornithine transcarbamylase. Gene names (all of which are italicized by convention): *ARG1*, encodes for the arginase protein; *ASL*, encodes for the argininosuccinate lyase protein; *ASS1*, encodes for the argininosuccinate synthetase protein; *CPS1*, encodes for the carbamoylphosphate synthetase protein; *NAGS*, encodes for the N-acetylglutamate synthase protein; *OTC*, encodes for ornithine transcarbamylase protein; *SLC2525A13*, encodes for the citrin protein; *SCL25A15*, encodes for the ornithine translocase protein (ORNT1), an aspartate transporter. (Adapted from Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2017 Jun 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. GeneReviews® is a registered trademark of the University of Washington, Seattle. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1217.)

clinical phenotypes.[3,66,98] The prognosis for neonates with hyperammonemic encephalopathy depends on the severity of the underlying genetic defect and the duration of symptoms before treatment is started. Long-term neurologic sequelae are common, even for patients who are recognized and treated early.

The first step in the urea cycle is the formation of carbamoyl phosphate from ammonia by carbamoyl phosphate synthetase 1 (CPS1). N-acetylglutamate synthetase (NAGS) catalyzes the conversion of acetyl-CoA and glutamate to N-acetylglutamate, which is required for activation of CPS1. The next enzyme in the cycle, ornithine transcarbamylase (OTC), converts carbamoyl phosphate and ornithine to citrulline. Citrulline and aspartate are converted to argininosuccinate by argininosuccinic acid synthetase (ASS). Argininosuccinic acid is then cleaved by argininosuccinic acid lyase (ASL) to produce arginine and fumarate. Finally, arginine is cleaved by arginase to form urea and ornithine. The urea is excreted in the urine, and the ornithine is available to restart the cycle. Ornithine, citrulline, argininosuccinate, arginine, and aspartate are all amino acids. In addition to these enzyme reactions, two amino acid transporters are required to provide substrates for the urea cycle: an ornithine transporter (ORNT1) and an aspartate transporter (citrin). The role of these enzymes and transporters is illustrated in Fig. 90.4.

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Urea cycle disorders can be differentiated from each other by performing plasma amino acid analysis, urine amino acid analysis, and urine orotic acid analysis (see Specialized Biochemical Testing).[3] The amino acids proximal to the enzyme deficiency are increased, whereas the amino acids distal to the enzyme deficiency block are decreased. Except in the case of arginase deficiency, the urea cycle disorders are characterized typically by an increased plasma concentration of glutamine, glycine, and alanine, and a decreased plasma arginine concentration.

The plasma citrulline and argininosuccinate concentrations provide the initial keys to distinguishing among the urea cycle defects that manifest with hyperammonemia in the neonatal period (see Fig. 90.5). The plasma citrulline concentration is generally low in NAGS deficiency, CPS1 deficiency, and OTC deficiency, because citrulline synthesis requires the sequential action of these enzymes. Measurement of urinary orotic acid, which is formed from excessive amounts of carbamoyl phosphate that leave the mitochondrion and enter the cytosolic pyrimidine biosynthetic pathway, can be used to distinguish among NAGS deficiency, CPS deficiency, and OTC deficiency. The urinary orotic acid concentration is low or normal in NAGS deficiency and CPS1 deficiency but elevated in OTC deficiency.

Once formed, citrulline is converted to argininosuccinate by ASS. In the absence of ASS, citrulline produced by the earlier steps of the urea cycle accumulates in high concentration. For this reason, ASS deficiency is commonly called citrullinemia type I. Argininosuccinate lyase deficiency leads to increased excretion of argininosuccinate (and its anhydrides) and moderate elevation of plasma citrulline. Deficiency of the last step in the urea cycle, arginase, is rarely a cause of hyperammonemia in the neonatal period but is a cause of neurologic disease and occasionally hyperammonemia in later childhood. N-acetylglutamate synthetase deficiency resembles CPS1 deficiency, and it requires enzyme analysis of a liver biopsy or genetic testing to distinguish between the two disorders. Plasma and urine amino acid analysis are required to distinguish ORNT1 deficiency and citrin deficiency from the other urea cycle disorders and from each other.[3]

Treatment for the acute phase of the urea cycle disorders includes stopping dietary protein intake, suppressing endogenous protein catabolism through hypercaloric parenteral administration of glucose and intralipids (using an insulin infusion if necessary to avoid hyperglycemia), and providing drugs that serve as alternate pathways for ammonia detoxification and excretion. Hemodialysis is required for severe cases in which the patient has a plasma ammonia concentration greater than 200 umol/L that has not responded to the previously listed modes of therapy and in severe cases in which the patient presents with a plasma ammonia concentration greater than 400 umol/L.[3,96,107,112] Physicians who are unable to offer these forms of therapy should consider transferring their patients to centers that have such capability.

The protocols for detoxifying ammonia employ drugs that form excretable compounds with amino acids that accumulate during hyperammonemic crisis. The first drug to be developed was sodium benzoate, which conjugates with glycine to form benzoylglycine (hippurate); formation and excretion of one molecule of hippurate eliminates one molecule of ammonia. The second drug to be developed was sodium phenylacetate, which conjugates with glutamine to form phenylacetylglutamine; formation and excretion of one molecule of phenylacetylglutamine eliminates two molecules of ammonia. Sodium phenylacetate is still available for intravenous use, but it has been replaced for oral use by sodium phenylbutyrate and more recently by glycerol phenylbutyrate (Ravicti).

In addition to these drugs, arginine (or citrulline, if diagnosis has been made and indicates that citrulline is the preferred medication) is provided to prime the urea cycle (i.e., regenerate ornithine), which is the precursor for the next turn of the cycle. N-carbamylglutamate (Carbaglu) is an analogue of N-acetylglutamate that can be taken orally and appears to be an effective treatment for N-acetylglutamate synthetase deficiency. Long-term management of these disorders after the acute illness entails modification of this basic plan.[3]

The prognosis for neonates who present with a urea cycle defect in the newborn period is guarded.[5,61] Without treatment, the mortality rate is high. With treatment, the mortality is reduced, but survivors are often left with significant neurologic impairments and a lifelong illness that predisposes them to recurrent life-threatening metabolic crises. The prognosis is particularly guarded for patients with defects affecting the early part of the cycle, namely, NAGS deficiency, CPS deficiency, and OTC deficiency. The prognosis for patients with more distal defects in the urea cycle (i.e., ASS deficiency and ASL deficiency) is better, although these patients also experience recurrent hyperammonemic crises. The guarded prognosis for these patients has led many groups to perform early liver transplantation for these patients, especially those with severe NAGS, CPS, and OTC deficiency. The results of these efforts appear promising.[69,80,112]

Secondary Hyperammonemias

As noted above in the Differential Diagnosis section, the secondary hyperammonemias are differentiated from the primary hyperammonemias (the urea cycle disorders) by the presence of acidosis, an increased anion gap, and/or ketosis (see Fig. 90.5). The secondary hyperammonemias can, in turn, be distinguished from each other by further laboratory testing, including plasma amino acid analysis, plasma carnitine analysis with an acylcarnitine profile, plasma lactate analysis, and urine organic acid analysis. This testing will permit identification of five groups of disorders: fatty acid oxidation disorders, lactic acidemias (gluconeogenic disorders and mitochondrial disorders), organic acidemias, and a miscellaneous group (see Fig. 90.1, Fig. 90.2, and Fig. 90.3 for the diagnostic algorithms

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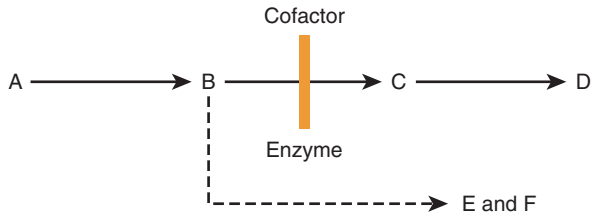
for metabolic acidosis, lactic acidemia, and hypoglycemia, respectively). Further discussion of these disorders is presented in the sections of this chapter that accompany these figures.

Although the secondary hyperammonemias are a clinically diverse group of disorders, they all exhibit hyperammonemia as the result of a defect outside the urea cycle that indirectly affects urea cycle function via enzyme inhibition or substrate deficiency. The secondary hyperammonemias can be classified into three groups of disorders based on their pathophysiology:

- Enzyme inhibition
  - *Organic acidemias*. Several organic acidemias, including the three most common organic acidemias—methylmalonic acidemia, propionic acidemia, and isovaleric acidemia—lead to overproduction of toxic metabolites that interfere with the ability of NAGS to produce N-acetylglutamate, which is required for activation of CPS1, the first step in the urea cycle. Thus, these disorders lead to a CPS1-like syndrome, which can present with plasma ammonia concentrations >1000 umol/L in the neonatal period. These disorders are discussed elsewhere in this chapter (see Metabolic Acidosis subsection under Abnormal Newborn Infant: Laboratory Phenotypes).
- Substrate deficiencies
  - *Fatty acid oxidation and carnitine cycle disorders.* One of the final products of mitochondrial fatty acid oxidation or the carnitine cycle is acetyl-CoA. Defects in either fatty acid oxidation (especially those affecting long-chain fatty acid oxidation) or the carnitine cycle (which is required for transport of long-chain fatty acids into the mitochondria where they undergo oxidation) leads to decreased acetyl-CoA production and possibly acylation and decreased activity of the VLCAD enzyme. These disorders may also lead plasma ammonia concentrations >1000 µmol/L in the neonatal period. These disorders are discussed elsewhere in this chapter (see Fatty Acid Oxidation Disorders in the section Abnormal Newborn Infant: Laboratory Phenotypes).
  - *Mitochondrial disorders.* Several mitochondrial disorders are associated with hyperammonemia including several mtDNA depletion syndromes and respiratory chain deficiencies. One proposed mechanism for the hyperammonemia in these disorders is that they interfere with ATP production, which is a required substrate for the CPS1-mediated synthesis of carbamyl phosphate. It is also likely that the several of these disorders also lead to more global structural impairment of mitochondrial structure and indirectly affect the urea cycle and related pathways. Two recently described examples of these severe mitochondrial phenotypes are associated with mutations in *FBXL4* and *TMEM70*. Both are inherited in an autosomal recessive manner because of mutations in these nuclear genes.

    Encephalomyopathic mitochondrial DNA depletion syndrome, type 13 (MTDPS13) is caused by mutations in the *FBXL4* gene, which appears to encode for a protein required for maintaining intramitochondrial architecture.[75] Patients with this deficiency may manifest intrauterine growth failure, cardiomyopathy, congenital heart defects, feeding difficulties, failure to thrive, global developmental delay, and brain atrophy. Laboratory abnormalities include lactic acidemia (and increased CSF lactic acid), hyperammonemia, elevated serum creatine kinase activity, nonspecific mitochondrial respiratory chain enzyme deficiencies, and mtDNA depletion. The diagnosis is established by genetic testing of the *FBXL4* gene. No specific treatment is available. The *TMEM70* gene encodes for *t*rans*mem*brane protein *70*, a mitochondrial membrane protein that is required for biogenesis of the mitochondrial ATP synthase (also known as complex V of the oxidative phosphorylation system).[62] *TMEM70* deficiency is characterized by neonatal onset of hypotonia, hypertrophic cardiomyopathy, and apneic spells, accompanied by lactic acidosis, hyperammonemia, decreased concentrations of tricarboxylic acid (TCA) cycle intermediates, and 3-methylglutaconic aciduria. No specific treatment is available.
  - *Pyruvate carboxylase (PC) deficiency.* PC converts pyruvate to oxaloacetate, which is in turn converted to aspartate. Aspartate is a required substrate for argininosuccinate synthetase (ASS). Thus, PC deficiency leads to hyperammonemia. The clinical features and management of PC deficiency are provided elsewhere in this chapter (see Gluconeogenic Disorders in the section The Abnormal Newborn Infant: Laboratory Phenotypes).[136]
- Others
  - *Glutamine synthetase (GS) deficiency.* GS catalyzes the conversion of glutamate to glutamine, which is an alternate mechanism of ammonia detoxification. GS deficiency increases the ammonia load that the urea cycle must handle. This disorder leads to moderate hyperammonemia and neonatal seizures (see Seizures subsection under Abnormal Newborn Infant: Clinical Phenotypes).[39,40]
  - *Hyperinsulism/hyperammonemia (HI/HA syndrome).* The HI/HA syndrome is caused by an autosomal dominant mutation in the *GLUD1* gene, which encodes for glutamate dehydrogenase.[82] Glutamate dehydrogenase plays a key role in insulin release in response to a protein-containing (specifically, more leucine) meal. This disorder is associated with postprandial hypoglycemia and mild-moderate hyperammonemia. The hyperinsulinism associated with this disorder is diazoxide-responsive, whereas the hyperammonemia is not. See Chapter 86 for more details about the clinical features and management of this disorder.

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• **Fig. 90.6** Schematic depiction of the pathogenesis of many inborn errors of metabolism. See text for details.

Treatment

It is not possible in an overview of inborn errors of metabolism to discuss treatment of all the individual diseases that might be encountered in the newborn period. Treatments for some of these inborn errors of metabolism were discussed in the relevant sections of this chapter. General principles that are relevant to many of these diseases are discussed in the following section.

With few exceptions, the inborn errors of metabolism expressed in the newborn period are inherited as recessive traits. Disorders inherited in this manner generally have a common mechanism of pathogenesis, which is depicted in Fig. 90.6. In simple terms, patients with these metabolic diseases are lacking a specific enzyme that converts substance B to substance C. In some cases, the enzyme requires one or more cofactors for its activity. Deficient enzyme activity may be caused by an error in apoenzyme function or cofactor availability.

The absence of enzyme activity can produce disease in a number of different ways. First, there is accumulation of substance B proximal to the enzyme block, leading to increased concentrations of substance B that might be toxic. The congenital hyperammonemias are a good example of this mechanism. Without one of the urea cycle enzymes, ammonia accumulates and causes significant neurotoxic effects. Second, excess substance B can be converted by alternate pathways to toxic metabolites E and F. It is thought that tyrosinemia type I, for example, produces its hepatotoxic and neurotoxic effects through overproduction of toxic secondary metabolites. Third, the disease state may be caused by deficiency of substance C or D, which is distal to the enzyme block. Defects of gluconeogenesis, such as pyruvate carboxylase deficiency, presumably work through this mechanism. Hypoglycemia results from impaired production of gluconeogenic precursors.

The disease state may be produced by a combination of these mechanisms. It is thought that many of the organic acidemias produce their toxic effects through a combination of mechanisms. In many of these disorders, acyl-CoA molecules accumulate proximal to the enzyme block and interfere with a number of other metabolic pathways (e.g., the urea cycle), and there is underproduction of metabolites distal to the enzyme deficiency that are essential for other cellular processes.

TABLE 90.18 Approaches to Treatment of Inborn Errors of Metabolism

Approach	Examples
Treatment at the metabolite level	Dietary modification to reduce production of toxic metabolites Diversion of toxic metabolites Reduction of the effects of toxic metabolites Supplementation of metabolite deficiencies
Treatment at the protein level	Stimulation of residual enzyme activity Inhibition of toxic metabolite production Replacement of missing enzyme Substrate reduction therapy
Treatment by transplantation	Hematopoietic stem cell transplantation (HSCT) Organ transplantation
Treatment at the genetic level	Somatic cell gene therapy

Traditional approaches to treating inborn errors of metabolism have focused on this model of pathogenesis. The general approaches in use or under development include: (1) treatment at the metabolite level; (2) treatment at the protein (or enzyme) level; (3) treatment by transplantation; and (4) treatment at the genetic manipulation level (Table 90.18).[18,34]

Treatment at the Metabolite Level

The most common form of metabolite manipulation is dietary modification or restriction, which decreases the amount of precursor A that the impaired enzyme must handle. The dietary management of PKU is an example of successful application of this approach. Dietary restriction is often combined with other treatment approaches, such as metabolite diversion.

The therapy for the urea cycle defects is perhaps the best studied of the metabolite diversion strategies. Two drugs, sodium phenylacetate and sodium benzoate, are provided to these patients to serve as ammonia traps (see Hyperammonemia). Phenylacetate can also be provided as phenylbutyrate. Phenylacetate conjugates with glutamine to form phenylacetylglutamine, eliminating two ammonia molecules per molecule of drug as the nitrogen component of glutamine; benzoate conjugates with glycine to form benzoylglycine (hippurate), eliminating one ammonia molecule per molecule of drug as the nitrogen component of glycine. Arginine is also provided to prime the urea cycle, because it is the last amino acid in the urea cycle and is split to release urea and ornithine, the precursor for the next turn of the cycle.

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Another example of diversion of toxic metabolites is carnitine supplementation for the organic acidurias. Carnitine is transesterified with acyl-CoAs to form acylcarnitines. These transesterifications release free CoA, making it available for essential intracellular processes, whereas the potentially toxic acyl groups are excreted in the urine as acylcarnitines and acylglycines.

Reduction of the effects of toxic metabolites is another approach to treatment. One example of this approach is the use of N-methyl D-aspartate (NMDA) receptor agonists such as dextromethorphan or ketamine to treat patients with nonketotic hyperglycinemia. These medications block the excitatory effects that excess glycine has on the NMDA receptors of the central nervous system. The result is reduction (but not complete resolution) of seizure activity in these patients.[45,128]

The deficiency of substances distal to the enzyme block (e.g., C or D) can be overcome by supplementing with exogenous C or D. An example of this approach is the feeding of uncooked cornstarch to patients with the hepatic forms of glycogen storage disease who cannot generate glucose from endogenous glycogen and are predisposed to fasting hypoglycemia. The uncooked cornstarch is metabolized slowly to provide a steady source of glucose while these patients are sleeping.

Treatment at the Protein Level

There are several approaches to treating at the protein level. Historically, the first example of this approach was to stimulate residual enzyme activity by providing pharmacologic amounts of cofactor required by the deficient enzyme. This approach has been used successfully to reduce the clinical severity of several vitamin-dependent enzymopathies, including vitamin B_6–responsive homocystinuria, vitamin B_{12}–responsive methylmalonic acidemia, thiamine-responsive MSUD, and tetrahydrobiopterin (BH4)–responsive phenylketonuria. Unfortunately, only a fraction of patients with any of these disorders respond to vitamin supplementation for reasons that are still not completely understood.

The converse of the first approach is to inhibit enzyme activity at a step proximal to production of toxic metabolites. The use of NTBC to treat tyrosinemia type I is an example of this approach. Tyrosinemia type I is a defect in the distal portion of the catabolic pathway for tyrosine. The enzyme deficiency that causes tyrosinemia type I leads to overproduction of toxic metabolites that produce the hepatic and neurologic complications of the disease. NTBC is a drug that inhibits an enzyme, *p*-hydroxyphenylpyruvate dioxygenase, which is proximal in the catabolic pathway to the enzyme deficiency that causes tyrosinemia type I. NTBC successfully suppresses overproduction of the toxic metabolites that produce the hepatic and neurologic complications of tyrosinemia type I.

A more direct approach to treating an enzyme deficiency is to replace the dysfunctional enzyme. It has been very difficult to provide "enzyme in a bottle" for a number of reasons, including the need to produce large amounts of pure enzyme; the need to direct the enzyme to the organ, cell, or organelle where it is needed; the tendency of the body to reject foreign proteins; and the great expense of such efforts. Among the earliest successes of this approach has been for the hematologic clotting disorders, such as factor VIII deficiency (see Chapter 79), and for α_1-antitrypsin deficiency (see Chapter 91). In the case of α_{1+}-antitrypsin deficiency, enzyme replacement therapy is effective for the adult-onset pulmonary manifestations of the disease but not for the hepatic problems expressed in the neonatal period.

Direct enzyme replacement therapy is now available for several lysosomal storage disorders.[8,113] In the case of nonneuropathic Gaucher disease, enzyme replacement therapy has been successful in treating the hematologic and visceral manifestations but less successful in treating the skeletal manifestations of children and adults. Enzyme replacement therapy is now available for Fabry disease, Hurler syndrome (MPS I; mucopolysaccharidosis I), Hunter syndrome (MPS II), Maroteaux-Lamy syndrome (MPS VI), Morquio syndrome (MPS IVA; mucopolysaccharidosis IV type A), and Pompe disease (GSD II; glycogen storage disorder type II).[8,113,152]

Another approach that can be used is substrate reduction therapy, either alone or in conjunction with enzyme replacement therapy. In this approach, a drug is provided that inhibits the production of the storage material. This approach is most commonly used for patients with Gaucher disease type 1; however, this disorder rarely manifests in the newborn period. This form of therapy (miglustat) is also effective for patients with Niemann-Pick disease type C, which can present in the newborn period with fetal ascites or cholestatic jaundice and pulmonary infiltrates (see Lysosomal Storage Disorders in the section The Abnormal Newborn Infant: Clinical Phenotypes).[113]

Treatment by Transplantation

This approach is being pursued vigorously for a number of inborn errors of metabolism. Perhaps the best-studied approach is liver transplantation, which has been performed successfully for about two dozen different inborn errors of metabolism, including glycogen storage disorders, organic acidemias, urea cycle disorders, and several other disorders.[69,71,80] This approach has been particularly successful for disorders in which the liver is the sole source of the enzyme and the only organ affected by the disease. Heart transplantation has been used successfully for patients with propionic acidemia. Many inborn errors of metabolism cannot be treated with liver transplantation or even multiple organ transplantation, because the abnormal genotype produces a multisystem disease and the overall prognosis remains poor. This appears to be the case for some patients with a mitochondrial disorder, but not all.[80,100]

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Bone marrow transplantation or stem cell transplantation is sometimes used to treat multiorgan disease, because the pluripotent cells provided by these transplants can serve as precursors for many related cell types in different organs. The benefit of bone marrow transplantation or stem cell transplantation for several of the lysosomal storage diseases appears promising and is an area of intense interest.[12,81,87,113] For example, these forms of transplantation are the treatment of choice for patients with Hurler syndrome who are diagnosed early, since they are essentially curative except for the skeletal manifestations that still develop.

Treatment at the Genetic Level

Treatment of inborn errors of metabolism has focused on modification of the phenotype rather than the genotype, but vigorous efforts have been under way for many years to develop methods for manipulating the genotype of somatic cells (i.e., cells other than germ cells).[34] Efforts have focused on somatic cell gene therapy rather than altering germ cells for numerous ethical reasons. Additionally, there is the very practical reason that most children born with inborn errors of metabolism are not known to be at risk before they manifest symptoms of disease.

Somatic cell gene therapy requires insertion of a functional gene into a patient's somatic cells in such a way that they are introduced into the appropriate target organs, are functionally active, and are appropriately regulated. Somatic cell gene therapy has the goal of treating the affected patient's disease; it cannot correct the affected patient's germline. Successful somatic cell gene therapy has not been demonstrated conclusively for any inborn error of metabolism. The approaches to somatic cell gene therapy employ viral vectors or physicochemically modified DNA as a means of delivering a suitably tailored normal gene to its appropriate target. In vivo and ex vivo approaches also are being used to introduce the corrective gene. One source of concern with this approach has been that gene insertion into the patient's genome would be random and could lead to harmful mutagenesis. Homologous recombination has been explored as a means of circumventing this risk. In homologous recombination, a new gene (or DNA fragment) is inserted in exchange for the defective gene (or DNA fragment) rather than inserted randomly into the patient's genome. Homologous recombination could, therefore, provide a means of selectively excising the deleterious gene in exchange for the normal gene without the risk of producing harmful random insertional mutagenesis. Recent efforts have focused on altering gene functioning, such as genome editing, RNA interference, and cell reprogramming. None of these approaches has reached the stage of clinical availability.[34]

Along with these efforts to surmount the technical difficulties of somatic gene therapy, considerable effort is being expended to address the larger clinical, ethical, and societal issues of this form of treatment. These issues will undoubtedly prove to be as formidable a challenge as the technical issues, and they deserve the same attention.

Conclusion

Inborn errors of metabolism are an important cause of morbidity and mortality in newborn infants. These disorders are probably underdiagnosed because of their relative rarity, the nonspecific way many of them are expressed, and the difficulty clinicians have with recognition and diagnosis. This chapter hopefully reduces this difficulty by providing a practical approach to the diagnosis of these disorders based on sets of common clinical and laboratory findings.

Key Points

- Inborn errors of metabolism are an underdiagnosed cause of neonatal morbidity and mortality, because they are individually relatively uncommon, they manifest with a wide diversity of symptoms and signs, they may not be identified by the usual battery of diagnostic laboratory testing, and many physicians are relatively unfamiliar with these disorders.
- Recent expansion in the scope of newborn screening has increased the awareness of physicians and other medical professionals who care for newborns regarding the need to understand better the scope, benefits, limitations, and follow-up care of patients who are found to have an abnormal newborn screen.
- Key clinical and laboratory findings will alert the physician caring for a sick newborn to the possibility that the newborn might have an inborn error of metabolism.
- The sick newborn with a suspected inborn error of metabolism should be evaluated expeditiously, because many inborn errors of metabolism can lead to rapid clinical deterioration, often with irreversible consequences. The evaluation should start with broad-based laboratory tests that will provide a provisional diagnosis and direct initial therapy. The evaluation should then progress to more specialized laboratory testing to establish a definitive diagnosis and optimal treatment.
- The treatment for newborns with an inborn error of metabolism has improved both in the number of disorders that are treatable and the efficacy of treatment for many of these disorders. Treatment includes dietary modification, metabolite manipulation, enhancement of enzyme activity, enzyme replacement, cell or organ transplantation, and genetic therapies.

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91

Neonatal Jaundice and Liver Diseases

MICHAEL KAPLAN, RONALD J. WONG, JENNIFER C. BURGIS, ERIC SIBLEY, AND DAVID K. STEVENSON

Bilirubin is one of three biologically active end-products of heme catabolism. Its clinical significance in the neonate relates to its propensity for deposition in the skin and mucous membranes, producing easily identifiable jaundice (French *jaune*, yellow) or icterus (Greek *ikteros*). The yellow color, or the serum (or plasma) total bilirubin (TB) concentration at any point in time, represents the combined processes of bilirubin production and bilirubin elimination from the body, the latter process comprising bilirubin uptake into the hepatocyte, bilirubin conjugation, and excretion of the conjugated product. As long as these functions remain in balance, a moderate degree of jaundice may develop but should not endanger an otherwise healthy, nonhemolyzing infant. Imbalance between bilirubin production and its elimination may result in increasing jaundice or hyperbilirubinemia. In rare cases, the degree of bilirubin production relative to bilirubin elimination may be so great that bilirubin may deposit in the brain, where it may cause dysfunction in the form of acute bilirubin encephalopathy (ABE). Although some cases of ABE may be transient and reversible, chronic bilirubin encephalopathy with resultant permanent neuronal damage, a form of cerebral palsy known as kernicterus, may ensue. As many as 80% of otherwise healthy, term newborns develop some degree of elevated TB levels. In contrast, severe hyperbilirubinemia with its potentially devastating sequelae is rare. It is, therefore, important to distinguish between normal processes of bilirubin physiology from pathologic metabolism. Medical caretakers of newborns should possess a thorough understanding of normal bilirubin physiology as well as its abnormal metabolism and the potential complications of severe hyperbilirubinemia.

Bilirubin Metabolism

Bilirubin Biochemistry

Overview

Throughout life, there is a continuum of bilirubin production and elimination from the body. Ongoing lysis of red blood cells (RBCs), whether physiologic or at increased rates (e.g., due to hemolysis), releases iron protoporphyrin (heme), the oxygen-carrying component of hemoglobin. Catalyzed by heme oxygenase (HO), heme is then converted to biliverdin and subsequently to bilirubin (Fig. 91.1). This bilirubin in its unconjugated form is transported to the liver bound to albumin. In the hepatocyte, bilirubin is conjugated to glucuronic acid by the enzyme uridine diphosphoglucuronate (UDP)-glucuronosyltransferase 1A1 (UGT1A1). Water-soluble conjugated bilirubin can be now excreted into the bile from which it reaches the bowel and is ultimately eliminated from the body. This simplified overview of bilirubin biochemistry will be reviewed in greater detail later in this chapter.

Heme Degradation

Heme oxygenase-1 (HO-1), the inducible isoform of HO, is a membrane-bound enzyme found in cells of the liver and other organs that catalyzes the first step in the pathway by which heme is converted to biliverdin through oxidation of the former molecule's α-methene bridge carbon (Fig. 91.2). HO-1 is inducible by its substrate heme. This rate-limiting step produces biliverdin; free iron (which can be reutilized for hemoglobin synthesis); and carbon monoxide (CO), which is excreted in the lungs in equimolar amounts. This process occurs in all nucleated cells except for mature, anucleated RBCs. Biliverdin is a blue-green water-soluble pigment that can be readily excreted by the liver and kidneys. In amphibians, reptiles, and certain avian species, the major pigmented end-product of heme catabolism is biliverdin. In mammals, however, biliverdin is converted to bilirubin by biliverdin reductase in the cytosol.

The degradation of 1 g of hemoglobin forms 34 mg of bilirubin. The isomeric form of bilirubin produced in this two-step process is IX-α (*Z,Z* isomer), defining the relative positions of the four pyrrole rings and the hydrogen molecules on the two linking lateral carbons. This form of bilirubin is water-insoluble, owing to tertiary structural changes that internalize the keto and carboxy groups that would otherwise interact with water molecules. Intramolecular hydrogen bonding maintains this folded bilirubin structure.

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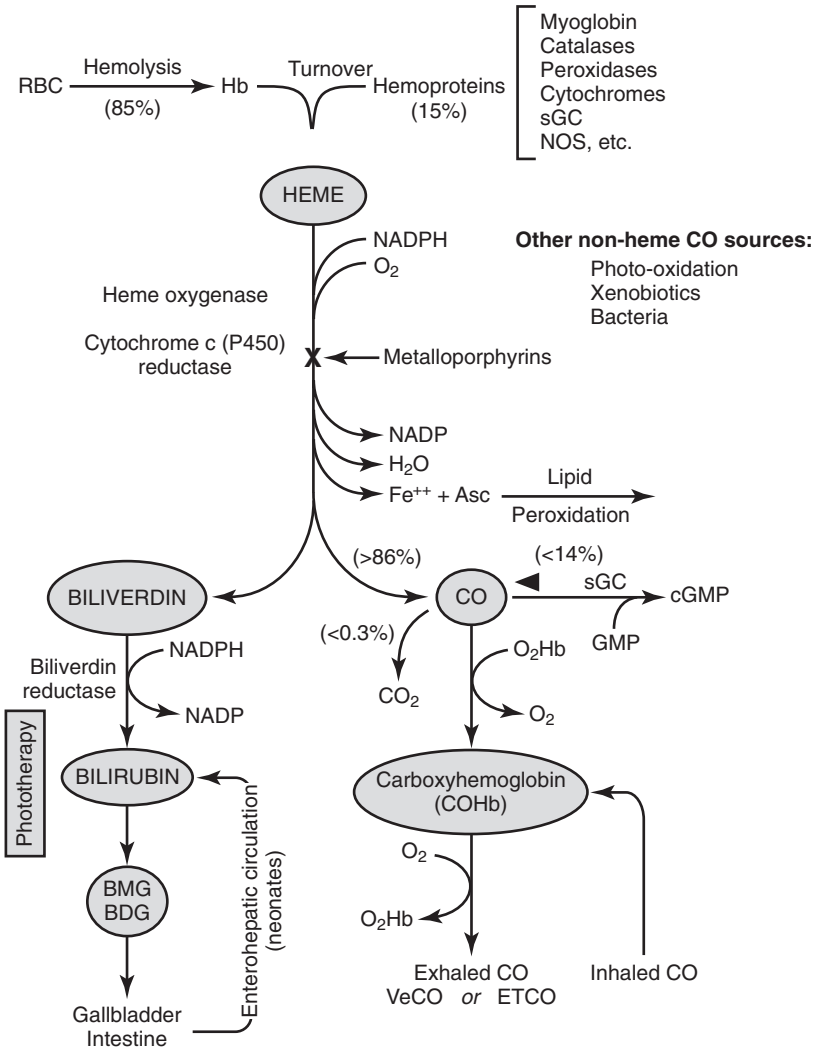
Abstract

Neonatal hyperbilirubinemia, usually transient and benign, is one of the most common neonatal problems, but if extreme and untreated, can potentially cause bilirubin neurotoxicity, manifesting as chronic choreoathetotic cerebral palsy (kernicterus) and death, or bilirubin-induced neurologic dysfunction (BIND). In industrialized countries, bilirubin neurotoxicity has been limited to a large extent, but the condition still occurs in developing countries and is a major cause of mortality and morbidity globally. The etiology of hyperbilirubinemia stems from conditions increasing bilirubin production (e.g., hemolysis) and those diminishing bilirubin elimination, resulting in an imbalance between these two processes. Hemolysis appears to be a primary risk contributor to developing bilirubin neurotoxicity. Bilirubin conjugation is immature in the newborn and even more so in the preterm infant. The total serum/plasma bilirubin, when primarily indirect or unconjugated, is used for clinical assessment and therapeutic decision making. While unbound bilirubin may be a better prognostic value, its measurement is not universally available clinically. The mainstay of treatment is intensive phototherapy, with the option of exchange transfusion in those infants not responding to that treatment. Drug therapy using metalloporphyrins has potential for the treatment of hyperbilirubinemia in the future. Conjugated hyperbilirubinemia results from interference with the hepatic excretion of conjugated bilirubin into bile. Idiopathic neonatal hepatitis and biliary atresia together account for the majority of cases of conjugated hyperbilirubinemia. Extrahepatic biliary atresia requires early surgical intervention with hepatoportoenterostomy. Clinical management of conditions with prolonged cholestasis includes supportive measures to prevent sequelae of malabsorption of dietary fat and fat-soluble vitamins.

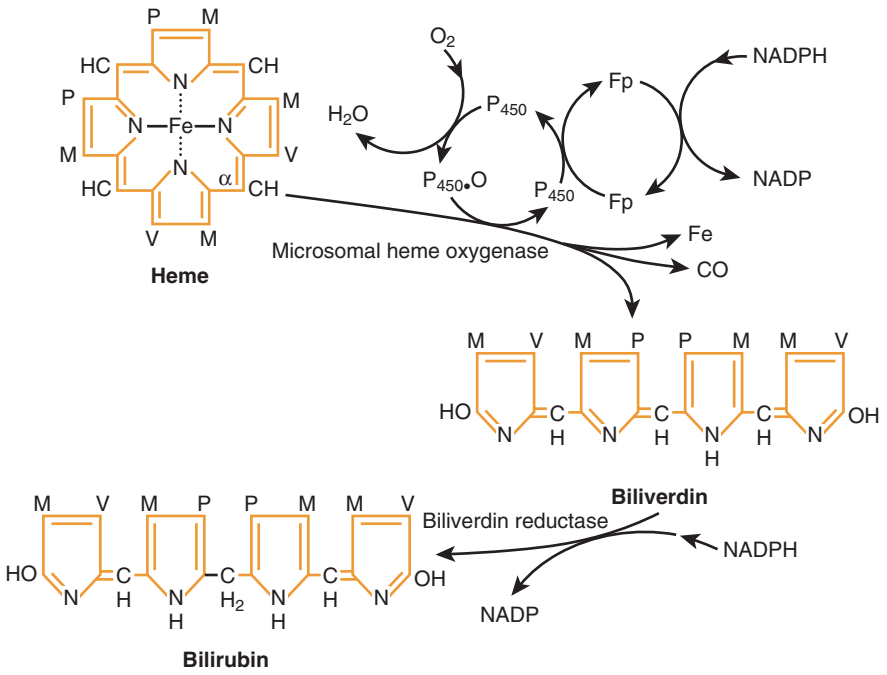
Keywords

biliary atresia
bilirubin encephalopathy/neurotoxicity
cholestasis
hemolysis
idiopathic neonatal hepatitis
kernicterus
phototherapy

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• **Fig. 91.1** Metabolic pathway of the degradation of heme and the formation of bilirubin. Heme released from the hemoglobin of red blood cells or from other hemoproteins is degraded by heme oxygenase (HO), the first and rate-limiting enzyme in a two-step reaction requiring nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen, and resulting in the release of iron and the formation of carbon monoxide (CO) and biliverdin. Metalloporphyrins, synthetic heme analogs, can competitively inhibit HO activity (indicated by the *X*). Biliverdin is further reduced to bilirubin by the enzyme biliverdin reductase. CO can activate soluble guanylyl cyclase (sGC) and lead to the formation of cyclic guanosine monophosphate (cGMP). It can also displace oxygen from oxyhemoglobin or be exhaled. The bilirubin that is formed is taken up by the liver and conjugated with glucuronides to form bilirubin mono- or diglucuronide (BMG and BDG, respectively), in reactions catalyzed by uridine diphosphoglucuronate glucuronosyltransferase (UGT1A1). The bilirubin glucuronides are then excreted into the intestinal lumen but can be deconjugated by bacteria so that the bilirubin is reabsorbed into the circulation, as shown. (Modified from Vreman HJ, et al. Carbon monoxide in breath, blood, and other tissues. In: Penney DG, ed. *Carbon monoxide toxicity*. Boca Raton, FL: CRC Press; 2000:22-30.)



• **Fig. 91.2** Catabolism of heme to bilirubin by microsomal heme oxygenase and biliverdin reductase. (From Tenhunen R, et al. The enzymatic conversion of hemoglobin to bilirubin. *Trans Assoc Am Physicians*. 1969;82:363.)

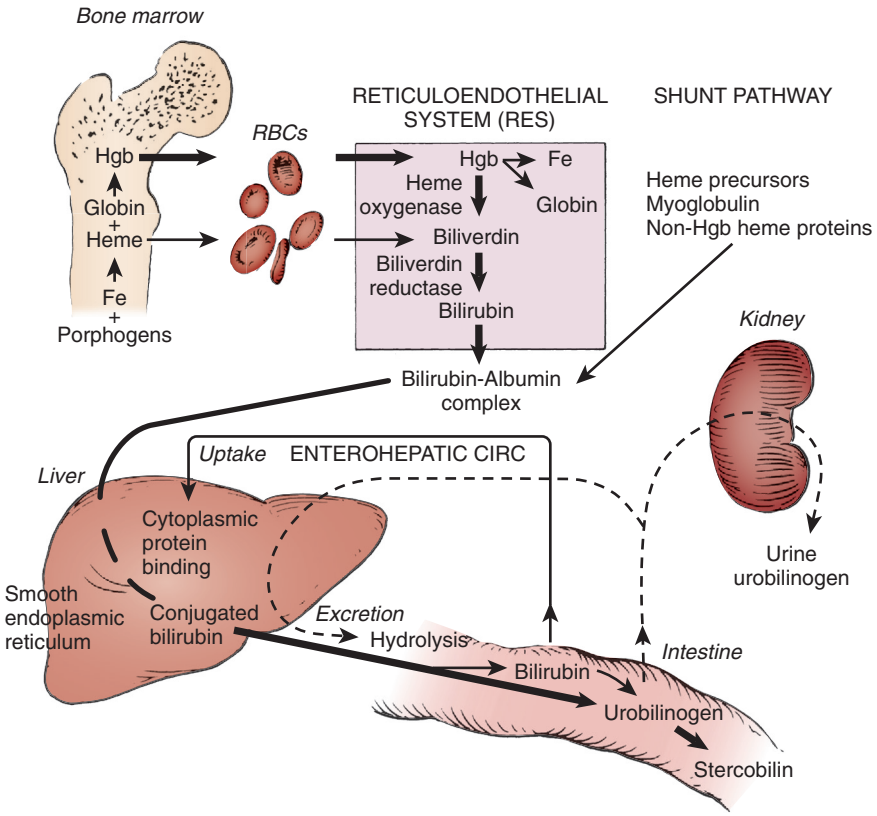
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Because bilirubin is a weak acid and is neither water soluble nor readily excreted at pH 7.4, to facilitate its excretion the molecule must be conjugated to mono- and diglucuronic acids by the specific hepatic enzyme isozyme (UGT1A1).[130] The evolutionary advantage derived by mammalian species in the development of such an intricate energy-dependent system that first produces bilirubin from a water-soluble precursor and then converts it back to a water-soluble form for excretion is presently uncertain. The mammalian placenta is capable of removing unconjugated bilirubin but not biliverdin. Biliverdin accumulation in the mammalian fetus would presumably result in the accumulation of large amounts of potentially toxic metabolites. Evidence has shown that bilirubin[257] and even CO may be biologically useful molecules.[175] The inducibility of HO-1 would appear to indicate that bilirubin production is helpful to cells when they are stressed. Bilirubin is a potent antioxidant that readily binds to membrane lipids and is capable of limiting membrane damage by preventing peroxidative injury. Biologic evidence of potentially beneficial effects of moderate concentrations of bilirubin is tempered by the association of high levels of unconjugated bilirubin with neuronal dysfunction and necrosis. Although cells may be potential beneficiaries of small amounts of bilirubin, in greater circulating quantities, the same bilirubin molecule may be a causative factor of severe neuronal damage. The dilemma that faces the clinician is determining the desirable or "safe" level of bilirubin appropriate for a particular neonate.

The CO formed by heme degradation binds to hemoglobin to form carboxyhemoglobin (COHb) and is then transported in the circulation to the lung. Here, the CO separates from hemoglobin and is exhaled in breath. Although there are other potential endogenous and exogenous sources of CO, such as lipid peroxidation and photo-oxidation, the main source of endogenous CO is derived from heme catabolism. Therefore, quantitative estimation of its synthesis or excretion (in infants without significant lung disease or oxygen exposure) offers a reasonably accurate assessment of the rate of heme degradation from which the rate of bilirubin production can be derived. It is believed that other hemoproteins undergo the same degradative process.

Bilirubin Production

The pathway of bilirubin synthesis, transport, and metabolism is summarized in Fig. 91.3. In the normal adult, bilirubin is derived primarily from the degradation of heme, which is released from senescing RBCs in the reticuloendothelial cells. Normally, about 20% of the bilirubin excreted into bile is derived from heme and other hemoproteins (mainly cytochromes, catalase). CO excretion in humans and more direct measurements in animals have demonstrated that, on the first day of life, bilirubin production



• **Fig. 91.3** The pathways of bilirubin synthesis, transport, and metabolism. Hgb, hemoglobin; RBCs, red blood cells. (From Assali NS. *Pathophysiology of gestation*. New York: Academic Press; 1972.)

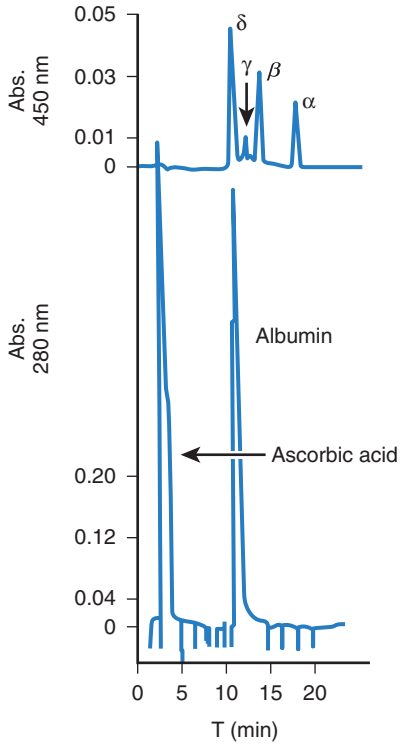
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is increased two to three times the rate of adults, to an estimated average of 8-10 mg/kg body weight per day. Bilirubin production decreases rapidly during the first 2 postnatal days. Several factors may explain this increased production in the newborn. The circulating RBC life span is shortened to 70-90 days compared with 120 days in the adult. Increased heme degradation arises from the very large pool of hematopoietic tissue, essential to intrauterine well-being, but ceases to function shortly after birth. An additional factor may possibly include an increased turnover of cytochromes. Another major contributor to the bilirubin pool in the neonate is an increase in bilirubin absorbed from the bowel as part of the enterohepatic circulation. This mechanism results from both reformation of unconjugated bilirubin from conjugated bilirubin in the bowel and enhanced absorption of unconjugated bilirubin by the intestinal mucosa back to the circulation (see Enterohepatic Absorption of Bilirubin).

Transport of Bilirubin in Plasma

Unconjugated bilirubin is mostly insoluble in water at pH 7.4, with a solubility of less than 0.01 mg/dL, and when released into the circulation by the reticuloendothelial cells, it is rapidly bound to albumin. Each molecule of adult albumin is capable of binding at least two molecules of bilirubin; the first molecule is more tightly bound than the second. Additional binding sites with weaker affinities may also exist but are probably of little clinical importance. On average, 7-8 mg/dL of unconjugated bilirubin can be bound to each gram of albumin. Physiologically, newborns have a lower plasma-binding capacity for bilirubin compared with adults or older children. This occurs because of reduced neonatal albumin concentrations and reduced molar binding capacities. Binding of unconjugated bilirubin by albumin is believed to be of importance in determining bilirubin neurotoxicity, because the unbound bilirubin fraction is thought to be a more sensitive predictor of bilirubin-induced neurologic dysfunction (BIND) than the TB used clinically.[284] However, except for Japan, there is currently no reliable and clinically available measurement to make the determination of unbound bilirubin concentrations a useful clinical tool in evaluating a newborn's risk for developing BIND[32,123] or in the therapeutic decision-making process.

The TB (serum or plasma) concentration is the conventional clinical laboratory measurement of bilirubin and is the basis for decision making for the management of hyperbilirubinemia. Bilirubin exists in four different forms in circulation: (1) unconjugated bilirubin reversibly bound to albumin, which makes up the major portion; (2) a relatively minute, but potentially neurotoxic, fraction of unconjugated bilirubin not bound to albumin (known as free or unbound bilirubin); (3) conjugated bilirubin, comprising mainly mono- and diglucuronides, which have effluxed from the hepatocyte to the circulation and are readily excretable through the renal or biliary systems; and



• **Fig. 91.4** Separation of serum bilirubin fractions by high performance liquid chromatography, showing bilirubin profiles at 450 nm (*upper tracing*) and 280 nm (*lower tracing*). α, Unconjugated bilirubin; β, monoconjugated bilirubin; δ, delta fraction bilirubin; γ, diconjugated bilirubin; Abs, absorption. (From Wu TW. Bilirubin analysis: the state of the art and future prospects. *Clin Biochem*. 1984;17:221.)

(4) conjugated bilirubin covalently bound to albumin, known as δ-bilirubin. Indirect, or unconjugated, bilirubin may increase in the serum or plasma in the presence of exaggerated hemolysis or diminished bilirubin glucuronidation. Conjugated or direct bilirubin will increase in association with excretory immaturity or with cholestatic diseases in which bilirubin is conjugated but its excretion is impaired.[179] A similar effect may be seen following acute hemolytic episodes in which indirect bilirubin is conjugated, but the large amounts of conjugated bilirubin are unable to be excreted via the bile. δ-Bilirubin has a plasma disappearance rate similar to that of serum albumin (Fig. 91.4).

"Conjugated" versus "Direct" Bilirubin

Conjugated bilirubin, but not δ-bilirubin, gives a "direct" reaction with standard diazo reagents; whereas, bound or unbound unconjugated bilirubin yields an "indirect" reaction. The terms *indirect* and *direct* bilirubin tend to be used interchangeably with unconjugated and conjugated bilirubin, respectively. However, the terms are not identical and measure differing bilirubin components. Direct bilirubin assays measure all conjugated bilirubin including mono- and diglucuronides as well as δ-bilirubin and some unconjugated bilirubin. Conjugated bilirubin implies measurement of mono- and diglucuronides only.

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Therefore, conjugated bilirubin determinations may be lower than direct measurements performed on an identical serum sample.[110]

Conjugated bilirubin usually comprises a small fraction of the TB concentration. δ-Bilirubin can be measured only with newer techniques. It is found in detectable amounts in normal older neonates and children and in significantly increased concentrations in those with prolonged conjugated hyperbilirubinemia resulting from various liver disorders. However, it is virtually absent from the serum during the first 2 weeks of life.

Hepatic Uptake of Bilirubin

Bilirubin dissociates from circulating albumin before entering the liver cell. The latter process occurs partly by a passive process of carrier-mediated diffusion and partly by mediation by organic anion transporter proteins. In the liver cell cytoplasm, the unconjugated bilirubin is bound to glutathione-S-transferase A, also known as ligandin, or with B-ligandin (Y protein). These are major intracellular transport proteins, and their bilirubin binding ability helps keep the potentially toxic unbound level low. Z protein, another hepatic cytoplasmic carrier, also binds bilirubin but with a lower affinity.

Equilibrium Between Bilirubin Production and Elimination Processes—The Major Determinant of TB Levels

The equilibrium between the rates of bilirubin entry into the circulation, including *de novo* synthesis, enterohepatic circulation, and tissue shifts, and the bilirubin elimination process, including hepatic cell uptake and conjugation and excretion of bilirubin, determines the TB concentrations at any specific time. This concept is equally applicable under normal physiologic and pathologic circumstances alike.

A reduced capacity of net hepatic uptake of unconjugated bilirubin has been implicated in the development of physiologic jaundice. In the newborn monkey, deficiency of B-ligandin and reduced clearance of sulfobromophthalein were demonstrated in the first 3 days of life, the period during which this animal frequently has physiologic jaundice. Studies in the human indicate that a deficiency of bilirubin uptake is probably of less importance in the pathogenesis of unconjugated hyperbilirubinemia than an immaturity of the bilirubin conjugation system during the first 3 or 4 postnatal days. However, the relative contribution of uptake deficiency may be greater during the second week of life, when the rate of bilirubin conjugation increases and approaches that of normal adults.

Conjugation of Bilirubin

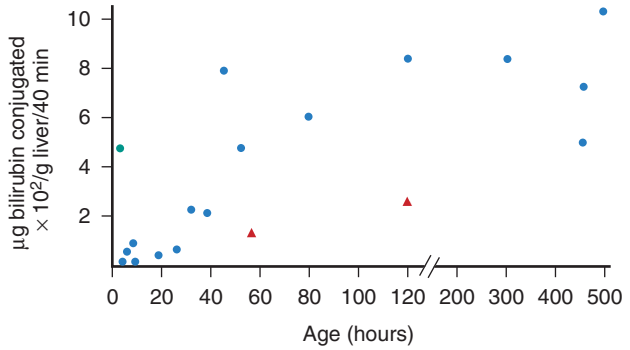
In order for bilirubin to be excreted into the bile, the nonpolar, water-insoluble unconjugated bilirubin must be converted to a more polar, water-soluble substance. The aim of this process is to alter the bilirubin molecule by solubilizing bilirubin IX-α. Bilirubin is presumed to be transported by hepatic ligandin from the liver cell plasma membrane to the endoplasmic reticulum, where the conjugating enzyme UGT1A1 is situated. Conjugation is a two-step enzymatic process in which each molecule of bilirubin is conjugated with two molecules of glucuronic acid. Glucuronic acid derives from activated uridine diphosphoglucuronic acid (UDPGA), itself synthesized by the soluble cytoplasmic enzyme uridine diphosphoglucose dehydrogenase from uridine diphosphoglucose, which is, in turn, synthesized from free glucose. The UGT1A1 enzyme first catalyzes the transfer of one glucuronic acid molecule from one of the two propionic acid side groups on one of the central pyrrole rings of bilirubin, in an ester linkage, to form bilirubin monoglucuronide. The physiologic reduction in enzyme activity in the newborn to less than 1% of normal may, therefore, result in unconjugated hyperbilirubinemia.

Although bilirubin monoglucuronide is water-soluble and capable of being excreted into bile without further alteration, about two-thirds of the total bilirubin excreted into bile in the adult human is in the form of a diglucuronide. The second step of the enzymatic conjugation process involves the esterification of a second glucuronide molecule to the now monoconjugate. This process is catalyzed primarily by the same UGT1A1 enzyme on the endoplasmic reticulum, although a second enzyme, UDP-glucuronate glucuronosyltransferase (transglucuronidase), located in the canalicular portion of the hepatocyte plasma cell membrane, may also play a role. The substrate for the canalicular transglucuronidation is believed to be bilirubin monoglucuronide. The enzyme transfers one molecule of glucuronic acid from one molecule of bilirubin monoglucuronide to another, resulting in the formation of one molecule of bilirubin diglucuronide. The latter molecule is excreted into the bile canaliculus; whereas, the remaining molecule of now unconjugated bilirubin is returned to the endoplasmic reticulum for subsequent reconjugation. In circumstances such as in severe chronic hemolysis, increased loads of bilirubin are delivered to the liver. Limited excretory ability may result in retention of conjugated bilirubin in the form of bilirubin monoglucuronide.

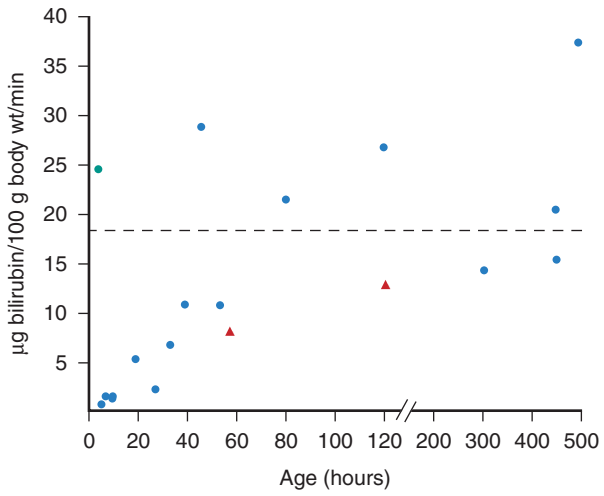
The result of the esterification is to disrupt the intramolecular hydrogen bonds, thereby opening the molecule and rendering the conjugated bilirubin water-soluble. The water-soluble form of bilirubin is excretable in the bowel. Water solubility also decreases the amount of bilirubin reabsorbed from the bowel, because hydrophilic agents do not pass through the intestinal wall easily.

In the normal adult, glucuronide conjugation accounts for the disposal of about 90% of all bilirubin. The remaining portion is converted to water-soluble substances by conjugation with substances other than glucuronic acid, or by oxidation, hydroxylation, or reduction. In humans, bilirubin forms a conjugate with glucose, xylose, possibly other carbohydrates, sulfates, and taurine. These non-glucuronide

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• **Fig. 91.5** Hepatic bilirubin uridine diphosphoglucuronate glucuronosyltransferase (UGT) activity in term (*blue circles*), premature (*red triangles*), and post-mature (*green circle*) newborn rhesus monkeys. (From Gartner LM, et al. Development of bilirubin transport and metabolism in the newborn rhesus monkey. *J Pediatr*. 1977;90:513.)



• **Fig. 91.6** Maximal hepatic bile bilirubin excretion in term (*blue circles*), premature (*red triangles*), and post-mature (*green circle*) newborn rhesus monkeys. The *horizontal dashed line* represents mean normal hepatic bile bilirubin excretion for nine adult rhesus monkeys (18.2 ± 1.0 SEM). (From Gartner LM, et al. Development of bilirubin transport and metabolism in the newborn rhesus monkey. *J Pediatr*. 1977;90:513.)

conjugates account for no more than 10% of the TB conjugates excreted in the bile.

A number of *in vitro* studies have demonstrated the existence of deficiencies in hepatic UGT1A1 activity in newborns of many species, including humans. In newborn rhesus monkeys, hepatic bilirubin conjugating capacity is extremely low during the first hours of life and functions at about 5% of adult capacity (Fig. 91.5). However, by 24 hours of age, UGT1A1 activity increases sufficiently to process the bilirubin load presented to the liver, and the TB concentration begins to fall. In 1-day-old rats, the proportion of both xylose and glucose conjugates of bilirubin equals that of glucuronide conjugates. Total conjugating capacity increases to adult levels by the fourth day of life, when a mature pattern of glycoside distribution is present, with 75% of all conjugates being glucuronides. In human newborns, the monoglucuronide conjugate is the predominant bile pigment conjugate. UGT1A1 activity in term infants is about 1% of that of healthy adults (and even less in premature infants), and increases at an exponential rate until 3 months of age, when adult levels are reached. Non-glucuronide conjugates are insignificant in this period.

Excretion of Bilirubin

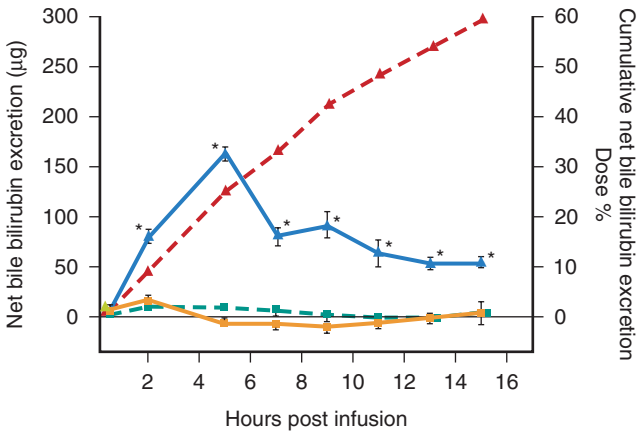
Excretion of the now polar, water-soluble bilirubin appears to be an energy-dependent concentrative process. The bilirubin conjugates are incorporated into mixed micelles along with bile acids, phospholipids, and cholesterol. The conjugates are excreted against a concentration gradient, and as a result, bile bilirubin concentration is about 100-fold that of the hepatocyte cytoplasm. Although the capacity for bilirubin excretion into bile is limited in newborn rhesus monkeys (Fig. 91.6), excretory deficiency is not a rate-limiting factor in the overall hepatic elimination of bilirubin in the human newborn. In newborn babies, bilirubin uptake into the hepatocyte and the enzyme-mediated conjugation processes are the more restrictive steps and may result in a "bottleneck" effect. However, a large bilirubin pool requiring elimination, such as in hemolytic disease of the newborn, may overwhelm the excretory capacity with efflux of backed up conjugated bilirubin into the circulation.[251] By contrast, in older humans and in the mature rhesus monkey and other mammals beyond the newborn period, hepatic excretion of conjugated bilirubin into bile predominates as the rate-limiting step in the presence of a large bilirubin load. At any age, in the presence of hepatic cell injury and biliary obstruction, hepatic excretory transport is the step most severely restricted, resulting in efflux of conjugated bilirubin from the hepatocyte to the serum with resultant conjugated hyperbilirubinemia. Thus, the hepatic excretory step may have the least reserve capacity of all the processes contributing to bilirubin elimination.

Enterohepatic Absorption of Bilirubin

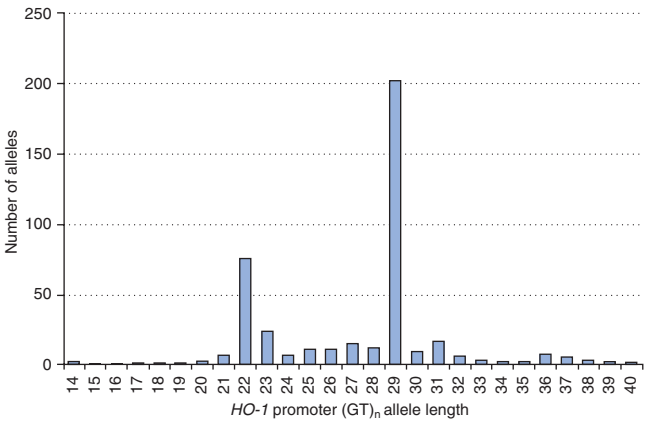
Conjugated bilirubin is not absorbed from the intestine. However, the mono- and diglucuronides of bilirubin are relatively unstable conjugates that are readily hydrolyzed to unconjugated bilirubin. Reverted unconjugated bilirubin may now be readily absorbed across the intestinal mucosa, contributing, through the enterohepatic circulation, to the circulating unconjugated bilirubin pool and again being presented to the liver for conjugation. Of importance in the mechanism of the enterohepatic circulation is the enteric mucosal enzyme β-glucuronidase, which is present in both term and premature neonates in high concentrations. Mild alkaline conditions present in the duodenum and jejunum contribute to the deconjugation process.

A study in adult rats demonstrates that enteric absorption of unconjugated bilirubin occurs predominantly in the duodenum and colon. The extent of absorption varies widely, depending on diet and caloric intake (Fig. 91.7). Although quantitative estimates of the disposal of bilirubin

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• **Fig. 91.7** Net rate of bilirubin excretion in adult rat bile over 15 hours after intraduodenal administration of 1000 mg unconjugated bilirubin in normal human milk at pH 8.6 (*orange squares*, mean ± SEM; *N* = 5) and human milk from mothers of infants with breast milk jaundice syndrome, pH 8.6 (*blue triangles*, mean ± SEM; *N* = 5). Cumulative net bilirubin excretion in bile for the same experiments expressed as a percentage of administered dose (*green squares*, bilirubin in normal human milk; *red triangles*, bilirubin in human milk from mothers of infants with breast milk jaundice syndrome). *Asterisks* indicate $p < 0.01$ for bilirubin in normal human milk versus bilirubin in human milk from mothers of infants with breast milk jaundice syndrome. (From Gartner LM, et al. Development of bilirubin transport and metabolism in the newborn rhesus monkey. *J Pediatr*. 1977;90:513.)



• **Fig. 91.8** Distribution of *HO-1* (GT)n repeats according to allele length of 199 newborns. Note the bimodal distribution common to other population groups. (From Kaplan M, et al. Heme oxygenase-1 promoter polymorphisms and neonatal jaundice. *Neonatology*. 2014;106:323.)

have been performed only for adult humans, these data do indicate that about 25% of the TB excreted into the intestine is reabsorbed as unconjugated bilirubin. About 10% of the total is excreted in stool as unaltered bilirubin. The remaining pigment is converted to urobilinoids, most of which are excreted in stool, with a small portion being reabsorbed in the colon for subsequent excretion by both the liver and kidney.

Neonates have relatively high concentrations of unconjugated bilirubin in the intestine, which contribute to the enterohepatic circulation. Intestinal bilirubin is derived from increased bilirubin production, exaggerated hydrolysis of bilirubin glucuronide, and high concentrations of bilirubin found in meconium. The relative lack of bacterial flora in the newborn bowel to reduce bilirubin to urobilinogen further increases the intestinal bilirubin pool in comparison with that of the older child and adult. The increased hydrolysis of bilirubin conjugates in the newborn is enhanced by high mucosal β-glucuronidase activity and the excretion of predominantly monoglucuronide conjugates (in the newborn) rather than diglucuronides (in the adult). Oral administration of nonabsorbable bilirubin-binding substances, such as agar, activated charcoal, or a lipase inhibitor (e.g., Orlistat),[104,199] may retain bilirubin in the bowel, thereby further increasing stool bilirubin content and reducing bilirubin reabsorption, thereby decreasing TB levels. Studies of intestinal bilirubin binding contribute to our understanding of the contribution of the enterohepatic circulation to unconjugated hyperbilirubinemia of the newborn.[70]

Genetic Control of Bilirubin Production

Heme Oxygenase-1

HO-1 is the rate-limiting enzyme that catabolizes heme to biliverdin and then to bilirubin, with the simultaneous release of equimolar quantities of ferrous iron (Fe^{3+}) and CO. Polymorphisms of the HO-1 gene promoter region may modulate its transcriptional activity, with increased HO activity being associated with the overproduction of bilirubin.

The *HO-1* Gene and Its Promoter Polymorphisms

The *HO-1* gene promoter region has a polymorphic $(GT)_n$ repeat sequence with lengths ranging from 12-40 repeats. As can be seen in Fig. 91.8, the $(GT)_n$ repeat distribution is bimodal with the main alleles at or around 23 and 30 repeat lengths.[137] The number of $(GT)_n$ repeats can modulate the rate of transcriptional activity (hence, gene expression), with short sequences (less than 25) being associated with increased transcriptional activity compared with those with long (25 or greater) sequences.

The prevalence of the short $(GT)_n$ lengths is cardinal to the analyses of the gene's contribution to the pathophysiology of hyperbilirubinemia. Higher HO activity associated with short alleles should lead to increased heme catabolism and hyperbilirubinemia. Newborn studies, however, have shown contradictory results. Most published studies demonstrated no effect of *HO-1* promoter polymorphisms on the TB levels. In two studies, however, from Taiwan and Japan, a modulating effect of short $(GT)_n$ repeats in increasing TB was reported.[142,283] A potential role of short $(GT)_n$ repeats to exacerbate hyperbilirubinemia in the presence of hemolysis in which large amounts of released hemoglobin result in *HO-1* induction has been suggested.

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Genetic Control of Uptake of Bilirubin into the Hepatocyte

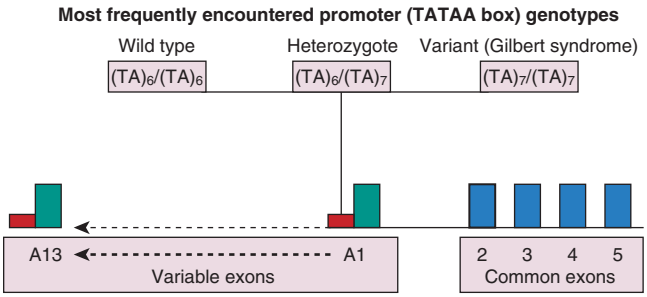
This process by which unconjugated bilirubin is taken up from the hepatic sinusoids and crosses the hepatocyte membrane to enter into that cell is facilitated by a carrier molecule, organic anion-transporting polypeptide-2 (*SLCO1B1*). In humans, this carrier may play an important role in the metabolism of bilirubin and in the prevention of hyperbilirubinemia by facilitating the entry of bilirubin into hepatocytes. A mutation in the gene leading to an impaired maturation of the protein with reduced membrane localization and abolished transport function has been described,[182] and a number of single-nucleotide polymorphisms (SNPs) have been identified, some of which are associated with an altered *in vitro* transport capability.[261]

Genetics of Diminished Bilirubin Conjugation

Perhaps one of the most important advances in our understanding of the genomics of bilirubin metabolism is the elucidation of the *UGT1A1* gene encoding the bilirubin-conjugating enzyme, UGT1A1. It is becoming more apparent that the modulation of bilirubin metabolism and whether TB levels remain within physiologic or hyperbilirubinemic ranges lie within genetic control. Although not limited to the neonatal age group, Skierka et al. demonstrated that 146/181 neonatal and pediatric age group patients referred for hyperbilirubinemia had at least one heterozygous *UGT1A1* variant, indicating that many cases of unconjugated hyperbilirubinemia could be attributed to variations at the *UGT1A1* locus.[248] Next is a short overview to allow the reader to comprehend mutations of this gene and interactions of these mutations with genetic or environmental factors in the mechanism of jaundice.[38,65,160,262]

The *UGT* Gene

The *UGT* gene is a superfamily of genes whose function is to encode a biochemical reaction leading to the conjugation of glucuronic acid to certain target substrates to facilitate their elimination from the body. The *UGT2* genes are located on chromosomes 4q13 and 4q28. The enzymes encoded by this family preferentially conjugate endobiotic substances, such as steroids and bile acids, and although of physiologic and pharmacologic importance, they are of little relevance to bilirubin metabolism. In contrast, the UGT1A1 gene isoform, which belongs to the UGT1 gene family, is of major importance to the conjugation and, therefore, elimination of bilirubin. This gene isoform has been mapped to chromosome 2q37. *UGT1A1* was cloned by Ritter and associates in 1991.[226] The gene consists of 4 common exons (exons 2, 3, 4, and 5) and 13 variable exons, of which only variable exon A1 is of any importance regarding bilirubin conjugation; the remaining exons play a role in the detoxification of a diverse range of chemical substances



• **Fig. 91.9** The human *UGT1* gene locus. Schematic representation of the genomic structure of the *UGT1* gene complex. Variable exon 1A1 and common exons 2 to 5 of the gene complex have been identified as those sites encoding the bilirubin conjugating enzyme, UDP-glucuronosyltransferase. Variable exons 1A2 to 1A13 do not participate in bilirubin metabolism. Genetic mutations associated with absent or decreased enzyme activity, which cause deficiencies of bilirubin conjugation, have been localized to this variable exon 1A1 (*green boxes*), its promoter (*red boxes*), or the common exons 2 to 5 (*blue boxes*). The upper section of the diagram demonstrates the common exon 1A1 promoter TATAA box genotypes. (Redrawn from Kaplan M, Hammerman C. Bilirubin and the genome: the hereditary basis of unconjugated neonatal hyperbilirubinemia. *Curr Pharmacogenom*. 2005;3:30.)

(Fig. 91.9). The variable exon A1 functions in conjunction with common exons 2 to 5: in response to a specific signal, transcription processing splices mRNA from the variable exon to the common exons. This process provides a template for the synthesis of an individual enzyme isoform. Upstream of each variable exon is a regulatory noncoding promoter that contains a box sequence of thymidine-adenine (TA) repeat (TATAA) of nucleic acids. Mutations of variable exon A1, its promoter, or the common exons 2 to 5 may result in deficiencies of bilirubin conjugation. Single nucleotide polymorphisms of the noncoding promoter area affect bilirubin conjugation by diminishing expression of a normally structured enzyme, whereas mutations of the gene coding area may affect enzyme function by altering the structure of the enzyme molecule. Further information is supplied in the section on Conjugated Hyperbilirubinemia.

Co-expression of Genes Modulating the Risk of Neonatal Hyperbilirubinemia

In a genome-wide study performed on adults in Sardinia, three loci were associated with the modulation of TB levels: UGT1A1, glucose-6-phosphate dehydrogenase (G6PD), and SLCO1B3, the latter a member of the SLC family implicated in bilirubin uptake into the hepatocyte.[233] Pursuing this finding in relation to neonatal hyperbilirubinemia, Lin et al.[152] studied the allele frequencies of mutations and polymorphisms of UGT1A1, G6PD, and SLCO1B1 in DNA samples, which were obtained from the DNA Polymorphism Discovery Resource of the National Human Genome Research Institute, and thought to be representative of the current US population. Although no clinical information was available for the individuals whose DNA was

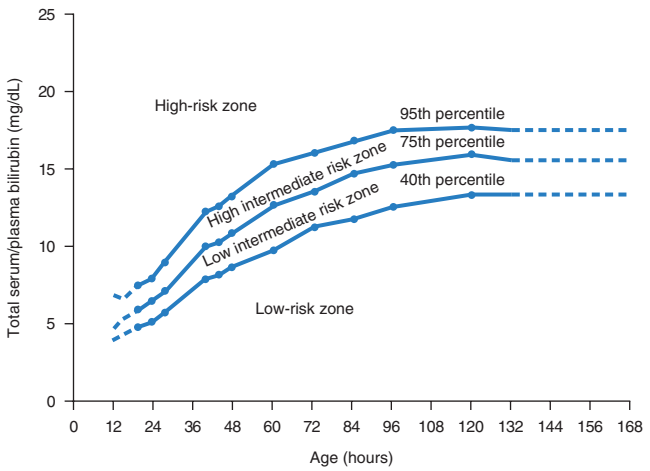
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included in the sampling, a high rate of gene co-expression does suggest a potentially important role for genetic polymorphism co-inheritance in neonatal hyperbilirubinemia. Co-expression of genes with another, with mutations or polymorphisms, or with environmental factors may potentiate their role and exacerbate the pathophysiology of neonatal hyperbilirubinemia to a greater extent than each gene individually.[152]

Nonpathologic Unconjugated Hyperbilirubinemia

Elevations in unconjugated bilirubin occur ubiquitously in the human neonatal population. In a sense, this "normal" increase in TB levels is not true hyperbilirubinemia when compared with a reference group of all newborns. A more appropriate term that would add to our understanding of the phenomenon and distinguish the normal or physiologic state from the pathologic entity implied in the term *hyperbilirubinemia* may be *physiologic bilirubinemia*. Although the 40th percentile is spuriously elevated, the hour-specific TB nomogram (Fig. 91.10), or more recently published transcutaneous bilirubin (TcB) nomograms, reflect the natural increase in TB during the first days of life, reaching a peak at about 5 days.

Unconjugated hyperbilirubinemia in the human, regardless of age, is defined as an indirect-reacting bilirubin concentration of 2.0 mg/dL (34 μmol/L) or greater, depending on the standard used in calibration of the reaction. Nearly all adults and older children normally have indirect-reacting bilirubin concentrations in circulation of less than 0.8 mg/dL (14 μmol/L) and δ-bilirubin of 0.2-0.3 mg/dL (3-5 μmol/L). Conjugated hyperbilirubinemia is defined as an elevation of the direct-reacting fraction in the van den Bergh diazo reaction of greater than 1.5 mg/dL (26 μmol/L) provided it comprises more than 10% of the TB concentration. The latter portion of the definition is added to guard against over-interpretation of direct reactions in newborns with markedly elevated indirect-reacting bilirubin concentrations, because up to 10% of the unconjugated pigment behaves as direct-reacting pigment in the van den Bergh–type methods.



• **Fig. 91.10** Zones of risk for pathologic hyperbilirubinemia based on hour-specific TB levels. (Reproduced with permission from Bhutani VK, et al. Predictive ability of a pre-discharge hour-specific TB level for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6. Copyright © 1999 by the American Academy of Pediatrics.)

Clinical situations in which the direct-reacting bilirubin concentration is equal to or close to the TB concentration are extremely rare, especially in the newborn period. In the neonate with conjugated hyperbilirubinemia, the hyperbilirubinemia is usually "mixed," the elevated direct-reacting fraction accounting for 20%-70% of the total pigment. Thus, a neonate with mixed hyperbilirubinemia should be considered primarily to have *conjugated* hyperbilirubinemia. Except in cases of extreme hemolysis, such as in hemolytic disease of the newborn, pathology resulting from interference with hepatic cell excretion and bile transport, rather than from abnormalities of increased bilirubin production or deficient hepatic bilirubin uptake or conjugation, should be sought.

Fetal Bilirubin

During the last stages of human gestation, the normal degradation of erythrocytes formed earlier in fetal life results in about a 150% increase in bilirubin production per unit of body weight compared with adults. The mammalian fetus of all species appears to be capable of degrading heme without limitation through the two enzymatic steps responsible for the formation of unconjugated bilirubin IX-α, CO, and biliverdin (see Fig. 91.2). However, notable species differences exist in the pattern of development of hepatic bilirubin conjugation. Marked deficiency in UGT activity is noted in rat, rabbit, guinea pig, sheep, dog, monkey, and human fetuses. At term, UGT activity in the rhesus monkey is only 1%-5% of that in the adult. In the human fetus, UGT activity is extremely low before 30 weeks of gestation at about 0.1% of adult activity and gradually increases to about 1% at term.

Diminished UGT activity is the central rate-limiting step that, in conjunction with additional processes, including increased bilirubin production, enhanced enterohepatic circulation, and diminished uptake into the hepatocyte, manifests as physiologic jaundice in monkeys and humans.

Significant hyperbilirubinemia is unusual in the human fetus, because the placenta transports unconjugated bilirubin from the fetus to the mother. Administration of radioactive unconjugated bilirubin into the fetal circulation of a dog, guinea pig, or monkey shows a rapid disappearance from the fetal side and recovery in the maternal bile. Even in states of severe intrauterine hemolysis from conditions such as Rh or other isoimmunizations, the degree of anemia by far exceeds the level of hyperbilirubinemia, and clinical jaundice is usually mild at birth.[36] Indeed, intrauterine therapeutic interventions in this condition are indicated by fetal anemia rather than fetal hyperbilirubinemia. After delivery and separation of the placenta from the infant,

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increases in TB may be expected and may be excessive in the face of hemolytic disorders. By contrast, the placenta is barely permeable to conjugated bilirubin. Thus, in the absence of evidence of hemolytic disease, if clinical jaundice is present at birth, a conjugated hyperbilirubinemia caused by intrauterine hepatic pathology should be suspected.

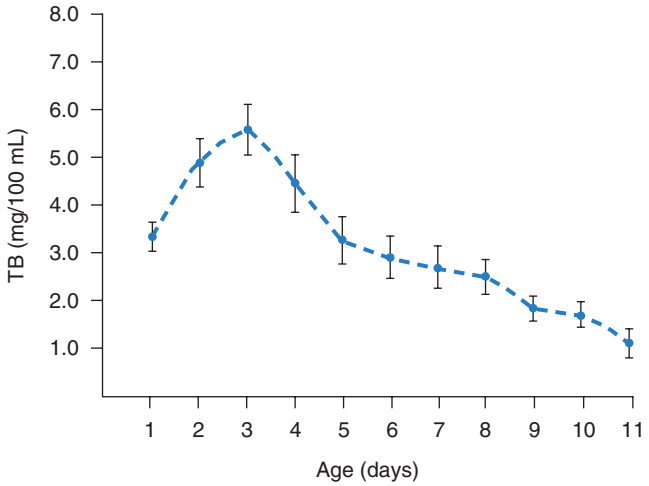
A large amount of bilirubin is found in meconium, indicating appreciable activity of fetal hepatic bilirubin conjugation. A significant level of β-glucuronidase activity is found in meconium, suggesting that conjugated bilirubin in the fetal intestine can be hydrolyzed back to unconjugated bilirubin and then absorbed from the bowel into the portal circulation. This absorbed bilirubin may reenter the hepatocyte for subsequent reconjugation and re-excretion or may be transferred through the placenta into the maternal circulation. The efficiency of this process is protective to the fetus against severe hyperbilirubinemia, even when hemolysis is severe.

Conjugated hyperbilirubinemia in the mother, which may occur in hepatitis or recurrent jaundice of pregnancy, is not reflected in the cord blood. Severe hemolytic disease in the fetus results in small, but significant increases in amniotic fluid bilirubin concentrations. How bilirubin enters the amniotic fluid pool is not known, but suggestions have ranged from direct transfer across the placenta from the maternal circulation, to transudation of pigment across the amniotic membranes or cord vessels, to secretion of bilirubin in the pulmonary fluids flowing from the fetal lung into the fetal pharynx and oral cavity and then into the amniotic fluid. Although to a great extent replaced by noninvasive measurement of anterior cerebral artery flow as an index of fetal anemia, in recent decades, measurement of amniotic fluid bilirubin concentrations by spectrophotometry, combined with percutaneous umbilical blood sampling allowing for serial hematocrit determinations and fetal intravascular transfusions, resulted in markedly improved outcome for the now rare fetus and infant with Rh erythroblastosis (see Chapter 23).

Neonatal Hyperbilirubinemia

Term Neonate

In the full-term newborn, physiologic jaundice is characterized by a progressive rise in TB concentration from about 2 mg/dL (34 μmol/L) in cord blood to a mean peak of 5-6 mg/dL (86-103 μmol/L) between 48 and 120 hours of age in Caucasian and African-American infants, with most TB levels peaking at 72-96 hours of age, and 10-14 mg/dL (171-239 μmol/L) between 72 and 120 hours of age in Asian-American infants. This is followed by a rapid decline to about 3 mg/dL (51 μmol/L) by the 5th day of life (Fig. 91.11) in Caucasian and African-American neonates and by the 7th-10th in Asian-American neonates. This early period of physiologic jaundice has been designated as *phase 1* physiologic jaundice. During the period from the 5th-10th days of life in Caucasian and African-American infants, TB concentrations decline slowly, reaching the normal adult



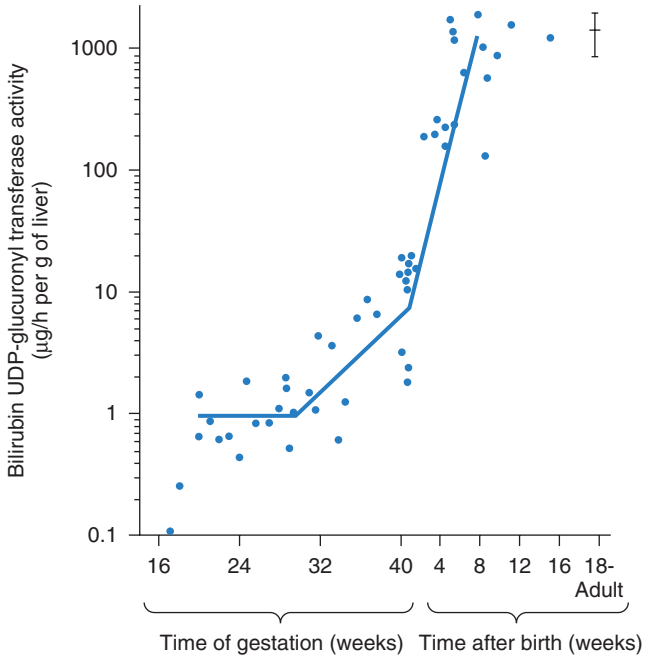
• **Fig. 91.11** Mean total bilirubin (TB) concentrations in 22 full-term normal white and African-American infants during the first 11 days of life. *Vertical bars* represent standard error of the mean. (From Gartner LM, et al. Development of bilirubin transport and metabolism in the newborn rhesus monkey. *J Pediatr*. 1977;90:513.)

value of less than 2 mg/dL (34 μmol/L) by the end of that period. This late neonatal period of minimal, slowly declining hyperbilirubinemia has been designated as *phase 2* physiologic jaundice. The epidemiology is dependent, in part, on the prevalence of breastfeeding in a population, because lower peak TB values will be found among predominantly formula-fed infants.

Studies in the newborn rhesus monkey, an animal with a pattern of physiologic jaundice of the newborn that is similar to that in humans, show that phase 1 results from the combination of a six-fold postnatal increase in the load of bilirubin presented to the liver combined with a markedly diminished UGT activity. The presence of either of these factors alone would result in retention of unconjugated bilirubin to a lesser extent than when in combination. Hepatic uptake and excretion of bilirubin are also decreased during this period, although their function as rate-limiting steps in the transport of bilirubin from plasma into bile is dwarfed by the combination of increased bilirubin load to the liver and diminished conjugative capacity. The very large increase in bilirubin load appears to result from both increased *de novo* bilirubin synthesis and enteric reabsorption of unconjugated bilirubin. In the newborn monkey, the markedly increased load persists for 3-6 weeks, primarily because of enhanced intestinal bilirubin absorption. Similar data are not yet available for the human neonate.

In the human, UGT1A1 activity is extremely low in the fetal period. After birth, UGT1A1 activity increases at an exponential rate, reaching the adult level by 6-12 weeks of age (Fig. 91.12). The early deficiency in enzyme activity may result from insufficient enzyme synthesis, inhibition of enzymatic activity by naturally occurring substances, deficient synthesis of the glucuronide donor UDPGA, or a combination of these factors. Phase 2 physiologic jaundice appears to result from an imbalance in which hepatic uptake

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• **Fig. 91.12** Developmental pattern of hepatic bilirubin uridine diphosphoglucuronate (UDP)-glucuronosyltransferase activity in humans. (From Kawade N, Onishi S. The prenatal and postnatal development of UDP-glucuronyltransferase activity towards bilirubin and the effect of premature birth on this activity in the human liver. *Biochem J*. 1981;196:257. Reprinted by permission of the Biochemical Society, London.)

of bilirubin remains diminished while an increased bilirubin load presented to the liver persists. Developmental deficiency of B-ligandin may contribute to deficient uptake of bilirubin.

Despite the development of physiologic jaundice of some degree in nearly every newborn, only half of all Caucasian and African-American term newborns become visibly jaundiced during the first 3 days of life. A greater proportion of exclusively breastfed infants can be expected to display some degree of jaundice. Cutaneous icterus in the newborn will not become evident until TB concentrations exceed 5-6 mg/dL (86-103 μmol/L). This situation contrasts with that of the older child and adult, in whom jaundice may be noticeable in the conjunctiva and skin at TB concentrations as low as 2 mg/dL (34 μmol/L). Variations in duration of hyperbilirubinemia, in skin color, and in perfusion may account for these differences. As the intensity of jaundice increases, clinical icterus progresses in a caudal direction. At lower levels of TB, only the head and conjunctiva may be affected, with the chest, abdomen, legs, and feet becoming jaundiced in parallel to increasing TB concentrations. Because routine daily TB determinations are not usually performed on full-term or even premature newborns, in the past, careful scrutiny of the nursery population several times a day by experienced personnel was essential to detect infants who were becoming jaundiced, as some of these may subsequently develop significant hyperbilirubinemia and require further TB testing. Visual assessment of jaundice, however, is largely subjective, inaccurate, and dependent on observer experience. More recent developments of TcB monitoring devices intended to measure the skin color objectively and noninvasively and convert this color reading to a bilirubin estimation may improve on the reliability of visual estimation. Daily noninvasive TcB determinations may enhance the predictive value of the technique by allowing the actual trajectory to be plotted against those of the hour-specific TB or TcB nomograms (see Transcutaneous Bilirubinometry). This is especially important in predischarge assessment of newborns, especially those discharged before 72 hours of age.

Preterm Neonate

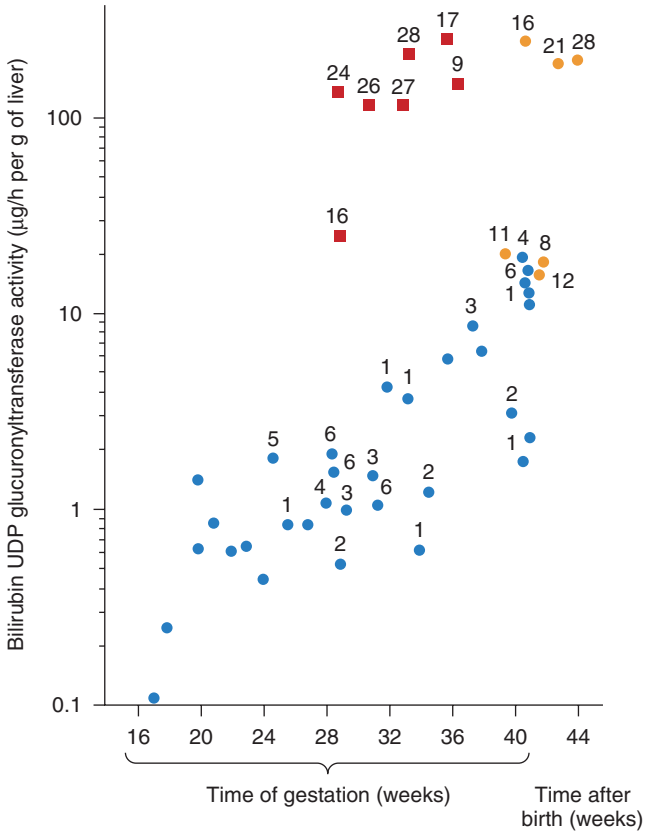
Physiologic jaundice in premature neonates is more severe than in term neonates. In larger preterm infants, mean peak TB concentrations may reach 10-12 mg/dL (171-205 μmol/L) by the 5th day of life. This delay in reaching the maximal concentration compared with term neonates primarily reflects the delay in maturation of hepatic UGT1A1 activity. Because mean peak unconjugated bilirubin concentrations as low as 10-12 mg/dL (171-205 μmol/L) may be associated with ABE or kernicterus in certain high-risk, low birth weight neonates, all degrees of visible jaundice in premature neonates should be monitored closely and investigated fully. Small premature infants cared for in an intensive care nursery will rarely be allowed to reach the TB levels mentioned but will be treated with phototherapy at much lower levels. The natural peak TB level in small premature infants is, therefore, mainly unknown.

Despite lower UGT1A1 activity in premature neonates than in term neonates at birth, UGT1A1 activity increases rapidly, far exceeding the expected maturational rate noted in utero (Fig. 91.13). This observation indicates that there are two components in the maturational process of hepatic UGT1A1: (1) chronologic maturation and (2) accelerated maturation related to birth. Nevertheless, normal TB concentrations in premature neonates may not be reached in many cases until the end of the first month of life.

Late Preterm Neonate

Late preterm gestation (34 0/7 to 36 6/7 weeks) is an important risk factor for the development of severe neonatal hyperbilirubinemia and kernicterus. These infants are physiologically immature and have limited compensatory responses compared with term infants. They are at greater risk of morbidity and mortality than term counterparts. Among the infants registered in the voluntary US-based Kernicterus Registry, late preterm infants were disproportionately represented compared with term. At this point of gestation, hepatic conjugative capacity is still immature and may contribute to the greater prevalence, severity, and duration of neonatal jaundice in these infants. Additional risk factors increasing the incidence of severe hyperbilirubinemia in these infants include feeding with human breast milk, large-for-gestational-age status, male sex, G6PD deficiency, and others. Suck-swallow immaturity

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• **Fig. 91.13** Effect of premature birth on development of hepatic bilirubin uridine diphosphoglucuronate (UDP) glucuronosyltransferase (UGT) activity in humans. Numbers beside symbols represent age (days) at which activities were measured. Symbols represent enzyme activities for premature (*red squares*) and full-term (*orange circles*) infants who lived more than 8 days after birth, and for fetuses and premature and full-term infants who died within 7 days of delivery (*blue circles*). (From Kawade N, Onishi S. The prenatal and postnatal development of UGT activity towards bilirubin and the effect of premature birth on this activity in the human liver. *Biochem J*. 1981;196:257. Reprinted by permission of the Biochemical Society, London.)

may also contribute to the risk of hyperbilirubinemia.[113] These infants are at increased risk for readmission, primarily for hyperbilirubinemia. In a US survey, late prematurity increased the risk for neonatal hyperbilirubinemia more than fivefold.[224] Scrupulous attention to screening for jaundice in the newborn nursery, adequate lactation support, parental education, and appropriate postdischarge follow-up should facilitate institution of treatment when clinically indicated.[84,277]

Early-Term Neonate

Although within the definition of term, newborns born at the early end of term (37-38 weeks' gestation) may be, as a result of relative immaturity, at higher risk for neonatal hyperbilirubinemia than full-term counterparts, and unexplained jaundice may be twofold greater.[153] In a Canadian study, 37- and 38-week neonates had a higher risk of readmission for hyperbilirubinemia than those born ≥39 weeks.[230] Similarly, in Utah, late-term and early-term neonates had higher rates of readmission for hyperbilirubinemia than those born at term.[291]

Term Infant

Neonatal hyperbilirubinemia is the most common cause for readmission of otherwise healthy term infants. Many readmissions can be avoided by discharging the mother–infant dyad when both are ready to be discharged, when the mother has recovered sufficiently and is able to care for her newborn. Jaundice, if present, must be evaluated, and appropriate treatment or follow-up arranged according to the 2004 American Academy of Pediatrics (AAP) Practice Guideline.[12,22]

Post-Term Neonate

Nearly all post-term neonates and about half of all term neonates who are small-for-gestational age may be expected to have little or no physiologic jaundice, with peak TB concentrations of less than 2.5 mg/dL (43 µmol/L). The mechanism for this acceleration of hepatic maturation is unknown. Similarly, neonates of mothers treated with phenobarbital, a drug known to stimulate hepatic UGT activity and the concentration of ligandin, and neonates of heroin users have less than the anticipated severity of physiologic jaundice. Other drugs, less well investigated, also may have similar "maturing" effects.

Genetic, Ethnic, and Cultural Effects

The severity of physiologic jaundice varies significantly among different ethnic populations. Mean maximal TB concentrations in Chinese, Japanese, Korean, Native-American, and other Asian term newborns are 10-14 mg/dL (171-239 µmol/L), about double those of the Caucasian and African-American populations. The incidence of bilirubin toxicity as defined by autopsy-proven kernicterus is also increased significantly in Asian newborns. There is no clinical evidence for increased hemolysis in Asian newborns to account for these dramatic differences,[89] although some studies of CO production have suggested that bilirubin synthesis may be slightly increased compared with that in Caucasian or African-American neonates. A mutation (Gly71Arg) known as UGT1A1*6 in the gene for UGT frequently found in Japanese, Koreans, and Chinese, but rare in Caucasians, is associated with Gilbert syndrome in Asian populations and has been shown to be associated with an increased incidence of neonatal hyperbilirubinemia in these groups.[5,157] In contrast, variation in the number of TA repeats in the promoter for the *UGT1A1* gene are commonly encountered in Caucasians and are associated with Gilbert syndrome in that population group (see previous section Genetics of Diminished Bilirubin Conjugation). The promoter polymorphism is rare in Asian communities.[24] Thus, there is mounting evidence that the phenotypic variability in neonatal TB levels seen in different populations results in part from genotypic heterogeneity.

In contrast to Asians, the African-American race is often considered protective against hyperbilirubinemia, with a

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lower risk of developing TB levels greater than 20 mg/dL (342 μmol/L) than Caucasian infants.[12] However, African-American infants are over-represented, relative to population statistics, in both the US-based Kernicterus Registry and a British and Irish series of severe hyperbilirubinemia. They also appear at greater risk of developing TB levels greater than 30 mg/dL (513 μmol/L) with resulting increased risk of kernicterus than Caucasian counterparts. This phenomenon may be explained in part by the high incidence of G6PD deficiency within this ethnic group.[135,173]

Certain geographically distinct populations may demonstrate a markedly increased incidence of neonatal unconjugated hyperbilirubinemia without associated hemolysis. The most dramatic of these are from certain Greek islands, especially the islands of Lesbos and Rhodes. Although the incidence of G6PD deficiency in these populations is markedly increased compared with the remainder of the Greek population and the world, the incidence of hyperbilirubinemia was not directly correlated with the frequency of G6PD deficiency, suggesting interaction of additional icterogenic factors. Unless aggressively treated with phenobarbital prophylaxis, phototherapy, and/or exchange transfusion, the incidence of kernicterus was also much greater in the newborns from these Greek islands than in those of the mainland population.

It has been speculated that the increased incidence of neonatal unconjugated hyperbilirubinemia in Asian and geographically identifiable populations may result either from environmental influences, such as the maternal ingestion of certain ethnically characteristic herbal medications or foods, or from a genetic predisposition to slower maturation of bilirubin metabolism and transport. Asian-origin infants born in the United States and Greek newborns born in Australia appear to be at similar risk for neonatal jaundice as natives of Asia and Greece, respectively, suggesting that geographic factors alone are not determinants. Differentiating the influence of drugs, foods, or traditional practices from that of genetic factors requires further investigation. Severe hyperbilirubinemia can result from hemolysis associated with sepsis or, if genetically vulnerable (e.g., in G6PD deficiency), exposure to chemicals (such as naphtha in mothballs) or pharmaceutical agents (such as antimalarials, sulfonamides, sulfones, antipyretics, and analgesics). In some societies with a high incidence of G6PD deficiency, application of henna to the skin or use of menthol-containing umbilical potions may precipitate severe hyperbilirubinemia and potentiate bilirubin encephalopathy. Even though some of these agents and stressors have received public attention, others represent generally unsuspected dangers, such as the intramuscular (IM) injection of vitamin K_3 (menadione) or the inhalation of paradichlorobenzene, which is used in moth repellents, air fresheners, and bathroom deodorizers.[247] In addition, newborn exposure to a hemolytic agent, especially in the presence of G6PD deficiency, can occur transplacentally or through breast milk as in the case of maternal ingestion of fava beans, or directly by inhalation, ingestion, or injection.

Pathologic Unconjugated Hyperbilirubinemia

Elevated concentrations of unconjugated bilirubin are of concern because of the danger of bilirubin encephalopathy or neuropathy associated with this fraction of bilirubin. Although there have been some reports of bilirubin encephalopathy associated with elevated levels of conjugated bilirubin, the role of conjugated hyperbilirubinemia in the mechanism of bilirubin encephalopathy is not clear. Most studies of kernicterus have related to the TB concentration, of which the conjugated fraction usually comprises only a small fraction. Elevated levels of conjugated bilirubin frequently indicate disease processes of hepatic origin. The following discussion, therefore, relates primarily to unconjugated, or indirect, hyperbilirubinemia and is followed by a section on conjugated hyperbilirubinemia.

The TB level at any point in time reflects a multiplicity of forces in delicate balance. Processes including bilirubin production, transport, uptake, conjugation, excretion, and reabsorption are not only interdependent, but are also influenced by tremendous physiologic flux present in this complex system in the first few days of the neonatal period. Examples of such changes include differences in the rate of heme catabolism and progressive maturation of the bilirubin conjugation system. Physiologically, the net result is an increase in TB levels up to about the fifth day of life, after which point TB values level off and then gradually decrease. Superimposed on these physiologic alterations of bilirubin metabolism may be specific disorders that may further exaggerate or prolong the normal pattern of an elevated TB level. These conditions may affect the entire spectrum of bilirubin metabolism and include disorders of bilirubin production as well as bilirubin conjugation and elimination.

Causes of Unconjugated Hyperbilirubinemia

Disorders of Bilirubin Production

Although increased bilirubin production could result from pathologic states in which degradation of nonhemoglobin heme (i.e., hemoproteins such as cytochromes, catalase) and erythrocyte hemoglobin precursor heme are increased, such disorders in fact have not been identified in the newborn period. The most common pathologic hemolytic causes of unconjugated hyperbilirubinemia in the newborn include isoimmune hemolytic disease, caused by blood group incompatibility between mother and fetus, and G6PD deficiency. Disorders associated with increased erythrocyte destruction are listed in Box 91.1 (see Chapter 23).

Neonates who are acutely hemolyzing appear to be at a higher risk for developing bilirubin-induced brain damage compared with those without hemolysis. Indeed, the first association to be recognized between increasing TB levels and the risk for kernicterus was made in newborns with Rh isoimmunization. Some reports suggested that kernicterus in hyperbilirubinemic newborns with hemolytic disease may occur more frequently than that in their counterparts without evidence of hemolytic disease. Surveying

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• BOX 91.1 Conditions Associated With Increased Erythrocyte Destruction

Isoimmunization
- Rh incompatibility
- ABO incompatibility
- Other blood group incompatibilities

Erythrocyte Biochemical Defects
- Glucose-6-phosphate dehydrogenase deficiency
- Pyruvate kinase deficiency
- Hexokinase deficiency
- Congenital erythropoietic porphyria
- Other biochemical defects

Structural Abnormalities of Erythrocytes
- Hereditary spherocytosis
- Hereditary elliptocytosis
- Infantile pyknocytosis
- Other

Infection
- Bacterial
- Viral
- Protozoal

Sequestered Blood
- Subdural hematoma and cephalohematoma
- Ecchymoses
- Hemangiomas

the literature up to 1983, Watchko and Oski reinforced the concept that hyperbilirubinemia among neonates without hemolytic disease was less dangerous with regard to the development of kernicterus than in cases in which hemolysis was present.[280] However, there are few data to substantiate this view. A study shedding some light on this question was performed by Ozmert and colleagues.[213] In 102 children aged 8-13 years, indirect hyperbilirubinemia ranging from 17-48 mg/dL (291-821 µmol/L) associated with a positive direct Coombs' test (also known as the direct antiglobulin test [DAT]), presumed to reflect ongoing hemolysis, was associated with lower intelligence quotient (IQ) scores and a higher incidence of neurologic abnormalities. In these same children, the incidence of detected neurologic abnormalities increased as the time of exposure to high TB levels became more prolonged. Similarly, in Norway, Nilsen and coworkers found that of males born in the early 1960s who developed neonatal hyperbilirubinemia, those with a positive Coombs' test and hyperbilirubinemia for greater than 5 days had significantly lower IQ scores than average for that country.[198]

In a reanalysis of the data from the Collaborative Perinatal Project, no relationship was found between maximum TB levels and IQ scores. However, in those children who had had a positive DAT, a TB of greater than 25 mg/dL (428 µmol/L) was associated with a decrease in IQ scores.[147] A study of severe neonatal hyperbilirubinemia from Egypt reported the threshold TB level in identifying infants with bilirubin encephalopathy was lowered in those with identifiable risk factors associated with hemolysis, including Rh isoimmunization, ABO blood group incompatibility, and sepsis.[93]

Although there is to date no hard evidence demonstrating higher levels of unbound bilirubin in hemolyzing neonates, many believe hemolysis to be a potential factor that increases the risk for bilirubin-related brain damage. Although a TB concentration of 20-24 mg/dL (342-410 µmol/L) may be associated with kernicterus in a neonate with Rh isoimmunization, a healthy, term infant without an obvious hemolytic condition will rarely be endangered by TB in this range. Conditions associated with hemolysis, including direct Coombs'-positive Rh and ABO immunization or other isoimmunizations and G6PD deficiency, may pose an increased threat to an otherwise healthy newborn. The Subcommittee on Hyperbilirubinemia of the AAP includes jaundice developing within the first 24 hours, blood group incompatibility with a positive DAT, and other known conditions including G6PD deficiency, all associated with increased hemolysis, as major risk factors for the development of severe hyperbilirubinemia.[12] The AAP recommends initiating phototherapy or performing exchange transfusions at lower levels of TB in neonates with hemolytic conditions than in apparently nonhemolyzing counterparts. However, it is not proposed that a hyperbilirubinemic newborn without an obvious hemolytic condition will be unaffected by bilirubin encephalopathy. Patients with kernicterus have been reported in whom no evidence of hemolysis was evident.[168] Crigler-Najjar syndrome, a condition not associated with increased hemolysis, is frequently complicated by bilirubin encephalopathy.

Absence of a defined diagnosis associated with hemolysis should not lead to a state of complacency or belief that hemolysis is not, in fact, taking place. Blood counts are notoriously unreliable indicators of hemolysis in newborns. Studies utilizing the endogenous production of CO, an accurate index of heme catabolism, have demonstrated increased hemolysis in many jaundiced newborns, even in the absence of evidence of a specific hemolytic disorder. The term *nonhemolytic jaundice* should be used cautiously so as not to unwittingly potentiate bilirubin neurotoxicity in a possibly hemolyzing infant in whom it could have been prevented.[164,255]

Hemolytic conditions in the newborn are generally divided into two major etiologic groups: immune and nonimmune.

Isoimmunization

The hallmark of isoimmunization is a positive DAT (also known as the Coombs' test). This is indicative of a maternally produced antibody that has traversed the placenta and is now found within the fetus. The test is termed *direct* if the antiglobulin is adhered to the RBCs. An *indirect* test refers to the antibody being detected in the serum.

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Rh Disease. In past decades, Rh hemolytic disease was the most common cause of severe hemolytic hyperbilirubinemia and a frequent cause of kernicterus. However, maternal prophylaxis with high-titer anti-D immunoglobulin G (RhoGAM), combined with aggressive fetal surveillance and intrauterine blood transfusions, has greatly reduced the incidence and severity of this disease. Mothers sensitized before the development of immune serum prophylaxis are no longer commonly encountered in industrialized countries. Additional technologies used antenatally, which have led to improvement in outcome, include antenatal blood group genotyping by polymerase chain reaction (PCR) from fetal cells obtained by amniocentesis or even from maternal blood samples.[34,184] Assessment of the degree of fetal anemia and determination of the need for intrauterine transfusion noninvasively by determining middle cerebral artery peak systolic velocity by the Doppler technique has reduced the need for invasive procedures.[88]

Those without access to preventive treatment, immigrants from countries in which prophylaxis is not widely available, or those who did not receive prophylaxis following abortion or invasive procedures may continue to deliver affected infants. The problem continues to be rife in developing countries. Although the incidence of Rh negativity is lower in countries such as India, Nigeria, Pakistan, Kenya, and Thailand than in North America or in Europe because of their large populations, large numbers of women from these countries may be at risk. Zipursky and Paul estimate that in these low income countries more than 1 million women annually do not receive anti-D prophylaxis[293] and that more than 100,000 children are born with Rh disease.[33]

The Rh blood group proteins are a highly antigenic group of proteins capable of causing severe isoimmunization with a high risk for fetal hydrops and death. Although several systems of nomenclature exist, the CDE system is most commonly used. These three loci each contain two major alleles (C,c; D,d; E,e) and several minor alleles. The D antigen may produce maternal sensitization with a fetomaternal hemorrhage as small as 0.1 mL. Whereas C and E alleles are relatively uncommon causes of isoimmunization, they can, on occasion, lead to severe hemolysis and hyperbilirubinemia. Indeed, Rh C disease may be as severe as Rh D isoimmunization.[222] Furthermore, women with multiple RBC antibodies may develop significant hemolytic disease of the fetus and newborn to a greater extent than those with a single antibody, especially in the presence of anti-(Rh)D. The pathophysiology of this phenomenon may represent a more aggressive immune response in those with more than one RBC antibody.[174] Rh disease in pregnancy is highly associated with both intrauterine hemolysis and severe hemolytic disease following delivery. Untreated, the condition can lead to intrauterine anemia and severe *hydrops fetalis*, with rapid postnatal evolvement of hyperbilirubinemia with the potential of kernicterus.

The immunization process may begin if an Rh-negative woman, usually D negative, is exposed to a D antigen. This usually occurs by ante- or intrapartum transplacental fetomaternal transfusion of fetal RBCs containing a D antigen, or by transfusion of Rh-positive RBCs during abortion, blood administration, or procedures including amniocentesis, chorionic villus sampling, or fetal blood sampling. Following exposure to the D antigen on the fetal RBCs, the mother's immune system responds by forming anti-D immunoglobulin G (IgG) antibodies. The IgG then crosses the placenta and adheres to fetal RBCs containing the D antigen. The subsequent antigen–antibody interaction leads to hemolysis and anemia. The immune response may become more severe and more rapid with progressive pregnancies. Resultant anemia causes bone marrow stimulation, with increased numbers of immature RBCs appearing in the circulation (*erythroblastosis*) and extramedullary hematopoiesis. *Fetal hydrops*, a condition characterized by generalized tissue edema and pleural, pericardial, and peritoneal effusions, may result from a combination of hypoproteinemia, tissue hypoxia, and capillary leak. Anemia with resultant poor myocardial function may further exacerbate the hydrops by causing congestive cardiac failure and venous congestion.

Elevated COHb levels detected in blood obtained by cordocentesis in affected fetuses of nonsmoking isoimmunized mothers confirm that destruction of erythrocytes begins in utero. However, the primary manifestation of the in utero hemolysis is that of anemia. Although large amounts of bilirubin are produced concomitantly, erythroblastotic infants are not severely icteric at birth. Concentrations of TB are usually kept below 5 mg/dL (86 μmol/L) by transfer of unconjugated bilirubin across the placenta. Jaundice may appear, however, shortly after delivery. Classically, in the initial stages, the TB is all indirect-reacting, although small amounts of conjugated bilirubin have been noted. After some days of excessive bilirubin load, the excretory system may become overwhelmed with efflux of conjugated bilirubin into the serum, and an increasing conjugated bilirubin fraction is not uncommonly seen.[251] Hepatic conjugation may mature more rapidly than excretory function as a result of stimulation by chronic exposure to high concentrations of bilirubin in utero. Furthermore, hepatic excretory function may also be adversely affected by development of hepatic congestion secondary to heart failure and swelling caused by extramedullary hepatic hematopoiesis, anemia, and poor hepatic perfusion.

ABO Heterospecificity. With the reduction of the incidence of Rh isoimmunization by immune prophylaxis, DAT-positive ABO incompatibility in industrialized countries with functional medical systems is now the single most prominent cause of immune hemolytic disease in the neonate. The clinical picture is usually milder than that of Rh disease, although infrequently severe hemolysis with hyperbilirubinemia may occur. In recent series of infants with either bilirubin encephalopathy/kernicterus or extreme hyperbilirubinemia reported from diverse countries including the United States, Canada, the United Kingdom,

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Ireland, Denmark, Switzerland, China, and Nigeria, in whom the etiology of the hyperbilirubinemia was determined, infants with blood group A or B born to group O mothers comprised 19% to 55%.[35,122,173,204,242,292,294]

ABO blood group heterospecificity is the situation in which a blood group A or B infant is born to a group O mother, a setup occurring in about 12% of pregnancies. In some instances, women with blood group O have a high titer of naturally occurring anti-A or anti-B antibodies. High titers of anti-A or anti-B antibodies can sometimes be found in blood group O women even before their first pregnancy. This contrasts to Rh isoimmunization, in which immune sensitization occurs progressively with subsequent pregnancies. In contradistinction to blood group A or B individuals, in whom their respective anti-B or anti-A antibodies are IgM molecules with limited ability to cross the placenta, the respective antibodies of blood group O individuals are predominantly smaller IgG molecules and may cross the placenta. Attachment to corresponding fetal RBCs may follow, provided these cells have the A or B antigen. Extravascular hemolysis of the IgG-coated RBCs is thought to be mediated within the reticuloendothelial system by Fc-receptor-bearing cells. As with Rh isoimmunization, the immune process may commence in utero. However, unlike the Rh situation, there is little danger of severe hyperbilirubinemia, anemia, or hydrops in utero, and prenatal intervention is not indicated. Infants may sometimes be born with moderate anemia. After delivery, there is a potential danger of hyperbilirubinemia.

About one-third of blood group A or B neonates born to a blood group O mother will have a positive direct Coombs' test. Measurements of endogenous formation of CO, reflective of heme catabolism, have demonstrated, overall, an increased rate of heme catabolism in affected infants compared with controls.[239,255] In one study, those infants who developed hyperbilirubinemia (TB >95th percentile on the Bhutani nomogram) had even higher COHb values than the already high values of those who were nonhyperbilirubinemic.[134] Strength of DAT may also be predictive: ABO-heterospecific neonates with ++ DAT had a higher incidence of hyperbilirubinemia and higher COHbc values than those with ± or + DAT.[133] Not all DAT-positive neonates, however, develop severe hyperbilirubinemia. In one study, only 20% of DAT-positive neonates actually developed TB levels greater than 12.8 mg/dL (219 μmol/L); whereas, in another study, only 19.6% required phototherapy. Despite this apparent clinical mildness, newborns with severe hyperbilirubinemia of early onset who do not respond to phototherapy and require intravenous immune globulin (IVIG) therapy or exchange transfusion are occasionally encountered. In contrast to the above-mentioned studies, a study from Israel found that 52% of 164 DAT-positive, ABO-incompatible newborns developed a TB >95th percentile, many of these within the first 24 hours. At the extreme end of the spectrum, as already mentioned, kernicterus has been described.[242]

ABO blood group incompatibility with a negative DAT, not usually predictive of hemolysis or hyperbilirubinemia, may sometimes cause early and rapidly progressing jaundice, reminiscent of DAT-positive hemolytic disease.

Paucity of A and B antigenic sites on neonatal RBCs or weak expression of these antigens in neonates compared with adults may explain, in part, absence of clinical disease in many DAT-positive newborns. A or B antigenic sites situated in sites other than the RBC may bind with transplacentally acquired antibodies, limiting their availability to the RBC.

Because many ABO-incompatible, direct Coombs'-positive neonates have no evidence of ongoing hemolysis and do not develop early jaundice or hyperbilirubinemia, ABO heterospecificity with a positive DAT does not necessarily indicate ABO hemolytic disease. Some or all of the following criteria are necessary to support the diagnosis of ABO hemolytic disease:

1. Indirect hyperbilirubinemia, especially during the first 24 hours of life
2. Mother with blood group O; infant with blood group A or B
3. Spherocytosis on blood smear
4. Increased reticulocyte count
5. Evidence of hemolysis based on increased endogenous production of CO as assessed using end-tidal CO measurements, corrected for ambient CO (ETCOc) levels

In DAT-negative, ABO-heterospecific newborns, an interaction with a polymorphism for the $(TA)_7$ sequence in the promoter of the gene encoding UGT1A1, significantly increases the incidence of TB of at least 15 mg/dL (257 μmol/L) compared with controls and has been described.[131]

It is essential to closely observe any newborn born to a blood group O mother and to perform a TcB or TB measurement at the first appearance of jaundice. Routine blood group and DAT determination on umbilical cord blood is an option, which may allow for additional risk determination.

Isoimmunization Caused by Antibodies Other Than RhD. More than 50 RBC antigens may cause hemolytic disease of the newborn. The most important of these with regard to prenatal hemolysis include anti-C, anti-Kell, and anti-E,[103,124] although others may also infrequently be problematic. Alloimmunization caused by these autobodies can sometimes cause severe hemolytic disease of the fetus requiring prenatal intervention. Fetal surveillance protocols and clinical strategies developed for RhD alloimmunization are useful in monitoring all alloimmunized pregnancies. Similarly, the postnatal management should be based on the principles outlined in the management of the RhD-immunized newborn (see Therapy for Unconjugated Hyperbilirubinemia). Anti-Kell isoimmunization warrants special mention because fetal anemia, rather than hyperbilirubinemia, often predominates the clinical picture. This may be due to erythropoietic suppression in addition to a hemolytic process.[268]

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Nonimmune Hemolysis

Erythrocyte Enzymatic Defects. The mature human erythrocyte lacks a nucleus and the organelles necessary for protein and lipid syntheses. Most of the protein present within its cell membranes is hemoglobin. Because the uptake and release of oxygen and carbon dioxide by hemoglobin in the tissues does not require energy, the erythrocyte relies on glycolysis (through the anaerobic Embden-Meyerhof pathway and the aerobic pentose phosphate pathway) and not on mitochondrial oxidative phosphorylation to generate adenosine triphosphate (ATP). Thus, defects in the glycolytic enzymatic machinery may have profound effects on erythrocyte function and life span.

G6PD Deficiency. An entity that is highly associated with extreme neonatal hyperbilirubinemia and bilirubin encephalopathy is G6PD deficiency. Because G6PD deficiency has major neonatal public health implications, it is discussed in some detail.[129]

G6PD deficiency is a common enzyme deficiency estimated to affect hundreds of millions of people worldwide.[200] From its original indigenous distribution, including areas in south Europe, Africa, the Middle East, and Asia, immigration patterns have transformed it into a condition that may now be encountered virtually in any corner of the globe. It is not surprising that in low- and middle-income countries with a high frequency of G6PD deficiency, the condition is associated with a high incidence of neonatal mortality and neurodevelopmental disorders.[208] It is remarkable, though, that the condition has been over-represented in reports of neonates with extreme hyperbilirubinemia and bilirubin encephalopathy relative to the background frequencies of this condition among the populations of the United States, Canada, the United Kingdom, and Ireland.[173,242] In the US-based Pilot Kernicterus Registry, more than 20% of reported neonates were diagnosed with G6PD deficiency, whereas its overall frequency in that country is estimated at only 4%-7%.[200] Recent immigration from African and Middle Eastern countries to Europe may increase the frequency of this condition in that continent, as demonstrated by detection of G6PD A– and G6PD-Mediterranean mutations among African and Middle Eastern immigrants to Denmark.[276]

Function of G6PD. G6PD plays a major part in stabilization of the RBC membrane against oxidative damage. The enzyme catalyzes the first step in the hexose monophosphate pathway, oxidizing glucose-6-phosphate to 6-phosphogluconolactone, thereby reducing nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. NADPH is essential for the regeneration of reduced glutathione from oxidized glutathione, a substance that plays an integral part in the body's antioxidative mechanisms. The pathway is also instrumental in stimulating catalase, another important antioxidant. In the absence of G6PD, NADPH will not become available, reduced glutathione will not be regenerated, and cells may be rendered susceptible to oxidative stress. Unlike other body cells, no alternative source of NADPH is available in the RBC, which explains the extreme vulnerability of the G6PD-deficient RBC to oxidative damage. Oxidative membrane damage incurred to the cell membrane may manifest as hemolysis.

Genetics of G6PD Deficiency. Because G6PD deficiency is an X-linked condition, males may be normal hemizygotes or deficient hemizygotes, whereas females may be either normal or deficient homozygotes or heterozygotes. Because of X-inactivation, heterozygotes have two RBC populations: one G6PD deficient, the other G6PD normal. Because X-inactivation may be nonrandom, unequal ratios of normal and enzyme-deficient RBCs may coexist. Heterozygotes may, as a result, have either a normal, intermediate, or deficient phenotype. It was previously thought that heterozygotes had sufficient enzyme activity to protect them from the dangers of G6PD deficiency. However, reports suggest that heterozygotes may not be without risk, and fatal kernicterus has been described in a heterozygote.[112,126,132] The most commonly encountered mutation is G6PD A–, found in Africa and southern Europe and in African Americans. G6PD Mediterranean, regarded as a more severe type than G6PD A–, is found in Mediterranean countries, the Middle East, and India. Another variant encountered primarily in Asia is G6PD Canton. The number of mutations discovered is continually increasing and total 217 at the time of this writing.[95]

G6PD Deficiency and Hemolysis. Most G6PD-deficient individuals lead perfectly normal lives and will, for the most part, be unaware of their inherited condition. However, G6PD deficiency may be associated with severe hemolytic episodes with resultant jaundice and anemia, following exposure to a hemolytic trigger. Classically, these episodes often occur after ingestion of or contact with the fava bean (favism). Medications and chemical substances may be suspected, but sometimes no offending trigger is identified. Infection may play a role in the pathogenesis of acute hemolysis.

In neonates, extreme hemolytic hyperbilirubinemia may develop suddenly and without previous warning. Some identifiable substances associated with neonatal hemolysis include naphthalene (used to store clothes), herbal medicines, henna applications, or menthol-containing umbilical potions. Frequently, the trigger cannot be recognized and the hemoglobin concentration may not drop, leading to the erroneous diagnosis that hemolysis is not occurring. There can, however, be no other viable explanation for the exponential increase in TB to dangerous levels. G6PD deficiency may, therefore, be the one reason that kernicterus may not be completely preventable. Exchange transfusion may be the only recourse. Early hospital discharge with delayed follow-up may place these patients at risk for severe sequelae.

In a Nigerian neonatal cohort, G6PD-deficient and -intermediate (presumable heterozygotes) had higher TB, lower hematocrit values, and a greater need for phototherapy during the first postnatal week than G6PD-normal counterparts, suggestive of increased hemolysis.[20] Frequently, hematologic indices typical of hemolysis in older

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children and adults, including falling hemoglobin and hematocrit values and increasing reticulocyte counts, may be absent despite a clinical picture of hemolysis. However, studies of endogenous CO formation, reflective of the rate of heme catabolism, have demonstrated an important role of increased hemolysis in association with this condition. Significantly higher levels of COHb have been reported in Nigerian G6PD-deficient neonates who developed kernicterus compared with neonates who were hyperbilirubinemic but did not develop signs of kernicterus.

More frequently and less life threatening, G6PD-deficient neonates may have a moderate form of jaundice, which occurs at a rate several-fold that of controls. The jaundice usually responds to phototherapy, although exchange transfusion may also be necessary. These infants have a low-grade hemolysis that cannot be implicated as the primary icterogenic factor.[135] Diminished bilirubin conjugation has been shown to be of major importance in the pathogenesis of the hyperbilirubinemia. An intriguing interaction has been noted between G6PD deficiency and a noncoding area $(TA)_7$ promoter polymorphism in the gene encoding UGT1A1.[138] This polymorphism, also known as UGT1A1*28, is associated with Gilbert syndrome. The incidence of a TB of at least 15 mg/dL (257 μmol/L) increased in a stepwise, dose-dependent fashion in G6PD-deficient neonates who were heterozygous or homozygous, respectively, for the polymorphism. This effect was not seen in the G6PD-normal control group. Furthermore, G6PD deficiency alone, in the absence of the promoter polymorphism, did not increase the incidence of hyperbilirubinemia over and above that of G6PD-normal counterparts. In Asians, in whom the $(TA)_7$ promoter polymorphism is rare, a similar interaction was noticed between G6PD deficiency and coding area mutations of the *UGT1A1* gene.[115] In a recent study of African-American neonates, although 20.6% had variations in both *UGT1A1* and *SLCO1B1* genes, these genetic variants did not have an effect on the incidence of hyperbilirubinemia.[238] This may be because very few neonates in that cohort were G6PD-deficient, confirming the concept of a gene interaction necessary to influence the incidence of hyperbilirubinemia.

The apparent mildness of this form of hyperbilirubinemia may be deceiving. Inherent to these infants is increased hemolysis, as demonstrated by endogenous CO production studies, in combination with a predilection for diminished bilirubin conjugation related to *UGT1A1*28*. Any further hemolysis, or additional conjugation decrease such as associated with prematurity, may upset the equilibrium between bilirubin production and elimination, thereby precipitating severe hyperbilirubinemia. Unlike the acute hemolytic form of jaundice, this milder form of jaundice can be predicted by predischarge bilirubin testing. G6PD-deficient neonates, who had a predischarge TB concentration below the 50th percentile, were unlikely to develop subsequent hyperbilirubinemia. However, as the predischarge TB increased progressively above the 50th percentile, the risk for subsequent hyperbilirubinemia increased in tandem.[128]

Testing and Screening for G6PD Deficiency. Many qualitative or quantitative screening tests are available that should accurately determine the hemizygous state in males or the homozygous state in females. Because many heterozygotes may have intermediate to normal G6PD enzyme activity, the result of nonrandom X chromosome inactivation, the heterozygote state is difficult to determine using standard biochemical tests. Females of high-risk groups (Mediterranean origin, African American, African, Middle Eastern or Asian, and Sephardic Jews) should have close follow-up to detect the development of jaundice despite a normal screening result. Also, biochemical tests may give a false normal result if performed during an acute hemolytic episode. The reason is that older RBCs, depleted in G6PD enzyme activity, may be destroyed, leaving younger cells with higher enzyme activity intact. In such cases, G6PD testing should be performed several weeks after the acute hemolysis has subsided. An alternative method is to analyze DNA for the specific suspected mutation. Some countries have introduced neonatal screening for G6PD deficiency combined with parental education in the hope that identification of an infant with G6PD deficiency should lead to avoidance of known triggers of hemolysis and speed the process of evaluation and treatment should an affected neonate become jaundiced. Reports have demonstrated a decrease in the number of cases of kernicterus following introduction of screening programs, as recently reviewed.[127] G6PD screening with rapid turnaround time is feasible.[7,201,225] Although discussion regarding neonatal screening for G6PD deficiency has started in the United States, there is as yet no national consensus regarding its need, effectiveness, or the best approach.[278]

The treatment of neonatal hyperbilirubinemia associated with G6PD deficiency should follow the 2004 AAP Practice Guideline[12] for neonates with hemolytic risk factors.

Pyruvate Kinase Deficiency. Pyruvate kinase catalyzes the conversion of phosphoenolpyruvate to pyruvate and the formation of ATP from adenosine diphosphate in the Embden-Meyerhof pathway. Deficiency of this enzyme results in a lack of ATP for erythrocytic metabolic activity and in chronic anemia. Pyruvate kinase deficiency, a condition prevalent in northern Europeans and inherited in an autosomal recessive manner, results in a lack of ATP, an important source of energy for RBC metabolism. In the newborn period, anemia, reticulocytosis, and severe, early, hemolytic jaundice may ensue.[59] Exchange transfusion may be required, and kernicterus has been reported.

Four isozymes are encoded by two genes, among which 250 mutations and 6 polymorphisms have been described.[48] Diagnosis is determined by an enzyme assay, which should be performed in cases of hemolysis and hyperbilirubinemia not associated with a positive direct Coombs' test or spherocytosis. Molecular studies may also confirm the diagnosis.[100]

Hexokinase catalyzes the conversion of glucose to glucose-6-phosphate, the initial step in glycolysis. Hexokinase deficiency predisposes the erythrocyte to oxidant damage and thus is another cause of hemolysis and neonatal

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hyperbilirubinemia. Inheritance is autosomal recessive, and the gene has been localized to chromosome 10.

Congenital erythropoietic porphyria is an extremely rare, recessively inherited disorder of heme metabolism in which deficient uroporphyrinogen III cosynthase activity affects the conversion of hydroxymethyl bilane to type III uroporphyrinogen. Normal heme synthesis can occur only in the presence of greatly elevated levels of type I uroporphyrinogen and type I coproporphyrinogen. These porphyrins are deposited in massive quantities throughout the cells of the body, including the erythrocytes. The disease may present at birth with anemia, jaundice, and splenomegaly. Pink to brown staining of diapers soaked with porphyrin-rich urine is an early clue to the diagnosis. Because porphyrins are photoreactive, the diapers readily fluoresce under ultraviolet light. The same photoreactive properties of porphyrins lead to hemolysis, hyperbilirubinemia, and cutaneous photosensitivity with subepidermal bullae formation.

Deficiencies of other enzymes in the glycolytic pathway, including glucose phosphate isomerase, can produce severe hemolysis and hyperbilirubinemia in the neonatal period.

Erythrocyte Structural Defects. Defects in erythrocyte membrane and cytoskeletal structure (see Chapter 79) alter the shape and deformability of the cell and result in sequestration within the narrow splenic sinusoids. Hemolysis, hyperbilirubinemia, and splenomegaly are the clinical hallmarks of these disorders.

Hereditary Spherocytosis. Of the hereditary RBC membrane defects that may lead to acute hemolysis and hyperbilirubinemia in the newborn, hereditary spherocytosis is probably the most common.[119] In spherocytosis, the normal biconcave shape of the erythrocyte is altered such that the cell assumes a spherical shape—the shape with the smallest possible diameter for its volume. In addition to a reduction in surface area with consequential diminished oxygen uptake and delivery, the limitation in deformability may result in massive splenic sequestration. This condition may be inherited in both an autosomal dominant and recessive fashion, and frequently there may be a history of acute hyperbilirubinemia in a sibling or parent. The condition should be suspected in individuals of Northern European ancestry. Microvesiculization of the RBC membrane results from deficiency of proteins, including ankyrin, band 3, α-spectrin, β-spectrin, and protein 4.2 in that membrane. These osmotically fragile RBCs are trapped in the spleen, the microvesicles aspirated by macrophages, and the cell destroyed. The diagnosis can be made microscopically by identifying spherocytes in the peripheral blood smear, with confirmation by the osmotic fragility test. The latter test may be especially important in differentiating infants with hereditary spherocytosis from those with DAT-positive ABO isoimmunization, a condition that may also result in microspherocytosis. Mutations of at least five genes encoding the previously mentioned proteins have been recognized.

Hereditary spherocytosis is frequently associated with neonatal hyperbilirubinemia. Of 178 affected Italian term, predominantly breastfed newborns, 112 (63%) developed neonatal hyperbilirubinemia requiring phototherapy. The incidence of hyperbilirubinemia was even higher in those who also had a genetic variation of the *UGT1A1*28* gene promoter, similar to that described in G6PD deficiency.[119] Kernicterus has been described.[23] A mean corpuscular hemoglobin concentration (MCHC) of 36.0 g/dL or greater had an 82% sensitivity and a 98% specificity for identifying hereditary spherocytosis and should alert caregivers to the possibility of this diagnosis.[62]

Hereditary Elliptocytosis, Hereditary Pyropoikilocytosis, Hereditary Ovalocytosis, and Hereditary Stomatocytosis. These are rare conditions affecting the erythrocyte membrane. The diagnosis may be made by microscopic examination of the peripheral blood smear. Hemolysis may occur in the neonatal period and result in anemia and hyperbilirubinemia.

Infantile pyknocytosis is a transient abnormality of erythrocyte morphology associated with hemolysis and neonatal jaundice. Small, irregular, dense RBCs with spiny projections are seen in the peripheral smear and account for more than 5% of the total RBC population. Anemia and hemolysis persist throughout the first month of life and often into the second and third months. Jaundice is most severe during the first 2 weeks of life.

Blood Transfusion. In preterm infants, increases in TB levels have been documented, sometimes warranting phototherapy following blood transfusion. This may be because of a large bilirubin load caused by lysis of the transfused RBCs either prior to, during, or following the transfusion.[58]

Infection. Bacterial infection is a known cause of hemolysis and hyperbilirubinemia. Sepsis causes hyperbilirubinemia by increasing TB concentrations through hemolysis, or by impairing conjugation, thereby resulting in decreased excretion of bilirubin. Several theories have been proposed for the mechanism of hyperbilirubinemia in the septic neonate. Neonatal erythrocytes are particularly susceptible to cell injury and Heinz body formation in response to oxidative stress. In addition, HO-1 can be induced by oxidants, which could lead to increased catabolism of heme to bilirubin. Because bilirubin is a protective antioxidant, initially in infection, TB levels may decrease as a result of its consumption. However, the frequent manifestation of hyperbilirubinemia associated with sepsis suggests that this protective mechanism may be overwhelmed in septicemia. Furthermore, disseminated intravascular coagulation resulting from sepsis may produce hemolysis as erythrocytes traverse the deposition of fibrin within the microvasculature. In addition, conjugated hyperbilirubinemia may result from hepatitis secondary to bacterial, viral, fungal, and protozoal infections.

Sequestration. Sequestration of blood within body cavities can result in increased bilirubin production as the body metabolizes and recycles the heme released as erythrocytes are catabolized. Birth trauma resulting in the collection of RBCs within the layers of tissue covering the skull and brain (cephalohematoma, subdural hematoma, subgaleal hematoma) or elsewhere (bruising associated with precipitous or

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instrument-assisted delivery) has the potential to produce hyperbilirubinemia (see Chapter 29).

Large hemangiomas, as in Kasabach-Merritt syndrome, may be associated with hemolysis and hyperbilirubinemia in addition to thrombocytopenia and depletion of fibrinogen and other clotting factors.

Polycythemia. An increase in RBC mass with resultant increased breakdown of these cells has the potential to overload the already immature capacity of the newborn to eliminate heme degradation products. Polycythemia may be associated with delayed cord clamping, maternal–fetal transfusion, and twin–twin transfusion. Infants of diabetic mothers, especially those who are large-for-gestational age, are known to be at risk for polycythemia. Although the mechanisms underlying polycythemia in this group are unclear, CO excretion studies have shown that increased RBC breakdown, even in the absence of polycythemia, is the source of the hyperbilirubinemia in these neonates[254] (see Chapter 79).

Disorders of Hepatic Uptake and Conjugation

Uptake into hepatocytes may be affected by polymorphisms of the *SLCO* gene. Liu et al. reported that SLCO1B1 388G>A was associated with an increased risk of neonatal hyperbilirubinemia in Chinese but not in Caucasian, Thai, Malaysian, or Latin-American populations.[155]

Gilbert syndrome is a benign disorder that affects about 6% of the population and produces a chronic unconjugated hyperbilirubinemia. Both defective hepatic uptake of bilirubin and decreased hepatic UGT1A1 activity have been demonstrated. The basis of the reduced activity of UGT1A1 lies in the presence of additional TA repeats in the TATAA box in the promoter region of the gene.[37] The mutation is also known as *UGT1A1*28*. Because the noncoding, rather than coding, area of the gene is affected, individuals with Gilbert syndrome have a normally structured UGT1A1 enzyme but with diminished expression. The latter leads to a decrease in UGT1A1 enzyme activity. Although this disease usually does not manifest until after the second decade of life, some neonates with Gilbert syndrome may exhibit hyperbilirubinemia secondary to diminished uptake of bilirubin.[21] When mutations in both the gene for G6PD and the promoter for UGT1A1 occur, the degree of neonatal hyperbilirubinemia has been shown to be dose dependent.[138] In addition, in G6PD-deficient infants who had the wild-type $(TA)_6$ (normal) gene promoter, the incidence of hyperbilirubinemia was similar to that in infants who were G6PD-normal, with the wild-type promoter (9.7% versus 9.9%). The variant *UGT1A1* promoter, rather than the rate of heme catabolism as measured by blood COHb, was subsequently shown to be the crucial factor in determining the TB level and had a similar incidence of hyperbilirubinemia (>15 mg/dL [257 µmol/L]) to those infants with and without G6PD deficiency. However, in G6PD-deficient infants who were both hetero- and homozygous for the Gilbert variant, hyperbilirubinemia was more frequent in a stepwise, dose-dependent manner (32% versus 50%, respectively).[24,138] Polymorphisms of the *UGT1A1* promoter TATAA box, even in the heterozygotic form, may also play roles in the generation of extreme hyperbilirubinemia in G6PD deficiency-associated hemolytic episodes. Several studies have shown that *UGT1A1*28* in and of itself, in the absence of G6PD deficiency, is not associated with significant hyperbilirubinemia.[216]

As described earlier, UGT1A1 catalyzes the conjugation of bilirubin in the liver. Disorders of conjugation include both those in which there is a primary alteration in UGT1A1 and those in which UGT1A1 function is secondarily altered.

Crigler-Najjar Syndrome Type I

Crigler-Najjar syndrome type I is a rare autosomal recessive disease characterized by an almost complete absence of hepatic UGT1A1 activity. Because the coding area of the *UGT1A1* gene is mutated, the enzyme produced is structurally abnormal, with no bilirubin conjugating capacity. In the homozygous form, severe unconjugated hyperbilirubinemia develops during the first 3 days of life and progresses in an unremitting fashion, with TB concentrations reaching 25-35 mg/dL (428-599 µmol/L) during the first month of life. Kernicterus often occurs in the neonatal period, especially when the etiology of the disease is unsuspected and aggressive treatment is not initiated. Stools are pale yellow, and bile bilirubin concentrations are less than 10 mg/dL (171 µmol/L) (normal being 50-100 mg/dL [855-1710 µmol/L]), with total absence of bilirubin glucuronide in bile. Bilirubin glucuronide formation measured in vitro with liver obtained by biopsy is absent. Formation of most nonbilirubin glucuronides is either severely reduced or absent.

With either direct hepatic enzymatic assay or indirect measurement of glucuronide formation, both parents are found to have partial defects (about 50% normal). Enzyme activity reserve should be sufficient to keep TB concentrations within normal limits. Unless a family is known to be affected by the condition, the recognition of this disorder during the first week of life may be difficult because of confusion with other types of conditions causing exaggerated unconjugated hyperbilirubinemia. Persistence of unconjugated hyperbilirubinemia at TB concentrations of greater than 20 mg/dL (342 µmol/L) beyond the first week of life, or repeated need for phototherapy in the absence of obvious hemolysis, should prompt concern for existence of this syndrome.

Indirect methods of diagnosis, including microassay of UGT1A1 activity from a percutaneous liver biopsy specimen or analysis of bile conjugates, have been largely replaced by gene analysis. An update of the genetic mutations known to date has recently been published[49] (Fig. 91.9 includes many of the mutations known to be associated with the condition). Occurrence of the identical mutation in both parents of an affected homozygous infant suggests parental consanguinity.

The management of these neonates requires maintenance of TB concentrations to less than 20 mg/dL (342 µmol/L)

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during at least the first 2-4 weeks of life. The risk for kernicterus persists into adulthood, but aggressive management may diminish this risk while awaiting liver transplantation.[258] Today, nearly all neonates with this disorder are treated with phototherapy as initial therapy or after one or more exchange transfusions. Phototherapy is generally continued throughout the early years of life in the hope that this will prevent the development of kernicterus. Despite attempts to expose older children to phototherapy at the highest intensities and longest durations possible, the response to phototherapy progressively decreases with years of use. This may result from increased skin thickness or a changing distribution of the bilirubin pool. Prompt management of all intercurrent infections, febrile episodes, and other types of illness may help prevent later development of kernicterus. Inducers of UGT1A1, such as phenobarbital, are not effective in Crigler-Najjar syndrome type I disease.

Liver transplantation offers the only definitive treatment for the disease. This procedure should not be delayed indefinitely, because phototherapy may become less effective with the passage of time, and intercurrent illnesses may precipitate high levels of TB, with the potential of kernicterus, even in children whose TB concentrations had appeared to be under control and who had appeared to be neurologically intact. In a multicenter report of a world survey, 7 of 21 (33%) transplanted children had already developed some form of brain damage at the time of their transplantation. Average age at transplantation was 9.1 ± 6.9 years (range, 1-23 years). Hepatocyte transplantation has been used.[91] Gene therapy may also have promise for these patients in the future.[183,228] Stem cell therapy using hepatocyte-like cells differentiated from human-induced pluripotent stem cells reduced bilirubin levels in Gunn rats, indicating that the transplanted cells expressed UGT1A1 activity.[53]

Crigler-Najjar Syndrome Type II

Crigler-Najjar syndrome type II (also known as Arias disease) is more common than type I and typically benign. Although unconjugated hyperbilirubinemia occurs in the first days of life, TB levels generally do not exceed 20 mg/dL (342 μmol/L). Fasting, illness, and anesthesia may cause temporary increases in bilirubin to above baseline. The occurrence of kernicterus is rare. Evidence of hemolytic disease is absent (although it may occur coincidentally), stool color is normal, and neonates are otherwise healthy.

Unconjugated hyperbilirubinemia persists into adulthood. Biochemically, hepatic UGT1A1 activity is nonexistent and indistinguishable from that found in type I disease. Less than 50% of the daily bilirubin production is excreted in bile, and the monoglucuronide is the predominant form.

Another difference between type II and type I diseases lies in the response to phenobarbital.[259] Jaundiced neonates and adults with type II disease respond readily to oral administration of phenobarbital with a sharp decline in TB levels, whereas individuals with type I disease demonstrate no such change. Phenobarbital may be used as a simple clinical tool to differentiate the two syndrome types. Beyond the neonatal period, there should be no long-term risk for kernicterus unless there is coincidental hemolytic disease.

Crigler-Najjar syndrome type II occurs both as an autosomal recessive and dominant inheritance. The range of expression in one or both parents can be from an asymptomatic defect in conjugation on testing to severe icterus. Other members of the family also may either appear icteric or have detectable low-grade unconjugated hyperbilirubinemia. Screening of the parents and other close relatives for hyperbilirubinemia is a useful method for supporting the diagnosis when it is suspected. Testing of the neonate and the parents for the capacity to form glucuronides of bilirubin were used diagnostically in the past, but these methods have been largely replaced by sequencing of the *UGT1A1* gene.[125]

Transient Familial Neonatal Hyperbilirubinemia (Lucey-Driscoll Syndrome)

Lucey-Driscoll syndrome is a rare familial disorder in which neonates of certain mothers may develop severe unconjugated hyperbilirubinemia during the first 48 hours of life. Kernicterus has been reported in untreated newborns. The sera of these neonates and their mothers contain high concentrations of an inhibitor of UGT1A1 when tested in vitro. The serum inhibitory effect gradually declines after delivery coincident with gradual decline in TB levels.

Pyloric Stenosis

Pyloric stenosis may be associated with unconjugated hyperbilirubinemia at the time vomiting begins. Hepatic UGT1A1 activity is markedly depressed in the jaundiced neonates. The mechanism of diminished UGT1A1 activity may be due to presence of the variant $(TA)_7$ *UGT1A1* gene promoter, which is associated in adults with Gilbert syndrome.

Duodenal and jejunal obstructions are also associated with exaggerated unconjugated hyperbilirubinemia. Surgical relief of the obstruction results in a decline of TB levels to normal within 2-3 days. Lower intestinal obstruction, as in Hirschsprung disease, also may result in unconjugated hyperbilirubinemia, although usually of a milder degree than with upper intestinal tract disease. In this situation, as well as when there is upper intestinal tract obstruction, hyperbilirubinemia may result from increased reabsorption of unconjugated bilirubin from the intestine due to stasis of the intestinal contents (see Chapter 84).

Hypothyroidism

UGT1A1 activity in congenital hypothyroidism is deficient and may remain suboptimal for weeks or months. Because about 10% of congenitally hypothyroid neonates may develop prolonged, exaggerated jaundice, testing for thyroid function should be performed in these cases. Treatment with thyroid hormone promptly alleviates the hyperbilirubinemia. The mechanism of this association in the human newborn is unknown, but in rats, hypothyroidism impairs hepatic uptake and reduces hepatic ligandin concentrations.

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Thyroid hormone is also instrumental in many maturational processes. Its absence may delay hepatic bilirubin enzyme and transport development (see Chapter 88). It has also been suggested that thyroid hormone can cause changes in UGT1A1 protein expression.

Disorders of Excretion

Impaired hepatic excretion of bilirubin from disorders such as hepatocyte injury results in conjugated hyperbilirubinemia and is discussed later in this chapter.

Disorders of Enterohepatic Circulation

Jaundice Associated with Breastfeeding. Jaundice associated with breastfeeding is common, and breastfed newborns are more likely to develop prolonged hyperbilirubinemia than those fed formula. Two pathophysiologic mechanisms have been suggested for the early-onset association of jaundice with breastfeeding, although this differentiation is not clear, and overlap may exist between these suggested entities. Breastfeeding failure jaundice, or breastfeeding-associated jaundice, has been so labeled to distinguish it from breast milk jaundice. Breastfeeding failure jaundice is so labeled because the cause appears to be associated with poor feeding practices and not with any change in milk composition. In contrast, breast milk jaundice is apparently related to a change in the composition or physical structure of the milk. Both types result in an exaggerated enterohepatic circulation of bilirubin—one through "starvation" and the other through altered milk chemistry.

Breastfeeding Failure Jaundice. Breastfeeding failure jaundice occurs in the first weeks of life in breastfed newborns. Establishing effective breastfeeding may be difficult, especially in first-time mothers, who may find lactation to be an intricate process. Maternal factors, such as lack of proper technique, engorgement, cracked nipples, and fatigue may impair effective breastfeeding. Neonatal factors such as ineffective suck also may hamper attempts at breastfeeding. Even if the mother is experienced in breastfeeding and her baby is interested, her milk supply is usually limited to small amounts of colostrum in the first 24-48 hours after birth. A genetic predisposition including a $(TA)_7$ promoter polymorphism, or G71R mutation, both of the *UGT1A1* gene, can lead to the development of hyperbilirubinemia in breastfed infants and may contribute to the development of prolonged jaundice.[56,178,185,234] Breastfed newborns are more likely to develop prolonged hyperbilirubinemia than those fed formula.[235]

All these factors may act in combination, resulting in infrequent or ineffective breastfeeding. As a result, there may be little stimulus for milk production. Formula supplementation may further impair successful lactation. Exclusively breastfed neonates are, therefore, at risk for being relatively underhydrated and less well-nourished than formula-fed counterparts. Poor enteral intake may lead to a state of relative starvation with delayed meconium passage. Intestinal content stasis may lead to increased enterohepatic reuptake of bilirubin, increasing the bilirubin load presented to the liver, leading to unconjugated hyperbilirubinemia. This process is similar to "starvation jaundice" seen in older human patients as well as other animal species fasted for more than 24 hours.

Prevention of breastfeeding failure jaundice includes encouraging frequent (at least 8-12 times per day for the first several weeks) breastfeeding,[10] avoiding supplementation with water or glucose solutions,[71] and accessing maternal lactation counseling. Intensive support of the breastfeeding mother is necessary, especially in view of early discharge policies in place at many hospitals. Both during birth hospitalization and after hospital discharge, the newborn should be closely monitored for weight gain, adequate urination and stool formation, and the development of jaundice.[219]

Breast Milk Jaundice. Late breast milk jaundice occurs after the first 3-5 days of life and may last into the third week of life or beyond. Epidemiologic studies report that 10%-30% of breastfed infants in the 2nd-6th week of life are affected, with some having hyperbilirubinemia into the third month. In a recent study of predominantly breastfeeding North American Caucasian neonates at 3-4 weeks of age, 34%-43% had TcB levels >5.0 mg/dL, and many were clinically jaundiced.[163] Presence of the variant $(TA)_7$ *UGT1A1* (UGT1A1*28) gene promoter may be associated with prolonged breast milk jaundice in Caucasian populations[185] and G71R (UGT1A1*6) in Japanese.[178]

Typically, the TB level rises steadily, peaking at 5-10 mg/dL (86-171 μmol/L) at about 2 weeks of age, with a gradual decline over the first several months of life. More severely affected neonates may achieve peak levels as high as 20-30 mg/dL (342-513 μmol/L). There is no evidence of hemolysis, nor do these neonates appear ill; weight gain and intestinal function are normal. Pregnane-3-α,20-β-diol, a progesterone metabolite found in the breast milk fed to affected neonates, was historically thought to be the cause of this disorder, because this substance was shown to be a competitive inhibitor of UGT1A1 in vitro. Although milk and urine of mothers of these neonates contain this pregnanediol isomer, the inhibitory effect of this hormone has been questioned. Studies have indicated that the milk associated with this syndrome also contains high concentrations of non-esterified long-chain fatty acids. This suggests that certain of these fatty acids act as inhibitors of hepatic UGT1A1, causing retention of unconjugated bilirubin. It is unlikely that the non-esterified long-chain fatty acids would reach the sites of conjugation in smooth endoplasmic reticulum of hepatocytes without prior esterification. Triglycerides of these long-chain fatty acids do not inhibit in vitro activity of UGT1A1. Neither the pregnanediol nor the fatty acids have ever been substantiated as an inhibitor of hepatic conjugation in vivo, and their role in the cause of the breast milk jaundice syndrome remains questionable.

Studies of the enterohepatic circulation of bilirubin in the rat suggest that milk from mothers of neonates with this syndrome contains β-glucuronidase, an enzyme that could deconjugate bilirubin and, consequently, enhance enteric

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reabsorption of bilirubin, thereby increasing the hepatic bilirubin load. The presence of this enhancer of intestinal bilirubin absorption in human milk strongly correlates with the presence of mild to moderate unconjugated hyperbilirubinemia in neonates during the second and third weeks of life. With more than 50% of all breastfed neonates manifesting this effect of breast milk, this phenomenon may be a normal physiologic development comparable to, and an extension of, physiologic jaundice of the early newborn period.

Usually, other than jaundice, the neonates appear healthy, and no abnormal findings are noted. Although not recommended unless TB concentrations reach phototherapy levels or those that might be of danger to the infant, interruption of nursing and substitution with formula feeding for 1-3 days frequently causes a prompt decline of TB levels. On resumption of nursing, TB levels do not usually increase substantially. Brief interruption of nursing may be useful to confirm the diagnosis, thereby allaying parental anxiety. Failure to respond in this manner indicates that the neonate's jaundice may be unrelated to breastfeeding, and other causes should be sought. Supplementation with milk formula may have an effect similar to complete cessation of nursing. An alternative to temporary cessation of breastfeeding would be to confirm that the TB is primarily unconjugated, that thyroid function tests are normal, and that there is no evidence of urinary infection. In the situation where the infant is thriving and the TB does not reach levels indicating the need for phototherapy, it may be prudent to just observe the infant. It should not be forgotten, however, that rare disorders of bilirubin conjugation may occur in breastfeeding infants and may lead to erroneous diagnoses. Effective nursing practices that prevent early "starvation" in breastfed newborns may reduce not only the incidence of breastfeeding failure jaundice but also the severity of breast milk jaundice.[8,177]

Sequelae of Unconjugated Hyperbilirubinemia

The recognition that unconjugated bilirubin may penetrate the brain cell under certain circumstances and its association with neuronal dysfunction and death are reasons for carefully managing newborn infants with significant hyperbilirubinemia.[9,11] There is some evidence that, despite the publication of national guidelines for the prevention and management of hyperbilirubinemia in several countries (United States, Canada, South Africa, the United Kingdom, Norway, Israel, Japan, and the Netherlands), kernicterus continues to occur in industrialized countries in which the condition was thought to have been "extinct."[69,79,172,242] ABE (defined as the acute manifestations of bilirubin neurotoxicity) and its resultant sequelae, kernicterus (defined as chronic and permanent sequelae of bilirubin neurotoxicity) should, for the most part, be preventable conditions. Concerns that risks for ABE or kernicterus have been exaggerated with regards to term, otherwise healthy neonates have been outweighed by the perpetuation of cases up to present times.[14]

There is no single TB concentration that can be regarded as safe or categorically dangerous. The TB level, although used clinically to determine the need for phototherapy and exchange transfusion, is a poor predictor of subsequent neurodevelopmental outcome. In a study of 140 newborns with TB values greater than 25 mg/dL (428 µmol/L) who were treated with phototherapy or exchange transfusion, 5-year outcomes were not significantly different from those of randomly selected controls. Re-analyzing data from the Collaborative Perinatal Project, Kuzniewicz and Newman found no relationship between maximum TB levels and IQ scores.[148,195] However, in both aforementioned studies, the presence of a positive DAT did result in a poorer prognosis than the general population studied. Of 249 newborns admitted to a children's hospital in Cairo, Egypt, with TB values 25 mg/dL (428 µmol/L) or greater, Gamaleldin et al. found little correlation between admission TB levels and ABE.[93]

It is unlikely that in an otherwise healthy term infant with no obvious hemolytic condition, bilirubin neurotoxicity will occur at TB concentrations below 25 mg/dL (428 µmol/L), or even higher.[265] In the presence of hemolysis, prematurity, or other risk factors (see later), or in the presence of poor relative health, the danger point may be reached at lower levels of TB.[68,121] In a term infant thought to be actively hemolyzing, a TB concentration of 18-20 mg/dL (308-343 µmol/L) should probably not be exceeded.[42,50] In California, any TB >30 mg/dL is rare (8.6 per 100 000 births), and chronic bilirubin-induced neurotoxicity is uncommon and occurrs only in the setting of additional risk factors and TB values substantially above the AAP exchange transfusion thresholds.[149] Until definitive scientific data indicate otherwise, hyperbilirubinemia should be seen as being capable of producing a spectrum of neurologic dysfunction in the newborn, ranging from transient mild encephalopathy to permanent severe neurologic impairment secondary to neuronal necrosis (kernicterus). In addition, it is important to understand that bilirubin metabolism is a dynamic process influenced by many factors. An isolated TB level obtained at one point in time is inadequate to fully assess the risk for sequelae for a particular neonate. Many other factors, including the gestational age and relative health of the newborn, need to be carefully evaluated.

Epidemiology of Kernicterus and Extreme Hyperbilirubinemia

Did Kernicterus Really Disappear and Then Resurface?

Some authorities refer to a disappearance and resurgence of kernicterus in Westernized countries during the last decades.[107] Others claim that the condition never completely disappeared and as a result is still being seen. Undoubtedly, phototherapy and exchange transfusion, along with

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immune prophylaxis of Rh isoimmunization, have prevented many cases of kernicterus. The disappearance theory cannot explain cases of kernicterus still occurring owing to G6PD deficiency and DAT-positive ABO immunization, both common to this day.

The evidence for and against the disappearance/resurgence theory is inconsistent. In favor is a dearth of reported cases followed by several case reports and culminating in the US-based Kernicterus Registry report.[159,168] In Denmark, cases of bilirubin encephalopathy were found between 1994 and 2001 but not during the 20 years preceding that period. However, in the United States, Burke et al. reported a 70% decrease in the number of hospitalizations between 1988 and 2005 for kernicterus.[46] There was a constant incidence of kernicterus in California occurring during two time epochs: 1988-1993 and 1994-1997, whereas on a national United States basis, mortality data due to kernicterus from the Centers for Disease Control and Prevention databases remained consistent between 1979 and 2006.[46] Overshadowing this debate is the fact that cases of kernicterus with major public health implications are still occurring.

How Frequent Is Kernicterus?

The incidence of kernicterus varies from country to country, as well as between industrialized countries and countries with developing medical systems. Estimates in developed countries range from about 0.4-2 per 100,000.[45] Table 91.1 summarizes the frequency of the condition in some Westernized countries. In addition, recent cases of kernicterus have been reported from Italy and Germany.

These reports shared several common epidemiologic and etiologic features, including ABO heterospecificity, G6PD deficiency, other isoimmunizations, late prematurity, breastfeeding, sepsis, male gender, and discharge prior to 48 hours. It is remarkable that many of the infants were discharged as healthy from birth hospitalization but were subsequently readmitted for extreme hyperbilirubinemia.

TABLE 91.1 Incidence (per Live Births) of Kernicterus in Westernized Countries

Country/State	Years of Birth	Incidence of Kernicterus
Denmark	1994-1998	1/64,000
Denmark	1994-2003	1/79,000
United Kingdom	2003-2005	1/150,000
Canada	2007-2008	1/43,000
California*	1988-1997	0.44/100,000

*California data from Brooks JC, Fisher-Owens SA, Wu YW, Strauss DJ, Newman TB. Evidence suggests there was not a "resurgence" of kernicterus in the 1990s. *Pediatrics*. 2011;127:672-679.
Adapted, in part, from Maisels MJ. Neonatal hyperbilirubinemia and kernicterus—not gone but sometimes forgotten. *Early Hum Dev*. 2009;85:727-732.

African-American ethnicity and minority groups were over-represented, relative to the baseline population, in the United States and United Kingdom/Ireland reports.

Kernicterus in Developing Countries

Kernicterus, with a high incidence of bilirubin-attributable neonatal mortality, continues to occur in countries where G6PD deficiency is indigenous, as well as in developing countries with underdeveloped health services or in war zones as illustrated in a recent report from Baghdad, Iraq.[105] Other recent reports derive from Nigeria, Oman, Turkey, Kuwait, and Egypt.[93]

Surrogates for Assessing the Incidence of Kernicterus: Extreme Hyperbilirubinemia and Readmission

Although a devastating condition, kernicterus is in fact rare, and it is difficult to assess its incidence in any specific population group. Surrogates for the potential to develop bilirubin neurotoxicity have been sought, including the incidence of extreme hyperbilirubinemia [TB >25 mg/dL (428 μmol/L) or 30 mg/dL (513 μmol/L)] or the incidence of readmission for hyperbilirubinemia.[87] Overall, the rate of extreme hyperbilirubinemia or one of the alternatives should be low, provided surveillance for hyperbilirubinemia both during birth hospitalization and postdischarge is effective, although a zero rate will be difficult to obtain.

The reported range for readmission for hyperbilirubinemia lies between 0.17% and 3.2%.[40,180] The main reasons for readmission include lower gestational age, late prematurity, early discharge, unsuccessful breastfeeding, and lack of predischarge assessment of the risk for subsequent hyperbilirubinemia. The high risk for readmission of early term newborns in combination with early discharge was recently documented in Australia: Neonates born at 37 weeks' gestation and who were discharged at ≤48 hours were readmitted for hyperbilirubinemia at a ninefold higher frequency than those born at 39 weeks' gestation and remained in hospital for 3-4 days.[150] In Utah, late preterm and early term newborns were readmitted at higher rates than term counterparts, emphasizing the need to assess these babies' readiness for discharge and to vigilantly follow them for the development of hyperbilirubinemia after discharge.[291] Extreme hyperbilirubinemia, despite the close surveillance and ready availability of treatment in an organized health system in California, occurred in 0.14% of newborns (TB ≥25 mg/dL [428 μmol/L]), while 0.01% had TB values ranging from 30.5-45.5 mg/dL (522-778 μmol/L).[196] Within a health system in Detroit, Michigan, only 0.6% of infants compared to 2% in the California survey developed a TB of 20 mg/dL (342 μmol/L) or greater.[57] This difference was attributed to rigorous bilirubin screening, follow-up, and treatment.

Again in California, 0.12% of 18,089 newborns 35 weeks' or greater gestational age developed TB levels that exceeded the AAP[12] indications for exchange transfusion. It is remarkable that the majority of the affected infants were less than 38 weeks' gestational age.[90]

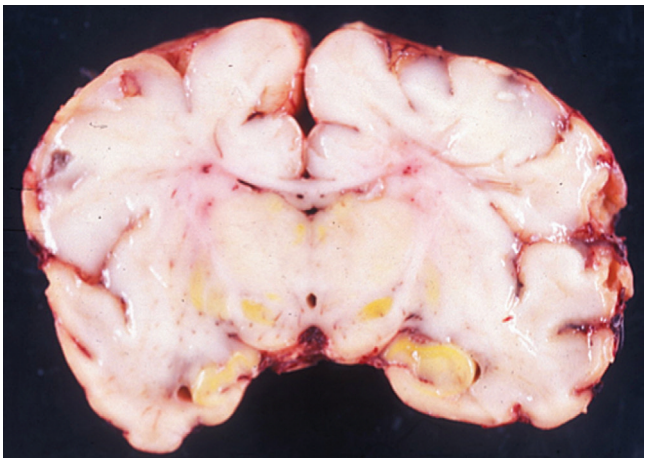
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Transient Encephalopathy or Acute Bilirubin Encephalopathy (ABE)

ABE is characterized by lethargy, poor feeding, hypotonia, and a high-pitched cry in a severely jaundiced infant. Hyperextension of the extensor muscles and back arching may ensue.[241] Early bilirubin toxicity may be transient and reversible, and not all infants displaying signs of ABE will necessarily go on to the full-blown clinical picture of kernicterus.[35,108,111,173] This is suggested by clinical observations of increasing lethargy and other signs in tandem with rising TB levels, with reversal of the symptoms after exchange transfusion. In Egyptian newborns with severe hyperbilirubinemia, a BIND score, based on mental status, muscle tone, and cry patterns, was used to predict residual neurologic and hearing dysfunction at 3-5 months of age. Those with high scores either died or were left with residual neurologic and auditory impairments. Low BIND scores were associated with a high rate of normalcy at follow-up after aggressive intervention. However, the BIND score was not an absolute predictor; some infants with low BIND scores but very high TB levels did have neurologic residua at follow-up.[83] Moreover, extreme hyperbilirubinemia in the absence of clinical evidence of ABE may be indicative of a favorable prognosis. In a 10-year Danish study, no evidence was found of an increased risk of deficits in motor development, executive function, or hearing in children who had had extreme neonatal hyperbilirubinemia but did not have intermediate or advanced bilirubin encephalopathy.[266]

Brainstem auditory-evoked responses (BAERs) may show changes in the wave latency and magnitude, characteristic of early signs of ABE.[245] BAER signs typically encountered in neonates with moderate unconjugated hyperbilirubinemia (10-20 mg/dL [171-342 µmol/L]) include prolongation of latencies of waves III and IV-V, and interpeak I-III and I-V, compared with neonates of similar gestational and postnatal ages without hyperbilirubinemia. Prolonged latencies in peak IV-V and interpeak I-V suggest interference with brainstem conduction. These changes in evoked responses reverse with either exchange transfusion or spontaneous decline in TB levels.

Long-term follow-up of children with neonatal abnormalities in brainstem responses believed to be caused by hyperbilirubinemia is not yet available, and the significance of abnormal BAER findings remains unknown.[285] An abnormal BAER suggests an injury of the VIII cranial nerve. Bilirubin neurotoxicity affects the neural tissues of the auditory center and nerve but not the cochlea. Therefore, bilirubin-induced auditory neuropathy may occur even in the context of normal cochlear function as measured by otoacoustic emission (OAE). This emphasizes the need to perform BAER testing, and not to rely on OAE, in neonates who are suspected of having auditory damage due to hyperbilirubinemia. During the early stages of bilirubin neurotoxicity, a characteristic signal signature can be seen by magnetic resonance imaging (MRI) using T1- and T2-weighted imaging.[99] Consequently, the presence of an abnormal BAER, normal OAE, and focal changes in the globus pallidus and medial lobe of the hippocampus by MRI is highly suggestive of ABE (Fig. 91.14).



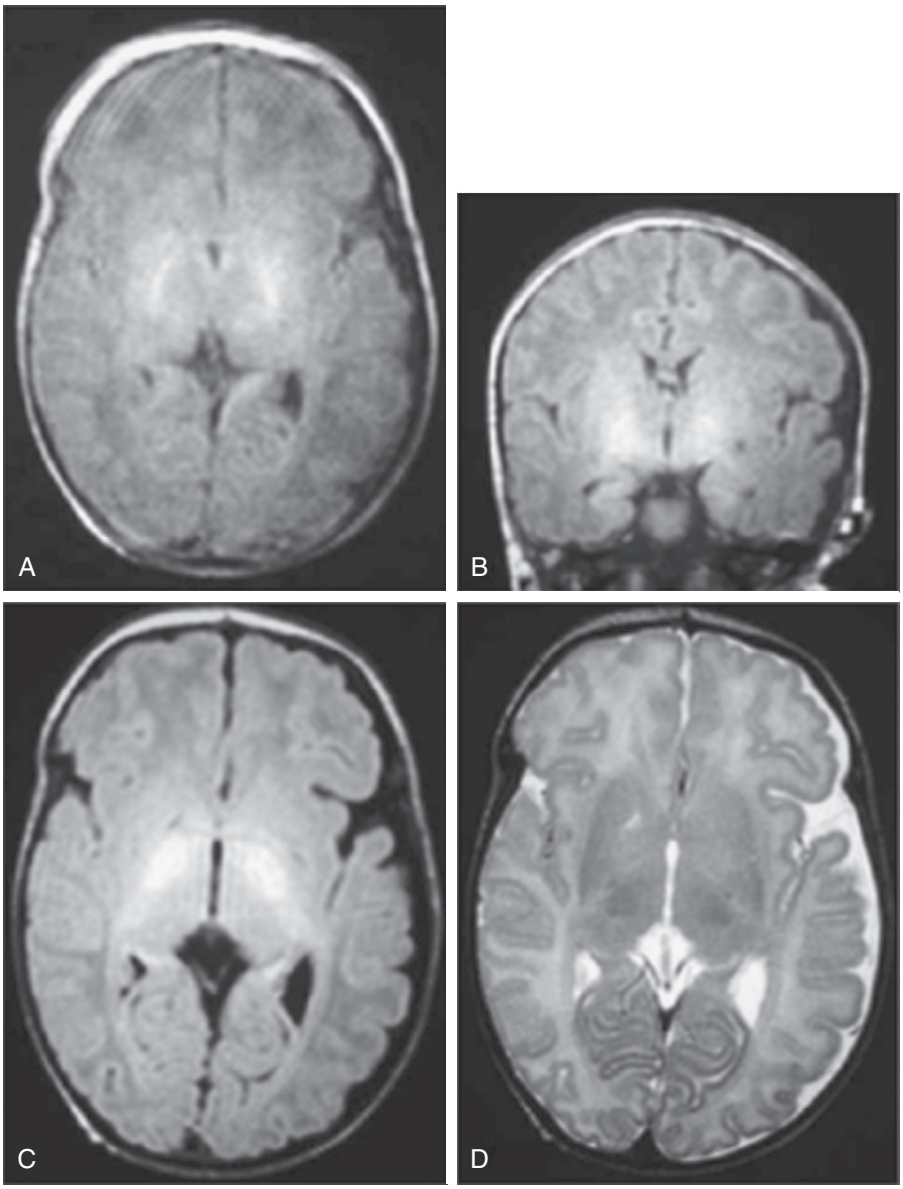
• **Fig. 91.14** Acute bilirubin encephalopathy. Coronal section through parietotemporal lobes. Note selective symmetric yellow discoloration in the hippocampus and subthalamic nuclei. Thalamus and globus pallidus are focally stained. (From Zangen S, et al. Fatal kernicterus in a girl deficient in glucose-6-phosphate dehydrogenase: a paradigm of synergistic heterozygosity. *J Pediatr*. 2009;154:616-619.)

Kernicterus

If early ABE is unrecognized or untreated, it may progress to permanent neurologic impairment. The term *kernicterus* (German *kern*, kernel or nucleus, and *ikteros*, jaundice) has been traditionally used to describe the pathologic findings of bilirubin toxicity within the brain: staining and necrosis of neurons in the basal ganglia, hippocampal cortex, subthalamic nuclei, and cerebellum, followed by gliosis of these areas in survivors (Fig. 91.15). The cerebral cortex is generally spared. About half of all infants with kernicterus observed at autopsy also have extraneural lesions of bilirubin toxicity. These include necrosis of renal tubular cells, intestinal mucosa, and pancreatic cells in association with intracellular crystals of bilirubin. Gastrointestinal hemorrhage may accompany these lesions.[263]

Kernicterus is also used to describe the clinical presentation of worsening encephalopathy. In the term newborn, several phases have been classically described, progressing from ABE in the early stages to chronic athetoid cerebral palsy later. Phase 1 is marked by poor sucking, hypotonia, and depressed sensorium. Fever, retrocollis, and hypertonia that may progress to frank opisthotonos are seen in phase 2. The hypertonia becomes less pronounced in phase 3, but high-pitched cry, hearing and visual abnormalities, poor feeding, and athetosis are manifest. Seizures may also occur. The usual time course for progression of the disease is about 24 hours. Long-term survivors often demonstrate the classic signs of kernicterus. These include a tetrad of: (1) choreoathetoid cerebral palsy; (2) upward gaze palsy; (3)

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• **Fig. 91.15** Magnetic resonance images of a 21-day-old, preterm male neonate with acute kernicterus. Axial (**A**) and coronal (**B**) T1-weighted and axial FLAIR (**C**) images at the level of the basal ganglia show symmetric, hyperintense globus pallidus involvement. This is not apparent on the axial T2-weighted (**D**) image. (From Coskun A, et al. Hyperintense globus pallidus on T1-weighted MR imaging in acute kernicterus: is it common or rare? *Eur Radiol*. 2005;15:1263.)

sensorineural hearing loss; and (4) dental dysplasia during later infancy and childhood.[244] The intellect may be spared, and mental retardation is not universally encountered. However, children with normal intelligence frequently have severe physical handicaps, making rehabilitation, education, and independent living unlikely. These sequelae of bilirubin toxicity may also develop in neonates who never manifested clinical signs of ABE during the newborn period. In addition, some neonates may have sequelae of subclinical bilirubin encephalopathy characterized only by the later development of mild disorders of motor function or abnormal cognitive function, or both.

A recent report of 25 California cases of strictly defined kernicterus illustrates the dismal picture of these unfortunate children. At a mean age of 7.8 ± 3.9 years old, 60% did not walk at all, and only 16% were able to walk unaided. Self-feeding was possible in only 52%, while a feeding tube was in place in 12%. Severe or profound mental retardation or severe disabilities were found in 36%, with only 32% having no evidence of mental retardation. Epilepsy and severe, profound or untestable visual and auditory impairment were common, with only 36% having normal hearing. Motor spasticity, ataxia and dyskinesis, and hypotonia completed the clinical picture in many others.

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Kernicterus in Preterm Infants and Low-Bilirubin Kernicterus

Presentation in preterm neonates is less stereotypical, and these patients may simply appear ill without signs specific for kernicterus. Bilirubin may enter the brain at lower levels of TB than would be expected in term infants. Moreover, bilirubin staining of central nervous system (CNS) structures in premature neonates may not be indicative of overt kernicterus and may result from developmental differences in CNS permeability to bilirubin and in situ bilirubin metabolism. Mortality occurs in about 50% of term newborns but may occur more frequently in the preterm population with kernicterus.[2,206,207] Based on a recent Japanese survey, it is estimated that 2/1000 preterm infants <30 weeks' gestational age developed kernicterus. Many did not have TB levels in the hyperbilirubinemic range, suggesting that the unbound bilirubin component may have been high in those affected.[186]

Low-bilirubin kernicterus can and does occur in premature infants at TB levels lower than what would be expected to be associated with neurotoxicity and at levels lower than those indicating phototherapy or exchange transfusion. Low-bilirubin kernicterus is a condition that was encountered in the past during autopsy examinations of premature infants in whom TB did not reach excessive levels that were thought to be neurotoxic. It is still encountered today in premature infant survivors who did not have very high TB levels, but who have clinical and MRI evidence of kernicterus. Low-bilirubin kernicterus has been defined as the occurrence of kernicterus at TB levels below commonly recommended exchange transfusion thresholds.[279] Because of the low nature of the TB in this situation, in the range not necessarily obligating phototherapy, the condition is unpredictable and the consequences refractory. Adherence to an accepted guideline is not a guarantee that some infants will not be unscathed. No guideline can be expected to prevent illness in every individual. It is not known what factors potentiate bilirubin neurotoxicity at low TB levels. Some factors that have been implicated include low serum albumin (almost ubiquitous in sick, unstable premature infants) and co-morbid CNS injury, including intraventricular hemorrhage, periventricular leukomalacia, and infection. Given the occurrence of the condition at low TB levels, it is unlikely that the condition will be eliminated barring a significant lowering of exchange transfusion thresholds, with the potential of bringing in its wake a plethora of complications (infections, hemorrhage, blood pressure instability, necrotizing enterocolitis, complications related to blood transfusion in general) associated with this procedure.

Bilirubin Entry into the Brain

Bilirubin is thought to enter the brain through multiple mechanisms. These include: (1) bilirubin production that overwhelms the normal buffering capacity of the blood and tissues; (2) alterations in the bilirubin-binding capacity of albumin and other proteins resulting in the presence of unconjugated bilirubin in the circulation; (3) increased CNS permeability to bilirubin secondary to disruption of the blood–brain barrier; and (4) other factors that may affect those previously mentioned or act through novel independent mechanisms.

Unconjugated bilirubin is nonpolar and lipid soluble, and its aqueous solubility in plasma water is extremely small, mandating its binding in plasma primarily to albumin. Binding to other components of blood (β-globulin, RBC membranes, and platelets) may also occur when the albumin-binding capacity for bilirubin is exceeded. It has long been believed that bilirubin toxicity occurs when the albumin-binding capacity for bilirubin is saturated and the unbound or "free" bilirubin (bilirubin in aqueous phase) concentration rises in blood. Whether this is, in fact, the basic pathophysiologic mechanism of kernicterus remains unresolved.

The human albumin molecule is capable of binding at least two molecules of bilirubin, with the first molecule more tightly bound than the second. Additional classes of binding sites, if operative in vivo, have much lower affinities than the first two. At a molar ratio of 1, each gram of human albumin binds 8.2 mg of bilirubin. Thus, at an average albumin concentration of 3 g/dL, the first binding site should be capable of binding 25 mg of bilirubin/dL of serum or plasma. The second binding site should be capable of binding an additional 25 mg/dL for a total binding capacity of 50 mg/dL.

Various techniques have been proposed to measure albumin binding of bilirubin, but their application and interpretation in clinical management are not generally accepted. The dye-binding methods using 2-(4'-hydroxybenzeneazo) benzoic acid and direct-yellow-7 are based on the measurement of reserve binding sites on the albumin molecule and should be capable of indicating impending risk. The column chromatographic methods (Sephadex G-25), the salicylate displacement spectrophotometric method (saturation index), the RBC uptake method, and the oxidation technique (peroxidase method) should all be capable of detecting small increases in unbound bilirubin or "loosely bound" bilirubin, in theory, denoting increased risk for developing kernicterus.[3,4] However, current laboratory and clinical data are still insufficient to permit a recommendation for the use of either a single method or a combination of methods to guide the clinical management of infants with neonatal unconjugated hyperbilirubinemia. Furthermore, it may be falsely reassuring to assume that in vitro binding capacities will remain reliably static in an in vivo system that changes so dynamically during the first postnatal days.

The bilirubin-binding capacity of albumin is thought to be decreased in sick term and premature human neonates. In addition, the serum albumin concentration is often lower in these patients than in healthy, term counterparts. Theoretically, both of these factors may act to place the sick term or premature neonate at higher risk for kernicterus at lower TB levels than seen in the healthy term newborn. There

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is still debate about whether the bilirubin-binding capacity of albumin decreases as pH drops below 7.4, despite the known solubility decrease of bilirubin with increasing acidity. Numerous agents compete with bilirubin for binding sites on albumin, acting to displace bilirubin and increase the ratio of free to bound bilirubin. Free fatty acids, which are elevated in sepsis and hypoxemia, are capable of displacing bilirubin. Similarly, IV lipid emulsions rarely can contribute to elevated free fatty acids and thus displacement of bilirubin. Sulfisoxazole and other sulfa drugs, indomethacin, and salicylates readily displace bilirubin. Even ampicillin, when injected rapidly, has the potential to act in a similar manner. Benzyl alcohol, once used as a preservative in various medications, has been shown to competitively inhibit bilirubin binding. Finally, certain substances used in the preparation of albumin solutions may act to decrease its bilirubin-binding capacity.[275]

Disruption of the blood–brain barrier allows the passage of molecules otherwise prevented from entering the CNS. Hypertonicity of the serum, meningitis, and hypoxemia all increase CNS permeability to bilirubin.[109] It has been reported that unconjugated bilirubin is a substrate for phosphorylated glycoprotein (P-GP) and that P-GP in the blood–brain barrier may play a role in limiting the entry of bilirubin into the CNS. P-GP is an integral plasma membrane transport protein, dependent on ATP, which can transport a wide variety of substrates across biologic membranes.

Many other factors may play a role in regulating bilirubin entry into the brain. Kernicterus has been reported to occur in adults with Crigler-Najjar syndrome type I, but only when TB levels have reached 45-55 mg/dL (770-941 μmol/L). This contrasts with the situation in the full-term newborn in which kernicterus may be anticipated at somewhat lower concentrations, suggesting presence of a maturational process in the blood–brain barrier integrity.

In addition to bilirubin produced within the reticuloendothelial system, bilirubin may be produced within the brain. The mammalian brain has two isoforms of HO, HO-1 and HO-2, which convert heme to biliverdin. HO-1 normally shows little baseline activity in the brain but is capable of being rapidly upregulated in response to stress. Most HO activity in the brain is the result of the constitutive isoform HO-2. HO-1 and HO-2 are distributed in selected areas of the brain, many of which play roles in motor and auditory function. Biliverdin reductase is also found in the brain, catalyzing the conversion of biliverdin to bilirubin. Although bilirubin thus formed is normally rapidly cleared by bilirubin oxidase, it is possible that this fraction of the bilirubin pool does contribute to the development of kernicterus. These enzyme systems are developmentally regulated and may also be influenced by any of the disease states previously mentioned. Because the bilirubin produced and metabolized in situ must be transported out of the brain, interference with this transport mechanism may be another potential mechanism of contributing to kernicterus.

Once bilirubin has gained access to the CNS, there are several postulated mechanisms of neuronal injury: (1) passage through lipid moieties of cell membranes into the lipids of subcellular organelles such as mitochondria, interfering with critical steps in energy metabolism; (2) binding to specific membrane, organelle, or cytoplasmic proteins and inhibiting their function; and (3) damage and direct interference with the function of DNA.[64]

The neurotoxicity of bilirubin is currently being debated. As described earlier, HO catalyzes the conversion of heme to biliverdin, releasing equimolar amounts of CO. CO may function as a neurotransmitter within the CNS and has been implicated as playing a role in memory. However, CO may also act as a neurotoxin and have deleterious effects, including neuronal necrosis. The deposition of bilirubin in the brain of patients with kernicterus may not be the primary insult but rather may be a relatively innocuous marker of neuronal damage produced by other means. Bilirubin has antioxidant properties and may, at physiologic levels, provide protection from oxidative injury. Whatever the mechanism of bilirubin neurotoxicity, clinical decisions regarding the management of hyperbilirubinemia and the institution of therapy are based on the TB level, and given its apparent effectiveness in reducing the incidence of kernicterus, it would be unwise to alter the current approach to therapy.

Bilirubin-Induced Neurologic Dysfunction (BIND)

BIND represents a spectrum of neurologic disorders, less severe than classic choreoathetotic cerebral palsy, but nevertheless, attributable to bilirubin neurotoxicity. Neonates are usually exposed to TB levels of lesser severity than encountered in classic kernicterus, but the clinical picture may manifest as a range of subtle processing disorders including disturbances of vision, motor ability, auditory and speech function, cognition, and language.[32,122]

Diagnosis of Unconjugated Hyperbilirubinemia

About two-thirds of the more than 4 million neonates born annually in the United States become clinically jaundiced. Clearly, the number of jaundiced neonates who will develop sequelae of hyperbilirubinemia is substantially less than this. The challenge to the pediatrician is to determine which newborns may become or are already abnormally jaundiced and, therefore, are at risk for severe sequelae. The recommendations by the AAP[12] for the laboratory evaluation of the jaundiced infant at 35 weeks of gestation or later are listed in Table 91.2.

Total Bilirubin (TB) Measurements

When the clinical screening examination detects a jaundiced newborn, the mainstay of clinical management includes

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TABLE 91.2 Laboratory Evaluation of the Jaundiced Infant ≥35 Weeks of Gestation

Indications	Assessments
Jaundice in first 24 hours	TcB and/or TB
Jaundice appears excessive for age	TcB and/or TB
Infant receiving phototherapy or TB rising rapidly (i.e., crossing percentiles [see Fig. 91.16]) and unexplained by history and physical examination	Blood type and Coombs' test, if not obtained with cord blood CBC and smear Direct or conjugated bilirubin Optional: reticulocyte count, G6PD, ETCOc, if available Repeat TB in 4-24 hours, depending on infant age and TB level
TB concentration approaching exchange levels or not responding to phototherapy	Reticulocyte count, G6PD, albumin, ETCOc (if device available)
Elevated direct (or conjugated) bilirubin level	Urinalysis and urine culture Evaluate for sepsis indicated by history and physical examination
Jaundice present at or beyond age 3 weeks, or if the infant is sick	Total and direct (conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen; evaluate for signs and symptoms of hypothyroidism

CBC, Complete blood count; ETCOc, end-tidal carbon monoxide, corrected for inhaled CO; G6PD, glucose-6-phosphate dehydrogenase; TB, total bilirubin; TcB, transcutaneous bilirubin.
From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297.

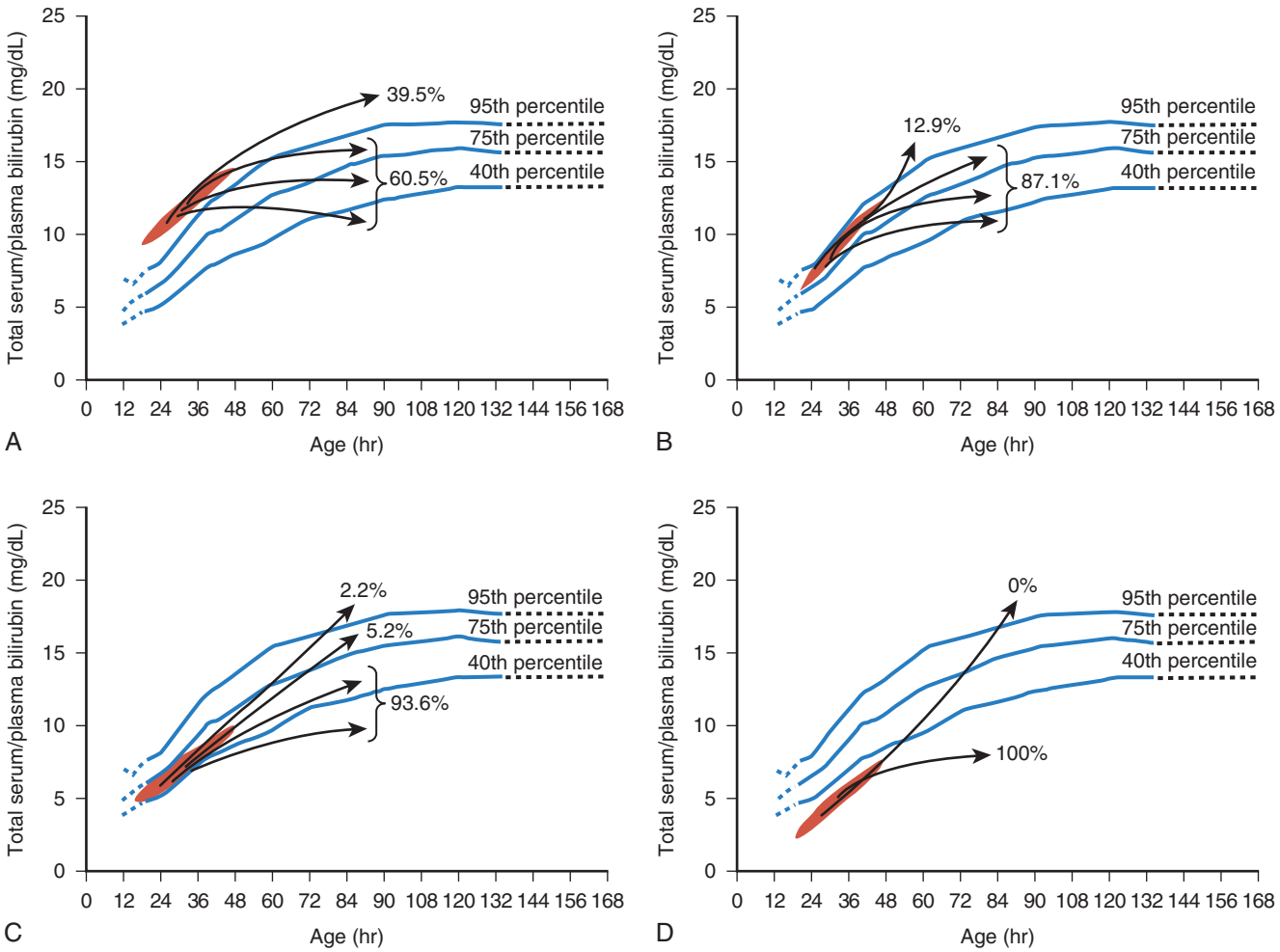
determination of TB concentrations in serum or plasma. Direct bilirubin measurements will not contribute much information in the early stages of jaundice but should be performed in cases of prolonged hyperbilirubinemia or of hyperbilirubinemia not responding to therapy, or if a disease process is suspected. In most patients, repeat determinations will be necessary in the acute stage of jaundice to determine the trajectory, the peak TB level, and whether indications for instituting therapy have been reached. Following that, an at least daily determination should be performed until a clear pattern of decline is observed. Clinical judgment is necessary to determine whether TB concentrations may be monitored on an ambulatory basis, thereby eliminating the need for prolonged hospitalization, or whether the risk for severe hyperbilirubinemia warrants in-hospital observation. Thus, the clinician must determine whether any individual neonate is at high or low risk for developing severe hyperbilirubinemia or kernicterus. Neonates at high risk for kernicterus include those presenting with jaundice in the first 24 hours of life, with pallor or hepatosplenomegaly, and with documented immune or nonimmune hemolytic conditions.

Bhutani and colleagues, in a study performed in 1999 on a racially diverse population of term healthy newborns, established that a percentile-based, hour-specific bilirubin nomogram of predischarge TB levels can accurately predict an infant's level of risk for developing hyperbilirubinemia[26] (see Fig. 91.10). Infants with a predischarge TB in the 95th percentile or higher (high-risk zone) had a 57% risk for developing severe hyperbilirubinemia (TB of 17 mg/dL [291 µmol/L] or greater). Risk was 13% for infants in the high-intermediate zone (TB between the 75th and 95th percentiles). Infants with TB levels between the 40th and 75th percentiles (low-intermediate risk) had a risk of 2.1%. Infants with TB in the 40th percentile or less had no risk. However, an analysis of predischarge TB values in 143 neonates who were readmitted for hyperbilirubinemia demonstrated a false negative predischarge bilirubin screen in 6 (4.2%) in the low-risk zone (<40th percentile) and 40 (28%) in the intermediate low-risk zone (41st-75th percentile).[40] The results of this and another study[249] suggest that predischarge TB values in the low-risk zones may not be benign, confirming the 2004 AAP recommendations for follow-up for all neonates within a few days of discharge.[12]

All TB measurements should be plotted on the hour-specific Bhutani nomogram, which takes into account the rapidly occurring changes in TB concentrations. It is clear from a study of the nomogram that an individual TB reading may have different connotations depending on the postnatal hour at which the blood was sampled. The closer the TB reading to the 95th percentile, the greater becomes the risk for subsequent hyperbilirubinemia. Conversely, a TB reading below the 40th percentile is usually associated with a low risk for hyperbilirubinemia. A useful method of assessing whether the rate of rise of TB is greater than normal (0.2 mg/dL/h or greater) is to plot several TB points on the graph and determine whether the trajectory runs in parallel with the graph or at a more rapid rate or "jumping" to a higher percentile track (Fig. 91.16). TcB may provide a useful, quick, and painless method of assessing these bilirubin modalities (see Transcutaneous Bilirubinometry later).

Classification of hyperbilirubinemia as conjugated or unconjugated requires fractionation of serum or plasma bilirubin into direct- and indirect-reacting pigments, respectively. Simple techniques that fail to distinguish direct- from indirect-reacting fractions are not recommended, but they may be useful as less expensive methods for screening and frequent repeat determinations and in emergency situations. The prototype of colorimetric methods is the van den Bergh test, a modification of the Ehrlich diazo reaction. The Jendrassik-Grof method has also been used widely as an automated procedure in many hospital laboratories.

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• **Fig. 91.16** Outcome of newborns as defined by the percentage of newborns that remain or move up to the high-risk zone after their risk assessment with the predischarge total serum/plasma bilirubin (TB) value (represented by the *red shaded areas*). **A,** Outcome for newborns designated in the high-risk zone ($N = 172$). **B,** Outcome of newborns in upper-intermediate-risk zone ($N = 356$). **C,** Outcome of newborns in the lower-intermediate-risk zone ($N = 556$). **D,** Outcome of newborns in the low-risk zone ($N = 1756$). (From Bhutani VK, et al. Predictive ability of a pre-discharge hour-specific TB level for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6.)

Newer automated methods such as the Ektachem system provide greater precision and the ability to measure the covalently bound δ-bilirubin. Compared with the values of direct bilirubin obtained by high-performance liquid chromatography, the Jendrassik-Grof and other diazo methods exaggerate this fraction to variable degrees. These older, nonspecific diazo reaction methods also fail to measure the δ-bilirubin fraction, underestimating TB by 0.2-0.3 mg/dL (3-5 μmol/L) in the normal adult. High-performance liquid chromatography probably provides the most accurate measurement of TB but is impractical for routine clinical laboratory use. The Ektachem method has gained wide acceptance. It uses a dry film system for measurement of TB and subfractions (indirect, direct, and δ) for general clinical laboratory use. The adult upper limit of normal for TB by this method is 1.3 mg/dL (22 μmol/L) and for the conjugated fraction, 0.3 mg/dL (5 μmol/L), of which two-thirds is in the form of δ-bilirubin. For newborns younger than 2 weeks, a simpler and less expensive single-film method can be used, omitting measurement of δ-bilirubin, which is not found in this age group.

High levels of direct-reacting bilirubin reflect a different set of pathologic entities that do not respond to the usual interventions for unconjugated hyperbilirubinemia and will be considered later in this chapter. It is useful to consider four groups of newborns when making decisions regarding laboratory evaluation and therapy of unconjugated hyperbilirubinemia: (1) healthy term (more than 37 completed gestational weeks); (2) sick term; (3) healthy premature; and (4) sick premature neonates. Studies to date have dealt almost exclusively with the healthy term newborn. Although unconjugated hyperbilirubinemia is a disease of multiple causes, and neonates should be treated differently based on gestational age and relative state of health, some general comments can be made.

Further laboratory investigation should be considered when TB concentrations are: (1) 4 mg/dL (68 μmol/L) or greater in cord blood; (2) increasing at a rate of 0.5 mg/dL

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(9 µmol/L) or greater per hour over a 4- to 8-hour period; (3) increasing at a rate of 5 mg/dL (86 µmol/L) or greater per day; (4) 13-15 mg/dL (222-257 µmol/L) or greater in full-term infants at any time; (5) 10 mg/dL (171 µmol/L) or greater in premature neonates at any time; or (6) when clinical jaundice persists beyond 10-14 days of life.

Further diagnostic studies are based on a thorough history and physical examination, which can narrow the differential diagnosis. A careful history from the parents may reveal familial patterns of neonatal hyperbilirubinemia or anemia or ethnic patterns associated with severe neonatal jaundice. Observation of the parents for jaundice and even determination of TB concentrations in them also may be useful in the diagnosis of familial types of hemolytic disease or inherited hepatic dysfunction. Patterns of feeding, the time of onset, and the frequency of breastfeeding also may be important. A careful physical examination with special attention to liver and spleen size, skin appearance, and neurobehavioral status should be performed in the evaluation of a jaundiced neonate.

Initial studies that may be indicated include determination of maternal blood group and Rh type; a screen for antibodies directed against minor erythrocyte antigens; determination of neonatal blood group and Rh type; direct antiglobulin titer (DAT), formerly known as the Coombs' test; hemoglobin or hematocrit; RBC morphology by peripheral blood smears; and reticulocyte counts. In the presence of significant jaundice with a potential ABO incompatibility (type O mother and type A or B infant), the DAT should be repeated at least once if originally negative, because initial false-negative results have often been noted. Hematologic indexes indicative of hemolysis in older children and adults may not be useful in the diagnosis of increased hemolysis in neonates because of overlap in these indices between hemolytic and nonhemolytic conditions. An elevated ETCOc level may be indicative of ongoing hemolysis (see End-Tidal Carbon Monoxide Measurements). Determination of erythrocyte G6PD activity may be useful in cases of unexplained hyperbilirubinemia, an exponential bilirubin trajectory, or hyperbilirubinemia not responding to intense phototherapy. Consideration of the family's ethnic group may be useful in deciding whether to perform a G6PD test. Cord blood should be saved in the event further testing is indicated.

More extensive studies for rarer forms of hemolytic disease and enzyme assays or genetic testing for UGT1A1 activity may be deferred until the chronicity of the disease has been established. Studies for hepatocellular disease (such as hepatitis and obstructive biliary disease), including serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, and cholesterol, need to be performed only when there is a significant elevation of conjugated bilirubin or liver disease.

Until a laboratory method is proved to accurately assess the risk for developing bilirubin neurotoxicity, the need for treatment and the progression from phototherapy to exchange transfusion must be based on clinical judgment in conjunction with consideration of TB, risk factors, gestational age, and the presence of hemolysis. The method of management chosen for an individual neonate is determined in part by the TB concentration at which therapy is instituted. The 2004 AAP Practice Guideline has formulated an established and uniform policy regarding the methods to be used and criteria for initiation of therapy.[12] The risk factors for the development of severe hyperbilirubinemia in infants 35 weeks' gestation or more are listed in Box 91.2.

Another problem in the assessment of any particular TB concentration involves variation within and between laboratories. High interlaboratory and interinstrument variations in the measurements of TB were reported. It was found that imprecision for a specific method or a given laboratory was acceptable, but inaccuracy was highly variable and should be taken into account in the interpretation of all TB measurements. Another factor contributing to these variations is the lack of appropriate bilirubin standards and consistent handling of clinical specimens. All these

• BOX 91.2 Risk Factors for Development of Severe Hyperbilirubinemia in Infants ≥ 35 Weeks of Gestation

Major Risk Factors

- Predischarge TB or TcB level in the high-risk zone (see Fig. 91.10)
- Jaundice observed in the first 24 hours
- Blood group incompatibility with positive DAT, other known hemolytic disease (e.g., G6PD deficiency)
- Gestational age 35-36 weeks
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, particularly if nursing poorly and weight loss is excessive
- East Asian race

Minor Risk Factors

- Predischarge TB or TcB in the high intermediate-risk zone
- Gestational age 37-38 weeks
- Jaundice observed before discharge
- Previous sibling with jaundice
- Macrosomic infant of diabetic mother
- Maternal age ≥25 years
- Male sex

Factors Associated with Decreased Risk of Significant Jaundice*

- TB or TcB in the low-risk zone (see Fig. 91.10)
- Gestational age ≥41 weeks
- Exclusive bottle feeding
- African-American race
- Discharge from hospital after 72 hours

DAT, Direct antiglobulin test; G6PD, glucose-6-phosphate dehydrogenase; TB, total bilirubin; TcB, transcutaneous bilirubin.
*Listed in order of decreasing importance.
From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114:297.

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observations warrant the need for universal standardization of all bilirubin measurements. Lo and co-workers analyzed specimens of TB from the College of American Pathologists (CAP) Neonatal Bilirubin (NB) and Chemistry (C) surveys using the reference method.[156] They found that the use of different methods in the NB and C surveys, together with the presence of nonhuman protein base and ditaurobilirubin in the survey specimens, accounted for wide variations in accuracy and imprecision between instruments and laboratories. Furthermore, they recommend that survey samples should consist only of human serum enriched with unconjugated bilirubin.

The measurement of unbound or "free" bilirubin concentrations is another potential measure to assess the risk for developing bilirubin neuropathy or encephalopathy. Data are limited, but preliminary studies show that unbound bilirubin levels may be better correlated with BIND than the TB.[15,205,212,284] In late preterm and term infants with severe jaundice, it has recently been demonstrated that unbound bilirubin is a more sensitive and specific predictor of auditory neuropathy spectrum disorder than TB or bilirubin to albumin molar ratio (BAMR).[15]

Transcutaneous (TcB) Bilirubinometry

Historically, visual inspection has been the most commonly used means of screening newborns for hyperbilirubinemia. Jaundice progresses cephalocaudally. Digital pressure that blanches the skin diminishes the effects of pigmentation and local cutaneous perfusion and allows the detection of jaundice. Proper lighting is important in detecting subtle levels of jaundice. However, visual assessment is subjective, dependent on observer experience and is notoriously inaccurate.

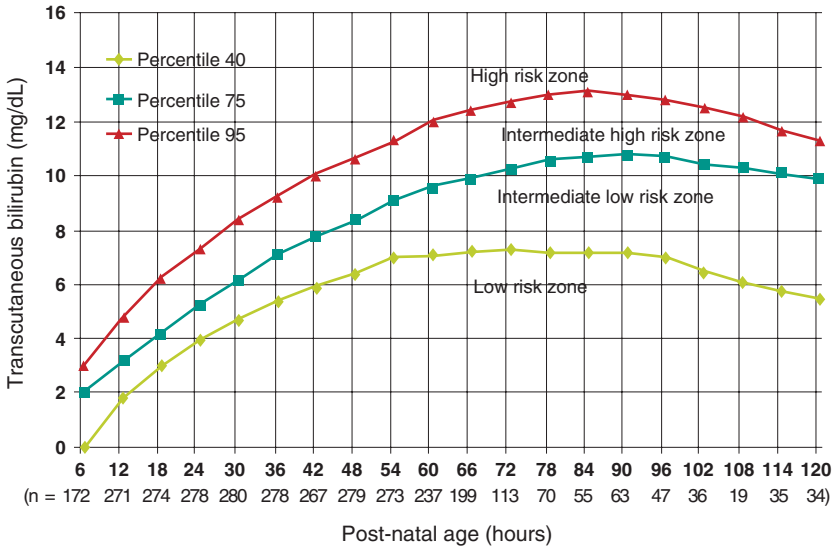
TcB is a method using reflectance photometry or transcutaneous colorimetry as a noninvasive estimate of TB levels. The technique offers an objective measurement of skin color, from which a reading, reflecting the TB, is derived. The two devices most commonly used include the BiliChek (Philips Childrens Medical Ventures, Monroeville, PA) and JM-103 Jaundice Meter (Konica Minolta/AirShields JM 103 Jaundice Meter, Draeger Medical AG and Co, Lubeck, Germany), but others are also commercially available. They differ in their ease of use and their propensity to be affected by variations in skin color. A number of studies have shown that these instruments provide fairly accurate estimates of TB in term and near-term newborn infants of varying races and ethnicities, generally providing values within 2-3 mg/dL (34-51 µmol/L) of the TB if the TB is less than 15 mg/dL (257 µmol/L).[81] The technology tends to underestimate the actual TB level and should be regarded as a screening mechanism rather than an accurate reflection of the TB. The devices have been evaluated as potential predischarge screening tools to identify infants at risk (i.e., TB level at the 95th percentile or higher). As a result of these studies, hour-specific nomograms based on TcB measurements have been established both for term and late preterm infants.[165,267] It may be more prudent to plot TcB readings on a TcB nomogram than on a serum bilirubin-based nomogram such as that of Bhutani et al. However, additional studies are warranted to establish a strong and reliable correlation between TcB and TB at levels of 15 mg/dL (257 µmol/L) and higher, as well as during and after phototherapy and in premature or low birth weight infants, before its routine use can be advocated. The device has also been used successfully in community TcB screening.[273] Clinicians should be aware that there may be variation in results between devices[218,220] and overestimation of results in African-American neonates.[209] Akin to the TB-based nomogram, a recently developed TcB nomogram from Israel demonstrated a greater than 100-fold increase in neonates meeting requirements for phototherapy, from 0 in those whose highest TcB reading fell below the 40th percentile, through 27/120 (22.5%) for the >95th percentile group (Fig. 91.17).[41]

End-Tidal Carbon Monoxide (ETCO) Measurements

The breakdown of heme by the rate-limiting enzyme HO-1 produces equimolar quantities of CO and biliverdin, the latter which is reduced to bilirubin. Therefore, the measurement of CO in the end-tidal breath, corrected for ambient CO to derive ETCOc, can be used as an index of in vivo heme degradation and bilirubin production and, hence, hemolysis. Portable devices that provided automatic sampling and bedside analysis of ETCOc yielded results comparable to gas chromatography and have been used to accurately estimate heme catabolism in neonates, children, and adults. A new device is now currently available and has been used successfully.[30,51,60,61]

In a large multicenter study, Stevenson and colleagues found that a measurement of ETCOc at 30 ± 6 hours of age, alone or in combination with a TB measurement, did not improve the predictive ability of the age-in-hours-specific TB level, although it was as good as a measurement of TB alone for this purpose.[255] They did find, however, that the use of an ETCOc measurement in combination with the TB level aids in the following: (1) the discrimination between infants with increased bilirubin production rates and infants with decreased elimination; (2) the identification of infants with increased bilirubin production due to ABO incompatibility or other causes of hemolysis; and (3) the identification of infants with impaired conjugation defects, who have a normal ETCOc level in the face of rising TB levels. In other words, high producers of CO and bilirubin are most likely undergoing a hemolytic process, whereas infants with high TB levels and normal bilirubin production rates most likely have a defect in bilirubin conjugation. The measurement of ETCOc could provide direct information of the rate of bilirubin production. Bhutani and co-workers, using data from this study, constructed an age-in-hours-specific ETCOc nomogram for measurements taken between 4 and 48 hours postnatal age, revealing that an ETCOc value at the 75th percentile at 30 ± 6 hours of age is 1.7 ppm or less and is considered the threshold of increased bilirubin production.[25] The importance of

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• **Fig. 91.17** Hour-specific transcutaneous bilirubin (TcB) nomogram constructed from 3303 measurements from 1059 neonates. The percentile values were divided into four groups following the pattern of the Bhutani hour-specific TB nomogram. (From Bromiker R, et al. Israel TcB nomogram predicts significant hyperbilirubinemia. *J Perinatol.* 2017;37(12):1315-1318.)

determining ETCOc levels and their application in identifying infants at risk for developing hyperbilirubinemia associated with hemolysis has recently been reviewed.[260]

Bilirubin-to-Albumin Molar Ratio (BAMR)

The molar ratio of bilirubin (mg/dL) to albumin (g/dL) correlates with unconjugated bilirubin levels in newborns and, therefore, can be used as a surrogate for unbound bilirubin or residual binding capacity of albumin. The serum albumin concentration is inherently low in preterm infants, and in addition, albumin levels and the ability of albumin to bind bilirubin vary significantly in sick infants. It has also been shown that binding increases with increasing gestational and postnatal age. The bilirubin/albumin molar ratio (BAMR) may be used as an adjunct to measurements of TB in determining the need for exchange transfusion. A serum albumin level <3.0 gm/dL (4.4 µmol/L) is suggested as a risk factor for bilirubin neurotoxicity[162] and can be used as an option for lowering the indication for commencing phototherapy.[12] The AAP (2004) has suggested bilirubin/albumin ratios that can be used together with, but not in lieu of, the TB level as an additional factor to be considered in determining the need for exchange transfusion (Table 91.3). However, use of the bilirubin/albumin ratio in addition to TB for the management of hyperbilirubinemia in a preterm population did not improve long-term neurodevelopmental outcome when compared with controls in whom TB alone was used.[117] In an Egyptian study of severely hyperbilirubinemic neonates both TB and bilirubin/albumin ratio were strong predictors of neurotoxicity, although bilirubin/albumin did not improve prediction over TB alone.[120] In a recent study of paired TB and albumin levels in preterm and term neonates, both gestational and postnatal age influenced TB, albumin, and

TABLE 91.3 Bilirubin/Albumin Molar Ratio (BAMR) as a Determinant of the Need for Exchange Transfusion

Risk Category	BAMR at Which Exchange Transfusion Should Be Considered	
	TB (mg/dL)/Albumin (g/dL)	TB (µmol/L)/Albumin (µmol/L)
Infants ≥38 0/7 wk	8.0	0.94
Infant 35 0/7 to 37 6/7 wk and well or ≥38 0/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	7.2	0.84
Infant 35 0/7 to 37 6/7 wk if higher risk or isoimmune hemolytic disease or G6PD deficiency	6.8	0.80

If TB is at or is approaching the exchange level, send blood for immediate type and cross-match. Blood for exchange transfusion is modified whole blood (RBCs and plasma) cross-matched against the mother and compatible with the infant.
G6PD, Glucose-6-phosphate dehydrogenase; TB, total bilirubin.
From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297.

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bilirubin/albumin ratios. Furthermore, hypoalbuminemia and extreme bilirubin/albumin ratios were associated with an increased risk of death.[281]

Newer Methods of Diagnosis

In the past, the etiology of many cases of nonimmune hemolysis were unidentified and termed idiopathic. Modern methods of diagnosis, including flow cytometry-based eosin-5-maleimide uptake to identify RBC membrane defects, and next generation sequencing-based panels to identify mutations responsible for hemolysis, may shed light on specific hemolytic conditions, the etiology of which may have remained unknown.[290] The same authors emphasize using this methodology only if simpler and less expensive technologies have failed to arrive at a diagnosis. One such technique includes studying RBC morphology, which may lead to diagnoses of spherocytosis, elliptocytosis, bite and blister cells, echinocytes, and schistocytes.[63]

Therapy for Unconjugated Hyperbilirubinemia

The current mainstay of treatment is phototherapy, which has been proved to be instrumental in containing the rate of rise and lowering the TB. In cases of failure of phototherapy, or in newborns presenting with extremely high TB concentrations, exchange transfusion will definitively lower the TB to a level that will no longer be of danger to the neonate. IVIG and phenobarbital therapy also have a role in the management of hyperbilirubinemia. The intensity and invasiveness of therapy are determined by the many factors discussed thus far, including the gestational age and relative health of the neonate, the current level of TB, and an estimation of the rate of rise in view of the dynamic nature of bilirubin metabolism in the newborn. An example of a clinical pathway for the management of the newborn infant readmitted for phototherapy or exchange transfusion is given in Box 91.3.

Indications for Therapy

Guidelines for the management and prevention of neonatal hyperbilirubinemia have been formulated in many countries, including the United States, Canada, Norway, South Africa, Israel, and others. There is some evidence that guidelines, complemented by statewide learning collaboratives, are instrumental in decreasing the rates of extreme hyperbilirubinemia and exchange transfusion. In California, from 2007-2012 (3 years after publication of the AAP guideline, discussed later) the rates of TB ≥25 mg/dL and exchange

• BOX 91.3 Examples of Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

Treatment

- Use intensive phototherapy and/or exchange transfusion as indicated in Fig. 91.22 and Fig. 91.23.

Laboratory Tests

- TB and direct bilirubin level
- Blood type (ABO, Rh)
- Direct antiglobulin test (Coombs' test)
- Serum albumin
- CBC with differential and peripheral blood smear for RBC morphology
- Reticulocyte count
- ETCOc (if device available)
- G6PD screen, if indicated by ethnicity or geographic origin or if poor response to phototherapy
- Urinalysis for reducing substances
- If history or presentation suggests sepsis, perform blood culture, urine culture, and CSF examination for protein, glucose, cell count, and culture.

Interventions

- If TB ≥25 mg/dL (428 μmol/L) or ≥20 mg/dL (342 μmol/L) in a sick infant or infant <38 weeks of gestation, obtain a type and crossmatch, and request blood in case exchange transfusion becomes necessary.
- In infants with isoimmune hemolytic disease and a rising TB despite intensive phototherapy or rising to within 2-3 mg/dL (34-51 μmol/dL) of exchange level (see Fig. 91.22), administer IVIG (500-1000 mg/kg) over 2 hours and repeat if necessary.
- If infant's weight loss from birth is greater than 12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake in question, give IV fluids.

For Infants Receiving Intensive Phototherapy

- Breastfeed or bottle feed (formula or expressed breast milk) every 2-3 hours.
- If TB ≥25 mg/dL (428 μmol/L), repeat TB within 2-3 hours.
- If TB = 20-25 mg/dL (342-428 μmol/L), repeat TB within 3-4 hours.
- If TB <20 mg/dL (342 μmol/L), repeat TB in 4-6 hours.
- If TB continues to fall, repeat TB in 8-12 hours.
- If TB is not decreasing, or is moving closer to level for exchange transfusion, or the BAMR exceeds levels shown in Table 91.3, consider exchange transfusion.
- When TB is <13-14 mg/dL (222-239 μmol/L), discontinue phototherapy.
- Depending on the cause of the hyperbilirubinemia, it is an option to measure TB 24 hours after discharge to check for rebound hyperbilirubinemia.

BAMR, Bilirubin/albumin molar ratio; CBC, complete blood count; CSF, cerebral spinal fluid; ETCOc, end-tidal carbon monoxide, corrected for inhaled CO; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; IVIG, intravenous immunoglobulin; RBC, red blood cell; TB, total bilirubin.
From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114:297.

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transfusion both decreased significantly.[27] A similar report emanates from Canada, where national guidelines were published in 2007. In the period prior to 2007, neonates were 3.5 times more likely to develop a TB ≥25 mg/dL than in the period 2011-2013. This improvement was attributed to introduction of the Canadian Pediatric Society guidelines and improved physician awareness of severe neonatal hyperbilirubinemia.[243] A significant decrease in the number of exchange transfusions was reported from New South Wales, Australia, following publication of guidelines related to this procedure.[54]

Guidelines were derived from consensus and were not evidence based. In surveys from California, both bilirubin-induced neurotoxicity and sensorineural hearing loss occurred at TB levels well above the AAP recommendations for exchange transfusion.[149,287] Cerebral palsy consistent with kernicterus was limited to infants with TB levels >5.0 mg/dL (85.5 μmol/L) above exchange transfusion indications and at least two risk factors for neurotoxicity, including prematurity, G6PD deficiency, and hypoxic-ischemia.[289] It has been suggested that, as kernicterus is rare and occurs only at very high TB levels (>35 mg/dL or 599 μmol/L), previously recommended phototherapy and exchange transfusion treatment thresholds may be unnecessarily aggressive.[194] Similarly, Maisels asks that if 3000 newborns need to receive phototherapy to prevent one exchange transfusion, could phototherapy have been avoided in many of these neonates?[166]

Phototherapy

Phototherapy is the most widely used form of therapy for the treatment and prophylaxis of neonatal unconjugated hyperbilirubinemia. In nearly all neonates, phototherapy reduces or blunts the rise of TB levels (regardless of maturity, the presence or absence of hemolysis, and the degree of skin pigmentation). Extreme hemolysis, however, especially when combined with immature conjugation, may result in phototherapy failure. Given the decades of experience with its use worldwide and the lack of reported serious long-term side effects thus far, short-term phototherapy appears to be safe. The initial report from the Collaborative Study on the Effectiveness and Safety of Phototherapy undertaken under the auspices of the National Institute of Child Health and Human Development (NICHD) demonstrated that neonates receiving phototherapy require significantly fewer exchange transfusions. More important, these infants had an incidence of gross kernicterus and subsequent neurobehavioral performance that was lower than those who received only exchange transfusions to control hyperbilirubinemia. Furthermore, subsequent follow-up studies revealed no adverse outcome in the infants who received phototherapy in the neonatal period.

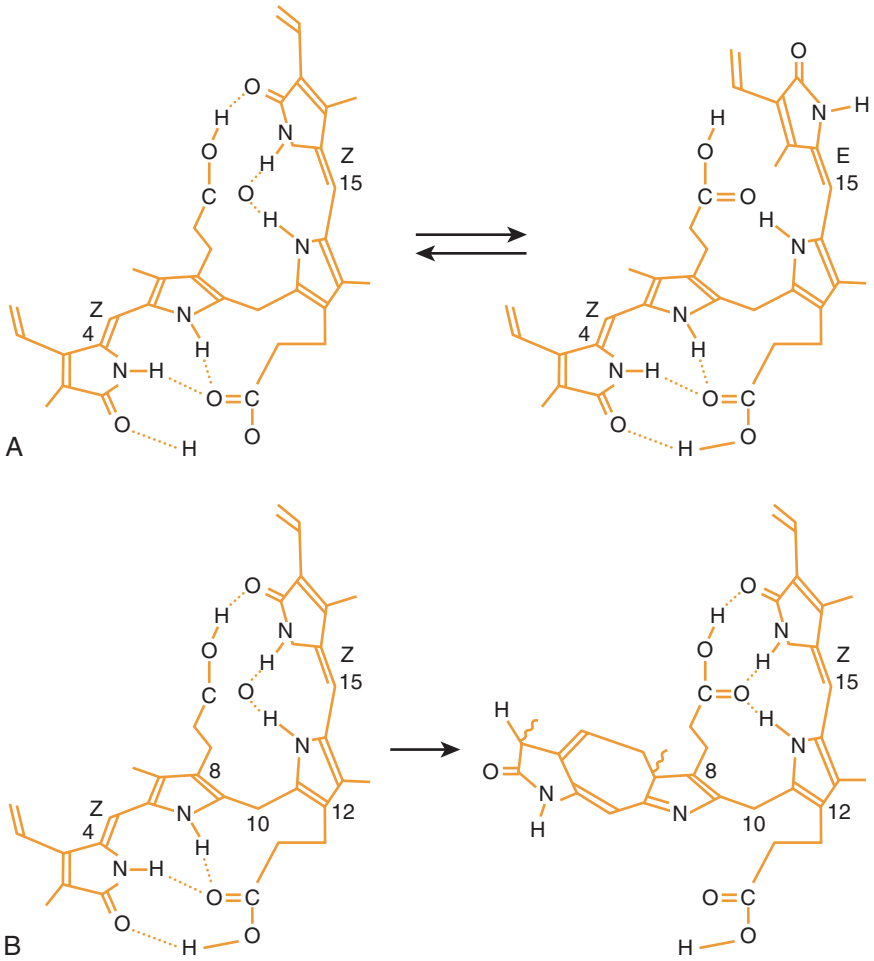
Mechanism of Action

Three independent mechanisms have been proposed to explain the action of phototherapy in reducing TB levels in neonates. The first and most important pathway is geometric photoisomerization of the native unconjugated bilirubin IX-α (Fig. 91.18). Unconjugated bilirubin IX-α is normally in the *4Z,15Z* configuration. In this form, the –COOH group of each carboxymethyl side chain interacts through three hydrogen bonds with the C=O and N-H groups of the pyrrole rings in the opposite half-molecule. As a result, ionization of the two –COOH and two keto groups is inhibited, making the molecule nonpolar and water insoluble. When illuminated by wavelengths (peak, 460 ± 10 nm), light is absorbed by bilirubin, and unconjugated bilirubin undergoes *Z* to *E* (configurational) isomerization at either one or both of the bridge double bonds to yield potentially three isomers: *4E,15Z*; *4Z,15E*; and *4E,15E*. The *E* configuration spatially precludes hydrogen bonding of the molecule which, therefore, remains open or unfolded and free to ionize. Thus, the *E* isomer is more polar and soluble than the *Z* isomer. Because the liver can transport only soluble bilirubin into bile, the *E*-isomers can be excreted without the need for conjugation.

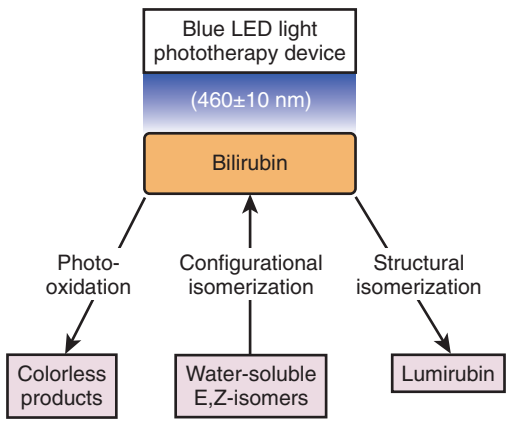
At least two pairs of geometric photoisomers have been identified *in vivo*. The first pair, photoisomers IA and IB, is presumably the two possible *E,Z* isomers. The second pair, photobilirubins IIA and IIB, is most likely two rotamers of the *4E,15E* isomer. Both pairs are presumably formed rapidly in the skin, subcutaneous tissue, and capillaries. Being more polar, all these isomers partition into the plasma, continuously shifting the equilibrium to promote more isomer formation. These isomers are rapidly taken up by the liver and transported into bile, where they are destabilized by bile acids, rapidly reverting to native unconjugated bilirubin IX-α in the bile ducts and intestine. The rotameric isomers remain mostly intact and are the major polar photoproducts found in bile. This photoisomerization pathway may be responsible for more than 80% of the augmented bilirubin elimination during phototherapy. Geometric photoisomerization is not, however, the only isomerization pathway open to photoexcited bilirubin. The proximity of the side-chain double bond at C-3 to the adjacent pyrrole ring allows an intramolecular cyclization, again rendering the bilirubin molecule more polar (see Fig. 91.18). This structural isomer of bilirubin is called *lumirubin*, and it is also excreted into bile without need for hepatic conjugation. Lumirubin, a soluble compound, is the major photoproduct excreted with the bile and urine, and its conversion is the rate-limiting step in the elimination of bilirubin by phototherapy.

The third pathway of phototherapy involves a variety of bilirubin oxidation reactions, resulting from an autosensitized reaction involving singlet oxygen. The products formed by these reactions are multiple but include biliverdin, dipyrroles, and monopyrroles. Many of these products are colorless, nonreactive in the van den Bergh test, and presumably excreted by the liver and kidney without need for conjugation. Compared with the photoisomerization pathway, the oxidation mechanism appears to play a very minor role in photocatabolism of unconjugated bilirubin in vivo (Fig. 91.19).[271]

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• **Fig. 91.18** Isomerization pathways for bilirubin during phototherapy. **A,** *Z-E* carbon double-bond configurational isomerization of bilirubin. **B,** Intramolecular cyclization of bilirubin to form lumirubin. (Modified from McDonagh AF, Lightner DA. "Like a shrivelled blood orange": bilirubin, jaundice, and phototherapy. *Pediatrics*. 1985;75:443. Used with permission of the American Academy of Pediatrics.)



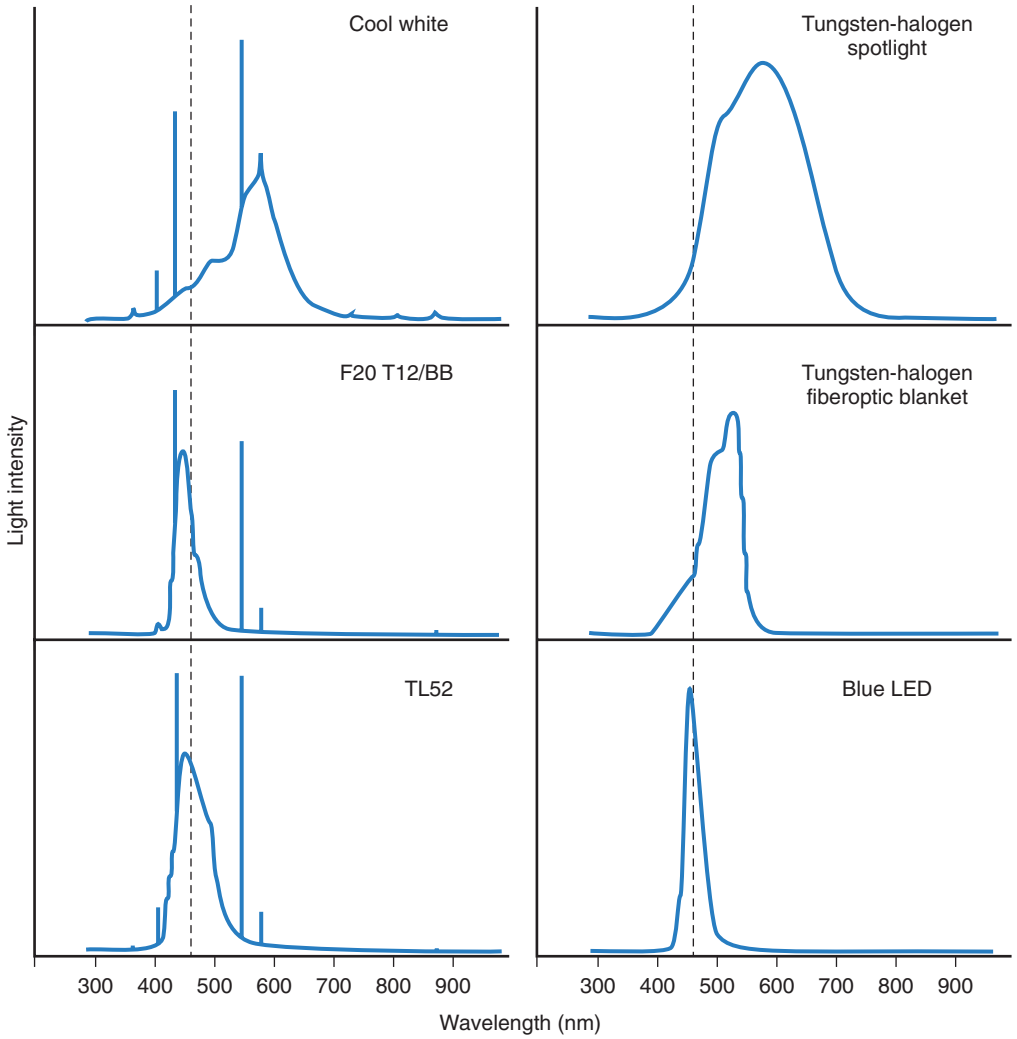
• **Fig. 91.19** The major mechanisms of bilirubin photoalteration. (Redrawn from Vreman HJ, et al. Light emitting diodes for phototherapy for the control of jaundice. In: Holick M, ed. *Biology of light 2001: proceedings of a symposium.* Boston: Kluwer Academic; 2002:355-367.)

Technique

Phototherapy is not a standardized practice in the United States at this time, and there exist many different devices capable of delivering phototherapy with varying efficacies. Any physician using one of these devices must be cognizant of the variables influencing the efficacy of phototherapy and ensure that the device is used appropriately. The efficacy of phototherapy units varies widely because of differences in light source and configuration and depends on emission of light in the blue-to-blue-green range that overlaps the in vivo bilirubin absorption spectrum (≈460-490 nm), irradiance of at least 30 μW/cm^2/nm, illumination of maximal body surface area, and demonstration of a decrease in TB levels during the first 4-6 hours of exposure.[28]

The first variable to consider is the wavelength of light used to induce photoisomerization (Fig. 91.20). Bilirubin absorbs light maximally in the blue range (340-540 nm), with peak absorption for albumin-bound bilirubin at about 460 nm and for unbound bilirubin at about 440 nm. Daylight and cool white lamps have a spectral emission of 380-720 nm with a peak of 578 ± 10 nm and are less effective than blue lamps (F20 T12/B), which have a narrower spectral range and peak between 420 and 480 nm. Special blue lamps (F20 T12/BB and TL52 tubes [Philips, The Netherlands]) emit narrower spectra of light with greater irradiance at the main therapeutic spectrum and have been shown to be most effective. The blue hue that is produced by these lamps can interfere with skin color assessment in jaundiced neonates, and it has been reported to produce dizziness and nausea variably in those caring for these patients. These side effects may be readily tempered by the addition

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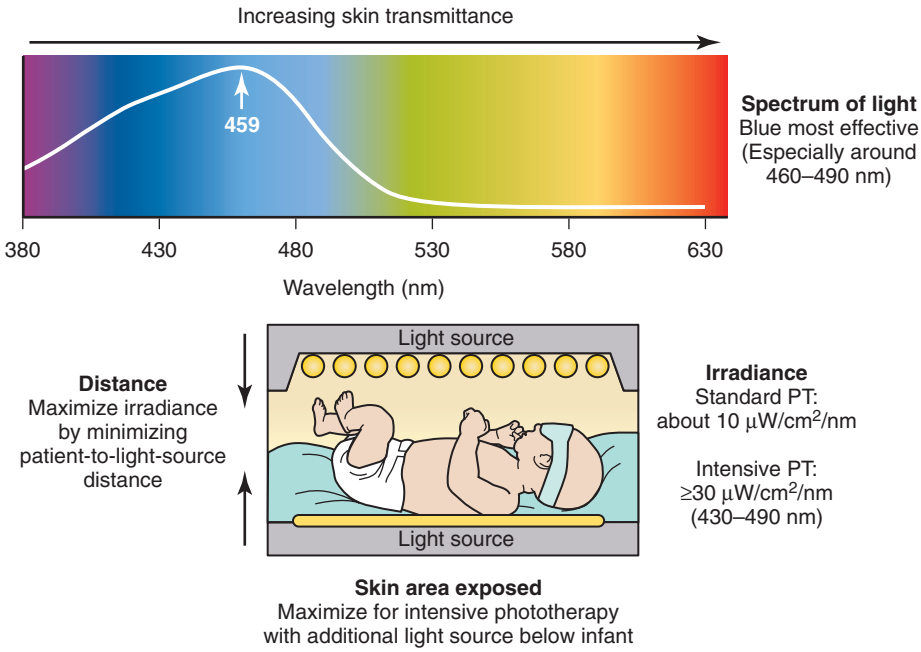
• **Fig. 91.20** Emission spectra of phototherapy devices. The intensities are shown on a linear relative scale. The spectra of the three fluorescent lamps (cool white and special blue [F20 T12/BB and TL52]), tungsten-halogen (spotlight [Olympic Medical Mini-Bililite, Seattle, WA] and fiberoptic blanket [Biliblanket, Ohmeda, Columbia, OH]), and blue light-emitting diodes (LEDs [neoBLUE, Natus Medical, Inc., San Carlos, CA]) were measured under identical conditions on an S-2000 spectrophotometer (Ocean Optics, Inc., Dunedin, FL). *Dotted line* represents the peak absorption of bilirubin at about 460 nm. (From Vreman HJ, et al. *In vitro* efficacy of an LED-based phototherapy device [neoBLUE] compared to traditional light sources. *Pediatr Res*. 2003;53:400A.)

of daylight fluorescent lamps to the phototherapy unit.[67,86] However, incorporation of white fluorescence "dilutes" the blue intensity, thereby dramatically decreasing the effectiveness of phototherapy.[271]

Several studies showed that phototherapy with blue-green to green light (peak at 525 nm) is as effective as that with blue light and better than white light in reducing bilirubin levels.[80,82] Green light lacks the untoward side effects often associated with intense blue light. However, further study is needed to definitively determine the clinical benefit of green light, because green light phototherapy has not been widely adopted.[19]

The second variable that influences the efficacy of phototherapy is energy output or irradiance as measured in units of microwatts per square centimeter per nanometer (μW/cm^2/nm). Effective phototherapy must provide irradiance well above the levels that have been determined to be minimally effective in producing bilirubin degradation while not exceeding levels beyond which no significant increases in response are evident. This also helps avoid potential side effects such as elevation in body temperature. A standard phototherapy unit operating under optimal conditions would provide clinically significant, but minimally effective, levels of phototherapy (about 6-12 μW/cm^2/nm). In intensive phototherapy, irradiance is increased to 30 μW/cm^2/nm or greater.[12] Standard phototherapy lamps are normally positioned within 40 cm from the infant, but should more intensive phototherapy be required, the lamps may be placed within 15-20 cm of the patient, provided blue fluorescent or light-emitting diode (LED) lamps, and not heat-producing halogen lamps with a potential danger of causing thermal injury, are used. Conversely, increasing the

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• **Fig. 91.21** Important factors in the efficacy of phototherapy (PT). The absorbance spectrum of bilirubin bound to human serum albumin (*white line*) is shown superimposed on the spectrum of visible light. Clearly, blue light is most effective for phototherapy, but because the transmittance of skin increases with increasing wavelength, the best wavelengths to use are probably in the range of 460-490 nm. Term and near-term infants should be treated in a bassinet, not an incubator, to allow the light source to be brought to within 10-15 cm of the infant (except when halogen or tungsten lights are used), increasing irradiance and efficacy. For intensive phototherapy, an auxiliary light source (fiberoptic pad, blue light-emitting diode [LED] mattress, or special blue fluorescent tubes) can be placed below the infant or bassinet. If the infant is in an incubator, the light rays should be perpendicular to the surface of the incubator in order to minimize loss of efficacy due to reflectance. (From Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. *N Engl J Med*. 2008;358:920.)

distance from the lamp to the skin surface of the neonate results in a theoretical diminution of light energy by a factor equal to the square of the increase in the distance (Fig. 91.21).[167]

Skin pigmentation does not reduce the effectiveness of phototherapy. With use, fluorescent lamp energy output declines to a degree that varies from one type of lamp to another. A meter for monitoring lamp energy output should be used to ensure optimal treatment. Although commercially available photometers have been found to vary in their absolute measurement of irradiance because of differences in meter sensitivity (i.e., peak and range) and the emission characteristics of their light sources, they are still useful in determining relative lamp decay. Lamps that have lost more than 20% of the acceptable output should be replaced.

All lamps should be housed behind Plexiglas to reduce the danger to the patient should a lamp explode. Also, it has been shown that Plexiglas provides protection from any harmful ultraviolet irradiation arising from the available light sources. Patients may be cared for on an open warmer or in a crib. Use of a closed incubator may increase the distance of the light source from the infant, thereby attenuating the irradiance delivered to the patient.

The third variable affecting the efficacy of phototherapy is the body surface area of the neonate exposed to light. Ideally, neonates should be naked when under phototherapy; however, use of diapers, folded back to cover as little of the baby's surface as practically possible, may improve on the obvious disadvantages of leaving the infant unclothed. Positioning of several phototherapy units around the newborn, or placing the baby on a phototherapy mattress in addition to the overhead lights, may increase exposure. A white sheet draped around the periphery of the bed may also act to reflect light onto relatively under-exposed areas, thereby increasing the overall light irradiance.

Other conventionally used devices incorporate tungsten-halogen lamps as their light source for use as spotlights. Another technique involves transmission of light through a fiberoptic bundle to a pad or blanket around the infant. The advantage of the latter technology is that the source of light and, therefore, heat will be at a distance from the infant. In infants with severe hyperbilirubinemia, the previously mentioned techniques can be used in combination to increase light intensity (irradiance) and body surface area exposure.[1,85] Too frequently, currently used doses of phototherapy are well below the optimal therapeutic range. The AAP recommends the use of intensive phototherapy, especially for infants readmitted for hyperbilirubinemia, or if the threshold for exchange transfusion is approaching. Intensive phototherapy implies the use of high levels of

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irradiance in the therapeutic range (usually ≥30 μW/cm²/nm) delivered to as much of the infant's surface area as possible.[12]

Use of arrays of blue LEDs, which can deliver high-intensity narrow band light in the absorption spectrum of bilirubin has nearly replaced fluorescent tube-based devices.[269,271] This technology has been shown to be an effective and safe alternative to other modes of phototherapy.[271] LED light sources are now available in many configurations, from mattresses, side panels, blankets, and overhead lights. Advantages of the LED technology include the ability to increase the light intensity to a level higher than many conventional technologies without significantly warming the baby and the long period during which the lamps remain effective without the need for replacement.[197]

Clinical studies comparing intermittent to continuous phototherapy have yielded conflicting results. Several studies failed to show effectiveness of the intermittent therapy. These results may have resulted from prolonged light-on and light-off cycles—for example, 6- to 12-hour on-off schedules. Photoisomerization of bilirubin occurs primarily in skin layers, and the restoration of the bilirubin pool in the skin takes about 1-3 hours. Thus, a prolonged on-off schedule may not be as effective as continuous therapy, but an on-off cycle of less than 1 hour is apparently as effective as continuous treatment. Phototherapy lights should be shut off and eye patches removed during feeding and family visiting for up to 1 hour, because this does not significantly reduce phototherapy effectiveness.

Some reports have demonstrated that home phototherapy may be an effective and safe alternative to prolonged hospitalization for healthy full-term neonates with jaundice. Clear advantages of home-centered phototherapy include: (1) reduced cost; (2) avoidance of parent–infant separation; and (3) parental satisfaction. However, complications of home phototherapy that might result from inadequate nursing supervision include corneal abrasion, eye patch misuse, excessive weight loss, temperature derangement, and ineffective bilirubin reduction. Whether there is any valid indication for phototherapy for those neonates who could be safely managed at home is questionable. Those with valid indications are generally too sick, too small, or too close to the exchange transfusion level to be safely treated at home. The Committee on the Fetus and Newborn of the AAP has not endorsed home phototherapy, but it has issued a strict guideline for its use.[13] Because the devices available for home phototherapy may not provide the same degree of irradiance or surface-area exposure as those available in hospital, the Subcommittee on Hyperbilirubinemia of the AAP recommends that home phototherapy should be used only in infants whose bilirubin levels are in the "optional phototherapy" range (see Indications).[12] It is not appropriate for infants with higher bilirubin concentrations or if the TB is approaching the exchange transfusion level. As with hospitalized infants, the TB must be monitored regularly.

Indications

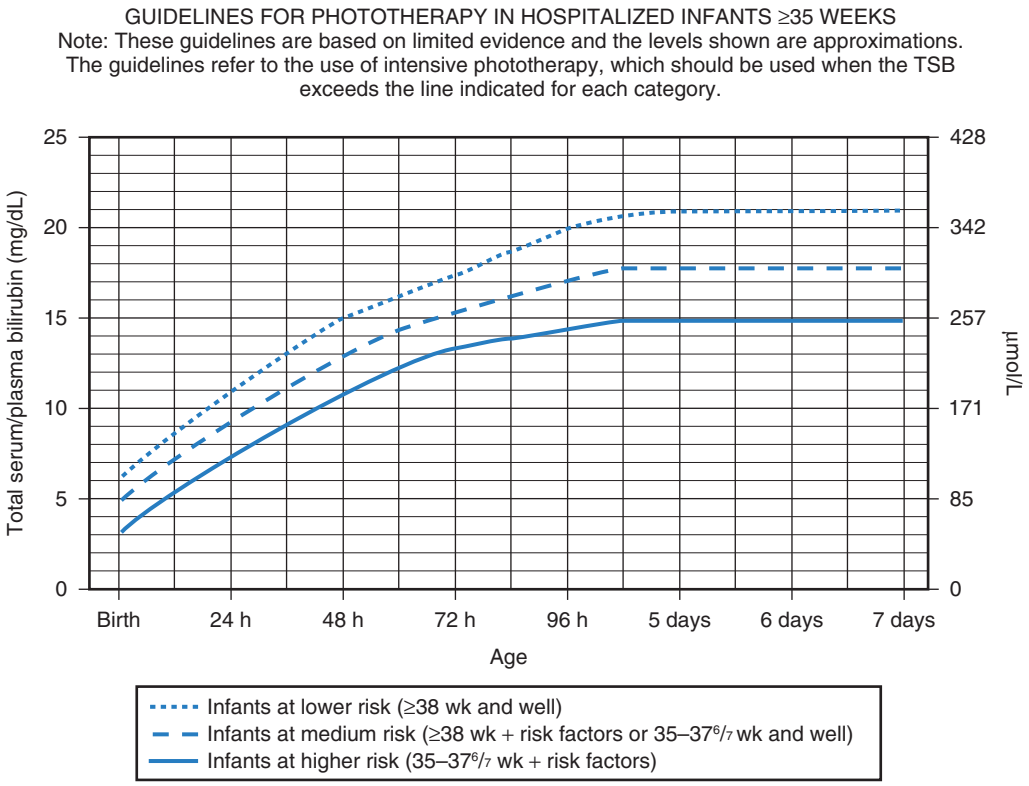
Although not "evidence-based," the AAP has issued a comprehensive guideline for the commencement of phototherapy in infants greater than 35 weeks' gestation (Fig. 91.22).[12] This guideline takes into account the presence of risk factors as well as late prematurity and also is adapted to the dynamic changes in TB levels during the first days of life. Thus, there is no single TB level at which phototherapy should be commenced, but each newborn must be assessed individually, taking into consideration postnatal age, gestational age, and other risk factors. The TB level at which phototherapy may be discontinued must also be decided in view of these factors. It may be useful to continue plotting the TB concentrations of the hour-specific bilirubin nomogram during phototherapy and discontinue phototherapy once the TB has decreased below the 75th percentile for hours of age, or even closer to the 40th percentile in infants with lower gestational age or in the presence of risk factors. Chang et al. recently proposed a formula by which rebound hyperbilirubinemia can be predicted by an infant's gestational age, age at initiation of phototherapy, and relative TB at phototherapy termination. The formula comprises: Score = 15 (if gestational age <38 weeks) − 7 × (age in days at phototherapy initiation) − 4 × (AAP phototherapy threshold − TB at phototherapy termination) + 50. With a prediction score of <20, phototherapy can be discontinued with <4% probability of rebound.[52] Follow-up for rebound, not necessarily requiring continued hospitalization, should be performed in cases of newborns younger than 37 weeks' gestation, those with positive DAT, and those treated at or before 72 hours' postnatal age.[136] Phototherapy should be used during transport of hyperbilirubinemic newborns to centers for exchange transfusion.[282]

The 2004 AAP Practice Guideline does not extend to premature infants younger than 35 weeks' gestational age.[12] Previously, guidelines suggested by Maisels and Watchko were used.[171] These suggest a wide range of indications for phototherapy and exchange transfusion, offering options based on gestational age and birth weight. Guidelines published by the National Institute for Health and Clinical Excellence (NICE) include graphs incorporating indications for phototherapy and exchange transfusion for each week of gestational age, starting at 23 weeks. TB values can be plotted directly on the graphs (available at http://www.nice.org.uk/CG98). More recently, a revised guideline, albeit non-evidence-based, for the management of hyperbilirubinemia in preterm infants was formulated in the United States by neonatologists who were involved in the preparations of either the 2004 AAP Practice Guideline, the 2009 clarification, or both (Table 91.4).[169] Additional guidelines for use in premature infants have been published from Norway, Holland, and South Africa.[39,114,264]

Aggressive versus Conservative Phototherapy in Premature Infants

In an NICHD study, 1974 premature infants were randomized to aggressive (earlier timing) or conservative

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- Use total bilirubin (TB). Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35–37⁶/₇ wk, can adjust TB levels for intervention around the medium risk line. It is an option to intervene at lower TB levels for infants closer to 35 wk and at higher TB levels for those closer to 37⁶/₇ wk.
- It is an option to provide conventional phototherapy in hospital or at home at TB levels 2–3 mg/dL (35–50 µmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

• **Fig. 91.22** Guidelines for phototherapy in hospitalized infants aged ≥35 weeks' gestation. Infants are designated as higher risk because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood–brain barrier, and the susceptibility of the brain cells to damage by bilirubin. (Adapted from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297. Used with permission of the American Academy of Pediatrics.)

phototherapy.[189] Two subgroups of infants, birth weight 501-750 g and 751-1000 g, respectively, were randomized at 12-36 hours to aggressive (phototherapy immediately after enrollment) or conservative (phototherapy started at 8.0 mg/dL [137 µmol/L] in the 501-750 g birth weight subgroup and 10.0 mg/dL [171 µmol/L] in the 751-1000 g subgroup). Aggressive phototherapy significantly reduced the mean peak TB, thereby confirming the efficacy of phototherapy in decreasing TB in the 1000 g or less birth weight group. In only seven infants were the criteria for exchange transfusion met. There was no difference (52% versus 55%) in the rate of the primary outcome (a composite of death or neurodevelopmental impairment (NDI), including blindness, severe hearing loss, moderate or severe cerebral palsy, or a Mental or Psychomotor Developmental Index [Bayley] <70). However, aggressive phototherapy was instrumental in reducing the rate of NDI when analyzed alone (26% versus 30%). This apparently was offset, however, by a 5% increase in mortality (39% versus 34%) in the very smallest infants (501-750 g birth weight), attributable to phototherapy. While aggressive phototherapy may be appropriate for relatively larger babies, these results emphasize the potential for phototherapy-related adverse effects. Aggressive phototherapy should be administered with caution in those less than 750 g birth weight. Suggested possible strategies for delivering safer but effective phototherapy to this premature very low birth weight group include reduced initial irradiance with subsequent increase should the TB increase,[170] use of narrow spectrum LEDs, and cycled phototherapy.[16]

Complications

Several potential complications may occur with the use of phototherapy.[227] The effect of high-intensity light exposure on the eyes of human neonates is uncertain, but animal studies indicate that retinal degeneration may occur after

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TABLE 91.4 Suggested Guidelines for Initiating Phototherapy or Exchange Transfusion in Premature Infants

Gestational Age (wk)	Phototherapy TB (mg/dL) [µmol/L]	Exchange Transfusion TB (mg/dL) [µmol/L]
<28 0/7	5-6 [86-103]	11-14 [188-239]
28 0/7-29 6/7	6-8 [103-137]	12-14 [205-239]
30 0/7-31 6/7	8-10 [137-171]	13-16 [222-274]
32 0/7-33 6/7	10-12 [171-205]	15-18 [257-308]
34 0/7-34 6/7	12-14 [205-239]	17-19 [291-325]

TB, Total bilirubin.
Adapted from Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks' gestation. *J Perinatol*. 2012;32:660-664.

several days of continuous exposure. It is essential, therefore, that the eyes of all newborns exposed to phototherapy be covered with sufficient layers of opaque material to guard against the possibility of damage. The use of fiberoptic phototherapy does not eliminate the need to cover an infant's eyes.

Phototherapy may produce an increase in body and environmental temperature. Fluid balance, especially in the premature neonate, is a key management issue in the patient being treated with phototherapy. There is increased insensible and intestinal water loss during phototherapy, which must be compensated for by an increase of about 25% above the estimated fluid need without phototherapy. In addition, stools may be slightly looser and more frequent. Fiberoptic phototherapy appears to result in lower insensible water losses and, therefore, slightly less need for increased maintenance fluids (see Chapter 92). Blue LED-based devices, however, do not release a significant amount of heat, and their use results in less insensible water loss. Term infants treated with blue LED light in open cribs should have their body temperatures monitored to detect excessive body cooling.

A well-recognized side effect of phototherapy is the *bronze baby syndrome*. In this disorder, the serum, urine, and skin become brown-black (bronze) several hours or more after a neonate is placed under the phototherapy lamps. All reported neonates with this syndrome have recovered without apparent sequela, except one term neonate who died and was found to have kernicterus on autopsy. In nearly all patients, conjugated hyperbilirubinemia and retention of bile acids have been noted either before light exposure or after the syndrome has developed. This syndrome has been reproduced in Gunn rats when their smaller bile ducts become obstructed by precipitated bile pigment during phototherapy. Photobilirubin II is shown to be degraded to brown pigments in vitro and when administered to Gunn rats in vivo. It seems likely that the bronze color of the plasma and urine in bronze baby syndrome results from retention of bile pigment photoproducts when biliary excretion is impaired by concomitant cholestasis. A study in two infants with this syndrome showed an increase in coproporphyrin in the blood, and photo-irradiation of this substance produced copper coproporphyrin degradation products similar to those found in neonates with this syndrome. It is generally recommended that phototherapy not be used in neonates with significant conjugated hyperbilirubinemia or other evidence of cholestasis. However, because there have been case reports of newborns who developed kernicterus in the presence of predominantly direct hyperbilirubinemia, the role of conjugated bilirubin in the pathophysiology of bilirubin encephalopathy is not clear, and affected infants should be assessed for the need for phototherapy on an individual basis.

Congenital erythropoietic porphyria is another syndrome in which phototherapy is contraindicated because it may lead to death. This rare disorder is characterized by hemolysis, splenomegaly, and pink to red urine that fluoresces orange under ultraviolet light. Exposure to visible light of moderate to high intensity and of wavelengths between 400 and 500 nm (blue to blue-green) produces severe bullous lesions on the exposed skin and accelerated hemolysis. Mixed hyperbilirubinemia with a significant direct-reacting fraction may also be seen in this disease.

Other theoretical dangers of phototherapy include electrical shock or fire from poorly grounded or defective equipment and unproven potential long-term effects on endocrine and sexual maturation and DNA repair mechanisms in skin epithelial cells. Phototherapy may cause DNA damage, but there is no evidence for long-term effects.[221]

In the main follow-up studies, except for the above-mentioned NICHD study, phototherapy-treated premature and full-term neonates have failed to demonstrate any increase in morbidity or mortality ascribed to the appropriate use of phototherapy. Recent studies have excluded phototherapy as an implication in the etiology of autism and diabetes mellitus,[288] although there may be a slight increase in the risk of infantile cancer.[286]

No scientific evidence exists indicating that hydration directly lowers TB levels. However, dehydration is not known to be beneficial to patients in this context and, therefore, all neonates should receive appropriate replacement and maintenance fluids. Conjugated bilirubin is water soluble and eliminated from the body in urine, bile, and stool. In as much as appropriate hydration maintains adequate urine output, bile flow, and stool excretion, fluid administration indirectly assists in the removal of unconjugated bilirubin. Ideally, this fluid is given enterally to stimulate gastrointestinal tract motility. The use of a milk-protein formula may be considered in infants not responding to phototherapy to inhibit enterohepatic reabsorption of bilirubin, thereby lowering TB levels.

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Pharmacologic Therapy

Phenobarbital

In experimental animals, UGT1A1 activity can be increased or induced with administration of phenobarbital, ethanol, chloroquine, antihistamines, heroin, and chlorophenothane (also known as DDT). These substances are not specific for any one enzyme but stimulate many hepatic membrane-bound enzyme systems and hepatic protein synthesis in general. Because of the known and potential toxicity of these agents, only phenobarbital has been used with regularity in humans.

After the demonstration that phenobarbital administration to a child with Crigler-Najjar syndrome type II disease reduced TB levels, phenobarbital administration to pregnant mothers and their offspring was shown to reduce peak TB levels caused by physiologic jaundice by about 50%. Studies in newborn rhesus monkeys have demonstrated that the major effect of this therapy is to increase hepatic UGT1A1 activity and the conjugation of bilirubin. It also may enhance hepatic uptake of bilirubin in the newborn. The administration of phenobarbital to newborns at the time jaundice is first observed or even immediately after delivery is much less effective than its administration to the mother during pregnancy for at least 2 weeks before delivery. The drug is much less effective in premature neonates. As a prophylactic measure, it would be necessary, therefore, to administer phenobarbital to large numbers of pregnant women for prolonged periods during pregnancy, because the time of delivery could not be predicted with certainty. Even then, the premature neonates most susceptible to the toxic effects of hyperbilirubinemia would receive little or no beneficial effect.

Phenobarbital is potentially addictive, may lead to excessive sedation of the newborn, and has other potent metabolic effects in addition to those on bilirubin metabolism. For these reasons, its use has not achieved wide application but has been reserved largely for specific high-risk populations. For example, in the pre-phototherapy era, in unexplained severe hyperbilirubinemia of newborns from the Greek coastal islands, the frequency of kernicterus was significantly reduced by general administration of phenobarbital to pregnant women during the last trimester. A dosage of 60 mg/day is sufficient for maternal administration and 5 mg/kg per day for neonatal treatment. Similar effects have been observed in full-term Korean newborns. Phenobarbital is also useful in the differentiation of Crigler-Najjar syndromes types I and II. Combining phenobarbital treatment with phototherapy has no advantage, the effect being no greater than that of phototherapy alone.

Metalloporphyrins

The pharmacologic basis for using this class of compounds to control bilirubin levels is the targeted blockade of bilirubin production through the competitive inhibition of HO, the rate-limiting enzyme in the bilirubin production pathway.[237,256] Originally proposed by Maines in 1981 for use in modulating bilirubin production,[161] these compounds have been extensively studied. The first metalloporphyrin to be evaluated for use in preventing neonatal unconjugated hyperbilirubinemia was tin protoporphyrin (SnPP). Administration of this compound was shown to decrease bilirubin concentrations in newborn rats, rhesus monkeys, and adult rats with hemolytic anemia, and it was the first synthetic heme analogue used for the purpose of inhibiting HO in human neonates.[78] Although highly efficacious, the photoreactivity of this metalloporphyrin made it a less desirable drug.[270] In newborn rhesus monkeys, administration of SnPP produced skin ulcerations, whereas in human neonates who also received phototherapy, some mild erythema of the skin was observed.[161] Human trials with tin mesoporphyrin (SnMP) in preterm neonates have shown a dose-dependent reduction in peak TB levels irrespective of gestational age and a reduction in the need for phototherapy compared with controls.[139,140,176,223] Mild transient erythema in patients requiring phototherapy was the only side effect noted. In human studies, it has been shown that a single IM dose of 6 μM SnMP/kg body weight eliminates the need for phototherapy during the postnatal period.[176] In a recent study using SnMP, the drug was administered intramuscularly to newborns whose predischarge TcB reading was >75th percentile. In treated infants, compared with controls, phototherapy time was halved, the natural TB trajectory was reversed, and the TB at 3-5 days was sixfold lower.[29] The efficacy of SnMP has been well described by several investigators in patients with Crigler-Najjar syndrome,[69,92] but SnMP does contain a foreign metal, it induces the HO-1 promoter,[74,187] and it can inhibit other enzymes such as nitric oxide synthase and soluble guanylyl cyclase. An alternative compound, zinc protoporphyrin (ZnPP), has been proposed, but it has a much lower inhibitory potency and is not well absorbed after oral administration. Nevertheless, it is a naturally occurring metalloporphyrin possessing both in vitro and in vivo inhibition of both HO-1 and HO-2 isozymes in studies using neonatal rodents and nonhuman primates. Moreover, ZnPP is minimally photoreactive in vivo.

Other Nonmetalloporphyrin Inhibitors

Some nonmetalloporphyrin inhibitors of HO-1 have been identified. Originally designed for use in transplantation survival studies, peptide inhibitors have been reported not only to be immunosuppressive in vitro and in vivo, but also to inhibit in vitro total HO enzyme activity dose-dependently. However, in mouse studies, it has been found that administration of peptides may upregulate HO-1 mRNA and protein in the liver, spleen, and kidney. These findings have precluded human studies investigating the efficacy of peptides for the treatment of hyperbilirubinemia.

Imidazole dioxolanes, inhibitors of cholesterol production,[47] have also been found to inhibit in vitro[72,146,188] and in vivo HO activity, despite being structurally different from metalloporphyrins. It has been demonstrated that these compounds are highly selective for inhibiting the inducible

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HO-1, but like metalloporphyrins, some imidazole dioxolanes may affect other important enzymes, such as nitric oxide synthase and soluble guanylyl cyclase.[146]

Miscellaneous Agents

As already discussed, reabsorption of unconjugated bilirubin may contribute to a significant portion of hepatic bilirubin load in the newborn period. Frequent milk feeding (cow or human) may slow the rise of TB levels and enhance the bilirubin-reducing effect of phototherapy. Oral administration of nonabsorbable substances that bind bilirubin in the intestinal lumen and presumably reduce enteric absorption of bilirubin may reduce peak TB levels in physiologic jaundice. Orlistat has been used to increase fecal fat excretion, thereby enhancing bilirubin elimination and decreasing the serum unconjugated bilirubin concentrations in Crigler-Najjar syndrome.[104] Feeding breastfed newborns β-glucuronidase inhibitors (L-aspartic acid or enzymatically hydrolyzed casein) during the first week reduced jaundice without affecting breastfeeding deleteriously.[98] Activated charcoal has been used but is effective only when administered during the first 12 hours of life.[70] Agar has also been shown to be effective. Further study of this type of therapy is needed before recommendations can be made regarding clinical applications. These pharmacologic agents may be no more effective than frequent milk feeding (every 2 hours).

Intravenous Immunoglobulin

High-dose IVIG (500-1000 mg/kg) administered over 2-4 hours has been shown in several small studies to reduce TB levels and the need for exchange transfusion in fetuses and neonates with Rh or ABO immune hemolytic disease.[229] COHb studies performed 24 hours after IVIG infusion in DAT-positive ABO-heterospecific neonates have demonstrated that, in those infants who responded to IVIG infusion with a decrease in TB, hemolysis was inhibited compared with the pre-administration status. Exchange transfusion was avoided in responding newborns, but not in those in whom there was no response. Lack of response was attributed to higher rates of hemolysis, in which case use of a higher dose of IVIG was suggested.[106] The use of IVIG administration should be considered in neonates with DAT-positive immune hyperbilirubinemia who are not responding to intense phototherapy and whose TB level is approaching exchange transfusion indications. This dose can be repeated after 12 hours if necessary. Recommendations for IVIG have been included in the revised 2004 AAP Practice Guideline. While the use of IVIG may be effective in preventing exchange transfusion in ABO-heterospecific neonates, it may not be as valuable in hemolytic disease of the newborn because of Rh isoimmunization, although its administration may delay the increase in TB, thereby allowing for stabilization of the infant.[253]

Exchange Transfusion

Exchange transfusion (see Chapter 80), first described by Diamond and associates,[76,77] is the standard mode of therapy for immediate treatment of hyperbilirubinemia to prevent kernicterus and for correction of anemia in erythroblastosis fetalis. Its use in the past decade has actually been reduced as a result of the use of RhoGAM to prevent Rh isoimmune disease, the application of phototherapy, and more recently, the administration of IVIG in cases of isoimmunity. In infants with severe hyperbilirubinemia caused by isoimmunity or other hemolytic conditions, especially G6PD deficiency, exchange transfusion may be the only effective method of adequately reducing TB levels.

Objectives

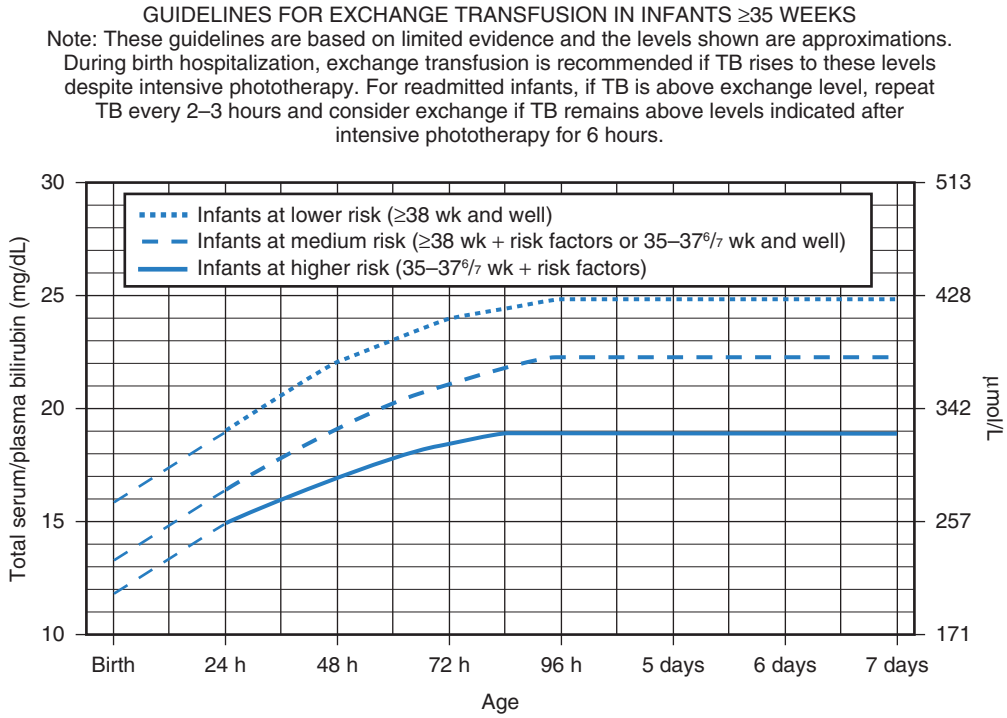
With this technique, the equivalent of two neonatal blood volumes (160 mL/kg of body weight) is replaced in aliquots not to exceed 10% of the total blood volume. This results in the replacement of about 85% of the circulating RBCs. Bilirubin concentrations are usually reduced by 50%. Although the procedure is relatively safe when performed by experienced practitioners in term neonates, it nevertheless carries a risk for both mortality (0.1%-0.5% in term neonates) and morbidity as well as being time consuming and expensive. The procedure usually takes 1-2 hours. Slower exchanges should theoretically increase the quantity of bilirubin removed by permitting equilibration of pigment from tissue, but the differences are too small to justify the increased risk of prolonging the duration of the procedure. The indications for exchange transfusion need to be individualized, taking into account gestational age and severity of illness (Fig. 91.23). During acute hospitalization, exchange is recommended if TB rises to the indicated levels despite intensive phototherapy. For readmitted infants, if TB is above the exchange transfusion threshold level, intensive phototherapy may be considered, provided the infant does not display clinical signs of acute bilirubin encephalopathy. Serial TBs should be performed every 2-3 hours, and if TB remains at or above levels indicated, exchange is recommended after 6 hours of intensive phototherapy.[12]

Indications

In the past, it was regularly recommended that TB, even in healthy term infants, be kept below 20 mg/dL (342 μmol/L) during the first 28 days of life. This has been questioned, and a growing consensus has developed that levels as high as 25 mg/dL (428 μmol/L) are acceptable for otherwise healthy, full-term, asymptomatic infants with no obvious hemolytic condition. When the exchange level is considered, conjugated bilirubin should not be subtracted from the total. Despite the inability of direct-reacting bilirubin to enter the CNS, it is possible that direct-reacting bilirubin can partially displace unconjugated bilirubin from albumin-binding sites to increase the risk for kernicterus.

In the face of rapidly rising TB levels, as may be seen in Rh erythroblastosis or other types of hemolytic disease, the decision to perform an exchange transfusion should anticipate the rate of rise (from previous TB levels, hemoglobin concentrations, and reticulocyte counts). Such prediction permits blood for the exchange to be ordered so that the

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- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of ABE (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TB is 25 mg/dL, (85 μmol/L) above these lines.
- Risk factors—isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate bilirubin/albumin (B/A) ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37⁶/₇ wk (median risk), can individualize TB levels for exchange based on actual gestational age.

• **Fig. 91.23** Guidelines for exchange transfusion in hospitalized infants aged ≥35 weeks' of gestation. Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. (Adapted from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297. Used with permission of the American Academy of Pediatrics.)

exchange transfusion is underway by the time the critical level is reached.

The indications for exchange transfusion are based on the infant's TB levels in combination with postnatal age, gestational age, and other risk factors, such as isoimmune hemolytic disease, G6PD deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, and BAMR. In 2004, the AAP published a comprehensive guideline for initiating exchange transfusion for term and near-term neonates.[12] Indications for low birth weight neonates or those with lower gestational ages than those specified in the AAP guideline have also been published (see Phototherapy, discussed previously).[171]

In the severely affected erythroblastotic neonate, clinical judgment rather than laboratory data should be used to decide whether the neonate requires immediate exchange transfusion after delivery. In this situation, a partial exchange transfusion using packed RBCs, coupled with reduction in blood volume if venous pressure is elevated, and with measures to ensure adequate ventilation and correction of acidosis and shock, will often be lifesaving. In most exchange transfusions, fresh whole or reconstituted citrate-phosphate-dextrose anticoagulated blood should be used. If blood older than 5 days must be used, the pH should be checked and sodium bicarbonate added to correct the pH to 7.1. Full correction to pH 7.4 may result in later excessive rebound alkalosis as the citrate is metabolized. Repeat exchange transfusion may sometimes be required. In a developing country, acute bilirubin encephalopathy and TB >30 mg/dL were predictive of the need for repeat exchange transfusion.[158]

Technique

Although there are numerous different combinations of blood components that can be used safely and effectively, there is no single combination or component that

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is superior. RBCs reconstituted with 5% albumin or fresh frozen plasma are most frequently used. Mixtures containing a citrate anticoagulant may cause hypocalcemia, but the administration of calcium during the exchange is seldom practiced. Transfused blood should not contain RBC antigens to which the mother has antibodies. Irradiation of blood is recommended for all exchange transfusions, especially if the infant had undergone an intrauterine transfusion, but may be omitted in clinical emergencies. Because the transfused blood is frequently deficient in platelets, the platelet count should be monitored after exchange transfusion, and platelet transfusion should be considered in infants who are severely thrombocytopenic or who have a bleeding tendency.

The administration of salt-poor albumin (1 g/kg) to neonates 1-2 hours before exchange transfusion to increase the efficiency of bilirubin removal by shifting more tissue-bound bilirubin into the circulation has been advocated and shown to increase the bilirubin removed by 40%. As the total amount of bilirubin removed during an exchange transfusion is only a small portion of the total-body pool of bilirubin, this increase may not significantly alter subsequent bilirubin concentrations or the need for additional exchange transfusions. In addition, theoretically, the transient increase in TB concentration after albumin administration could increase, rather than reduce, the risk for kernicterus if there are local phenomena at the brain level that enhance entry of bilirubin into neurons. Finally, constituents of some albumin solutions may act to displace bilirubin from its binding sites, potentially increasing the percentage of free bilirubin present in the plasma. Thus, pretreatment with albumin before exchange transfusion is not routinely recommended.

Complications

The AAP recommends that exchange transfusions be performed only by trained personnel in a neonatal intensive care unit with full monitoring and resuscitation capabilities.[12] Exchange transfusion is an invasive procedure, and complications may be related to the blood transfusion itself, catheter complications, and the procedure. The potential complications of exchange transfusion are listed in Box 91.4. Severe hemolysis caused by the use of incompatible RBCs may be life threatening. With modern-day screening for infection, there is only a slight chance of transmission of viral or bacterial infection. Hyperkalemia may result if the transfused blood has been stored for a long period. Rebound hypoglycemia may occur if the glucose load during exchange transfusion is large. Graft-versus-host disease is rare but may occur in premature infants or those who have had in utero transfusions. Umbilical venous catheterization may result in air embolism, hemorrhage, or infection.

Presently, serious complications of exchange transfusion are uncommon. Mortality rates are very low in healthy, term neonates but are increased for sick or extremely premature infants. In a study of 106 neonates who underwent 140 exchange transfusions between 1980 and 1995, the overall mortality was 2% but increased to 8% in the subset of infants who were ill. In a smaller series, no serious adverse effects or death occurred among 22 term neonates who had 26 exchange transfusions between 1990 and 1998.[55] In another review of 55 neonates who underwent 66 exchange transfusions between 1992 and 2002,[214] 74% had some form of adverse event, with the most common being thrombocytopenia, hypocalcemia, and metabolic acidosis. In a study of exchange transfusion in neonates with hemolytic disease of the newborn, the procedure was associated with an increased risk of sepsis, leukocytopenia, thrombocytopenia, hypocalcemia, and hypernatremia, but not mortality, when compared with a similarly affected group who did not undergo exchange transfusion.[252] Adverse events related to exchange transfusion, including thrombocytopenia, metabolic acidosis, hypocalcemia, seizures, and death were more frequent in preterm infants: 32 weeks or less (87%), 33-36 weeks (78%), and 37 weeks or more (67%).[214]

If performed under intensive care facilities and with appropriate expertise, the advantages of performing an exchange transfusion clearly outweigh the potential risk, albeit small, of serious complications. Preparations for emergency situations should be made before initiation of the procedure.

• BOX 91.4 Potential Complications of Exchange Transfusion

- Thrombocytopenia, particularly with repeat transfusions
- Portal vein thrombosis or other thromboembolic complications
- Umbilical or portal vein perforation
- Acute necrotizing enterocolitis
- Arrhythmia, cardiac arrest
- Hypocalcemia, hypomagnesemia, hypoglycemia
- Respiratory and metabolic acidosis, rebound metabolic alkalosis
- Graft-versus-host disease
- Human immunodeficiency virus, hepatitis B and C infections
- All other potential complications of blood transfusions

Individualization of Therapeutic Guidelines

The TB level is one of the major criteria to be evaluated when considering the initiation or escalation of treatment for unconjugated hyperbilirubinemia. Although it is believed that it is the unconjugated fraction that presents the danger of kernicterus, the exact ratio of unconjugated and conjugated bilirubin is difficult to assess, because its quantitation exhibits great variability among laboratories. In view of this, the conjugated bilirubin level should not be subtracted from the TB level unless it constitutes more than 50% of the total. As was stated previously, many variables other than the TB level influence the susceptibility of a particular patient to the sequelae of unconjugated hyperbilirubinemia; these include genotype, gestational age, chronologic age, and the presence of hemolytic or other disease

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states. Therefore, it is useful to consider four groups of patients at risk for kernicterus and modify treatment based on the category: the healthy term (>37 weeks' estimated gestational age), the sick term, the healthy premature, and the sick premature neonate.

In 1994, the Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia of the AAP published recommendations for the management of unconjugated hyperbilirubinemia in healthy term neonates.[14] The recommendations were revised in 2004,[12] clarified in 2009,[162] and are detailed in Figs. 91.16, 91.22, and 91.23. Whereas the 1994 AAP Practice Parameter did not offer suggestions for the management of newborns with hemolytic conditions, the 2004 AAP Practice Guideline takes into account both term and late preterm infants, with and without risk factors. Risk factors to be considered for the purpose of deciding whether to institute phototherapy or exchange transfusion include isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, and acidosis. Jaundice manifesting in the first 24 hours of life is emphasized as an important risk factor, and recommendations for infants with early jaundice are included in the therapeutic guidelines. Therefore, a more conservative approach should be taken to initiating therapy for hyperbilirubinemia (Table 91.4). Similarly, TB levels rising at a rate greater than 0.5 mg/dL per hour (9 µmol/L) or "jumping tracks" on the bilirubin nomogram indicate a state of active hemolysis; such patients should be considered as falling into the "sick," or risk factor, category. It is exceedingly important in these cases to institute and revise therapies on the basis not only of the current level of bilirubin but also of an estimate of the anticipated peak. Thus, early in the patient's course, phototherapy or exchange transfusion may be performed at a relatively lower TB level than for a similar level occurring at a later time (see Box 91.3).

Prediction of Hyperbilirubinemia and Postdischarge Follow-up

An examination of the hour-specific bilirubin nomogram will reveal that the TB continues to rise in a steady fashion throughout the first days of life, arriving at its peak at about 4-5 days. An infant who is discharged home at or around 48 hours of age will only have started to increase the TB, which will peak at home. Great responsibility is, therefore, placed on the parents to detect deepening jaundice and to approach the appropriate facilities should hyperbilirubinemia develop. Many cases of kernicterus have developed at home in newborns previously thought to be well and discharged from the newborn nursery as healthy. To assist in discharge planning and in an attempt to detect at least some of the infants with developing hyperbilirubinemia, the AAP has issued recommendations for postdischarge follow-up[12] (Table 91.5). It is recommended that every newborn should be seen by a pediatrician within 2-3 days of discharge, even those who were not jaundiced at the time of discharge.

TABLE 91.5 Post-Discharge Follow-Up

Infant Discharged	Should Be Seen by
Before age 24 hours	72 hours
Between age 24 and 47.9 hours	96 hours
Between age 48 and 72 hours	120 hours

From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2004;114:297.

Clinical judgment should be used when scheduling follow-up, and infants with risk factors for hyperbilirubinemia may be seen earlier than recommended in Table 91.5, as judged clinically necessary.

In a clarification[162] to the 2004 AAP Practice Guideline, a predischarge measurement of TB or TcB is recommended and the risk for hyperbilirubinemia detected based on an infant's age in hours and the TB measurement, which may require readmission to the hospital for treatment. Moreover, all infants should be screened for risk factors prior to discharge, when planning for the postdischarge visit. Predischarge TB percentile risk assessment in combination with gestational age may be the most sensitive index of subsequent hyperbilirubinemia requiring phototherapy or readmission,[31,144] while complete absence of clinical jaundice is highly predictive of infants who will not develop significant hyperbilirubinemia.[145]

Hyperbilirubinemia in Resource-Limited Countries

Severe hyperbilirubinemia, frequently with clinical evidence of ABE, is one of the most frequent causes for admission in countries with limited resources. Management of hyperbilirubinemia is compromised by long distances to travel to obtain medical care, lack of adequate phototherapy devices, and erratic electricity supply. Exchange transfusion is frequently performed under inadequate circumstances. To cite only a few examples: in Nigeria, severe hyperbilirubinemia accounted for one in five neonatal admissions and has been associated with case fatality and neurodevelopmental sequelae, including cerebral palsy and auditory impairments. G6PD deficiency, prematurity, low birth weight, infection, and ABO incompatibility were prevalent among the etiologies of hyperbilirubinemia.[211] In Myanmar, half of all neonatal hospital admissions are for hyperbilirubinemia with a high rate of exchange transfusion.[17] In an attempt to circumvent the inability to provide adequate phototherapy, Slusher et al. have devised a method by which filtered sunlight can be as a surrogate for electric-powered phototherapy by using window tinting films to filter the broad spectrum of sunlight, allowing transmission of only safe and efficacious

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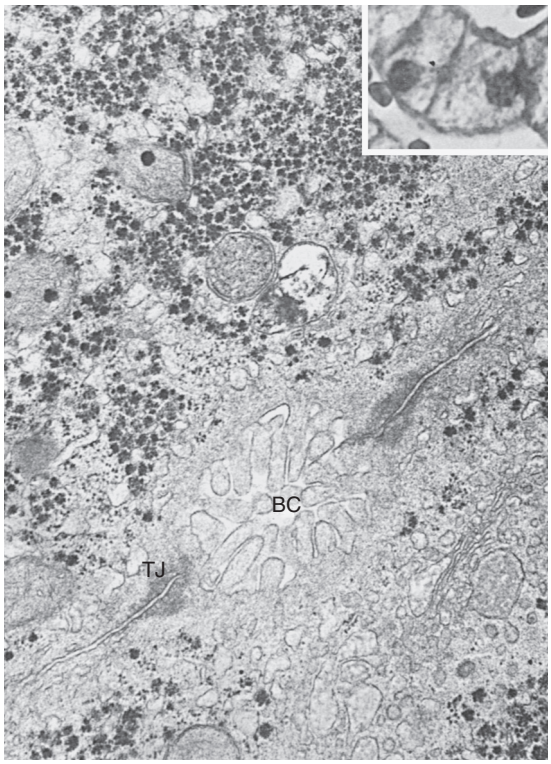
blue light. In a randomized, controlled noninferiority trial in which filtered sunlight was compared with conventional phototherapy for the treatment of hyperbilirubinemia in term and late-preterm neonates in Nigeria, filtered sunlight was noninferior to conventional phototherapy for the treatment of neonatal hyperbilirubinemia.[250] Because the need for exchange transfusion may be high, and blood banking and other supportive services lacking, it has been proposed that infants at high risk of kernicterus should be given priority over those at moderate risk. Factors to be taken into consideration include the presence of intermediate or advanced ABE, neurotoxicity risk factors, and TB levels.[210]

Conjugated Hyperbilirubinemia

Neonatal jaundice associated with a rise in conjugated bilirubin is indicative of a defect or insufficiency in bile secretion, biliary flow, or both and is always pathologic. It is commonly accompanied by a rise in serum levels of other constituents of bile, such as bile salts and phospholipids. The designation *cholestasis*, meaning reduction in bile flow, is used to describe this group of disorders. The rise of conjugated serum bilirubin may be the result of primary defects in the hepatocellular transport or excretion of bile, or secondary to abnormalities in bile duct function or structure.[18] Sequelae are specific to the many diverse diseases producing this clinical entity, and therefore treatment, when possible, is directed at the underlying disease.

The hepatocellular phase of bile secretion involves the transport of conjugated bilirubin across the hepatic cell membrane at the biliary pole. The lateral cell membrane at this site is folded to form microvilli and becomes part of the canalicular space, surrounded by two or more adjacent hepatocytes. Microvilli and the underlying cytoplasm contain microfilaments visible by electron microscopy. These structures consist of the contractile protein actin, which is necessary for normal canalicular contraction and microvillous motility, important elements in the generation of intrahepatic bile flow. At the border of the bile canaliculus, hepatocytes are joined in a "tight junction," which under normal circumstances forms an efficient barrier, preventing the contents of the bile canaliculus from entering the perisinusoidal space of Disse or the vascular compartments (Fig. 91.24). The bile canaliculus is an integral part of hepatocytes. It follows that any hepatocellular injury may result in impairment of the cellular phase of bile excretion and breakdown of the tight junctions, leading to the clinical and laboratory findings of cholestasis.

Hyperbilirubinemia resulting from hepatocellular injury may be associated with other abnormalities that reflect impairment of other hepatocellular functions. These abnormalities include hypoglycemia, fluid retention, toxin and medication metabolism, and bleeding. However, injury may selectively impair bile secretion at the biliary pole of hepatocytes, resulting in an isolated laboratory finding of conjugated hyperbilirubinemia. A liver biopsy taken in the early stages of one of the diseases caused by a hepatocellular

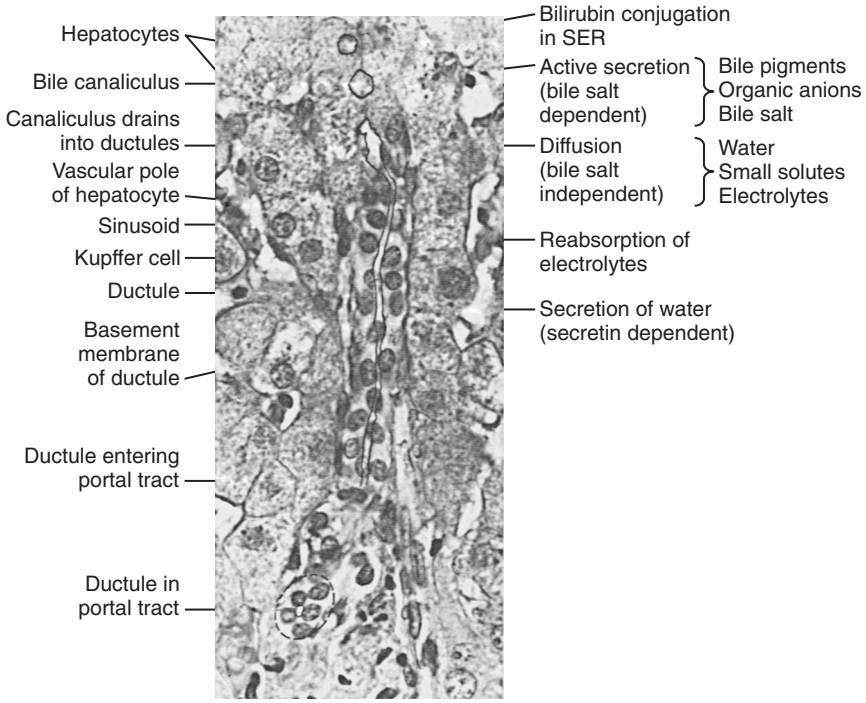


• **Fig. 91.24** Electron micrograph of two adjacent normal hepatocytes. Note the microvillar surface of the bile canaliculus (BC). Tight junctions (TJ) border the canaliculus. *Insert:* A high-power view of two adjacent hepatocytes as seen in the light microscope. In such preparations, bile canaliculi appear as poorly defined condensations of the cell membrane. Epon-embedded, x6000. (Courtesy of Dr. L. Biempica, Albert Einstein College of Medicine, Bronx, NY.)

defect in bile secretion would characteristically show bile pigment granules in hepatocytes and canaliculi, referred to as *intracellular* and *intracanalicular cholestasis*. Bile pigment granules are not seen in either hepatocytes or canaliculi of normal liver parenchyma. In fact, the canalicular lumen is not visualized in routine sections of normal liver parenchyma, because it is partially obliterated by microvilli identifiable only by electron microscopy. In cholestasis, there is usually blistering, blunting, or destruction of these microvilli, transforming the bile canaliculus into a widened, round space containing bile (the bile plug). On rare occasions, liver biopsies from patients with conjugated hyperbilirubinemia fail to show any abnormalities when examined with the light microscope.

The ductal phase of bile excretion includes those events that take place in the biliary system distal to the bile canaliculus (Fig. 91.25). The intrahepatic biliary system comprises the bile ductules (the initial portion of which is frequently referred to as the *canals of Hering*); the interlobular (portal) bile ducts, recognized by their constant association with a vein and an arteriole; and the right and left hepatic ducts, which in some individuals may partially extend beyond the liver capsule at the liver hilum. The extrahepatic component includes the common hepatic duct, the cystic duct, the gallbladder, and the common bile

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• **Fig. 91.25** Microscopic section of normal liver depicting transition between the bile canaliculus and bile ductule entering the portal tract. Anatomic structures are identified to the *left* of the illustration, and the corresponding physiologic events are listed on the *right*. SER, smooth endoplasmic reticulum.

duct (choledochus). The extrahepatic biliary system and the major right and left hepatic ducts contain intramural and periductal glandular structures. Although the role of these structures in humans is not clearly understood, information derived from animal experiments suggests they may play an important role in bile duct regeneration or failure to regenerate. This is suggested by the presence of glands or ductules in duct remnants resected during portoenterostomy for biliary atresia (see under specific disorders in the following paragraphs). Most diseases affecting the extrahepatic bile ducts, and occasionally the left and right hepatic ducts, are associated with segmental or diffuse luminal obliteration and are primarily expressions of mechanical disturbance in bile flow.

Diseases involving the intrahepatic ducts, in the absence of concomitant extrahepatic disease, are complex and probably result from a combination of mechanical obstruction to the flow of bile, abnormalities of the biochemical pathways involved in the process of bile secretion, and in some cases, persistence of infectious agents or viral antigens. In rapidly occurring duct obstruction, dilation of proximal branches is noted. This change may not be present when luminal obliteration is incomplete or when it develops slowly, because these cases are frequently complicated by reduction in intrahepatic bile secretion and flow. A constant and characteristic tissue response to complete mechanical obstruction of a major bile duct is dilation and proliferation of proximal portions of the intrahepatic biliary system, including the ductules and canals of Hering, structures that are outside the confines of the portal tracts. A constant accompaniment to bile duct proliferation is an increase in surrounding connective tissue, which eventually leads to fibrous bridging between adjacent portal tracts, causing biliary cirrhosis. Although bile secretory defects may initially be purely hepatocellular or ductal, any long-standing abnormality in the flow of bile leads to some degree of hepatocellular damage.

Box 91.5 lists diseases that may manifest as conjugated hyperbilirubinemia in the neonatal period. This list is divided into those disorders caused by a primary defect in the hepatocellular phase of bile secretion and those caused by ductal disturbances. In most of these disorders, direct-reacting bilirubin accounts for 50%-90% of the TB level. A small amount of indirect-reacting bilirubin is always present, reflecting mild hemolysis, defective uptake and excretion, or hydrolysis of conjugated bilirubin. Early in the onset of conjugated hyperbilirubinemia in the neonate, the direct-reacting portion may account for only 10%-25% of TB. As hepatic conjugation and uptake of bilirubin mature, the indirect-reacting portion decreases, whereas the direct portion increases.

Causes of Conjugated Hyperbilirubinemia

Conjugated hyperbilirubinemia results from interference with the hepatic excretion of conjugated bilirubin into bile. Idiopathic neonatal hepatitis and biliary atresia together account for about 60%-80% of all cases of conjugated hyperbilirubinemia. It is possible that similar pathogenetic mechanisms produce a spectrum of disease, with biliary atresia being the final possible, but not the inevitable, outcome. Because of this, it is useful to discuss these two entities simultaneously.

Idiopathic neonatal hepatitis is defined as prolonged conjugated hyperbilirubinemia without the apparent stigmata of a generalized viral illness, the evidence of identifiable

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• BOX 91.5 Diseases That May Manifest as Conjugated Hyperbilirubinemia in the Neonatal Period

Hepatocellular Disturbances in Bilirubin Excretion

Primary Hepatitis

Neonatal idiopathic hepatitis (giant cell hepatitis)
Hepatitis caused by identified infectious agents

- Hepatitis B
- Rubella
- Cytomegalovirus
- *Toxoplasma* organisms
- Coxsackie virus
- Echoviruses 14 and 19
- Herpes simplex and varicella-zoster viruses
- Syphilis
- *Listeria* organisms
- Tubercle bacillus

"Toxic Hepatitis"

Systemic infectious diseases

- *Escherichia coli* (sepsis or urinary tract)
- *Pneumococcus* organisms
- *Proteus* organisms
- *Salmonella* organisms
- Idiopathic diarrhea

Intestinal obstruction
Parenteral alimentation
Ischemic necrosis

Hematologic Disorders

Erythroblastosis fetalis (severe forms)
Congenital erythropoietic porphyria

Metabolic Disorders

α_1-Antitrypsin deficiency
Galactosemia
Tyrosinemia
Fructosemia
Glycogen storage disease type IV
Lipid storage diseases

- Niemann-Pick disease
- Gaucher disease
- Wolman disease

Cerebrohepatorenal syndrome (Zellweger syndrome)
Trisomy 18
Cystic fibrosis
Progressive familial intrahepatic cholestasis (PFIC)
Hemochromatosis
Idiopathic hypopituitarism

Ductal Disturbances in Bilirubin Excretion

Extrahepatic Biliary Atresia

Isolated
Trisomy 18
Polysplenia-heterotaxia syndrome

Intrahepatic Biliary Atresia (Nonsyndromatic Paucity of Bile Ducts)

Alagille Syndrome (Arteriohepatic Dysplasia)

Intrahepatic Atresia Associated with Lymphedema

Extrahepatic Stenosis and Choledochal Cyst

Bile Plug Syndrome

Cystic Disease

Tumors of the Liver and Biliary Tract

Periductal Lymphadenopathy

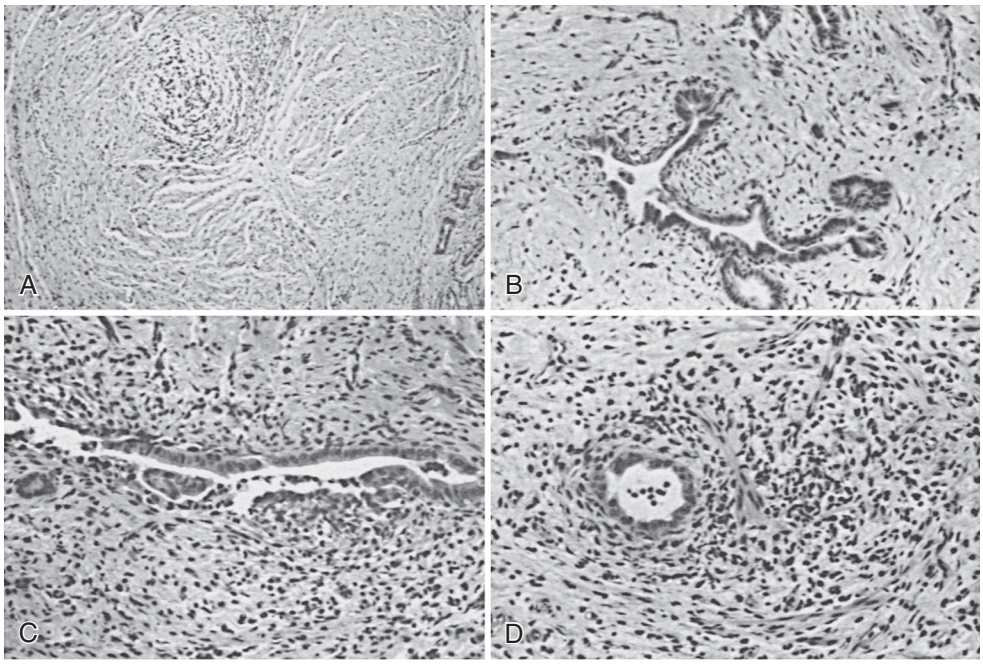
infectious agents, or an etiologically specific metabolic abnormality. On liver biopsy, this group is characterized by extensive transformation of hepatocytes into multinucleated giant cells, and it is, therefore, sometimes referred to as *neonatal giant cell hepatitis*. Giant cell transformation of hepatocytes does not reflect any specific etiology. It is caused by rupture of lateral cell membranes of adjacent hepatocytes, with consequent reduction in the number of bile canaliculi and retention of conjugated bilirubin. It is seen in various inherited metabolic disorders and some infections. Necrosis of hepatocytes and inflammation are usually present, although special stains (e.g., silver impregnation) may be necessary to demonstrate loss of hepatocytes. Necrosis and inflammation may be transient, with giant hepatocytes persisting for many months or even years.

Extrahepatic biliary atresia is defined as a condition in which there is luminal obliteration or apparent absence of segments or all of the extrahepatic biliary system.

Differentiation between these two groups of diseases may be difficult in the early stages; however, an early accurate diagnosis is essential for the choice of proper clinical management.[190] Extrahepatic biliary atresia requires early surgical intervention with hepatoportoenterostomy. Unrelieved by surgery, the defect inevitably leads to death from biliary cirrhosis in the first 3 years of life. The prognosis in idiopathic neonatal hepatitis is uncertain and cannot be predicted based on clinical or laboratory findings. Familial cases have a poor prognosis, with recovery rates of less than 30%. Sporadic cases have a recovery rate of 65%-83% in various series. The poor prognosis in familial cases may be indicative of a metabolic defect.

The causes of idiopathic neonatal hepatitis and biliary atresia remain undetermined. The long-held view that biliary atresia represents a simple congenital developmental anomaly with failure of canalization is now thought untenable. In most cases, biliary atresia and neonatal hepatitis occur as isolated abnormalities, and both are considered to represent acquired conditions that may be initiated by the same or similar noxious factors. In support of the acquired nature of most cases of biliary atresia is the absence of reported cases in stillborn fetuses and the relatively rare association with other malformations. Similarly, clinical evidence of total obstruction to the flow of bile (such as acholic stools or colorless meconium) is not detected in the early stages of jaundice. The onset of acholic stools and conjugated hyperbilirubinemia is frequently delayed

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• **Fig. 91.26** Microscopic preparations of fibrous remnant of extrahepatic biliary system resected during Kasai procedure for biliary atresia. **A,** Most distal portion of specimen, showing complete obliteration of lumen by fibrous tissue. **B** to **D,** More proximal segments, illustrating a spectrum of changes that includes necrosis of lining epithelium, acute and chronic inflammation, mural fibrosis with distortion of lumen, and great variation in size of ductlike structures. All micrographs x60.

until 2 weeks of life or later. Microscopic changes observed in the extrahepatic biliary system, or its fibrous remnant removed during the hepatoportoenterostomy (see Treatment of Extrahepatic Biliary Atresia, later), strongly suggest a sequence of changes that include acute cholangitis, necrosis, inflammation, attempted regeneration, and obliterative fibrosis (Fig. 91.26).

Clinical and pathologic observations over a long period indicate that some patients fulfill all known criteria for neonatal hepatitis, including surgical demonstration of patent biliary ducts in the early stages of jaundice, and then go on to develop extrahepatic biliary atresia.

Injury to the structures involved in bile secretion (hepatocytes and biliary epithelium) may occur either in utero or in the perinatal period, but the consequences of such injury and, therefore, clinically manifested disease, are delayed until sometime after birth. Clinical manifestations and eventual outcome may depend on the severity and persistence of lesions in a specific location. Thus, primary injury to hepatocytes may result in clinical manifestations of neonatal hepatitis, whereas injury to major bile ducts and gallbladder may result in biliary atresia. Reovirus type 3 has been implicated as an etiologic factor in extrahepatic biliary atresia as well as in neonatal hepatitis. These studies include an experimental model in which a hepatobiliary disease bearing a strong resemblance to human biliary atresia can be induced in very young mice by infection with reovirus type 3. No studies, however, have definitively proved a role for any of the known hepatotrophic viruses, including reovirus type 3 in the etiology of biliary atresia in humans.[231]

Other viruses such as cytomegalovirus and rubella virus have been implicated in intrahepatic bile duct destruction and paucity. Patients currently classified as having idiopathic neonatal hepatitis constitute a heterogeneous group that undoubtedly includes various, as yet undefined, hereditary metabolic disorders. A metabolic disorder may explain the recurrent incidence of this disease in some families.

Most patients with idiopathic neonatal hepatitis or biliary atresia represent isolated cases without familial incidence or associated anomalies. Neonatal hepatitis has a familial incidence of 10%-15%, whereas no familial cases of histologically proven extrahepatic biliary atresia have been observed.[94,151] Rare occurrences of neonatal hepatitis and biliary atresia in two siblings have been reported. Both neonatal hepatitis and biliary atresia occur more frequently in patients with trisomy 18 than in the general population. Biliary atresia has been observed in association with the polysplenia-heterotaxia syndrome in 10%-15% of cases. This syndrome is characterized by situs inversus of abdominal organs; intestinal malrotation; multiple spleens; centrally placed liver; and a variety of cardiac, pulmonary, and vascular malformations. The inferior vena cava is frequently absent.

Early clinical manifestations of both idiopathic neonatal hepatitis and biliary atresia may be limited to jaundice. In a small proportion of patients, especially among those who later develop neonatal hepatitis, jaundice may be apparent at birth, documented by increased concentrations of conjugated bilirubin in cord blood. No case of extrahepatic biliary atresia has ever been described in which elevation of

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direct-reacting bilirubin was found in the cord blood. Jaundice usually becomes apparent between the 2nd and 6th weeks of life. The dark yellow staining of diapers from the presence of bilirubin in the urine often prompts the parents to seek medical advice. Jaundice is frequently first noted by the physician during a well-baby visit. Hepatomegaly may be present in both neonatal hepatitis and biliary atresia. Splenomegaly is more frequently present in neonatal hepatitis, but this is not a constant finding. Its presence in biliary atresia usually signifies cirrhosis. Obstruction to the flow of bile is reflected by acholic stools and may be observed in both neonatal hepatitis and biliary atresia. It is always transient and incomplete in neonatal hepatitis, but its duration is variable and may extend beyond the crucial period during which an accurate diagnosis must be established if surgical correction is needed. Routine clinical and laboratory findings usually do not distinguish between extrahepatic biliary atresia and neonatal hepatitis. A routine series of diagnostic laboratory tests is suggested, however, to establish the severity of hepatic involvement and to screen for possible causes (Box 91.6). The failure of routine tests to distinguish between neonatal hepatitis and biliary atresia has led to a continued search for other distinguishing biochemical characteristics. α-Fetoproteins are frequently present in the sera of patients with neonatal hepatitis but may be absent in patients with biliary atresia.

A reliable method for the evaluation of patency of extrahepatic bile ducts is the use of technetium-99m acetanilidoiminodiacetic acid (IDA) or IDA derivatives, such as paraisopropyl iminodiacetic acid or di-isopropyl iminodiacetic acid. These compounds are efficiently extracted by hepatocytes and are excreted with bile into the intestines. When complete obstruction exists, no activity is detected in the intestines. Pretreatment with phenobarbital for 3-7 days before testing promotes excretion of isotope in neonates with severe intrahepatic cholestasis and thus reduces the chance for a mistaken diagnosis of extrahepatic obstruction. Phenobarbital is given orally at the dose of 5 mg/kg daily. Patients are given nothing by mouth for 1 hour before and 2 hours after injection of the radiotracer to avoid gallbladder contraction and dilution of radiotracer excreted into the intestines. Combining cholescintigraphy with a less commonly used string test (determination of color and radioactivity count in duodenal fluid) increases the sensitivity and specificity of the diagnosis. Infants with biliary atresia will have a negative hepatobiliary scan at 24 hours or a string radioactive count of less than 197,007 counts per minute.[191]

Ultrasonography has also been applied in the evaluation of neonatal cholestasis. Although the demonstration of a normal gallbladder is usually indicative of an intrahepatic cause for cholestasis, it may be seen in extrahepatic biliary atresia and is, therefore, not a reliable sign. As intrahepatic bile ducts are usually not dilated in extrahepatic biliary atresia, their presence should suggest another cause.

Histopathologic examination of the liver is an integral part of the evaluation of any patient with persistent conjugated hyperbilirubinemia. It is best performed and analyzed after all other pertinent laboratory data have been gathered. A percutaneous liver biopsy usually yields adequate tissue for microscopic and, if desired, electron microscopic and virologic studies. If a metabolic disorder is suspected, as for example in familial cases, a liver core should be frozen and saved at –70°C for possible subsequent biochemical analysis. In most patients (90%-95%), liver biopsy establishes or confirms the correct diagnosis, sparing the neonate with neonatal hepatitis an unnecessary surgical procedure. Before the biopsy, the prothrombin time and platelet count must be ascertained and assessed to determine the safety of performing the procedure and the need for correction. A prolonged prothrombin time may be corrected in some patients by administration of vitamin K. In

• BOX 91.6 Laboratory Tests Recommended for Evaluation of Neonatal Conjugated Hyperbilirubinemia

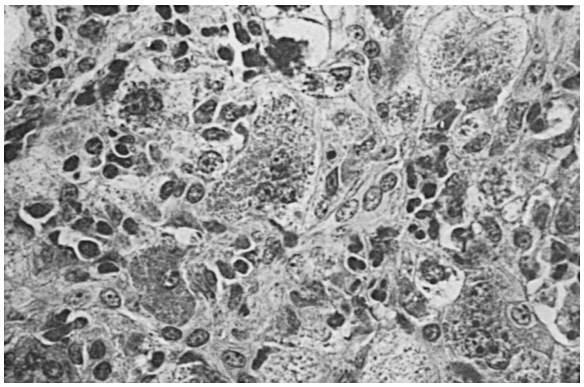
- Liver Function Tests
  - TB and direct-reacting bilirubin, total serum protein, and serum protein electrophoresis
  - SGOT (AST), SGPT (ALT), alkaline phosphatase (and 5′-nucleotidase if alkaline phosphatase elevated), and γ-glutamyl transpeptidase
  - Cholesterol
  - Serum and urine bile acid concentrations, if available
  - α_1-Antitrypsin
  - Technetium-99m iminodiacetic acid scan
  - α-Fetoprotein
- Hematologic Tests
  - Complete blood count, smear, and reticulocyte count
  - Direct Coombs' test and erythrocyte G6PD
  - Platelet count
  - Prothrombin time and partial thromboplastin time
- Tests for Infectious Disease
  - Cord blood IgM
  - VDRL; FTA-ABS; complement fixation titers for rubella, cytomegalovirus, and herpesvirus; and Sabin-Feldman dye test titer for toxoplasmosis
  - HBsAg in both infant and mother
  - Viral cultures from nose, pharynx, blood, stool, urine, and cerebrospinal fluid
- Urine Tests
  - Routine urinalysis, including protein and reducing substances
  - Urine culture
  - Bilirubin and urobilinogen
  - Amino acid screening
- Newborn Screen for Galactosemia and Hypothyroidism
- Liver Biopsy
  - Light microscopy
  - Specific enzyme assay (if indicated)
- Radiologic and Ultrasound Studies (if indicated)
- Additional Diagnostic Studies for Metabolic Disorders (if indicated)

ALT, Alanine transferase; AST, aspartate aminotransferase; FTA-ABS, fluorescent treponemal antibody absorption (test); G6PD, glucose-6-phosphate dehydrogenase; HBsAg, hepatitis B surface antigen; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transferase; TB, total bilirubin; VDRL, Venereal Disease Research Laboratory.

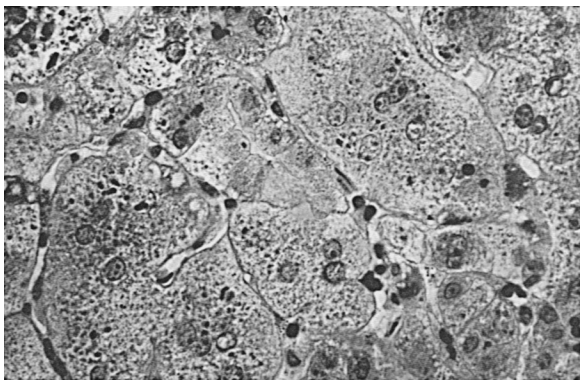
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some situations in which a biopsy is urgently required, fresh frozen plasma and/or platelets may be administered during the percutaneous biopsy. Postoperatively, neonates must be observed closely for vital signs or clinical changes that indicate significant bleeding, bile peritonitis, or pneumothorax, the rare but significant complications of the procedure. In the final analysis, the isotope scan and a percutaneous liver biopsy are the only reliable means available without surgical exploration to distinguish between neonatal hepatitis and extrahepatic biliary obstruction.

The liver biopsy in neonatal hepatitis is characterized by marked irregularity in the size of hepatocytes and, in some cases, by numerous giant hepatocytes (Fig. 91.27 and Fig. 91.28). Giant cells may contain from 4-100 nuclei. The cytoplasm of these giant cells is usually foamy and contains bile pigment. Bile canaliculi appear to be reduced in number and proportion to the number of giant hepatocytes. Necrosis and inflammation are frequently detected. Kupffer cells are swollen and contain bile pigment, lipofuscin, iron, and phagocytosed debris of destroyed hepatocytes. Extramedullary hematopoiesis is almost always present. Although these findings may also be present in biliary atresia, it is the relative absence of bile duct proliferation that distinguishes neonatal hepatitis from biliary atresia. In some cases of neonatal hepatitis, there is evidence of inflammatory injury to portal bile ducts, with epithelial reduplication interpreted as regenerative activity. The aforementioned changes are usually seen in early stages, soon after onset of jaundice. Biopsies taken after 3 months of age may show little necrosis and inflammation and, instead, demonstrate fibrosis or cirrhosis. Giant cell transformation of hepatocytes may persist for months or years.



• **Fig. 91.27** Neonatal hepatitis. Note the marked cellular irregularity obliterating the normal orderly plate arrangement. Intracanalicular bile is present. Small cells in sinusoids are Kupffer cells and elements of extramedullary hematopoiesis. Paraffin embedding and hematoxylin-eosin staining, x60.



• **Fig. 91.28** High-power view of transformed giant hepatocytes. Most of the intracytoplasmic granules represent bile pigment. Paraffin embedding and hematoxylin-eosin staining, x200.

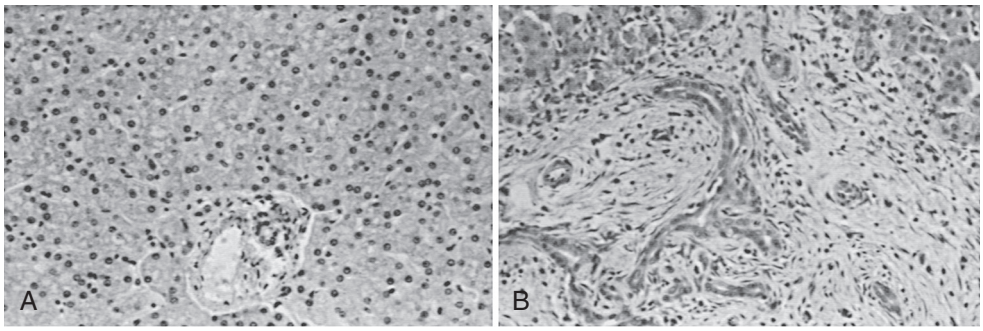
It has been shown in patients and in animal experiments that soon after obstruction of the common bile duct, ducts and ductules in portal tracts and in periportal zones begin to proliferate. This phenomenon involves most, if not all, portal tracts and is present even at the periphery of the liver, far removed from the site of obstruction. Therefore, in biliary atresia, changes suggesting blockage in the major (mostly extrahepatic) bile ducts are seen. At least three portal tracts should be available for examination. In biliary atresia, all tracts will show some degree of proliferation. In early stages, ductular proliferation may be present without increased fibrosis. The ducts have a varicose appearance and contain focal bile plugs. Later, ducts and ductules frequently appear distorted (Fig. 91.29) because of a discrepancy between the rate of proliferation of biliary epithelium and that of the surrounding fibrous tissue. An associated inflammatory exudate is occasionally seen around proliferated ductules, but a true cholangitis with epithelial necrosis and intramural inflammation is rarely encountered except in association with surgical complications. Other changes within portal tracts include dilated lymphatics and, occasionally, tortuous and thick-walled arterioles. In later stages of extrahepatic biliary atresia, ductular epithelium may disappear, having been replaced by collagen fibers, and this may lead to a secondary paucity of portal bile ducts.

Extensive paucity of bile ducts, whether primary or secondary, is associated with a clinical syndrome resembling that observed in primary biliary cirrhosis, or sclerosing cholangitis, with hypercholesterolemia, xanthomas, and pruritus. Hepatocytes in biliary atresia show intracellular and canalicular cholestasis, with the canalicular component predominating (Fig. 91.30). In about one-third of all patients with biliary atresia, there is giant cell transformation of hepatocytes. In most cases, this transformation is primarily centrolobular (around terminal branches of the hepatic vein) and is not associated with necrosis and inflammation. Extramedullary hematopoiesis may also be present.

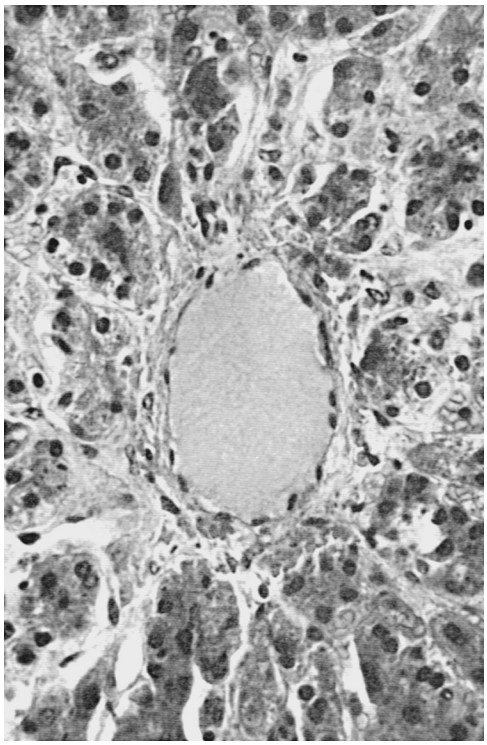
Treatment of Neonatal Hepatitis

Clinical management of neonatal hepatitis consists of supportive measures, because no specific therapy is known. Many neonates have a transient but significant reduction in bile flow, often requiring replacement of fat-soluble vitamins, particularly vitamins D and K. Subclinical rickets is common in these neonates and may contribute to the increase in serum concentrations of alkaline phosphatase. Persistence of acholic or very pale stools without significant lowering of direct-reacting serum bilirubin concentrations

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• **Fig. 91.29** **A,** Portal tract of normal neonate, containing a large, thin-walled vein and single cross section of a bile duct. **B,** Portal tract from neonate with biliary atresia. Note marked enlargement of tract from fibrosis that surrounds multiple elongated bile ducts. Both micrographs, x60.



• **Fig. 91.30** Extrahepatic biliary atresia. Central vein surrounded by hepatocytes. Intracanalicular bile plugs are present. In addition, hepatocytes contain intracytoplasmic bile pigment granules. Paraffin-embedding and hematoxylin-eosin staining.

after 1 month should be viewed as an indication for repeat clinical study, including liver biopsy. This practice permits detection of patients whose extrahepatic bile ducts sclerose after an initial phase of hepatitis and who are, therefore, suitable candidates for exploratory laparotomy and corrective surgery. On rare occasions, patients with neonatal hepatitis and complete obstruction, as evidenced by acholic stools, may recover rapidly after operative cholangiography that shows normal extrahepatic ducts. This phenomenon is probably the result of flushing out of inspissated bile in the extrahepatic biliary system, with consequent relief of obstruction. This situation may be seen in cystic fibrosis or severe dehydration. Fluctuations in stool color should alert the clinician to the possible existence of a choledochal cyst, which can usually be diagnosed with ultrasound and treated surgically. There are no early reliable criteria on which the prognosis of a particular patient can be based.

Treatment of Extrahepatic Biliary Atresia

When the clinical evaluation indicates complete biliary obstruction or proves inconclusive, the patient should undergo an exploratory laparotomy. On entry of the abdomen and after initial scrutiny of the biliary system, an operative cholangiogram should be performed to confirm and characterize the extrahepatic lesion and define its extent. The classification proposed by the Japanese Society of Pediatric Surgeons divides extrahepatic biliary atresia into three types based on gross observations during laparotomy:

Type I: Atresia of the common bile duct with patent proximal ducts
Type II: Atresia of the common hepatic duct with patent proximal ducts
Type III: Atresia of the right and left hepatic ducts at the porta hepatis

Operative examination of these neonates should be performed only by surgeons prepared to proceed with corrective procedures if necessary. Reoperation after exploratory laparotomy increases the technical difficulties and delays the institution of corrective measures. Reconstitution of normal biliary drainage by direct anastomosis of grossly identifiable segments of patent bile ducts to the gastrointestinal tract is possible in only a very small proportion of patients with biliary atresia (estimated at 5%-10%). These include the rare cases of choledochal cyst and occlusion of a short segment of the common bile duct by a valve, a membrane, or fibrosis. In most patients with biliary atresia, there are no grossly visible ducts proximal to the atretic segment. In the past, all these patients were considered inoperable. Untreated patients, although jaundiced, often appear clinically well in the first few months of life, but they deteriorate rapidly after cirrhosis develops, with clinical manifestations of portal hypertension, ascites, hypersplenism, infection, hyperammonemia, and hemorrhage.[116,236]

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In 1968, Kasai and associates described for the first time in American literature an operative procedure in which the periphery of the transected fibrous tissue of the porta hepatis, devoid of grossly identifiable ducts, was anastomosed to a Roux-en-Y loop of small intestine (portoenterostomy).[141] Kasai's portoenterostomy or variations of this procedure are currently performed in most medical centers.

The immediate goal for surgical correction is the reestablishment of bile drainage, which is now achieved in most neonates when operated on before 3 months of age. Cure rate, however, is still poor. In most operated patients, fibrosis increases with time and eventually progresses to cirrhosis despite adequate bile drainage. It is currently unclear whether progressive liver fibrosis represents a continuation of the same type of injury responsible for the initial obliterative process in extrahepatic ducts or if it is the result of ascending cholangitis complicating surgery. In addition to the age at the time of surgery, other factors that influence the outcome include the size and patency of microscopic ducts in the transected porta hepatis and the preservation of intact epithelial lining. Growth failure and TB between 2 and 6 mg/dL at 3 months after hepatoportoenterostomy was shown to be associated with need for transplantation or death by 24 months of age.[73]

Orthotopic liver transplantation is the definitive therapy for biliary atresia. Survival statistics have steadily improved since 1981, when cyclosporin A and steroid therapy were introduced. Other drugs that produce effective immunosuppression and fewer side effects, such as FK 506, lessen the mortality and morbidity of transplantation, resulting in longer and more productive lives for graft recipients.[236]

Known Infectious Causes

In a small proportion of neonates with neonatal hepatitis, a specific infectious agent may be identified either by direct isolation and culture or by serologic tests that detect specific antibodies. In addition, microbial antigens may be identified in liver biopsy using monoclonal antibodies and immunocytochemical staining methods. Among infectious agents reported in association with neonatal hepatitis are organisms, such as *Treponema pallidum* and *Listeria* species, and viruses such as rubella and Coxsackie virus, the herpes group of viruses (herpes simplex, varicella-zoster, cytomegalovirus), and adenovirus. The protozoan *Toxoplasma gondii* also has been implicated. Fetal infection may take place in utero either by transplacental spread or by an ascending infection of the amniotic fluid, usually after rupture of membranes. In some cases, infection may occur during delivery by aspiration or swallowing of vaginal contents. Clinically, patients in this group may appear sick and fail to thrive and also may have evidence of CNS and other organ involvement. In many patients, there are stigmata of generalized infection. Laboratory findings are similar to those seen in idiopathic neonatal hepatitis, but stools are not acholic, and therefore biliary atresia usually is not suspected. Although congenital infection with human immunodeficiency virus (HIV) is diagnosed with increasing frequency, cholestasis is rare in the neonatal period.

Liver biopsy may be helpful in the diagnosis of infectious agents, especially in infections with the herpes viruses. These DNA viruses replicate in the nucleus, resulting in intranuclear inclusion bodies that can be seen with the light microscope. Cytomegalic inclusion disease is characterized by marked enlargement of hepatocytes, biliary epithelium, and Kupffer cells caused by intranuclear as well as intracytoplasmic inclusions. In some cases, however, the virus has been isolated from patients in whom liver biopsy showed giant cell transformation of hepatocytes with no evidence of inclusions.

Hepatitis B surface antigen (HBsAg) may be transmitted from mother to infant, probably by aspiration of vaginal contents, including blood, during delivery. With few exceptions, infants born to HBsAg-positive mothers show no antigenemia in cord blood or in the first month of life. Repeated serologic tests indicate that HBsAg appears in the serum of these infants between 5 and 7 weeks of life and reaches a peak at 10 weeks. Antigenemia in the newborn may be associated with liver injury, and both may persist for many months or possibly years. It is necessary, therefore, to closely observe all infants of HBsAg-positive mothers for many years for clinical and laboratory evidence of chronic liver disease. Severe and even fulminant neonatal hepatitis associated with HBsAg has been described in infants of chronic carriers and after neonatal transfusions. Prophylaxis with concurrent administration of hepatitis B immune globulin (HBIG) and hepatitis B vaccine is effective in preventing neonatal infection in greater than 90% of exposed newborns. HBIG (0.5 mL IM) should be given within 12 hours of birth. In addition, hepatitis B vaccine should be given IM concurrently within 12 hours of birth at a different anatomic site and repeated at 1-2 and 6 months of age (for preterm infants who weigh less than 2000 g at birth, a total of four doses of vaccine should be given according to the immunization schedule for preterm infants; see Appendix C). Concurrent use of HBIG and vaccine does not appear to interfere with vaccine efficacy. High HBV DNA level in HBeAg-positive mothers is the most significant risk factor for vertical transmission despite appropriate vaccination.[44] There is a growing consensus for the use of antiviral therapy in the second or third trimester for pregnant HBsAg-positive women with high viral loads to reduce the risk of perinatal transmission. There is limited data on the level of HBV DNA that antiviral therapy is recommended.[43] Breastfeeding is not contraindicated for mothers with chronic hepatitis B infection.[246]

Hepatitis C virus (HCV), a single-stranded RNA virus in the flavivirus family, has been found to be the etiologic agent in most cases previously referred to as non-A, non-B hepatitis. Transmission occurs through both the percutaneous and the non-percutaneous route. The incubation period varies from 2 weeks to 6 months. The signs of acute disease include malaise, fever, elevation in hepatic transaminases, and jaundice. Fulminant hepatitis and acute hepatic failure

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are rare. Although about three-fourths of acute infections are asymptomatic, about one-half of affected patients will develop chronic hepatitis, with 20% of these patients progressing to cirrhosis. Progression of the disease is slow, with an average of 10 years to chronic hepatitis, 20 years to cirrhosis, and 30 years to hepatocellular carcinoma. Although infected infants manifest biochemical features of hepatocellular injury, other manifestations of the disease are relatively mild throughout childhood.

The overall risk for vertical transmission of HCV has been shown to be as high as 10% in several studies. Women who are infected with both HCV and HIV and those with HCV viremia are at the greatest risk for transmitting HCV to their offspring.[101] The persistence of maternal antibody in the infant is variable but may be as long as 8-12 months. Diagnosis in the neonate and infant is made by measuring serial anti-HCV (IgG) titers (using enzyme immunoassays followed by recombinant immunoblot assays detecting antibody against HCV core antigen or other nonstructural proteins) or by directly detecting the presence of HCV ribonucleic acid through the reverse-transcriptase polymerase chain reaction. No proven therapy is currently available to neonates infected with HCV. The safety and efficacy of HCV therapies, including new direct-acting antiviral agents, are currently being investigated in children. HCV has been detected in the breast milk of HCV-infected mothers. Although theoretically possible, transmission of HCV through breastfeeding has not been documented in HCV-positive, HIV-negative mothers. Thus, according to most authorities, breastfeeding is not currently contraindicated in HCV-positive, HIV-negative women.

Sepsis

Microorganisms and their biologic products may have direct toxic effects on the cells and structures responsible for the hepatocellular and ductal phases of conjugated bilirubin excretion. This may be complicated by sepsis-induced hemolysis, further adding to the bilirubin load. Postmortem examination of neonates with severe sepsis has shown centrilobular cholestasis, focal hepatocellular necrosis, and giant cell transformation in some patients. In others, no hepatic lesions can be demonstrated by light microscopy. Severe urinary tract infection, particularly with coliform bacilli, is associated with this syndrome. In this case, generalized septicemia is not an essential feature, and cholestasis may be caused by massive endotoxin release. Antibiotic treatment is followed by prompt relief of hyperbilirubinemia.

Hepatic Metabolic Disease

Several metabolic disorders result in hepatocellular injury in the neonatal period and give rise to a clinical pathologic syndrome that may resemble neonatal hepatitis or biliary atresia. α_1-Antitrypsin deficiency in the homozygous state (PiZZ) may be manifested by neonatal liver injury. It is estimated that only 10%-20% of all individuals with this abnormality will have liver disease. Most PiZZ individuals never develop clinical evidence of liver disease, but they may develop pulmonary emphysema as adults. Patients with α_1-antitrypsin deficiency may show all the signs and symptoms of neonatal hepatitis or biliary atresia, including acholic stools. Liver biopsy also may show changes consistent with either one of the aforementioned conditions. Bile duct proliferation may be so pronounced that exploratory laparotomy is performed. Although in older children periportal hepatocytes frequently contain intracytoplasmic inclusions that give a positive reaction with periodic acid-Schiff stain and resist diastase digestion, these are rarely seen in the neonatal period. Immunocytochemical staining may be helpful in demonstrating granules of α_1-antitrypsin, present in hepatocytes of patients with deficient states but not in normal phenotypes. Phenotyping of the Pi system should be carried out in all suspected cases. In many infants, neonatal cholestasis may regress before the age of 6 months and reappear later in childhood or adolescence when the patient becomes cirrhotic. The pathogenesis of liver disease associated with this anomaly is not fully understood.[202] Studies suggest that the liver disease is a result of toxic gain-of-function mutations that cause the α_1-antitrypsin protein to fold aberrantly and be retained in the endoplasmic reticulum of hepatocytes rather than be secreted into the blood.[102,215]

Several defects in carbohydrate, protein, and lipid metabolism occur with conjugated hyperbilirubinemia. Deficient activity of galactose-1-phosphate uridyltransferase is inherited as an autosomal recessive disease with an incidence of about 1 in 50,000. It results in the accumulation of galactose-1-phosphate in the liver, producing hepatomegaly and conjugated hyperbilirubinemia. Other associated findings in galactosemia include hypoglycemia, emesis, failure to thrive, cataracts, and ascites. Mental retardation and cirrhosis occur if dietary treatment is not instituted early. The acute form of tyrosinemia is also an autosomal recessive disease and is characterized by elevations in plasma tyrosine and methionine accompanied by hepatic and renal dysfunction, emesis, and failure to thrive. A medication, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), has been shown to improve liver and renotubular function.[154] Dietary tyrosine restriction prevents cirrhosis and early death. Niemann-Pick disease (deposition of sphingomyelin and cholesterol) and Gaucher disease (deposition of glucosylceramide), both autosomal recessive diseases, have also been reported to be associated with conjugated hyperbilirubinemia (see Chapter 90).

Total Parenteral Nutrition–Induced Hepatic Injury

Prolonged use (2 weeks or greater) of total parenteral nutrition may produce conjugated hyperbilirubinemia, which may persist for some time after cessation of this mode of nutrition. Liver biopsy shows evidence of hepatocellular injury with swelling of hepatocytes, necrosis, cholestasis, and occasional giant cell transformation. Trace elements (specifically manganese and copper) should be removed from the total parenteral nutrition solution if conjugated

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hyperbilirubinemia occurs. Baseline copper levels and monthly monitoring are recommended to avoid copper deficiency.[118]

Mechanical Obstruction

Inspissated Bile (Bile Plug) Syndrome

Obstruction of a major bile duct by thick bile or mucus is known as the *bile plug syndrome* or the *inspissated* (Latin *inspissatus*, thickened) *bile syndrome*. Although it may be seen in cases of cystic fibrosis, most often the cause is obscure. The obstruction usually resolves gradually, with or without phenobarbital therapy. Severe cases may require irrigation of the biliary tree or direct surgical extraction of the plug.

Choledocholithiasis

Choledocholithiasis is most commonly seen in neonates with a history of severe intrauterine hemolysis. The excessive bilirubin load results in the formation of gallstones, which have the potential to block the secretion of conjugated bilirubin. Gallstones may also be seen in patients receiving total parenteral nutrition. The diagnosis is suspected because of the presence of conjugated hyperbilirubinemia, bilirubinuria, acholic stools, and a palpable gallbladder. It is confirmed with ultrasound. Spontaneous resolution is common, but cholecystectomy may be necessary in cases of cholangitis or progressive elevation of conjugated bilirubin levels.

Cystic Diseases

Cyst formation in the biliary system may result in obstruction of bile flow and produce conjugated hyperbilirubinemia. Congenital hepatic fibrosis is an autosomal recessive disease marked by hamartomatous and fibrotic changes of the interlobular bile ducts. Most cases are associated with cysts of the renal collecting tubules, and the prognosis depends greatly on the degree of renal impairment. *Caroli disease* is the name given to cystic dilation of the major intrahepatic ducts. Cholangitis is a chronic problem, and the outcome is variable. Cysts found along the extrahepatic biliary tree (common hepatic duct, common bile duct, gallbladder) are known as *choledochal cysts*. These are more commonly seen in females and may lead to portal hypertension, cirrhosis, and carcinoma. Complete surgical excision is the definitive treatment. It is believed that these three disease entities may have a common etiology that differentially manifests itself depending on the timing, duration, and location of the insult. Taken together, they are rare causes of conjugated hyperbilirubinemia presenting in the neonatal period.

Masses

Obstruction of the extrahepatic biliary ducts may also rarely occur with tumors such as primary hepatoblastoma and metastatic neuroblastoma, enlarged periductal lymph nodes, and distended loops of bowel. Treatment is directed at the underlying disorder.

Miscellaneous Causes of Conjugated Hyperbilirubinemia

Alagille syndrome (arteriohepatic dysplasia) is an autosomal dominant disease with clinical variability characterized by a paucity of intrahepatic bile ducts in the presence of patent extrahepatic ducts. Other findings include unusual facies; vertebral anomalies; peripheral pulmonary stenosis; posterior embryotoxon (incomplete iridocorneal separation); and retarded mental, physical, and sexual development.[6] Mutations in Jagged1 (chromosome 20p12) have been identified in about 70% of patients studied with Alagille syndrome.[203] Jagged1 is a cell surface ligand for the Notch receptor. The interaction between Jagged1 and Notch is critical for proper cell differentiation during early development. The majority of Alagille syndrome cases (≈97%) are caused by haploinsufficiency of the *JAG1* gene. A small percentage (<1%) is caused by mutations in *NOTCH2.*

Early clinical manifestations and laboratory findings are identical to those observed in patients with extrahepatic biliary atresia. Later in the first year of life, however, serum cholesterol concentrations rise well beyond those observed in other forms of infantile liver disease. Levels higher than 1000 mg/dL may be seen as early as the third month of life. Cutaneous xanthomas are prominent in the later stages of untreated disease, usually after 1 year of age. It is important to recognize this condition before exploratory surgery, because the patency of the very narrow and collapsed extrahepatic ducts may be extremely difficult to demonstrate. Not only is portoenterostomy unsuccessful in establishing bile flow in this condition, but it actually accelerates the progression of liver disease.[143]

A nonsyndromic form of intrahepatic bile duct paucity has also been described. A familial form of cholestasis and paucity of intrahepatic bile ducts is associated with development of lymphedema of the lower extremities around the time of puberty. Although initially described cases in this group were from families of Norwegian extraction, similar cases have been reported from England, France, and Sweden.

Progressive familial intrahepatic cholestasis (PFIC) results from defects in specific transporter proteins that are responsible for traffic of bile components from hepatocytes into the bile canaliculus.[272] In addition to cholestasis, the group of PFIC conditions can present with diarrhea and growth failure. PFIC-1, previously known as Byler disease and Greenland-Eskimo familial cholestasis, is caused by mutations in the gene coding for the canalicular surface protein FIC1. PFIC-2 is caused by defects in the gene that codes for the bile salt export pump (BSEP) resulting in toxic retention of bile salts within hepatocytes. PFIC-3 is caused by mutations in the gene encoding multidrug resistant protein 3 (MDR3), resulting in lack of phosphatidylcholine in bile and predisposing to cholangitis. PFIC-3, in contrast to PFIC-1 and PFIC-2, is therefore associated with elevations of γ-glutamyl transpeptidase levels. Recently, two new subtypes of cholestatic liver disease have been reported, including PFIC-4 caused by a mutation in the *TJP2* gene,[232]

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which results in a disruption of tight-junction structure and PFIC-5 caused by a mutation in the *NR1H4* gene, which encodes a bile acid–activated nuclear hormone (farnesoid X) receptor that regulates bile acid metabolism.[96]

Zellweger (cerebrohepatorenal) syndrome is a rare autosomal recessive disease marked by the absence of hepatic and renal peroxisomes. Because peroxisomes have many vital anabolic and catabolic functions within the cell, their absence results in profound cellular dysfunction. In addition to conjugated hyperbilirubinemia, affected patients manifest characteristic facies (high forehead, flat occiput, large fontanelle, shallow orbital ridges, micrognathia), feeding difficulties, hypotonia, seizures, and mental retardation. Death usually occurs early in infancy.

Isolated cases of conjugated hyperbilirubinemia have been described in connection with congestive hepatopathy associated with congenital heart disease, severe internal hemorrhage, gestational alloimmune liver disease, and rarely, in association with umbilical vein catheterization.

Clinical management of conditions with prolonged cholestasis includes supportive measures. Infants with chronic cholestasis are at risk for failure to thrive. Malabsorption of fat and fat-soluble vitamins results from poor solubilization of dietary fat in mixed micelles owing to reduced intestinal bile flow. In addition, excess catabolism predisposes infants with chronic liver disease to poor weight gain. Fat malabsorption and steatorrhea can be managed by providing a fat source enriched for medium chain triglycerides, which do not require bile salts for intestinal absorption. Fat-soluble vitamins should be supplemented and serum vitamin concentrations should be monitored. The hydrophilic bile acid ursodeoxycholic acid (UDCA, or Actigall) has been used in managing cholestatic disorders. Proposed anti-cholestatic mechanisms of UDCA action include stimulation of bile flow and displacement of more toxic bile acids from hepatocytes into the systemic circulation via Ca^{257+} and protein kinase C-α-dependent mechanisms and/or activation of p38 (mitogen-activated protein kinase [MAPK]) and extracellular signal-regulated kinases (ERK) to affect transporter molecules (e.g., bile salt export pump [BSEP] and the conjugate export pump [MRP-2]). UDCA can be helpful for severe pruritus associated with cholestasis, with the oral antibiotic rifampin often added for refractory pruritus.

Evidence is clear that a parenteral fish oil emulsion (Omegaven®, Fresenius Kabi, Bad Homberg, Germany), in contrast to the traditional soy-based products, reduces the risk of progressive intestinal failure–associated liver disease (IFALD).[217,240] Such a reduction can rescue patients from needing liver and/or intestinal transplants.[193] Recent studies suggest that the pro-inflammatory ω-6 polyunsaturated fatty acids in plant oil-based lipid emulsions (Intralipid, Liposyn III) and the presence of phytosterols contribute to the development of hepatotoxicity. In contrast, fish oil–based lipid emulsions are rich in anti-inflammatory ω-3 fatty acids, which are hepatoprotective and contain no phytosterols. In the United States, Omegaven® is not yet approved by the federal Food and Drug Administration (FDA), which means that institutions must obtain an IND from the FDA to provide Omegaven® for compassionate use. Expanding on the initial experience at the Children's Hospital in Boston, Omegaven® at 1 g/kg/d compared with patients on Intralipid has been demonstrated to improve IFALD in several case series from Canada, Hong Kong, and Seattle, as well as several national and international case reports. Although the reversal of cholestasis has been the most studied parameter in the fish oil and IFALD field, liver histology is lacking. Some studies indicate there may not be regression, but there may be stabilization of fibrosis despite resolution of cholestasis on fish oil emulsions.[181] Some centers are arguing for lipid minimization as the initial treatment for IFALD.[66] Other key factors in the management of IFALD include a focus on enteral autonomy, prevention of catheter line infection (including the use of ethanol locks), limitation of hepatotoxic medications, and multidisciplinary management by intestinal rehabilitation programs.[274] It is important to note that there is a risk of bleeding in patients receiving parenteral fish oil emulsions.[192] Finally, another lipid emulsion, SMOFlipid, also produced by Fresenius Kabi, which is composed of soybean oil, fish oil, olive oil, and medium-chain triglycerides, has been advocated by several groups.[75,97] It has a higher content of ω-3 fatty acids and a lower phytosterol content than soy-based emulsions, and there is some evidence suggesting that it may be beneficial in IFALD.

Key Points

- Neonatal hyperbilirubinemia is usually transient and harmless, but if severe and untreated, can lead to chronic choreoathetotic cerebral palsy (kernicterus) and death or bilirubin-induced neurologic dysfunction, including severe neurologic hearing impairment (auditory neuropathy/dyssynchrony).
- Although bilirubin neurotoxicity has been limited to a large extent in industrialized countries with functional medical systems, it is still rampant in developing countries and a major cause of mortality and morbidity globally.
- The etiology of hyperbilirubinemia results from an imbalance between the bilirubin production and elimination: hemolysis and prematurity appear to increase the risk of bilirubin neurotoxicity.
- The serum total bilirubin (TB), when primarily indirect or unconjugated, is used for clinical assessment and therapeutic decision making. While unbound bilirubin may offer better prognostic value, its measurement is not available universally in the clinical setting.
- The mainstay of treatment is intensive phototherapy, with the option of exchange transfusion in those infants

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not responding to that treatment. Therapies using metalloporphyrins have potential in the future.
- The rise of conjugated serum bilirubin may be the result of primary defects in the hepatocellular transport or excretion of bile, or secondary to abnormalities in bile duct function or structure.
- The two most common causes of conjugated hyperbilirubinemia are idiopathic neonatal hepatitis, a noninfectious, nonmetabolic hepatocellular injury, and biliary atresia, a progressive obliteration or absence of extrahepatic bile ducts.
- Abdominal imaging with ultrasound and/or percutaneous liver biopsy for histopathology is a key step to differentiating the many potential causes of neonatal cholestasis.
- Hepatoportoenterostomy to re-establish biliary drainage is an imperative early surgical intervention for biliary atresia.
- New fish oil lipid emulsions compared to traditional soybased products may reverse the progression of intestinal failure–associated liver disease (IFALD).

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Fluid, Electrolytes, and Acid-Base Homeostasis

KATHERINE MACRAE DELL

Fluid and electrolyte and acid–base management are essential components in the care of neonates who are considered high risk. This is particularly true for infants with very low birth weight (VLBW) for several reasons. Premature neonates typically require parenteral fluids, the quantity and composition of which can be highly variable. They also have important developmental limitations in renal homeostatic mechanisms. Finally, immature infants may be particularly susceptible to significant morbidity and mortality related to fluid and electrolyte and acid–base imbalances.

Fluid and Electrolyte Management

In this section, basic renal mechanisms for maintaining fluid and electrolyte homeostasis are reviewed, and factors that govern fluid and electrolyte requirements for term and preterm infants are outlined. Methods for monitoring fluid and electrolyte balance, and potential complications and treatments of fluid and electrolyte disorders, are discussed. Also, several specific situations in high-risk infants that require special consideration are addressed.

Body Fluid Composition in Fetuses and Newborns

Total body water (TBW) encompasses extracellular (interstitial and plasma) and intracellular water. Early in fetal development, TBW is almost 95% of the total body weight. As the fetus grows, there is a decrease in the proportion of body weight represented by water (Fig. 92.1).[20] At birth, TBW represents approximately 75% of body weight in a full-term infant. The progressive decrease in TBW is caused primarily by decreases in the extracellular water compartment. The TBW percentage in premature infants, therefore, is higher than that of term infants and is proportional to gestational age.[24] For instance, at 32 weeks, the infant's TBW is approximately 85% of the body weight, whereas that of a 23-week infant approaches 90%.[43]

During the first week of life, all healthy neonates experience a reduction in body weight. The major cause of this physiologic weight loss is a reduction in extracellular water.[56] In the first 24-48 hours after birth, infants have decreased urine output, followed by a diuresis phase, with urinary losses of water and sodium in the first week of life, resulting in weight loss.[34] Physiologic weight loss in the first few days of life in term and premature infants represents isotonic contraction of body fluids and seems to be part of a normal transitional physiologic process thought to be mediated through release of atrial natriuretic peptide.[40] In term infants, this weight loss can be up to 10%. In very premature infants, weight loss can be up to 15%.[58] Perturbations in this normal transitional physiology can lead to imbalances in sodium and water homeostasis. In ill term infants and premature infants, various factors (discussed subsequently) can lead to increased or decreased urinary or insensible water losses. Similarly, increased or decreased administration of intravenous fluids, with variable amounts of water and sodium, can have a significant impact on overall fluid balance.

Sodium Balance in Newborns

Sodium is the major component of the extracellular fluid (ECF) volume and plasma volume. The total sodium content (*not* the serum sodium concentration, which reflects only the relative relationship between salt and water) determines the volume of the ECF. Renal sodium handling is crucial in maintaining sodium balance and protecting against volume depletion or overload. Sodium is freely filtered by the glomerulus, and the bulk of the filtered sodium is reabsorbed in the proximal tubule. Additional sodium reabsorption occurs in the loop of Henle via the Na^+-K^+-2 Cl^- cotransporter, the therapeutic target of loop diuretics. In the distal convoluted tubule, sodium is further reabsorbed via the sodium chloride cotransporter, the therapeutic target of thiazide diuretics. The major site of fine regulation of sodium reabsorption is the collecting tubule, wherein aldosterone

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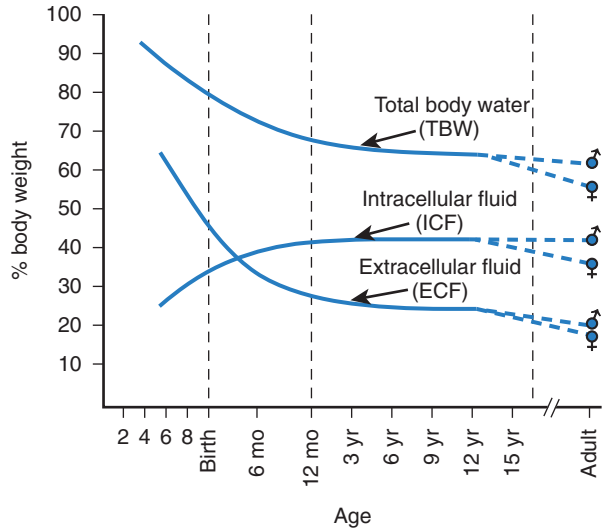
Abstract

Fluid and electrolyte and acid–base management are essential components in the care of neonates who are considered high risk. This is particularly true for infants with very low birth weight (VLBW) for several reasons. Premature neonates typically require parenteral fluids, the quantity and composition of which can be highly variable. They also have important developmental limitations in renal homeostatic mechanisms. Finally, immature infants may be particularly susceptible to significant morbidity and mortality related to fluid and electrolyte and acid–base imbalances.

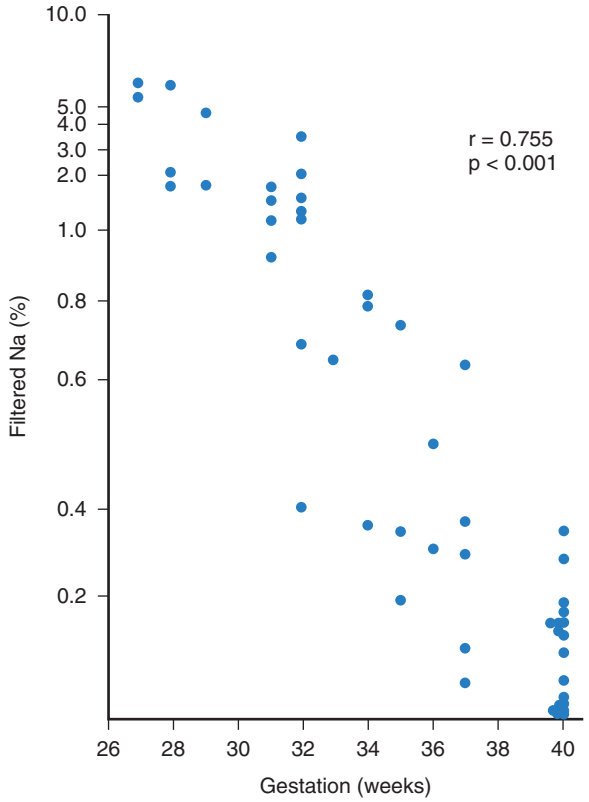
Keywords

fluid therapy
hyponatremia
hypernatremia
acidosis
alkalosis
inherited tubular disorders

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• **Fig. 92.1** Change with age in total body water and its major subdivisions. (From Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics.* 1961;28:169. Used with permission of American Academy of Pediatrics.)



• **Fig. 92.2** Scattergram showing the inverse correlation between fractional sodium excretion and gestational age. (From Siegel SR, et al. Renal function as a marker of human renal maturation. *Acta Paediatr Scand.* 1976;65:481.)

acts on the principal cells to promote reabsorption through sodium channels located on the luminal membrane.

Healthy term neonates have basal sodium handling similar to that of adults, with a fractional excretion of sodium (FE_{NA}) of less than 1%, although a transient increase in FE_{NA} occurs during the diuretic phase on the second and third days of life.[34] In premature infants, however, renal sodium losses are inversely proportional to gestational age, with FE_{NA} equaling 5%-6% in infants born at 28 weeks' gestation (Fig. 92.2).[60] As a result, preterm infants may display negative sodium balance and hyponatremia during the initial 2-3 weeks of life because of high renal sodium losses and inefficient intestinal sodium absorption.[66] The mechanisms responsible for increased urinary sodium losses in preterm infants are multifactorial. The immature kidney exhibits glomerulotubular imbalance, a physiologic state that is present when the glomerular filtration rate (GFR) exceeds the reabsorptive capacity of the renal tubules. This imbalance is attributable to numerous factors, including a preponderance of glomeruli compared with tubular structures, renal tubular immaturity, large extracellular volume, and reduced oxygen availability.[49] Decreased responsiveness to aldosterone is also characteristic of fetal and postnatal kidneys compared with adult kidneys and results in a decrease in sodium reabsorption.

Urinary sodium losses in preterm and term neonates may be increased in certain conditions, including hypoxia, respiratory distress, hyperbilirubinemia, acute tubular necrosis, and polycythemia. Pharmacologic agents such as dopamine, beta blockers, angiotensin-converting enzyme inhibitors, and diuretics may also increase urinary sodium losses in neonates. The abnormalities in sodium and water balance seen in premature infants are attenuated, to some degree, by prenatal steroid administration. Prenatal steroid treatment is associated with decreased insensible water loss, a decreased incidence of hypernatremia, and an earlier diuresis and natriuresis.[44] This beneficial effect on water and sodium balance in infants with extremely low birth weight is thought to be mediated by maturation of the renal epithelial transport systems controlling fluid and electrolyte homeostasis.

Water Balance in Newborns

Water balance is controlled primarily by antidiuretic hormone (ADH), which controls water absorption in the collecting duct. ADH secretion is regulated by hypothalamic osmoreceptors that monitor serum osmolarity and baroreceptors of the carotid sinus and left atrium that monitor intravascular blood volume. Stimulation of ADH secretion occurs when serum osmolarity increases to greater than 285 mOsm/kg or when effective blood volume is significantly diminished. Increases in serum osmolarity also stimulate thirst receptors in the anterior hypothalamus to promote increased water intake. Intravascular volume has a greater influence on ADH secretion than serum osmolarity. Patients with hyponatremia and concomitant volume depletion are unable to suppress ADH in response to the decrease in serum osmolarity.

At baseline, when the serum osmolarity and effective blood volume status are normal, the collecting duct

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is impermeable to water. In response to an increase in serum osmolarity or significant volume contraction, ADH produced in the hypothalamus binds to its receptor, arginine-vasopressin V2 receptor, located on the basolateral membrane of principal and inner medullary collecting duct cells. Receptor activation results in elevated levels of intracellular cyclic adenosine monophosphate. Downstream signaling pathways promote movement of preformed vesicles containing aquaporin 2 (AQ2) water channels to the apical surface. The presence of these water channels on the watertight apical membranes renders them permeable to water. Withdrawal of ADH stimulates endocytosis of AQ2-containing vesicles, which restores the collecting duct cells to a state of water impermeability.

This system may not be as straightforward as previously believed, however, because vasopressin V2 receptors have been shown to be expressed in nephron segments other than the collecting duct, notably the loop of Henle.[42] This study and others support the emerging concept of crosstalk between the ADH/vasopressin V2 receptor system (classically considered a regulator of water homeostasis only) and the renin-angiotensin system (classically considered a sodium regulator only), which may modulate renal handling of salt and water further.

Maximal renal concentration and dilution require structural maturity, well-developed tubular transport mechanisms, and an intact hypothalamic-renal vasopressin axis. In adults and older children, decreased water intake or increased water losses activate a highly efficient renal concentrating mechanism that can produce maximally concentrated urine with an osmolarity of 1500 mOsm/kg, resulting in fluid conservation. Conversely, excessive fluid intake triggers the diluting mechanism of the kidney that can produce maximally dilute urine with an osmolarity of 50 mOsm/kg, resulting in free water excretion.

Urinary concentrating ability is diminished in neonatal kidneys, particularly those of premature infants.[15,38] When challenged, term newborns can concentrate urine to an osmolarity of 800 mOsm/kg; preterm infants can concentrate urine to an osmolarity of only 600 mOsm/kg.[15] This diminished urinary concentrating ability, particularly in preterm infants, may limit a neonate's ability to adjust to fluid perturbations—notably perturbations that result in increased free water losses (e.g., increased insensible water losses). Multiple factors limit renal concentrating capacity in preterm infants. Structural immaturity of the renal medulla limits sodium, chloride, and urea movement to the interstitium. Preferential blood flow through the vasa recta limits generation of a medullary gradient. Diminished urea-generated osmotic gradient in the renal medulla limits production and maintenance of the countercurrent mechanisms that are essential in producing maximally concentrated urine. Finally, tubular responsiveness to vasopressin is diminished because of decreased transcription and protein synthesis of AQ2 water channels.[68]

Urinary dilution capability, in contrast, is normal in term neonates but diminished in preterm neonates. When challenged with a water load, term infants can produce dilute urine with an osmolarity of 50 mOsm/kg, similar to that of an older child or adult. The kidneys of preterm infants, however, may be capable of diluting the urine to an osmolarity of only 70 mOsm/kg.[38,52]

The diminished urinary diluting and concentrating capacities of neonates have important implications for their care. Excessive fluid restriction places newborns, particularly preterm neonates, at risk for dehydration or hypernatremia or both. Conversely, generous fluid intake poses the risk of intravascular volume overload or hyponatremia or both. High fluid intake has also been associated with an increased risk of symptomatic patent ductus arteriosus (PDA) and necrotizing enterocolitis.[7,10,11]

These facts underscore the importance of careful calculation of fluid and electrolyte requirements and close monitoring of fluid balance in high-risk neonates.

Calculation of Fluid and Electrolyte Requirements

Calculation of fluid and electrolyte requirements in newborns is based on maintenance needs, deficits, and ongoing losses. Crucial factors that determine these fluid requirements include gestational age, renal function, ambient air temperature and humidity, ventilator dependence, presence of drainage tubes, and gastrointestinal losses.[12]

Maintenance Fluids and Electrolytes

Maintenance fluid requirements represent the water required to maintain a newborn in neutral water balance. The total amount of maintenance fluid required is equal to urine production plus insensible losses. Table 92.1 summarizes maintenance fluid requirements during the first month of life for full-term and preterm infants. The numbers presented in Table 92.1 are only guidelines; they are to be used as a starting point for prescribing maintenance fluid for infants with low birth weight during the first week of life. Further adjustments must be based on the clinical situation. In particular, close attention to the patient's volume status and assessment of factors that may increase or decrease the baseline fluid requirements are essential to the appropriate management of these infants.

Insensible Losses

Insensible water losses (see Chapter 35) are primarily evaporative losses via the skin and respiratory tract. In newborns, one-third of insensible water loss occurs through the respiratory tract, and the remaining two-thirds occurs through the skin. Numerous physiologic, environmental, and therapeutic factors can influence insensible water loss, making it the most variable component of the maintenance fluid requirements in newborns. Table 92.2 summarizes the effect of various factors on the degree of insensible water loss in newborns. Transepidermal water loss contributes significantly to increased insensible losses of premature infants (Fig. 92.3).[21] There is an inverse relationship

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TABLE 92.1 Maintenance Fluid (Water) Requirements During the First Month of Life

Birth Weight (g)	Insensible Water Loss (mL/kg/d)	Total Water Requirements by Age (mL/kg/d)		
		Day 1-2	Day 3-7	Day 8-30
<750	100+	100-200	120-200	120-180
750-1000	60-70	80-150	100-150	120-180
1001-1500	30-65	60-100	80-150	120-180
>1500	15-30	60-80	100-150	120-180

Adapted from data from Veille JC. AGA infants in a thermoneutral environment during the first week of life. *Clin Perinatol*. 1988;15:863; Taeusch W, Ballard RA, eds. *Schaffer and Avery's diseases of the newborn*. 6th ed. Philadelphia: Saunders; 1991; and Lorenz J, et al. Phases of fluid and electrolyte homeostasis in the extremely low birth weight infant. *Pediatrics*. 1995;96:48.

TABLE 92.2 Factors Affecting Insensible Water Loss in Newborns

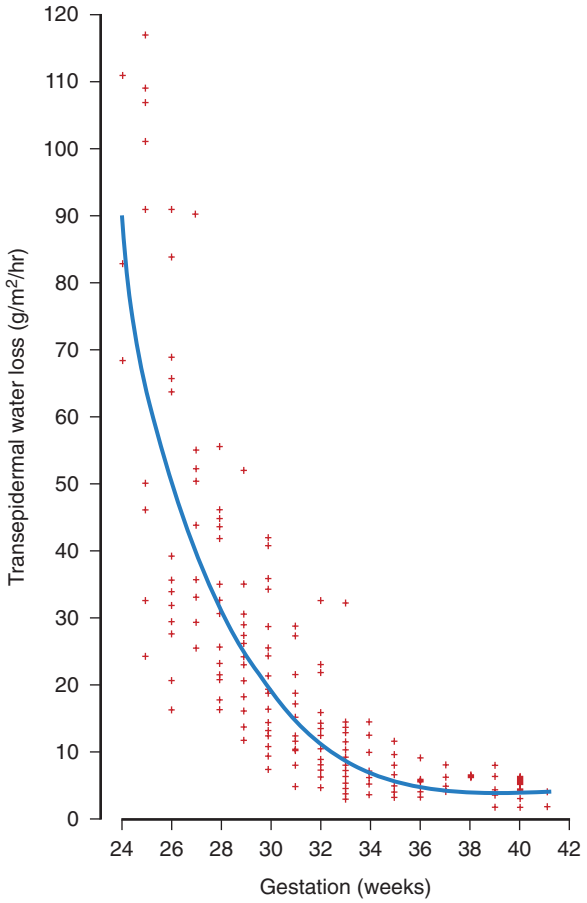
Factor	Effect on Insensible Water Loss
Level of maturity	Inversely proportional to birth weight and gestational age (see Fig. 92.3)
Environmental temperature above neutral thermal zone	Increased in proportion to increment in temperature
Elevated body temperature	Increased by up to 300% at rectal temperature >37.2°C
High ambient or inspired humidity	Reduced by 30% if ambient or respiratory vapor pressure equals skin or respiratory tract vapor pressure
Skin breakdown (e.g., burn)	Increased; magnitude depends on extent of lesion
Congenital skin defects (e.g., large omphalocele)	Increased; magnitude depends on size of defects
Radiant warmer	Increased by about 50% above values obtained in incubator setting with moderate relative humidity and neutral thermal environment
Phototherapy	Increased by up to 25%, depending on technique
Double-walled incubator or plastic heat shield	Reduced by 10%-30%

between body weight and insensible water loss in a neutral thermal environment with moderately high relative humidity.[67] Factors that contribute to these increased losses in preterm versus term infants include greater water permeability through a relatively immature epithelial layer of skin, a higher surface-area-to-body-weight ratio, and increased skin vascularity. Although prenatal glucocorticoids promote maturation of the renal tubules, they do not have a similar effect on skin maturation.[26] Infants who have conditions associated with skin breakdown, such as burns or large skin defects such as omphaloceles, also have increased transepidermal water loss. Phototherapy has been reported to increase insensible water losses by up to 26%.[35] However, with newer phototherapy techniques, this number may be substantially less.[36]

Ambient temperature and relative humidity play an important role in influencing transepidermal water loss.[8,9,21] An increase in ambient temperature results in increased insensible water loss. A decrease in ambient temperature has no effect on insensible water loss, however, despite the fact that it increases energy expenditure on the basis of cold stress. When ambient temperature is held constant, a lower ambient humidity increases skin water losses because of increased vapor pressure on the skin surface compared with the ambient vapor pressure; this is particularly true for very premature infants. A decrease in humidity from 60%-20% results in an increased water loss of 100% in infants of less than 26 weeks' gestation.[1] Use of newer humidified incubators has been reported to result in significant decreases in insensible fluid losses and fluid requirements in premature infants.[30] Alternatively, in the presence of high relative humidity, water evaporation is less. For example, infants on mechanical ventilation, which provides a humidified oxygen delivery system, have reduced water evaporation from the respiratory tract.

The quantity of water required for the formation of urine depends on two major factors: the degree of renal function and the renal solute load. Under normal conditions, a major determinant of renal water requirement is renal solute load. Renal solute load is derived from exogenous and endogenous sources. During the first 1-2 days of life, the exogenous solute load of infants with low birth weight may be low. Because these infants may not be fed enterally, caloric delivery by intravenous glucose-containing solutions

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• **Fig. 92.3** Effects of gestation on transepidermal water loss. Measurements were made from abdominal skin and carried out in the first few days of life. (From Hammarlund K, et al. Transepidermal water loss in newborn infants. III. Relation to gestational age. *Acta Paediatr Scand*. 1979;68:795.)

does not meet basal energy needs. In the first 1-2 days of life, the basal energy requirement for infants with low birth weight is approximately 50 kcal/kg body weight. Currently, many infants are started on total parenteral nutrition (TPN) on day 1-2. If they are started at 70-90 mL/kg per day of a 10% glucose solution, the caloric intake is 35 kcal/kg per day. These infants must derive the remaining mandatory energy requirement from an endogenous source (i.e., catabolism). This catabolic state produces approximately 6 mOsm/kg per day of endogenous solute load presented to the kidney. Assuming the infant can produce a maximal urinary concentration of 600 mOsm/kg, a minimum of 10 mL/kg per day of free water is required to excrete this solute load.

As the infant ages, the exogenous intake from parenteral or enteral sources increases, resulting in increased caloric intake. The result is that the exogenous solute load increases, whereas catabolism decreases, resulting in a decreased endogenous solute load. It estimated that by 2 or 3 weeks of age, an infant consuming 80-120 kcal/kg per day has a total solute load of approximately 15-20 mOsm/kg per day. Assuming that the infant can produce a maximal urinary concentration of 800 mOsm/kg by this age, 20-25 mL/kg per day of free water is required to excrete the solute load.

Other Fluid Losses

Water loss through the gastrointestinal tract from stool output is minimal during the first few days of life, particularly in infants with low birth weight. When enteral feeds begin, the water loss in the stool is 5-10 mL/kg per day. In a growing infant, the amount of water required for new tissue formation should be considered in the calculation of maintenance fluid requirements. Because infants grow at the rate of 10-20 g/kg per day, and new tissue contains 70% water, the maintenance fluid required should provide a net water balance of 10-15 mL/kg per day.

Electrolyte Requirements

Maintenance sodium and chloride should not be provided in the first 1-2 days of life because of the relatively volume-expanded state of the newborn. Avoidance of sodium supplementation is particularly important in very premature infants, who have increased water losses and for whom early administration of sodium supplementation is associated with an increased risk of hypernatremia.[57] In contrast, sodium supplementation initiated after the first few days of life in premature infants was associated with improved weight gain in the neonatal period and improved developmental outcomes at age 10-13 years compared with a group of premature infants who did not receive supplementation.[2,25]

Potassium is not provided in parenteral fluid until urinary flow has been established and normal renal function is ensured and a normal serum potassium is confirmed. From postnatal days 3-7, maintenance sodium, potassium, and chloride requirements are approximately 1-2 mEq/kg per day. Beyond the first week of life, 2-3 mEq/kg per day or more of sodium and chloride is required to maintain the positive electrolyte balance that is necessary for the formation of new tissue. Because of high urinary sodium losses, premature infants may require 4 or 5 mEq/kg of sodium per day during the first few weeks of life.

Pathogenic Losses and Deficit Replacement

Many clinical situations require careful estimates of ongoing pathogenic losses and replacement of deficits. Commonly encountered conditions include diarrhea with dehydration, chest tube drainage, surgical wound drainage, and excessive urinary losses from osmotic diuresis. The important guiding principle in managing patients with these conditions is to measure the volume and composition of the pathogenic losses accurately. Electrolyte losses can be calculated by multiplying the volume of fluid loss by the electrolyte content of the respective body fluids (Table 92.3).

Estimating replacement for pathogenic fluid and electrolyte losses can be difficult, particularly in infants who accumulate fluid and electrolytes in static body fluid compartments. This phenomenon, commonly referred to as "third spacing," occurs in several conditions, including sepsis, hydrops fetalis, hypoalbuminemia, intra-abdominal

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TABLE 92.3 Electrolyte Content of Body Fluids

Fluid Source	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)
Stomach	20-80	5-20	100-150
Small intestine	100-140	5-15	90-120
Bile	120-140	5-15	90-120
Ileostomy	45-135	3-15	20-120
Diarrheal stool	10-90	10-80	10-110

infections, and after abdominal or cardiac surgery. An infant with necrotizing enterocolitis often accumulates fluid in the mucosal and submucosal tissues of the small and large intestine and in the peritoneal cavity. Under these circumstances, large amounts of fluid, electrolytes, and protein may leak into the interstitial tissue and cannot be accurately quantitated. Because fluid lost into these tissue spaces does not contribute to effective arterial blood volume and circulatory balance in these patients, they may appear edematous even though their intravascular volume is decreased. The most appropriate strategic approach in the management of these infants is to replenish the extracellular fluid compartments with colloid and crystalloid, as able.

Fluid and Electrolyte Balance

Interpretation of key clinical feedback is a crucial part of successful fluid and electrolyte management strategies in newborns. Fluid and electrolyte balance can be achieved by using a meticulous and organized system that obtains pertinent data and applies the physiologic principles outlined in the beginning of this chapter. A careful assessment of clinical indicators of volume status, including heart rate, blood pressure, skin turgor, capillary refill, oral mucosa integrity, and fullness of the anterior fontanelle, is essential. Other pertinent data that must be monitored include body weight, fluid intake, urine and stool output, serum electrolytes, and urine osmolarity or specific gravity.

During the first few days of life, appropriate fluid and electrolyte balance is reflected by a urine output of approximately 1-3 mL/kg per hour, a urine specific gravity of approximately 1.008-1.012, and an approximate weight loss of 5% in term infants and 15% in premature infants with very low birth weight.[58] Microsampling of serum electrolytes can be done at 8- to 24-hour intervals, depending on illness severity, gestational age, and fluid-electrolyte balance. Extracellular volume depletion is manifest by excessive weight loss, dry oral mucosa, sunken anterior fontanelle, capillary refill greater than 3 seconds, diminished skin turgor, increased heart rate, low blood pressure, elevated blood urea nitrogen, or metabolic acidosis. Serum sodium, which reflects sodium concentration but not sodium content, may be normal, decreased, or increased in states of volume depletion. Bedside monitoring of weight gain, as an indicator of volume status and growth, is essential for monitoring the adequacy of fluid and caloric intake in sick neonates. Beyond the first week of life, infants should gain approximately 20-30 g per day.

Hyponatremia and Hypernatremia

Hyponatremia and/or hypernatremia are extremely common in premature infants as well as in term infants with significant medical issues (such as perinatal asphyxia or septic shock). Hyponatremia, defined as a serum sodium less than 130 mmol/L, occurs in up to 30% of very low birth weight infants in the first week of life and 25%-65% after the first week.[6] Hypernatremia, defined as a serum sodium greater than 150 mmol/L, may occur in up to 40% of preterm infants born at <29 weeks' gestation.[23] Both hyponatremia and hypernatremia have been associated with significant complications. Large changes in serum sodium (either an increase or decrease) in the first month of life in premature infants have been associated with adverse long-term neurologic outcomes.[6] Alternatively, the presence of hypernatremia itself rather than rapid changes in sodium (up to 15 mmol/liter/day) has been identified as a risk factor for intraventricular hemorrhage.[17] Whether these long- and short-term poor outcomes are caused by the serum sodium changes themselves or, instead, reflect the severity of the infant's clinical situation, has yet to be established. However, given the potential risks, it is prudent to try attempt to maintain serum sodium levels within the normal range and avoid large fluctuations.

Hyponatremia

Hyponatremia is caused by one of three general mechanisms: (1) an inability to excrete a water load, (2) excessive sodium losses, or (3) inadequate sodium intake. Most commonly, sick newborns are unable to excrete a water load because of a decreased effective arterial blood volume preventing the suppression of ADH secretion. Hyponatremia may also occur because of decreased fluid delivery to the distal nephron diluting segments. Two common etiologies of this decreased delivery are decreased GFR caused by acute kidney injury (AKI) and increased proximal tubular fluid and sodium reabsorption associated with volume depletion. Defects in sodium chloride transport in the cortical and medullary ascending limb of the loop of Henle, which is essential in producing an osmotic gradient for distal water absorption via the countercurrent multiplier, also limit the diluting capacity of the nephron. The treatment for hyponatremia varies depending on the underlying etiology. A patient with hyponatremia and volume depletion should receive increased fluids, whereas a patient with oliguric acute kidney injury should have fluids restricted. These examples highlight the importance of assessing the neonate's volume status when determining therapy.

Hyponatremia in the newborn has historically been delineated as *early onset* (occurring in the first week of life) or *late onset* (occurring in the latter half of the first month

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of life). Given the broad spectrum of gestational ages, underlying diseases, and clinical courses of neonates cared for in modern neonatal intensive care units, these distinctions may be less relevant. Assessing the individual neonate's clinical status is more important in determining the causes and appropriate interventions for hyponatremia. Increased free water load may be caused by one or more factors, including increased maternal free water intake during labor,[27] excess free water administration in the postnatal period, or perinatal nonosmotic release of vasopressin.[47] This latter phenomenon may be seen in conditions such as perinatal asphyxia, respiratory distress, bilateral pneumothoraces, and intraventricular hemorrhage[46] or with various medications, including morphine, barbiturates, or carbamazepine. Impaired free water clearance attributed to excessive vasopressin release has been reported in very low birth weight (VLBW) infants and may contribute to the development of chronic lung disease in those children.[64] Oliguric acute kidney injury or edematous disorders may also contribute to impaired ability to handle a water load. Alternatively, hyponatremia may be due to negative sodium balance. This condition may occur from either inadequate sodium intake or excessive renal losses because of a high fractional excretion of sodium, particularly in preterm infants of less than 28 weeks' gestation.[60]

Less common conditions, all of which result in pathologic urinary sodium losses, can cause hyponatremia in neonates and young infants. These conditions may be caused by inherited tubulopathies such as Bartter syndrome, or disorders of aldosterone production or responsiveness, respectively, including congenital adrenal hyperplasia (CAH) and pseudohypoaldosteronism. Aldosterone is a steroid hormone produced in the adrenal cortex that has a crucial role in maintaining sodium and potassium homeostasis in the kidney. It is produced in response to either volume depletion, via the renin-angiotensin-aldosterone axis, or an increase in serum potassium. Under the influence of aldosterone, apical epithelial sodium channels are inserted on the luminal (urinary) surface, allowing sodium to be reabsorbed down its concentration gradient. Potassium, as the primary intracellular cation, is excreted in return. This process is facilitated further by aldosterone-mediated increase in the activity of basolateral Na^+,K^+-ATPase.[51] Aldosterone also has a role in acid–base homeostasis and promotes hydrogen secretion (see Acid–Base Management) via actions on H^+-ATPase located on the luminal surface of adjacent intercalated cells. Abnormalities in either the production of, or the renal responsiveness to, aldosterone can result in variable degrees of renal sodium wasting, hyperkalemia, and metabolic acidosis.

Congenital adrenal hyperplasia (CAH) is an inherited disorder of cortisol synthesis that results in diminished aldosterone production[61] (See also Chapter 89). The most common form is complete absence of 21-hydroxylase activity, a key enzyme in the production of aldosterone. Affected girls have ambiguous genitalia at birth because of excess adrenal androgens. Patients typically present with shock and severe hyponatremia, hyperkalemia, and metabolic acidosis at 1-3 weeks of age as the result of a salt-losing crisis. Additional laboratory abnormalities typically seen with this disorder include elevated plasma levels of renin, adrenocorticotropic hormone, 17-hydroxyprogesterone, progesterone, androstenedione, and urinary 17-ketosteroids. Serum cortisol and aldosterone levels may be undetectable. Initial treatment is directed at correcting volume and electrolyte abnormalities, including fluid resuscitation and management of life-threatening hyperkalemia. Long-term glucocorticoid and mineralocorticoid replacement therapy should be instituted to facilitate normalization of serum electrolytes and to treat the underlying disease. Sodium supplements may be necessary for a prolonged period.

Pseudohypoaldosteronism (PHA) refers to a group of disorders characterized by renal tubular unresponsiveness to aldosterone as evidenced by hyperkalemia, metabolic acidosis, and variable degrees of renal sodium wasting. PHA can be primary (genetic) or secondary (acquired). The two subtypes of primary PHA include type I, which usually manifests in infancy with hypotension, severe sodium wasting, and hyperkalemia, and type II (Gordon syndrome), which typically presents later in childhood. Autosomal dominant type I PHA, previously designated the "renal" type I, is the most common type I PHA. Patients with this form usually present during early infancy with failure to thrive, weight loss, vomiting, dehydration, or shock. Sweat and salivary electrolytes are normal in this form of type I PHA. Although it is inherited in an autosomal dominant trait, expression may be variable. Treatment involves administration of large quantities of sodium chloride, 10 to 15 mEq/kg per day. Autosomal recessive type I PHA, previously designated "multiple target organ defects" type I PHA, is a severe, life-threatening systemic disease that affects sodium and potassium handling in the kidney, sweat glands, salivary glands, nasal mucosa, and colon.[22] Patients with this disorder usually present in the newborn period with severe salt wasting and life-threatening hyperkalemia. They also have increased sweat chloride that may mimic the presentation of cystic fibrosis. Sodium chloride supplementation alone often is inadequate in controlling hyperkalemia and metabolic acidosis in these patients. Dietary restriction of potassium intake and the use of rectal sodium polystyrene sulfonate resin (kayexalate), a sodium-potassium exchange resin, are often required. Indomethacin or hydrochlorothiazide may be necessary to control hyperkalemia and acidosis. Mutations in multiple different genes have been implicated in the pathogenesis of PHA type 1, including those encoding components or regulators of the mineralocorticoid receptor, epithelial sodium channels, and thiazide-sensitive sodium chloride co-transporter.[53] Secondary forms of PHA occur more commonly than primary forms and are typically caused by injury to the collecting tubules, the primary segment responsible for potassium balance. Causes of secondary PHA in the newborn period include unilateral renal vein thrombosis, neonatal medullary necrosis, urinary

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tract malformations, pyelonephritis, or other tubulointerstitial diseases. Patients with congenital obstructive uropathies such as posterior urethral valves are particularly prone to exhibiting aldosterone resistance, manifest as a hyperkalemic metabolic acidosis, even in the face of relatively intact renal function.

Hypernatremia

Hypernatremia occurs as the result of increased insensible or urinary water losses, inadequate water intake, or excess sodium administration. Hypernatremia occurring in the first week of life is typically caused by increased insensible water losses, often coupled with the excess sodium intake that may occur after resuscitation with sodium bicarbonate. Many other medications can contribute to large "inadvertent" sodium loads, particularly in sick premature infants, including calcium gluconate, gentamicin, dopamine, dobutamine, heparin, and intravenous fluids used to maintain arterial or venous vascular lines.[12] Onset of hypernatremia later in the first month of life usually is attributable to either excess sodium supplementation or inadequate free water intake.

Excess urinary losses can occur as the result of diabetes insipidus (DI), which is characterized by severe urinary water losses reflecting an inability to produce concentrated urine. Diabetes insipidus results from either low levels of circulating ADH (central DI) or impaired renal response to ADH (nephrogenic DI). Newborns with this disorder present with hypernatremia, polyuria, polydipsia, chronic dehydration, irritability, fever, poor feeding, and growth failure.

Nephrogenic DI can be inherited (congenital) or occur as the secondary result of processes that cause renal tubular damage. The most common inherited form of nephrogenic DI is caused by mutations in the gene encoding the vasopressin receptor V2R and is inherited as an X-linked recessive disease.[65] Causes of secondary nephrogenic DI include congenital structural disorders such as obstructive uropathy or nephronophthisis, chronic kidney disease, hypercalcemia, and hypokalemia. Treatment of nephrogenic DI includes placement on a low sodium formula to reduce solute intake and resultant obligate water loss associated with solute excretion. Thiazide diuretics are also used to reduce extracellular sodium content, which enhances sodium reabsorption in the proximal tubule and diminishes sodium and water delivery to the distal nephron. Amiloride may also be necessary to reduce urinary potassium losses that may occur with the use of thiazide diuretics. Although prostaglandin inhibitors have been successfully used to treat nephrogenic DI, long-term use of these agents is not recommended because of gastrointestinal, hematopoietic, and renal complications.

Central DI may be caused by midline central nervous system malformations, anoxic encephalopathy, cerebral edema, or trauma.[16] Although some ADH secretion may be present in central DI, levels are insufficient to promote appropriate water absorption in the distal nephron. Desmopressin acetate (DDAVP) is generally an effective therapy for this condition, and DDAVP responsiveness can help distinguish central versus nephrogenic causes when the underlying etiology is unclear.

Fluid and Electrolyte Therapy in Common Neonatal Conditions

Perinatal Asphyxia

Renal parenchymal injury from perinatal asphyxia frequently results in acute tubular necrosis, which is commonly accompanied by oliguria or anuria. In the presence of acute kidney injury, fluid restriction to amounts equal to urine output plus insensible losses is crucial to avoid volume excess. In a term infant, insensible water losses are approximately 20-25 mL/kg per day, and stool loss is minimal. Fluid requirements during the first day of life in an anuric term infant are approximately 30 mL/kg per day. Insensible losses for an anuric premature infant may be as high as 80 mL/kg per day, depending on gestational age. Fluid restriction is often difficult to accomplish when relatively large volumes of intravenous medications are necessary or when the absence of central venous access limits the concentration of dextrose-containing fluid that can be delivered. High caloric density parenteral nutrition, delivered in as small a volume as possible, is often necessary when fluid restriction is undertaken to avoid fluid overload and water intoxication. When urine production normalizes, fluid intake can be liberalized to reflect urine output and insensible losses.

If the cause of oliguria or anuria is unclear, and the infant is believed to be intravascularly depleted, a test dose of 10 mL/kg body weight of normal saline can be given. During the oliguric or anuric phase of acute tubular necrosis, potassium should not be given to avoid hyperkalemia. During the recovery phase of acute tubular necrosis, small infants may experience large urinary sodium and potassium losses, which should be quantitated and replaced.

In severe perinatal asphyxia, the renal parenchymal injury may be severe enough to produce acute kidney injury (AKI) lasting for several days to weeks, or may be permanent in cases with cortical necrosis. In the presence of hyperkalemia, defined as serum potassium greater than 7 mEq/L, the cardiac rhythm of the infant should be monitored by continuous electrocardiogram to detect any cardiac arrhythmia. Treatment options for hyperkalemia include insulin given with glucose; sodium polystyrene sulfonate resin (kayexalate); sodium bicarbonate, if metabolic acidosis is present; and peritoneal dialysis. If a significant arrhythmia is present, calcium chloride or calcium gluconate infusion is also indicated to antagonize the toxic effects of hyperkalemia on the cardiac membrane.

In addition to acute kidney injury, other factors may influence fluid management in patients with severe perinatal asphyxia. Fluid restriction has been advocated by some for infants with perinatal asphyxia even in the absence of acute kidney injury. However, no systematic randomized

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studies have determined whether this practice alters the long-term outcome for these patients. Over the last decade, use of hypothermia as a treatment for preventing mortality and neurologic sequelae of severe perinatal asphyxia has become common practice, although optimal duration and degree of hypothermia remains a subject of research.[37,59] To date, guidelines for fluid administration during hypothermia protocols have not been well delineated. However, hyponatremia has been reported as a complication of therapeutic hypothermia and has been associated with positive fluid balance, possibly related to decreased insensible losses from skin vasoconstriction.[45]

Hyperbilirubinemia

Severe hyperbilirubinemia (bilirubin >20 mg/dL after 72 hours of life) is not uncommon, occurring in approximately 1% of term neonates. Phototherapy is the mainstay of therapy[36]; however, several studies have also highlighted the importance of fluid therapy as an adjunct to phototherapy. A significant proportion of neonates with severe hyperbilirubinemia exhibit dehydration on admission.[39] In addition, intravenous fluids have been shown to accelerate the rate of decline in serum bilirubin and decrease the need for exchange transfusion in severely affected infants.[5] A recent meta-analysis, however, was unable to find evidence that intravenous fluids improve long-term neurologic outcome in otherwise healthy term infants.[31] It is still possible that intravenous fluids may prove to be beneficial to certain high-risk populations, including infants with dehydration or preterm infants, as these groups have been less well studied in this regard.

Symptomatic Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) with left-to-right shunt and pulmonary edema is a common cause of morbidity in preterm infants, particularly infants with respiratory distress syndrome in the first few days of life. Fluid overload during this period has been associated with an increased incidence of symptomatic PDA,[10] possibly caused by the lack of isotonic contraction of body fluids in this group of infants. Fluid restriction, however, may not convey beneficial effects on pulmonary or systemic hemodynamics,[18] and could convey risks of increasing the risk of acute kidney injury, especially in infants receiving medical therapy for the PDA with indocin or ibuprofen.

Bronchopulmonary Dysplasia

Infants with bronchopulmonary dysplasia (BPD) present complex challenges in fluid and electrolyte management. Because of higher basal metabolic rates and increased caloric requirements, the caloric density or volume, or both, of parenteral or enteral feedings needs to be maximized. Care must be taken to provide optimal fluid and nutrient intake without incurring volume overload and worsening pulmonary disease. In addition, therapies used to treat the underlying lung disease—most notably, diuretics—may have significant effects on fluid and electrolyte balance.[28]

Furosemide, a potent loop diuretic, causes a marked increase in urinary sodium, potassium, and hydrogen ion excretion, leading to hypokalemic metabolic alkalosis. Long-term use of this diuretic may also result in enhanced urinary excretion of calcium leading to osteopenia of prematurity, urolithiasis, or nephrocalcinosis. Furosemide should be used with caution in neonates, particularly premature infants with acute kidney injury and infants receiving concomitant aminoglycoside therapy, to avoid complications of ototoxicity. Chlorothiazide, a less potent thiazide diuretic that acts at the distal tubule, also causes a hypokalemic metabolic alkalosis. In contrast to loop diuretics, thiazides decrease urinary calcium excretion. Treatment with spironolactone, a potassium-sparing aldosterone inhibitor, may be associated with hyperkalemia. Strategies used to avoid complications of diuretic use include minimizing diuretic dosages, obtaining serum electrolyte measurements to detect electrolyte imbalance, monitoring urinary calcium excretion (when applicable), and supplementing calcium to prevent osteopenia of prematurity. Sodium supplementation should be avoided because it may further contribute to hypervolemia and/or hypertension if present.

Acid–Base Management

In this section, normal acid–base homeostasis in neonates is reviewed, and how these processes are influenced during the stages of nephron development is discussed. The diagnostic and therapeutic approach to acid–base disorders is presented, and common acid-base disorders are discussed.

Acid-Base Homeostasis in Neonates

Normal neonatal metabolism occurs within a tightly controlled extracellular pH ranging from 7.35-7.43. Normal growth and development critically depend on this homeostasis, which is threatened in ill term newborns or premature infants. The maintenance of serum pH (i.e., hydrogen ion concentration) within the physiologic range requires two major processes: (1) acute compensation, which is accomplished by rapid acid or base buffering by intracellular and extracellular buffers in response to acute decreases or increases in serum pH, and (2) long-term compensation, which is accomplished by renal excretion of acid or base, including an obligate daily acid load of approximately 1-2 mEq/kg per day. Renal and extrarenal homeostatic mechanisms contribute to the maintenance of acid-base balance.

Acute Compensation: Body Buffer Systems

After an acute change in serum pH caused by losses or gains of acid or base to the body, intracellular and extracellular buffering mechanisms respond rapidly to return the serum pH to a physiologic level. In response to a decrease in pH, H^+ enters the cell in exchange for K^+ by way of an H^+/K^+ exchanger. H^+ is buffered by intracellular buffers, including

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hemoglobin, organic phosphates, and bone hydroxyapatite. Conversely, when serum pH increases, H^+ leaves the cell in exchange for K^+. Acute acidosis often results in hyperkalemia, whereas alkalosis is associated with hypokalemia. Intracellular buffering accounts for about 47% of an acute acid load and can reach even higher levels during more prolonged episodes of acidosis. Much of this buffering capacity is in bone. In disorders characterized by chronic acidosis, increased bone resorption and loss of bone sodium, potassium, calcium, and carbonate occur. These effects on bone partially explain the invariable association of growth failure, a potentially significant issue for premature infants, with acidosis.

The major buffering mechanism in the extracellular fluid is mediated by the carbonic anhydrase system, as reflected in the following formula:

$$H^+ + HCO_3^- \overset{CA}{\leftrightarrow} H_2CO_3 \overset{CA}{\leftrightarrow} H_2O + CO_2$$

Regulation of carbon dioxide (CO_2) excretion by the respiratory system markedly improves the efficiency of this buffering system at physiologic pH. In the presence of carbonic anhydrase (CA), carbonic acid (H_2CO_3) is in equilibrium with CO_2. Addition or increased production of acid results in consumption of bicarbonate (HCO_3^-) and increased H_2CO_3 and CO_2. CO_2 then crosses the blood–brain barrier, resulting in a decrease in pH. This action stimulates central nervous system chemoreceptors, leading to increased respiration and resultant decreased CO_2 concentration within 12-24 hours. Similar respiratory compensation occurs in response to an alkali load, which leads to increased HCO_3^- concentration, resulting in hypoventilation and accumulation of CO_2.

Two formulas are particularly useful in understanding and evaluating acid–base disorders. The *Henderson-Hasselbach equation* expresses the relationship of pH, P_{CO_2}, and HCO_3^-:

$$pH = 6.1 + \log[HCO_3^- / (0.03 - P_{CO_2})]$$

where 6.1 is the pK_a of this equation.

The *Winters formula*[3] can be used to predict the appropriate respiratory response (i.e., decrease in P_{CO_2}) to a primary metabolic acidosis:

$$P_{CO_2} = (1.5 \times HCO_3^-) + 8 \pm 2$$

Respiratory compensation in response to either metabolic acidosis or metabolic alkalosis does not completely normalize the pH. The Winters formula predicts that a decrease in HCO_3^- to 10 mmol/L would result in a decrease in P_{CO_2} to 21-25 mm Hg. By the Henderson-Hasselbach equation, the resulting serum pH is 7.22-7.29. This is markedly better than the serum pH of 7.02 that would be seen if no respiratory compensation occurred but is still not within the normal range. With "simple" metabolic acidosis or alkalosis, the respiratory compensation does not fully correct the serum pH. If serum pH is found to be in the normal range (or higher or lower than predicted), a mixed acid–base disorder, with an added primary respiratory abnormality, should be considered.

Long-Term Maintenance of Acid–Base Balance

Long-term maintenance of a normal serum pH depends on the balance between the production or intake of acid and base and their metabolism or excretion. Dietary intake accounts for a small amount of preformed acid, but most of the daily acid load is a product of obligatory metabolic functions. A large proportion consists of CO_2, which is carried to the lung as bicarbonate and carbamino groups bound to hemoglobin and ultimately excreted through respiration. This is termed *volatile* acid. Hypoventilation or hyperventilation leads to either retention or enhanced excretion of CO_2 and results in acidosis or alkalosis. Metabolic activity also produces an obligate nonvolatile acid "load" of approximately 1-2 mEq/kg per day. Most of this acid load is sulfuric acid, which results from metabolism of the sulfur-containing amino acids, methionine and cysteine. The remainder consists primarily of incompletely oxidized organic acids, phosphoric acid and hydrochloric acid. Successful maintenance of acid–base balance depends on renal excretion of this daily acid load.

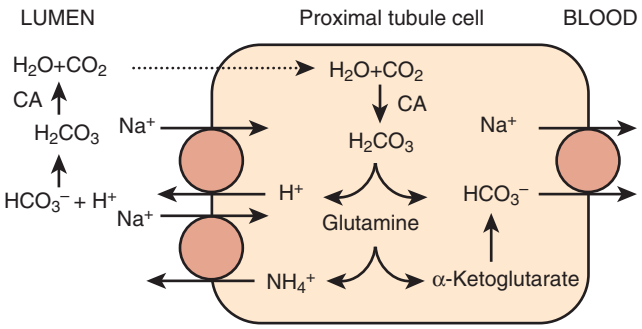
The kidney plays an essential role in maintaining acid–base homeostasis by three major mechanisms:

1. Reabsorption of filtered bicarbonate and excretion of excessive bicarbonate in response to metabolic alkalosis
2. Excretion of the obligate daily acid load and any additional acid load from pathogenic processes, such as lactic acidosis related to sepsis or bicarbonate loss from diarrhea
3. Compensation for changes in serum pH that result from primary respiratory disorders

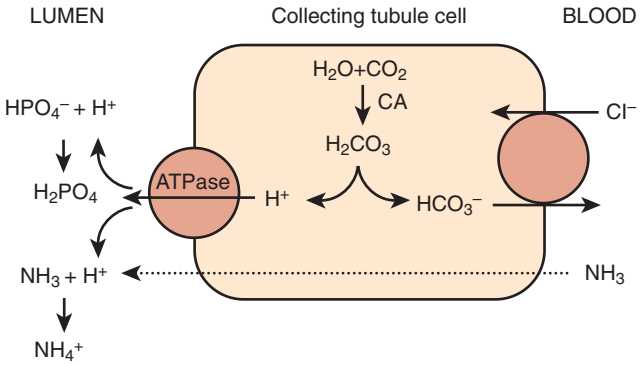
Bicarbonate reabsorption occurs primarily in the proximal tubule, wherein 60%-80% of the filtered bicarbonate load is reabsorbed. Bicarbonate is not reabsorbed via a specific transporter. Instead it is reabsorbed via an indirect mechanism. Bicarbonate present in the lumen is first buffered by H^+ that is secreted in exchange for sodium via a Na^+/H^+ exchanger located on the luminal membrane of proximal tubular cells (Fig. 92.4). Through the actions of carbonic anhydrase, CO_2 and H_2O are produced. CO_2 and H_2O diffuse into the cell, wherein HCO_3^- is regenerated and reabsorbed across the basal cell membrane in exchange for chloride. H^+ is also regenerated, making it available again for buffering of additional filtered bicarbonate. The net effect is that for every H^+ secreted, one molecule of filtered bicarbonate is reabsorbed.

Although proximal tubule bicarbonate reabsorption is essential in preventing bicarbonate wasting, no net H^+ excretion occurs in this process. Instead, excretion of the daily acid load is accomplished by two mechanisms: ammoniagenesis and production of titratable acids. Ammoniagenesis occurs in the proximal tubule (see Fig. 92.4) via the metabolic processing of glutamine produced in the liver. In the proximal tubule cell, glutamine is converted to ammonium (NH_4^+), which is secreted into the lumen in

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• **Fig. 92.4** Schematic drawing of proximal tubular HCO_3^- reabsorption and ammoniagenesis. See text for explanation. CA, Carbonic anhydrase.



• **Fig. 92.5** Schematic drawing of distal urinary acidification mechanisms. CA, Carbonic anhydrase.

exchange for Na^+. Deamination of glutamine also produces a-ketoglutarate, which buffers H^+. Through the actions of the intracellular carbonic anhydrase system, this process eventually results in the production of intracellular HCO_3^-, which can be reabsorbed across the basal membrane of the cell with Na^+. NH_4^+ secretion is the metabolic equivalent to H^+ excretion.

The remainder of acid secretion occurs in the cortical and medullary collecting tubule. H^+ is secreted into the collecting tubule against its pH gradient by H^+-ATPases located on the luminal membrane. This process is influenced by the luminal and peritubular pH, distal sodium delivery, and aldosterone. Secreted H^+ titrates filtered anions, including phosphates and sulfates, producing titratable acids (Fig. 92.5). The collecting tubule also secretes ammonia from the medullary interstitium, where it is buffered by H^+ to produce NH_4^+. Titratable acid formation and ammonia buffering require an acidic environment for protonation to occur. In addition to providing a source of H^+ for buffering, distal H^+ secretion is important in maintaining acidic urine (pH of 4.5-5.0).

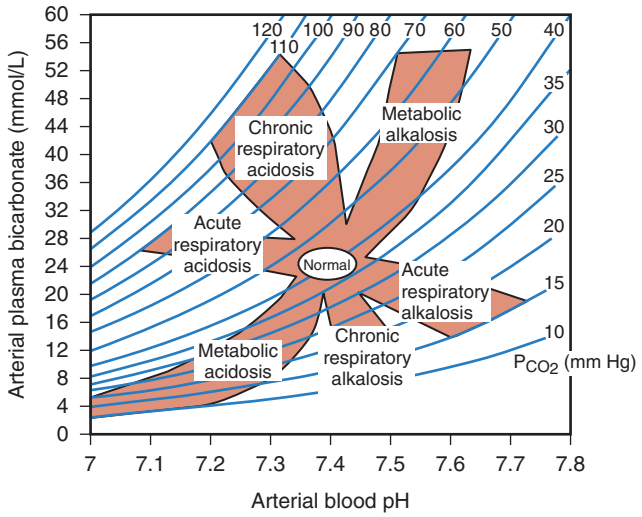
The net acid excretion by the kidney is equal to the sum of titratable acids plus ammonium minus any filtered bicarbonate that is not reabsorbed. During steady-state, total acid secretion equals the production of acid from diet and metabolism. In response to an acid load, ammoniagenesis can increase dramatically because of enhanced production of glutamine by the liver. Ammoniagenesis is stimulated by hypokalemia and inhibited by hyperkalemia. In contrast, titratable acids are relatively fixed in their production except in instances of diabetic ketoacidosis, in which the ketone bodies themselves can form titratable acids. Alternatively, the kidney has the capacity to alter HCO_3^- reabsorption in response to changes in the filtered load of bicarbonate, further minimizing changes in pH.

Developmental Aspects of Acid–Base Physiology

Although nephron formation is complete by 34 to 36 weeks of gestation, maturation and functional changes of the nephron continue during the first year of life. The relative immaturity of the kidney, which is more pronounced in preterm infants, affects basal acid–base status and the response to additional acid and alkali loads.[33] During the initial 24-48 hours of life, acid–base balance is influenced by the degree of perinatal stress and environmental factors such as temperature and diet.[62] In the first 2 weeks of life, neonates are in a state of mild metabolic acidosis. In some infants, blood pH may decrease to less than 7.25, or base deficit may exceed 8 mEq/L. In ELBW infants, that deficit is even higher, averaging closer to 10.6 meq/L.[13]

The causes of this metabolic acidosis in neonates are multifactorial. The threshold for bicarbonate reabsorption in the proximal tubule is lower in neonates, especially premature infants, compared with adults, so that neonates tend to "waste" bicarbonate at a lower blood HCO_3^- concentration (15-21 mEq/L). Thus, the normal bicarbonate level in a healthy neonate is lower than that of older children or adults. Low GFRs, particularly in premature or stressed neonates, decrease the availability of phosphates and other buffers, decreasing the formation and excretion of titratable acids. Tubular immaturity results in reduced tubular secretory surface for organic acid secretion, diminished number of organic acid transport sites per unit area of renal tubular surface, and diminished energy available for organic acid transport. Premature infants are also unable to acidify their urine maximally at birth, exhibiting a minimal urine pH of 6, in contrast to full-term neonates and adults whose urine pH may reach 4.5. The ability of premature infants to acidify their urine maximally and to excrete an acid load correlates with gestational age. By 6 weeks of age, the capacity of premature and term infants to excrete hydrogen ions matures to permit maximal acidification. Premature infants, particularly extremely low birth weight infants, demonstrate impaired ammoniagenesis.[54] As noted previously, this is an important compensatory mechanism for excreting an acute acid load. The impairment in both bicarbonate conservation and net acid excretion related to tubular immaturity significantly limits the ability of premature infants to respond to additional stresses associated with acute acid loading such as sepsis-induced lactic acidosis.

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• **Fig. 92.6** Acid–base map showing 95% confidence limits for compensatory responses. (From Cogan MG, et al. In: Brenner BM, et al., eds. *The Kidney*. Philadelphia: Saunders; 1986:462.)

TABLE 92.4 Expected Compensation in Acid–Base Disorders

	Primary Abnormality	Compensation
Respiratory	**ΔP_{CO_2}**	**ΔHCO_3^-**
Acute acidosis	↑ 1 mm Hg	↑ 0.1 mEq/L
Acute alkalosis	↓ 1 mm Hg	↓ 0.25 mEq/L
Chronic acidosis	↑ 1 mm Hg	↑ 0.5 mEq/L
Chronic alkalosis	↓ 1 mm Hg	↓ 0.5 mEq/L
Metabolic	**ΔHCO_3^-**	**ΔP_{CO_2}**
Acidosis	↓ 1 mEq/L	↓ 1.25 mm Hg
Alkalosis	↑ 1 mEq/L	↑ 0.2-0.9 mm Hg

Diagnostic Approach to Disorders of Acid–Base Balance

In generating a differential diagnosis of an acid–base abnormality, it is helpful to ask the following three questions:

1. What is the primary abnormality?
2. What is the secondary compensation?
3. Is the compensation appropriate?

The acid–base abnormality alone does not indicate if it is the primary disorder or a response to the primary disorder. A low serum bicarbonate level indicating metabolic acidosis could be caused by a primary metabolic acidosis or could represent a metabolic compensation for a primary respiratory alkalosis. Conversely, elevated serum bicarbonate could be a reflection of a primary metabolic alkalosis or a response to a primary respiratory acidosis. To distinguish the primary process from the secondary compensation, it is necessary to know the plasma pH, serum bicarbonate level, and CO_2 level. In addition to simple respiratory or metabolic acid–base disorders, "mixed" (combined) disorders may be seen, in which more than one primary process is present. Mixed disorders should be considered when the expected compensation falls out of the expected range.

The nomogram presented in Fig. 92.6 can aid in the diagnosis of simple and mixed acid–base disorders. It shows the 95% confidence limits of the expected compensatory response to a primary metabolic or respiratory acidosis or alkalosis. If the compensatory change in either P_{CO_2} or HCO_3^- falls beyond these limits (i.e., outside of the shaded region for each disorder), a combined disorder is present. Consider a newborn with pH of 7.17, P_{CO_2} of 34 mm Hg, and HCO_3^- of 12 mEq/L. The acidic pH and low serum HCO_3^- suggest a primary metabolic acidosis. When the values for pH, HCO_3^-, and P_{CO_2} are plotted on the nomogram, however, the convergence point falls out of the range for a simple metabolic acidosis, suggesting the possibility of a superimposed respiratory acidosis. To delineate this further, one can estimate the expected compensation (i.e., a respiratory alkalosis) based on the values presented in Table 92.4 or, alternatively, the Winters formula. With a decrease in serum HCO_3^- from 22 mEq/L to 12 mEq/L, P_{CO_2} should decrease by 12.5 mm Hg. The estimated compensation would result in a P_{CO_2} of 27 mm Hg. Similarly, the Winters formula predicts a compensatory P_{CO_2} of 24-28 mm Hg. The higher-than-expected P_{CO_2} confirms the presence of a superimposed primary respiratory acidosis.

Basic Principles of Therapy

Metabolic Acidosis

Metabolic acidosis is a common problem in critically ill neonates that results from either excess acid production or increased loss of base. Box 92.1 lists common causes of metabolic acidosis in neonates. Calculation of the anion gap allows differentiation into two groups. Increased anion gap metabolic acidosis is caused by the addition of exogenous acids (e.g., salicylates) or increased production of endogenous acids (e.g., lactic acid). In neonates, an increased anion gap is usually caused by increased production of endogenous acids, such as lactic acidosis in patients with sepsis or toxic metabolites in patients with inborn errors of metabolism. Increased anion gap metabolic acidosis is associated with a normal serum chloride.

In contrast, a normal anion gap metabolic acidosis is attributable to either bicarbonate loss in the urine (proximal renal tubular acidosis [RTA]) or the stool, or the inability to excrete acid because of a defect in distal nephron function (distal RTA). In this disorder, the serum chloride is elevated. Correction of the underlying cause is the most important therapeutic measure in the management of metabolic acidosis. The dose of alkali required to treat metabolic acidosis in newborns ranges from 1 mEq/kg per day for mild base deficits to 5-8 mEq/kg per day for more severe base deficits, such as seen in proximal RTA. Dialysis may be required

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• BOX 92.1 Common Causes of Metabolic Acidosis in Neonates

Increased Anion Gap

Lactic Acidosis

- Hypoxemia, shock, sepsis
- Inborn errors of carbohydrate or pyruvate metabolism
- Pyruvate dehydrogenase deficiency
- Pyruvate carboxylase deficiency
- Mitochondrial respiratory chain defects
- Chronic kidney disease

Ketoacidosis

- Glycogen storage disease (type I)
- Inborn errors of amino acid or organic acid metabolism

Normal Anion Gap

- Bicarbonate loss: acute diarrhea; drainage from small bowel, biliary, or pancreatic tube; fistula drainage; bowel augmentation cystoplasty; ureteral diversion with bowel
- Renal tubular acidosis
- Mineralocorticoid deficiency
- Administration of Cl-containing compounds: arginine HCl, HCl, $CaCl_2$, $MgCl_2$, NH_4Cl parenteral alimentation, high-protein formula
- Carbonic anhydrase inhibitors
- Dilution of extracellular fluid compartment

Adapted from Brewer E. Disorders of acid-base balance. *Pediatr Clin North Am*. 1990;37:429.

when acid production is severe, such as in lactic acidosis, acute kidney injury, or severe inborn errors of metabolism.

Administration of alkali, such as bicarbonate, has several potential adverse effects, including volume overload, hypernatremia, decreased oxygen delivery to the brain secondary to shifts in the hemoglobin dissociation curve, increased P_{CO_2}, and a paradoxical intracellular acidosis as CO_2 diffuses into cells.[48] Bicarbonate administration should be used with caution in most neonates.[4] The notable exception is cases of suspected RTA (primary or secondary to chronic kidney disease), in which bicarbonate supplementation has an important role in growth and maintenance of bone health and lean muscle mass.[19]

Metabolic Alkalosis

Metabolic alkalosis is generated by one of three general mechanisms: (1) loss of acid, such as hydrochloric acid loss with vomiting; (2) ingestion of base, such as sodium bicarbonate administration during resuscitation; or (3) contraction of the extracellular volume, with loss of fluid containing more chloride than bicarbonate. Box 92.2 lists common causes of metabolic alkalosis in neonates.[10]

Although the kidney is usually very effective in excreting excess alkali, several conditions maintain metabolic alkalosis when it is generated. Extracellular volume depletion limits bicarbonate excretion by several mechanisms. The decrease in GFR reduces the filtered load of bicarbonate, and the bicarbonate that is filtered is rapidly reabsorbed in

• BOX 92.2 Common Causes of Metabolic Alkalosis in Neonates

- Acid loss: vomiting (e.g., pyloric stenosis), nasogastric suction
- Diuretics
- Chloride deficiency: chronic chloride-losing diarrhea, Bartter syndrome, low-chloride formula, loss via skin secondary to cystic fibrosis
- Administration of alkali: bicarbonate, lactate, acetate, citrate

the proximal tubule as a result of avid sodium reabsorption. Volume depletion also stimulates renin-angiotensin system-mediated release of aldosterone, which leads to an increase in distal renal tubular absorption of sodium and excretion of H^+ and potassium. Other states of hyperaldosteronism, such as excess production of endogenous mineralocorticoids or administration of exogenous steroids, lead to enhanced distal renal tubular excretion of H^+ and potassium. Potassium depletion also maintains metabolic alkalosis by stimulating renal ammoniagenesis and inhibiting movement of H^+ out of the cell. Chloride depletion or respiratory acidosis, as evidenced by an elevated P_{CO_2}, can also maintain metabolic alkalosis.

Therapy for metabolic alkalosis consists of correction of the underlying disorder. Alkalosis resulting from volume depletion typically improves with saline administration and potassium repletion. Use of agents such as ammonium hydrochloride may be associated with life-threatening complications such as severe acidosis or a paradoxical intracellular alkalosis and is not supported by the literature. Acetazolamide has been used safely in patients with chronic contraction alkalosis associated with congenital heart disease.[41] However, no randomized studies have addressed the use of this agent in neonates or infants with chronic lung disease or other disorders requiring long-term diuretic therapy. As an alternative, aggressive repletion of potassium and chloride alone may facilitate correction of the hypokalemic metabolic alkalosis. Both oral and intravenous potassium supplementation may be required to correct significant total body potassium deficits. Although the long-term complications of chronic metabolic alkalosis are unknown, prolonged pH greater than 7.6 may increase the risk for sensorineural hearing loss.[32]

Respiratory Acidosis and Alkalosis

Respiratory acidosis results from any disorder with decreased alveolar ventilation, resulting in retention of CO_2. In neonates, this condition is usually caused by respiratory distress syndrome, meconium aspiration syndrome, pulmonary infections, or congenital diaphragmatic hernia. Correction of the underlying cause of respiratory acidosis is essential and frequently requires the use of assisted ventilation to increase excretion of volatile acid (CO_2). Administration of alkali to correct acidemia caused by a primary respiratory acidosis is generally inappropriate. The resultant increase

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in serum bicarbonate levels (and serum pH) promotes hypoventilation and a further increase in P_{CO_2}, exacerbating the respiratory acidosis. In instances in which a mixed acid–base disorder is present (i.e., a primary respiratory acidosis and a primary metabolic acidosis), bicarbonate administration should be used with caution, and assisted ventilation is typically required.

Respiratory alkalosis is rare in neonates; however, it may occur during excessive assisted ventilation or during central hyperventilation secondary to serious central nervous system disease. Patients with respiratory alkalosis who are dependent on ventilators are treated easily by adjusting the assisted ventilation settings. A search for underlying causes of central hyperventilation is necessary in other patients.

Specific Acid–Base Disorders That May Manifest in the Neonatal Period

Renal Tubular Acidosis

Renal tubular acidosis is a disorder characterized by a normal anion gap metabolic acidosis and is the sequela of either impaired reabsorption of bicarbonate or impaired urinary acidification/H^+ ion excretion. It may be the result of an inherited defect in the renal handling of H^+ ion or bicarbonate.[50]

More commonly, it is secondary to tubular damage from various causes, such as medications or obstructive uropathy. There are three main forms of RTA: type I (distal), type II (proximal), and type IV (hyperkalemic) (Box 92.3). Each form of RTA has a distinct pathophysiology and characteristic serum and urinary laboratory findings.

Type I (distal) RTA results from diminished distal H^+ secretion. Patients with distal RTA often present in the newborn period or during early infancy with lethargy, polyuria, vomiting, dehydration, and failure to thrive. Distal RTA is usually accompanied by hypokalemia, because potassium is secreted in lieu of H^+ to maintain electronegativity. Concomitant hypercalciuria and hypocitraturia predispose patients to the development of nephrocalcinosis and nephrolithiasis.

Distal RTA can occur as a sporadic form, although several well-characterized inherited forms have been described. In each instance, the genetic defect results in impairment of a specific component of the distal acidification mechanisms (see Fig. 92.5). Autosomal recessive and autosomal dominant forms have been described.[50] Acquired forms of type I RTA also can occur as the result of tubular injury. Certain medications cause damage to the distal nephron and result in backleak of H^+ from the lumen. Amphotericin toxicity is a classic example of this "gradient defect" form of acquired distal RTA. In addition, congenital lesions, most notably obstructive uropathies, may cause secondary RTA because of tubular damage from obstruction or infections.

The diagnosis of suspected distal RTA should be considered in any infant with a urinary pH that is greater than 6.5 in the presence of a nonanion gap metabolic acidosis.

• BOX 92.3 Classification of Renal Tubular Acidosis

Type I (Distal)

- Primary (autosomal dominant or recessive; sporadic)
- Secondary, associated with other renal disorders
  - Obstructive uropathy
  - Hypercalciuria/nephrocalcinosis
- Secondary, associated with acquired or other hereditary diseases
  - Osteopetrosis
  - Sickle cell anemia
  - Hereditary elliptocytosis
  - Marfan syndrome
  - Primary biliary cirrhosis
- Secondary, associated with drugs or toxins (e.g., amphotericin B)

Type II (Proximal)

- Primary (familial or sporadic)
  - Fanconi syndrome
- Primary
  - Cystinosis
  - Tyrosinemia
  - Oculocerebral renal syndrome (Lowe syndrome)
  - Hereditary fructose intolerance
  - Wilson disease

Type IV (Hyperkalemic)

- Pseudohypoaldosteronism
- Renal immaturity
- Obstructive uropathy
- Potassium-sparing diuretics
- Chloride shunt
- Hyporenin hypoaldosteronism
- Medications (e.g., cyclosporine)

Adapted from Brewer E. Disorders of acid-base balance. *Pediatr Clin North Am*. 1990;37:429.

Conversely, a urine pH of 5.5 or less indicates that distal acidification mechanisms are intact and effectively rules out distal RTA. The urine anion gap ($= Na^+ + K^+ - Cl^-$) indirectly assesses the amount of urine ammonium and can be helpful in distinguishing distal and proximal RTA. A positive value suggests a defect in urine ammonium excretion and deficient urinary acidification consistent with a distal RTA.[29]

Although primary distal RTA is a permanent defect, the prognosis for growth and the prevention of renal insufficiency is satisfactory when the condition is correctly treated. Therapy for distal RTA in infancy consists of the administration of alkali, usually in the form of an alkali-containing liquid such as Bicitra. The typical dose is 2-3 mEq/kg per day. Maintenance of normal blood pH and serum bicarbonate maximizes the opportunity for normal growth.

Type II (proximal) RTA is caused by a decrease in the threshold tubular maximum for HCO_3^- reabsorption in the proximal tubule, resulting in HCO_3^- wastage. The tubular maximum is decreased to approximately 15 mEq/L,

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so reabsorption of bicarbonate does not occur until the serum levels decrease to less than this value. The loss of HCO_3^- is often large because 60%-80% of the filtered HCO_3^- is normally reabsorbed in the proximal tubule. Distal urinary acidification is normal, and patients can appropriately acidify the urine (pH ≤5.5) when plasma HCO_3^- levels are less than 14-15 mEq/L. An increase in plasma HCO_3^- beyond the capacity of the proximal tubule results in HCO_3^- wastage and an alkaline urine pH of 7.6 or greater. Isolated inherited forms of proximal RTA occur rarely and can be inherited as an autosomal recessive (with ocular abnormalities) or autosomal dominant trait.[50] More commonly, proximal RTA is a component of Fanconi syndrome, a disorder of global proximal tubule dysfunction. In addition to bicarbonate wasting, patients with Fanconi syndrome exhibit tubular wasting of sodium, potassium, glucose, phosphorus, and amino acids. Fanconi syndrome is seen in many inherited metabolic disorders, including Lowe syndrome, galactosemia, tyrosinemia, and hereditary fructose intolerance. Patients with proximal RTA typically require larger amounts of bicarbonate supplementation than patients with distal RTA. Dosages of 10 mEq/kg or more per day may be required because of excessive HCO_3^- wastage.

As previously discussed, neonates display a mild degree of proximal RTA because of an altered threshold for proximal tubular HCO_3^- reabsorption, with maintenance of plasma HCO_3^- in the range of 15-21 mEq/L. Over the first year of life, the tubular maximum for HCO_3^- increases to adult levels as the proximal tubule elongates and transport function matures. Type IV (hyperkalemic) RTA is characterized by impaired ammoniagenesis as the result of hyperkalemia. Hyperkalemia results from abnormalities in aldosterone production or from altered tubular sensitivity to aldosterone. Disorders associated with abnormalities in mineralocorticoid production (e.g., congenital adrenal hyperplasia) or responsiveness (i.e., inherited or acquired pseudohypoaldosteronism) have been discussed earlier in this chapter. The symptoms of type IV RTA in infancy include dehydration and symptoms related to hyperkalemia. Laboratory abnormalities include a nonanion gap metabolic acidosis, hyperkalemia, elevated urine sodium, and diminished urine potassium. Therapy for type IV RTA consists of mineralocorticoid supplementation in conditions characterized by a deficiency of aldosterone. Treatment of hyperkalemia may reverse many of the abnormalities; however, alkali supplementation is generally required in patients with end-organ resistance to aldosterone, such as those with congenital obstructive uropathies. The need for such supplementation may decrease in the first few years of life, likely related to further maturation of the kidney.

Neonatal Bartter Syndrome

Bartter syndrome is a heterogeneous group of inherited tubular disorders characterized by hypokalemia, hypochloremia, and metabolic alkalosis. Typically, it is manifest as obligate and uncontrolled renal losses of sodium, potassium, and chloride. In the past, three clinically and genetically distinct variants of this syndrome were recognized: antenatal Bartter syndrome, "classic" Bartter syndrome, and Gitelman syndrome. However, in recent years, mutations in other tubular transporter-associated genes have been identified in patients with "Bartter-like" or "pseudo-Bartter" phenotypes, including antenatal presentations.[14,55]

The antenatal variant is typically the most severe form and manifests in the neonatal period with polyuria (leading to dehydration, hyponatremia, and hypokalemia). Urinary sodium and potassium losses can be massive. A history of polyhydramnios is also typical. Some patients will manifest characteristic dysmorphic facies, including triangular facies, protruding ears, strabismus, and a drooping mouth, but this is not invariant. Additional laboratory findings include markedly elevated plasma renin levels, normal serum magnesium levels, and elevated urine calcium excretion. Nephrocalcinosis may be evident on ultrasonography. This form of Bartter syndrome is inherited as an autosomal recessive trait and is often associated with mutations in genes encoding the rectifying potassium channel or the Na^+-K^+-2 Cl^- cotransporter both important for sodium and chloride reabsorption in the Loop of Henle. Treatment includes the use of indomethacin to inhibit prostaglandin and aldosterone production, sodium and potassium supplementation, and maintenance of adequate intravascular volume.

Key Points

- Neonates, especially premature neonates, are at increased risk of developing fluid, electrolyte, and acid–base disorders because of developmental differences in body water compensation and tubular immaturity compared with children and adults.
- Fluid and electrolyte therapy need to be tailored to the individual patient's clinical situation, taking into account gestational age, volume status, respiratory status, hemodynamic stability, and the presence of additional conditions, such as perinatal asphyxia, or mechanical devices, such as ventilators or phototherapy devices.
- Total body sodium determines overall volume status. Serum sodium is a reflection of the relationship between sodium and water but is generally not a reliable indicator of hyper- or hypovolemia.
- Hyponatremia is the result of an inability to excrete a water (fluid) load or renal tubular sodium wasting, which have different treatments. Assessment of overall volume status is an important consideration when assessing hyponatremia. Administration of sodium to treat hyponatremia in a patient suspected of having hypervolemia should be avoided.

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- Premature neonates have impaired urinary acidification mechanisms including impaired bicarbonate reabsorption, ammoniagenesis, and hydrogen ion secretion, all of which may contribute to development or persistence of acidosis, especially in the face of increased acid load.
- Rare inherited tubular disorders may present in the neonatal period with abnormalities in serum sodium, potassium, and/or bicarbonate and should be considered in the differential diagnosis of neonates with persistent electrolyte or acid–base disorders without a clear etiology.

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93

The Kidney and Urinary Tract of the Neonate

BETH A. VOGT AND TAMAR SPRINGEL

In the past 25 years, the field of clinical neonatal nephrology has expanded significantly in concert with major advances and changes in the care and survival of neonates, particularly premature neonates. The widespread use of invasive vascular catheters, for example, has resulted in a new set of complications, including acute kidney injury (AKI) and renovascular hypertension related to thromboembolic disease. The improved survival of infants with extremely low birth weight and bronchopulmonary dysplasia has led to the relatively new complication of neonatal nephrocalcinosis. The increased use of prenatal ultrasonography has created new paradigms for the prenatal management of urinary tract anomalies (see Chapter 11).

The goals of this chapter are to review the anatomic and functional development of the kidney, outline the recommended approach to the evaluation of the neonate with suspected renal disease, and provide an overview of the common nephrologic and urologic problems seen in preterm and term neonates.

Kidney and Urinary Tract Development

Kidney and urinary tract development is a complex process involving interactions between genes involved in the formation and maturation of the glomeruli, tubules, renal blood vessels, extracellular matrix, and uroepithelium. This carefully coordinated process involves the regulated activation and inactivation of hundreds of genes that encode transcription factors, growth factors and receptors, structural proteins, adhesion molecules, and other regulatory proteins.[63] Since the mid-1990s, the rapidly expanding field of molecular genetics has provided important new insights into the mechanisms involved in renal and urinary tract development. A detailed review of the genes and signaling pathways involved in renal development is beyond the scope of this chapter; therefore, the reader is referred to two detailed reviews of the subject.[22,40] This section highlights some of the important pathways involved in these processes and provides examples of human kidney diseases resulting from abnormalities in normal development.

Development of the Kidney

Kidney embryogenesis involves successive formation of three different kidneys: the pronephros, mesonephros, and metanephros. The formation of these structures during intrauterine development is illustrated in Fig. 93.1. The pronephros, a vestigial structure of 7-10 solid or tubular cell groups called nephrotomes, develops in the cervical region and disappears by the end of the fourth week of gestation. As the pronephros regresses, the mesonephros appears and is characterized by excretory tubules that form an S-shaped loop, with a glomerulus and Bowman capsule at the proximal end. At the distal portion, the tubule enters the collecting duct (also referred to as the mesonephric or Wolffian duct), which does not drain into the coelomic cavity. During the second month of gestation, the urogenital ridge, which is the forerunner of the gonads, develops. By the end of the second month of gestation, most portions of the mesonephros disappear. However, a few caudal tubules remain in close proximity to the testis and ovaries, developing into the vas deferens in males and remaining as remnant tissue in females.

The metanephric, or definitive, kidney is derived solely from intermediate mesoderm and begins forming at 5 weeks of gestation, when a portion of the Wolffian duct swells to form the ureteric bud (UB). The UB, composed of epithelium, then invades the nearby metanephric mesenchyme. The outgrowth and subsequent branching of the ureteric bud is dependent on interaction between glial cell–derived neurotrophic factor (GDNF) expressed by the metanephric mesenchyme and Ret receptors present on the UB. The GDNF-Ret interaction leads to patterned, progressive divisions of the UB (called "branching morphogenesis") that form the collecting ducts of the kidney as well as the major and minor caliceal system of the renal pelvis. At the tip of the branches, the mesenchymal cells of the metanephric blastema are induced by the advancing ureteric bud to differentiate into the epithelial cells that eventually become the glomeruli and renal tubules. The branching UB cells are dependent on the support of extracellular matrix

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Abstract

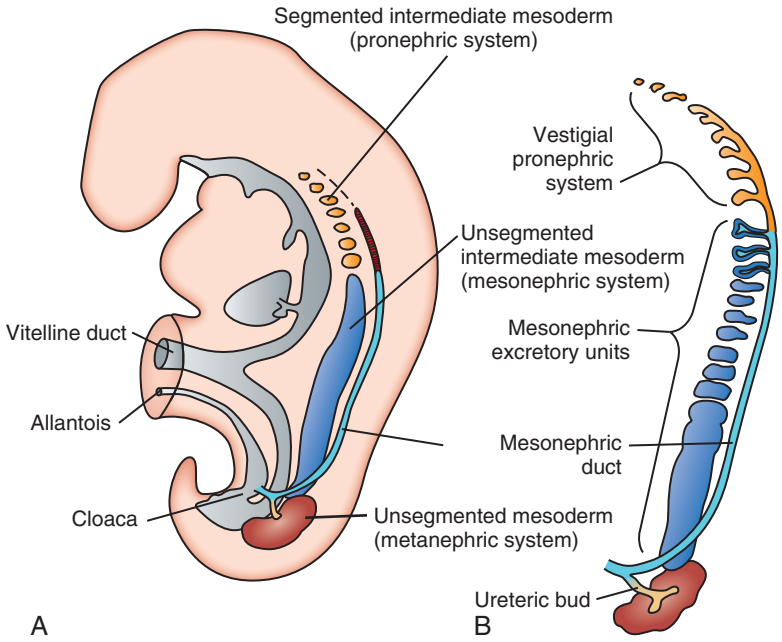
In the past 25 years, the field of clinical neonatal nephrology has expanded significantly in concert with major advances and changes in the care and survival of neonates, particularly premature neonates. The widespread use of invasive vascular catheters, for example, has resulted in a new set of complications, including acute kidney injury (AKI) and renovascular hypertension related to thromboembolic disease. The improved survival of infants with extremely low birth weight and bronchopulmonary dysplasia has led to the relatively new complication of neonatal nephrocalcinosis. The increased use of prenatal ultrasonography has created new paradigms for the prenatal management of urinary tract anomalies (see Chapter 11).

The goals of this chapter are to review the anatomic and functional development of the kidney, outline the recommended approach to the evaluation of the neonate with suspected renal disease, and provide an overview of the common nephrologic and urologic problems seen in preterm and term neonates.

Keywords

acute kidney injury
neonatal hypertension
neonatal nephrocalcinosis
renal vascular thrombosis
CAKUT (congenital anomalies of the kidney and urinary tract)
antenatal hydronephrosis
autosomal recessive polycystic kidney disease

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• **Fig. 93.1** Development of the early embryonic kidney. **A,** Schematic diagram showing the relation of the intermediate mesoderm of the pronephric, mesonephric, and metanephric systems. In the cervical and upper thoracic regions, the intermediate mesoderm is segmented; in the lower thoracic, lumbar, and sacral regions, it forms a solid, unsegmented mass of tissue known as the nephrogenic cord. Note the longitudinal collecting duct, initially formed by the pronephros but later taken over by the mesonephros. **B,** Schematic representation of the excretory tubules of the pronephric and mesonephric systems in a 5-week-old embryo. The ureteric bud penetrates the metanephric tissue. Note the remnant of the pronephric excretory tubules and longitudinal collecting duct. (From Langman J, ed. *Medical embryology.* 3rd ed. Baltimore: Williams & Wilkins; 1975:162.)

components such as laminins and integrins. Foci of the metanephric blastema become condensed adjacent to the branching ureteric bud to form comma-shaped bodies that then elongate to form S-shaped bodies. The lower portion of the S-shaped body becomes associated with a tuft of capillaries to form the glomerulus, because the upper portion forms the tubular elements of the nephron.

The metanephric kidney ascends from the pelvic to the thoracolumbar region. This process is thought to occur as the result of a decrease in body curvature and body growth of the lumbar and sacral regions. In the pelvis, the metanephric kidney receives its blood supply from a pelvic branch of the aorta. During ascent, the metanephric kidney receives its blood supply from arterial branches at higher levels of the aorta. Although the pelvic vessels usually degenerate, persistence of these early embryonic vessels can lead to supernumerary renal arteries. The metanephric kidney becomes functional during the second half of pregnancy. Nephrogenesis, which is the formation of new nephron units, is complete at 34 weeks of gestation, when each kidney contains its definitive complement of approximately 800,000 to 1.2 million nephrons.[3]

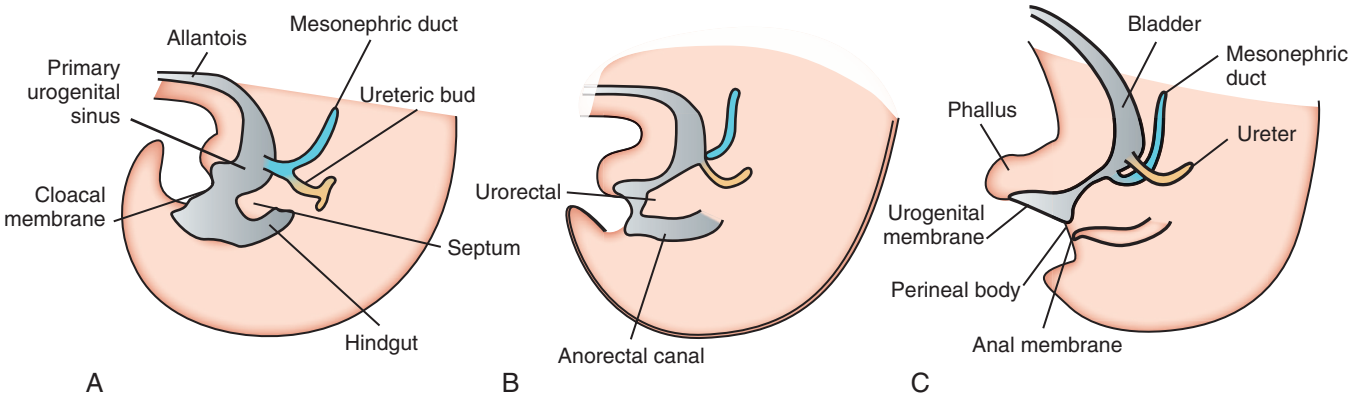
Development of the Bladder and Urethra

The bladder and urethra are formed during the second and third months of gestation, which is illustrated in Fig. 93.2. During the fourth to seventh week of development, the cloaca, which is located at the proximal end of the allantois and is the precursor to the urinary bladder and urethra, is divided by the urorectal septum into the primitive urogenital sinus (anterior portion) and the anorectal canal (posterior portion). The primitive urogenital sinus develops into the bladder (upper portion), prostatic and membranous urethra (pelvic portion) in males, and the penile urethra (males) or urethra and vestibule (females). As the cloaca develops, the caudal portion of the mesonephric ducts is absorbed into the bladder wall. Similarly, the caudal portions of the ureters, which originate from the mesonephric ducts, enter the bladder. During these processes, the ureteral orifices move cranially and the mesonephric ducts move closer together to enter the prostatic urethra, forming the trigone of the bladder. At the end of the third month of gestation, the epithelial proliferation of the prostatic urethra forms outbuddings that constitute the prostate gland in males. In females, the cranial portion of the urethra forms buds that develop into the urethral and paraurethral glands.[70]

Genetic and Prenatal Factors Affecting Renal Development

Studies in animal models have highlighted the important role of multiple proteins and signaling mechanisms in nephrogenesis, including growth factors such as fibroblast

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• **Fig. 93.2** Diagrams showing the division of the cloaca into the urogenital sinus and anorectal canal. Note that the mesonephric duct is gradually absorbed into the wall of the urogenital sinus and that the ureters enter separately. **A,** At the end of 5 weeks. **B,** At the end of 7 weeks. **C,** At the end of 8 weeks. (From Langman J, ed. *Medical embryology.* 3rd ed. Baltimore: Williams & Wilkins; 1975:168.)

TABLE 93.1 Genes Associated With CAKUT in Humans[63,66]

Type of Malformation	Renal Phenotype	Gene	Cause
Renal agenesis	Absence of the ureter and kidney	*RET, GDNF, FGF20, FRAS1, FREM2*	Lack of interaction between the ureteric bud and MM
Renal hypoplasia	Reduced number of ureteric bud branches and nephrons, small kidney size, often associated with dysplasia	*Pax2, Sall1, Six2, BMP4, HNF1B, UMOD*	Aberrant interaction between ureteric bud and MM
Renal dysplasia	Reduced number of ureteric bud branches and nephrons, undifferentiated stromal and mesenchymal cells, cysts, or cartilage	*PAX2, HNF1B, UMOD, Nphp1 BMP4, Six2, XPNPEP3*	Aberrant interaction between ureteric bud and MM
MCDK	Absent glomeruli and tubules	*HNF1B, UPIIIA, PEX26, ELN, HNF1B, ALG12, FRG1, FRG2, CYP4A11*	Aberrant interaction between ureteric bud and MM
Duplex ureters	Duplex ureters and kidneys or duplex ureters and collecting systems	*Robo2, FoxC1, FoxC2, BMP4*	Supernumerary ureteric bud budding from the MD
Horseshoe kidney	Kidneys are fused at inferior lobes and located lower than usual	*HNF1B*	Defects in renal capsule
VUR	Urine refluxes to various degrees from bladder up into the collecting system	*PAX2, ROBO2, SIX1, SIX5, SOX17, TNXB, CHD1L, TRAP1*	Aberrant insertion of ureter into bladder wall
Renal tubular dysgenesis	Absence of or incomplete differentiation of proximal tubule	*ACE, AGT, AGTR1, REN*	Impaired tubular growth and differentiation

CAKUT, Congenital anomalies of the kidney and urinary tract; MD; mesonephric duct; MCDK, multicystic dysplastic kidney; MM, metanephric mesenchyme

growth factor (FGF), adhesion molecules such as integrin alpha 8, the transcription factor WT-1, the canonical Wnt/beta catenin signaling pathway, and the GDNF/Ret tyrosine kinase signaling pathway.[22,40] Alterations in the actions of one or more of these proteins/pathways can result in renal or urogenital anomalies such as renal agenesis, renal dysplasia, cystic kidneys, and glomerulosclerosis.

A number of genes have been associated with congenital anomalies of the kidney and urinary tract (CAKUT) and often present with similar renal phenotypes (Table 93.1).[66] Genetic mutations associated with CAKUT may be inherited in an autosomal dominant or recessive pattern, but most often occur as sporadic, *de novo* mutations. In addition to monogenic causes, copy number variation (CNV) has

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TABLE 93.2 Normal Values for Renal Function

Age	GFR (mL/min/1.73 m^2)	RBF (mL/min/1.73 m^2)	Maximum Urine Osm (mOsm/kg)	Serum Creatinine (mg/dL)	Fe_{Na} (%)
Newborn					
Premature (30-34 weeks)	14 ± 3	40 ± 6	480	0.6-1.3*	2-6
Term	21 ± 4	88 ± 4	800	0.6-1*	<1
1-2 weeks	50 ± 10	220 ± 40	900	0.27-0.5*	<1
6 months-1 year	77 ± 14	352 ± 73	1200	0.18-0.29*	<1
1-3 years	96 ± 22	540 ± 118	1400	0.24-0.43†	<1
Adult	118 ± 18	620 ± 92	1400	0.6-1.3†	<1

Fe_{Na}, Fractional excretion of sodium; GFR, glomerular filtration rate; Osm, osmolality; RBF, renal blood flow.
*Based on enzymatic or Jaffe creatinine measurements.
†Based on IMDS-traceable creatinine measurements.
Adapted from references 8, 10, 27, 65.

been found in 10%-16% of patients with CAKUT, specifically in patients with posterior urethral valves or multicystic dysplastic kidneys.[17] However, identified genetic mutations do not account for all patients with CAKUT, and the majority of patients with anomalies do not have a known mutation identified.

Certain prenatal factors have been associated with increased risk of CAKUT. Maternal diabetes mellitus, older maternal age, gestational hypertension, and BMI greater than 25 were associated with higher likelihood of having renal dysplasia or obstructive uropathy in the infant.[30] Teratogenic effects of several drugs have been documented, most notably angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB). ACE-I fetopathy presents with renal tubular dysgenesis, neonatal anuria, pulmonary hypoplasia, and occasional central nervous system abnormalities, most often after exposure to ACE-I or ARB during the second trimester of pregnancy.[51] Animal studies have demonstrated nephrotoxic effects of nonsteroidal, anti-inflammatory drugs; immunosuppressive medications, such as corticosteroids, cyclosporine, and tacrolimus; and antibacterial medications, such as aminoglycosides and beta-lactams.[48] These drugs are mostly associated with reduced nephron mass, but their effects in humans are still uncertain. Finally, heavy metal exposure can potentially damage fetal kidney development, and there may be other unidentified environmental toxins that may cause developmental abnormalities of kidneys.[48]

Physiology of the Developing Kidney

During intrauterine life, the kidneys play only a minor role in regulating fetal salt and water balance, because this function is maintained primarily by the placenta. The most important functions of the prenatal kidneys are the formation and excretion of urine to maintain an adequate amount of amniotic fluid. After birth, there is a progressive maturation in renal function, which appears to parallel the needs of the neonate for growth and development (Table 93.2).

Renal Blood Flow

Absolute renal blood flow (RBF) and the percentage of cardiac output directed to the kidneys increase steadily with advancing gestational age. The kidneys of a human fetus weighing more than 150 g receive approximately 4% of the cardiac output, compared with approximately 6% in the term infant. The relatively low RBF of the fetus is related to high renovascular resistance caused by the increased activity of the renin-angiotensin-aldosterone and sympathetic nervous systems. The RBF dramatically increases postnatally, reaching 8%-10% of the cardiac output at 1 week of life, and achieves adult values of 20%-25% of the cardiac output by 2 years of age. This rise in RBF is caused primarily by decreasing renovascular resistance and increasing cardiac output and perfusion pressure.

Glomerular Filtration

The glomerular filtration rate (GFR) in the fetal kidney increases steadily with advancing gestational age. By 32-34 weeks' gestation, a GFR of 14 mL/min per 1.73 m^2 is achieved, which further increases to 21 mL/min per 1.73 m^2 at term. The GFR continues to increase postnatally, achieving adult values of approximately 120 mL/min per 1.73 m^2 by the age of 2 years. The achievement of adult GFR may be delayed in preterm infants, especially those with very low birth weights.[1,5] The progressive increase in GFR during the initial weeks of postnatal life primarily results from an increase in glomerular perfusion pressure. Subsequent increases in GFR during the first 2 years of life are caused primarily by increases in RBF and the maturation of superficial cortical nephrons, which lead to an increase in the glomerular capillary surface area.

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Concentration and Dilution of Urine

Newborn infants have a limited capacity to concentrate their urine, with maximal urinary osmolality of 800 mOsm/kg in a term infant compared to that of a 2 year old, which approximates adult values of 1400 mOsm/kg. In contrast, the term newborn infant has full ability to maximally dilute its urine in response to a water load, achieving adult values of 50 mOsm/kg. Preterm infants are unable to fully dilute their urine but can achieve urine osmolality of 70 mOsm/kg. However, the response of premature infants to an acute water load may be limited because of their low GFR and the decreased activity of sodium transporters in the diluting segment of the nephron. The excessive administration of water may place the newborn infant at a high risk for dilutional hyponatremia and hypervolemia. Urinary diluting and concentrating capacity in term and preterm infants is discussed in more detail in Chapter 92.

Evaluation of the Neonate With Renal Disease

History

The antenatal history should be reviewed thoroughly, with particular attention devoted to medications, toxins, and unusual environmental exposures during the pregnancy. Exposure to angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), particularly in the second and third trimesters, can result in oligohydramnios, renal failure caused by renal tubular dysgenesis, limb deformities, prolonged hypotension, pulmonary hypoplasia, and hypocalvaria.[51] Structural and functional alterations of the newborn kidney have also been described in infants with antenatal exposure to nonsteroidal anti-inflammatory drugs; selective COX-2 inhibitors; mycophenolate mofetil; certain antiepileptic medications; and chemotherapeutic agents, such as doxorubicin and cyclophosphamide.[48] A review of the family medical history is important, including any prior fetal or neonatal deaths. Certain congenital abnormalities of the kidney and urinary tract (CAKUT) (renal hypoplasia/dysplasia, multicystic dysplastic kidney, and vesicoureteral reflux) may have familial clustering. In other disorders, including polycystic kidney disease and congenital nephrotic syndrome, a clear genetic basis has been established. The results of prenatal ultrasonography should be carefully reviewed, with particular attention devoted to kidney size, echogenicity, structural malformations, amniotic fluid volume, and bladder size and shape (Box 93.1). Although the bladder may be identified and its volume discerned at 15 weeks of gestation, the kidneys are not visualized until after the 16th-17th week of gestation in most fetuses. The presence of small or enlarged kidneys, renal cysts, hydronephrosis, bladder enlargement, or oligohydramnios suggests significant renal or urologic pathology.

• BOX 93.1 Prenatal Ultrasonography as a Diagnostic Tool for Abnormalities of the Urinary Tract

Kidneys

- Dilated renal pelvis/hydronephrosis: physiologic, vesicoureteral reflux, obstruction
- Cystic kidney: MCDK, cystic dysplasia, ADPKD, severe obstruction
- Echogenic kidney: renal dysplasia, ARPKD
- Structural abnormalities: renal duplication, fusion abnormalities (e.g., horseshoe, crossed fused ectopia), ectopic kidneys (pelvic, thoracic)
- Lack of visualization: renal agenesis, hypoplasia, ectopic
- Enlarged kidneys: ARPKD, obstruction, overgrowth syndromes (Simpson-Golabi-Behmel, Perlman, Beckwith-Wiedemann)
- Renal mass

Ureter

- Hydroureter

Bladder

- Dilation
- Ureterocele
- With thickened wall: posterior urethral valves
- Without thickened wall: megacystis-megaureter syndrome, neurogenic bladder, EBS
- Bladder exstrophy, cloacal exstrophy
- Lack of visualization: minimal or absent fetal urine production; obstructive uropathy

Ascites

- Urinary ascites (typically associated with thickened bladder wall and/or abnormal kidneys)

Hydrops Fetalis

- Most often due to nonrenal causes; occasionally caused by bilateral renal cystic disease, urinary tract obstruction, congenital nephrotic syndrome

Oligohydramnios

- Bilateral renal dysplasia, urinary tract obstruction, ARPKD
- Rupture of membranes, postmaturity, subacute fetal distress

Polyhydramnios

- Renal tubular disorder with urinary concentrating defect (NDI, Bartter syndrome)
- Multiple gestation, upper gastrointestinal tract obstruction, neurologic disorders, maternal diabetes, fetal hydrops

Placental Edema

- Congenital nephrotic syndrome

ADPKD, Autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; EBS, Eagle Barrett syndrome; MCDK, multicystic dysplastic kidney; NDI, nephrogenic diabetes insipidus.

Physical Examination

The evaluation of blood pressure and volume status is critical in the newborn with suspected renal disease. Hypertension may be present in infants with polycystic kidney disease, acute kidney injury (AKI), renovascular or aortic

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thrombosis, or obstructive uropathy. Hypotension may be present in infants with volume depletion, hemorrhage, or sepsis, any of which may lead to AKI. Edema may occur in infants with AKI, hydrops fetalis, or congenital nephrotic syndrome. Ascites may be present in infants with urinary tract obstruction, congenital nephrotic syndrome, or volume overload. Special attention should be paid to the abdominal examination. In the neonate, the lower pole of each kidney is easily palpable because of the neonate's reduced abdominal muscle tone. The presence of an abdominal mass in a newborn should be assumed to involve the urinary tract until proved otherwise, because two-thirds of neonatal abdominal masses are genitourinary in origin. The most common renal cause of an abdominal mass is hydronephrosis, followed by a multicystic dysplastic kidney. Less common renal causes of an abdominal mass include polycystic kidney disease, renal vein thrombosis, ectopic or fused kidneys, and renal tumors. The abdomen should be examined for the absence of or laxity in the abdominal muscles, which may suggest Eagle-Barrett ("prune-belly") syndrome. Distention of the newborn bladder may suggest lower urinary tract obstruction or an occult spinal cord lesion.

A number of anomalies should alert the physician to the possibility of underlying renal defects, including abnormal external ears, aniridia, microcephaly, meningomyelocele, hemihypertrophy, persistent urachus, bladder or cloacal exstrophy, an abnormality of the external genitalia, cryptorchidism, imperforate anus, and limb deformities. Although screening renal ultrasonography of infants with a single umbilical artery had previously been recommended, in the era of routine prenatal ultrasonography, this practice is no longer recommended.

A constellation of physical findings designated the oligohydramnios (Potter) sequence may be seen in infants with severe neonatal kidney disease, including bilateral renal dysplasia, bilateral urinary tract obstruction, or autosomal recessive polycystic kidney disease. Marked reduction of fetal kidney function results in oligohydramnios or anhydramnios, which causes fetal deformation by compression of the uterine wall. The characteristic facial features include wide-set eyes; depressed nasal bridge; beaked nose; receding chin; and posteriorly rotated, low-set ears (Fig. 93.3). Other associated anomalies include a small, compressed chest wall; arthrogryposis; hip dislocation; and clubfoot. Such patients often have respiratory failure caused by pulmonary hypoplasia; complications include spontaneous pneumothorax and/or pneumomediastinum resulting from their requirement for high ventilator pressures.



• **Fig. 93.3** Potter facies. Photomicrograph demonstrates the characteristic findings, including epicanthal folds, hypertelorism, low-set ears, a crease below lower lip, and a receding chin.

Laboratory Evaluation

Urinalysis

The examination of a freshly voided urine specimen provides immediate, valuable information about the condition of the kidneys. A urine specimen collected by cleaning the perineum and applying a sterile adhesive plastic bag is useful for obtaining urine for urinalysis but is not recommended for urine culture, as it may be associated with a false-positive result caused by fecal contamination. Bladder catheterization is a more reliable method for collecting a sample for culture but may be technically difficult in preterm infants. Suprapubic bladder aspiration is an alternative urinary collection method in preterm infants without intra-abdominal pathology or bleeding disorders.

Analysis of the urine should include inspection, urinary dipstick assessment, and microscopic analysis. The newborn urine is usually clear and nearly colorless. Cloudiness may represent a urinary tract infection or the presence of crystals. A yellow-brown to deep olive-green color may represent large amounts of conjugated bilirubin. Porphyrins, certain drugs such as phenytoin, bacteria, and urate crystals may stain the diaper pink and be confused with bleeding. Brown urine may suggest AKI, hemoglobinuria, or myoglobinuria.

The specific gravity of neonatal urine is usually very low (<1.004) but may be factitiously elevated by high-molecular-weight solutes such as contrast agents, glucose or other reducing substances, or large amounts of protein. Urinary osmolality may be a more reliable measurement of the concentrating and diluting capacity of the kidney. Urinary dipstick evaluation can detect the presence of heme-containing compounds (i.e., red blood cells, myoglobin, and hemoglobin), protein, and glucose. White blood cell products such as leukocyte esterase and nitrite may also be detected on urinary dipstick evaluation and should raise the suspicion of urinary tract infection, mandating collection of a urine culture. The microscopic examination of urinary sediment may detect the presence of red blood cells, white blood cells, bacteria, casts, or crystals.

Assessment of Renal Function

Although 98% of term infants void during the first 30 hours of life,[20] a delay in urination for up to 48 hours should

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not be a cause for immediate concern in the absence of a palpable bladder, abdominal mass, or other signs or symptoms of renal disease. A failure to void for longer than 48 hours may suggest impairment of renal function and should prompt further investigation. The serum creatinine level is the simplest and most commonly used indicator of neonatal kidney function. Immediately after birth, the serum creatinine concentration reflects the maternal creatinine concentration. In term infants, the serum creatinine level gradually decreases from a range of 0.6-1 mg/dL (depending on the mother's serum creatinine) at birth to a mean value of 0.4 mg/dL within the first 2 weeks of life (Table 93.2). In preterm infants, the decline in serum creatinine level is slower and may not reach nadir for 1-2 months. In very preterm infants, the creatinine may actually rise transiently because of low GFR and tubular reabsorption of creatinine before falling to reach a nadir value at 2 months of age (Table 93.3).[11] Failure of the serum creatinine level to fall or a persistent increase in serum creatinine suggests impairment of renal function. Estimation of GFR is difficult in neonates, because formulas used in children have not been validated in infants less than 1 year of age. Measurement of serum cystatin C, a low molecular weight protein produced in all cells and filtered through the glomerulus, may offer more accurate estimation of neonatal kidney function but is not yet widely available for use.[27]

Radiologic Evaluation

Ultrasonography is the most common method of imaging the neonatal urinary tract, as it is a readily available, noninvasive test that does not involve exposure to contrast agents or radiation. Ultrasonography is indicated in infants with a history of an abnormal antenatal ultrasound, as well as in infants with an abdominal mass, AKI, hypertension, hematuria, or congenital malformations or genetic syndromes with increased risk of urinary tract anomalies. Ultrasonography can identify hydronephrosis, cystic kidney disease, and abnormalities of kidney size and position. It also may be used as a screening tool in preterm infants at increased risk of developing nephrocalcinosis due to chronic lung disease and long-term loop diuretic therapy. A Doppler flow study of the renal arteries and aorta may be helpful in the evaluation of infants with suspected renovascular hypertension, renal arterial or venous thrombosis, or AKI.

Importantly, nonurgent postnatal ultrasounds, such as those performed to follow up mild to moderate antenatal hydronephrosis, should be delayed until at least 48 hours after birth. Ultrasounds performed in the first 24-48 hours of life may not show hydronephrosis because of the low urine output of the neonate in the first few days of life.

Voiding cystourethrography (VCUG) should be considered an important part of the radiologic examination in infants with significant hydronephrosis, hydroureter, or documented urinary tract infection. Voiding cystourethrography involves the instillation of a radiopaque contrast agent into the bladder by urinary catheterization. This study is the procedure of choice to evaluate the urethra and bladder and ascertain the presence or absence of vesicoureteral reflux and posterior urethral valves. Other radiologic tests may occasionally be used for diagnostic purposes in the neonate (see

TABLE 93.3 Serum Creatinine Values for Very Preterm Infants

Age	50th Percentile Value mg/dL (micromol/L)	95th Percentile Value mg/dL (micromol/L)
7 days		
25-27 weeks' gestation	0.87 (76.9)	1.23 (108.7)
28-29 weeks' gestation	0.84 (74.3)	1.18 (103.9)
30-33 weeks' gestation	0.66 (58.3)	0.95 (83.9)
10-14 days		
25-27 weeks' gestation	0.75 (66.3)	1.10 (97.3)
28-29 weeks' gestation	0.69 (61)	1.02 (90.3)
30-33 weeks' gestation	0.57 (50.4)	0.84 (84.1)
1 month		
25-27 weeks' gestation	0.48 (42.4)	0.72 (63.6)
28-29 weeks' gestation	0.41 (36.2)	0.64 (57)
30-33 weeks' gestation	0.35 (30.9)	0.57 (50.2)
2 months		
25-27 weeks' gestation	0.31 (27.4)	0.51 (44.9)
28-29 weeks' gestation	0.33 (28.8)	0.58 (51.6)
30-33 weeks' gestation	0.25 (22.2)	Data not available

https://www.uptodate.com/contents/image?topicKey=PEDS%2F4989&rank=1~150&imageKey=PEDS%2F111831&source=machineLearning&view=machineLearning&sectionRank=1&sp=0&search=neonate%20creatinine Accessed November 29, 2017. Up to Date, data adapted from Bateman et al.[11]

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Chapter 38). Radioisotopic renal scanning may be of value in locating anomalous kidneys and identifying obstruction or renal scarring. Radioisotopic scans also provide information about the contribution of each kidney to overall renal function but may be difficult to interpret in the first few weeks of life because of the relatively low GFR in newborns. Abdominal computed tomography is useful in the diagnosis of renal tumors, renal abscesses, and nephrolithiasis.

Clinical Problems

Hematuria

Hematuria can be broadly classified into two categories: microscopic and macroscopic (gross). Microscopic hematuria is defined as ≥5 red blood cells on high-powered examination of the urine without visible discoloration of the urine. Macroscopic hematuria is defined as visibly discolored (red or brown) urine with ≥5 red blood cells on high-powered examination of the urine. When a neonate is suspected as having macroscopic hematuria, it is important to confirm that the discolored urine is caused by hematuria and not caused by a condition mimicking hematuria. Urate crystals, bile pigments, and porphyrins may discolor the urine and mimic hematuria, but in these conditions the urinary dipstick test is negative for blood and the microscopic examination reveals no red blood cells. Infants with myoglobinuria caused by inherited metabolic myopathy, infectious myositis, or rhabdomyolysis may have red or brown urine and test dipstick positive for blood, but the microscopic examination of the urine reveals no red blood cells. Similarly, infants with hemoglobinuria caused by hemolysis from ABO incompatibility or other forms of hemolytic disease will have a positive urinary dipstick for blood but no red blood cells present on microscopic examination. Vaginal bleeding or skin breakdown from diaper dermatitis can also mimic gross hematuria.

Once it is determined that an infant has macroscopic hematuria, there is a broad differential diagnosis.[38] Urinary tract infection should be ruled out with urine culture. Acute tubular necrosis (ATN) or cortical necrosis should be considered in infants with a history of perinatal asphyxia. Renal venous thrombosis must be considered in infants with risk factors, including birth to a diabetic mother, cyanotic congenital heart disease, volume depletion, or an indwelling umbilical venous catheter. Coagulopathy related to hemorrhagic disease of the newborn should be considered in at-risk infants who have not received vitamin K prophylaxis. Urolithiasis or nephrocalcinosis should be suspected in at-risk infants with a history of chronic lung disease and loop diuretic use. Other causes include trauma from bladder catheterization or suprapubic aspiration, obstructive uropathy, and tumors.

Evaluation of the neonate with macroscopic hematuria includes formal urinalysis with microscopic examination, catheter urine culture, complete blood count, serum electrolytes, creatinine, and kidney/bladder ultrasound. Further evaluation may include coagulation profile, urine calcium-to-creatinine ratio, abdominal computerized tomography scan, or urologic evaluation.

Proteinuria

Proteinuria is defined as a urinary dipstick value of at least 1+ (30 mg/dL), with a specific gravity of 1.015 or less, or a urinary dipstick value of at least 2+ (100 mg/ dL), with a specific gravity of more than 1.015. Normal urinary protein-to-creatinine ratio is less than 0.5 mg/mg in infants and toddlers younger than 2 years of age. Nearly any form of renal injury can result in a transient increase in urinary protein excretion, including ATN, fever, dehydration, cardiac failure, high doses of penicillin, and the administration of a contrast agent. Persistent heavy proteinuria, edema, and hypoalbuminemia in a neonate should prompt the consideration of congenital nephrotic syndrome, an autosomal recessive disorder characterized by massive proteinuria, failure to thrive, a large placenta, and chronic kidney disease (see section later in chapter). Proteinuria associated with glucosuria, phosphaturia, and metabolic acidosis raises concern for Fanconi syndrome, a rare condition characterized by generalized proximal tubular dysfunction; possible causes include cystinosis, Lowe syndrome, and mitochondrial disorders. False positive urinary dipstick values for protein may be the result of highly concentrated urine, alkaline urine, infection, and detergents.

Glycosuria

The diagnosis of glycosuria is established by the presence of glucose on a urinary dipstick. Glycosuria frequently occurs in infants with hyperglycemia, a condition in which the serum glucose exceeds the renal threshold for reabsorption. Common causes of hyperglycemia and resultant glycosuria in the NICU include sepsis or the administration of total parenteral nutrition. It is important to measure the serum glucose concentration in neonates with glycosuria on urinary dipstick evaluation. Correction of hyperglycemia normalizes the urinary dipstick findings. Isolated glycosuria with a normal serum glucose concentration raises concern for renal glycosuria, a benign inherited condition caused by an abnormality in the proximal tubular transport of glucose. No therapy is necessary other than the recognition of the condition, avoidance of confusion with diabetes mellitus, and provision of a normal intake of carbohydrates.

If glycosuria is accompanied by other evidence of renal tubular dysfunction, such as an excessive urinary loss of potassium, phosphorus, and amino acids, a generalized proximal tubulopathy (e.g., Fanconi syndrome) should be considered. Glycosuria may also be seen in infants with congenital renal diseases such as renal dysplasia, in which there is significant tubular dysfunction. Glycosuria in an infant with severe, watery diarrhea should raise the suspicion of congenital intestinal glucose-galactose malabsorption syndrome.

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Acute Kidney Injury

Acute kidney injury (AKI) is a common condition in the NICU, ranging from mild renal dysfunction to complete anuric kidney failure. AKI is characterized by a sudden decline in kidney function over hours to days, resulting in derangements in fluid, electrolyte, and acid–base balance. There has been difficulty in establishing a standardized definition of AKI in neonates because of a number of factors, including maturational difference in kidney function at different gestational ages, the overall low GFR of neonates, and the fact that serum Cr reflects maternal Cr for days to a week after birth. A consensus definition for neonatal AKI was recently established and termed the neonatal modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria.[60] These criteria define neonatal AKI in infants under 120 days of age as an increase in serum Cr ≥0.3 mg/dL or 50% or more from the previous lowest value and/or urine output <0.5 mL/kg/hr. Three stages of neonatal AKI are defined by relative changes in serum Cr from baseline (Table 93.4). Biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), urinary interleukin-18, and cystatin C may show promise in the earlier detection of neonatal AKI, potentially identifying earlier stages of kidney injury, which occur prior to the elevation of serum creatinine.[43,50]

Neonatal AKI is a common occurrence, occurring in 30% of critically ill neonates recently evaluated in a large multicenter retrospective cohort study.[37] The incidence of AKI varied by gestational age group, occurring in 48% of infants 22-29 weeks' gestation, 18% of infants 29-36 weeks' gestation, and 37% of infants ≥36 weeks' gestation.[37]

Neonates are at particularly high risk of developing AKI because of their intrinsically low GFR in the first week of life, immaturity of renal tubules, increased susceptibility of the kidney to impaired perfusion, high exposure to nephrotoxic agents including indomethacin and aminoglycosides, and frequent use of umbilical access catheters with potential for thrombosis.[60] Within the general NICU population, certain groups at heightened risk of developing AKI include term and near-term neonates with perinatal asphyxia, very low birth weight and extremely low birth weight infants, and infants requiring cardiac surgery or ECMO support.

Clinical signs of AKI may include oliguria, systemic hypertension, cardiac arrhythmia, evidence of fluid overload or volume depletion, decreased activity, seizure, vomiting, and anorexia. Laboratory findings may include elevated serum creatinine and blood urea nitrogen, hyperkalemia, metabolic acidosis, hypocalcemia, hyperphosphatemia, and a prolonged half-life for medications excreted by the kidney (e.g., aminoglycosides, vancomycin, theophylline). The causes of neonatal AKI are multiple and can be divided into prerenal, renal, and postrenal categories (Box 93.2).

Prerenal Azotemia

Prerenal azotemia is the most common type of AKI in the neonate and may account for up to 85% of all cases. Prerenal azotemia is characterized by inadequate renal perfusion, which if promptly treated, is followed by improvements in renal function and urine output. The most common causes of prerenal azotemia are hypotension, volume depletion, hemorrhage, septic shock, necrotizing enterocolitis, patent ductus arteriosus, and congestive heart failure. The administration of medications that reduce renal blood flow, such as indomethacin or ibuprofen, ACE inhibitors, and phenylephrine eye drops, can result in prerenal azotemia.

TABLE 93.4 Neonatal Modified KDIGO Criteria for Acute Kidney Injury

Stage	SCr (Serum Creatinine)	Urine Output
0	No change in SCr or rise <0.3 mg/dL	≥0.5 mL/kg/h
1	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥1.5-1.9 x reference SCr within 7 days	<0.5 mL/kg/h for 6-12 hr
2	SCr rise ≥2.0-2.9 x reference SCr	<0.5 mL/kg/h for ≥12 hr
3	SCr rise >3.0-2.9 x reference SCr or SCr >2.5 mg/dL or receipt of dialysis	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 hr

KDIGO, Kidney Disease: Improving Global Outcomes.
From Selewski DT, Charlton JR, Jetton JG, et al. Neonatal acute kidney injury. *Pediatrics* 2015;136:e463. Copyright © 2015 by the AAP.

• BOX 93.2 Causes of Acute Kidney Injury in the Neonate

Prerenal

- Volume depletion
- Hypotension
- Hemorrhage
- Sepsis
- Necrotizing enterocolitis
- Congestive heart failure
- Drugs: angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, indomethacin, ibuprofen, amphotericin

Renal

- Acute tubular necrosis
- Renal dysplasia
- Polycystic kidney disease
- Renal venous thrombosis
- Uric acid nephropathy

Postrenal

- Posterior urethral valves
- Bilateral ureteropelvic junction obstruction
- Bilateral ureterovesical junction obstruction
- Neurogenic bladder
- Obstructive nephrolithiasis

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Intrinsic (Renal) Acute Kidney Injury

The most common cause of intrinsic AKI in neonates is acute tubular necrosis (ATN). Risk factors for ATN include a prolonged prerenal state, perinatal asphyxia, sepsis, neonatal cardiac surgery, need for ECMO support, and nephrotoxic drug administration (acyclovir, aminoglycoside antibiotics, amphotericin B, ACE inhibitors, NSAIDs, radiocontrast agents, and vancomycin). The pathophysiology of ATN is complex and appears to involve interrelationships among renal tubular cellular injury, hypoxia, and altered glomerular filtration and hemodynamics. Other causes of intrinsic AKI in the newborn include renal dysplasia, autosomal recessive polycystic kidney disease, and renal arterial or venous thrombosis. Glomerulonephritis, although a common cause of AKI in older children and adolescents, is very uncommon in the neonatal population.

Obstructive (Postrenal) Acute Kidney Injury

Obstructive AKI in the neonate may be related to a variety of congenital urinary tract conditions, including posterior urethral valves, bilateral ureteropelvic or ureterovesical junction obstruction, obstructive urolithiasis, and neurogenic bladder. Rarer causes of obstructive AKI include extrinsic compression of the ureters or bladder by a congenital tumor such as a sacrococcygeal teratoma or intrinsic obstruction by renal calculi or fungus balls. Although relief of the urinary tract obstruction may yield improvement in urine output and GFR, many infants will develop chronic kidney disease because of variable degrees of associated renal dysplasia.

Evaluation

A careful history should focus on prenatal ultrasound abnormalities, perinatal asphyxia, the pre- or postnatal administration of potentially nephrotoxic drugs, and a family history of renal disease. The physical examination should focus on signs of volume depletion or volume overload, the abdomen, genitalia, and a search for other congenital anomalies or signs of the oligohydramnios (Potter) sequence. Levels of electrolytes, blood urea nitrogen, creatinine (Cr), calcium, phosphorus, albumin, and uric acid should be monitored at least daily or more frequently if significant metabolic abnormalities are present. Urine should be sent for urinalysis, urine culture, and urine sodium and creatinine determination. The fractional excretion of sodium (FE_{Na}), as well as other diagnostic indexes, may be useful in differentiating prerenal from intrinsic AKI (Table 93.5).

$$FE_{Na}\ (\%) = (UNa \times PCr)/(PNa \times UCr) \times 100\%$$

where U = urinary, P = plasma

Neonates with a FE_{Na} value of more than 3.0% generally have intrinsic AKI, whereas those with a FE_{Na} value of less than 2.5% have prerenal AKI. Baseline normal FE_{Na} values in preterm neonates may be as high as 6% at birth,[65] so the FE_{Na} measurement may be less helpful in distinguishing intrinsic versus prerenal AKI in that population. Renal ultrasound is helpful in the identification of congenital renal disease and urinary tract obstruction.

TABLE 93.5 Diagnostic Indexes in Acute Kidney Injury

Test	Prerenal AKI	Intrinsic AKI
BUN/Cr ratio (mg/mg)	>30	<20
FE_{Na} (%)	≤2.5	≥3.0
Urinary Na (mEq/L)	≤20	≥50
Urinary Osm (mOsm/kg)	≥350	≤300
Urinary specific gravity	>1.012	<1.014
Ultrasonography	Normal	May be abnormal
Response to volume challenge	Urine output >2 mL/kg/h	No increase in urinary output

AKI, Acute kidney injury; BUN, blood urea nitrogen; Cr, creatinine; FE_{Na}, fractional excretion of sodium; Osm, osmolality.

Prevention of AKI

The prevention of AKI in newborn infants requires maintenance of an adequate circulatory volume, careful fluid and electrolyte management, and prompt diagnosis and treatment of hemodynamic or respiratory abnormalities. Nephrotoxic medications such as acyclovir, aminoglycoside antibiotics, amphotericin B, ACE inhibitors, NSAIDs, radiocontrast agents, and vancomycin should be avoided if possible in neonates at high risk for AKI. Prophylactic theophylline (5 mg/kg IV) given within the first hour of life has been recommended to reduce the incidence of AKI in asphyxiated neonates, although its use must be weighed against potentially harmful neurologic side effects.[39] Therapeutic hypothermia protocols currently used for treatment of infants with perinatal asphyxia may have a beneficial effect in reducing the incidence of neonatal AKI.[61]

Medical Management

In the case of established oliguric AKI, a urinary catheter should be placed to exclude lower urinary tract obstruction. If there is no improvement in urine output after bladder drainage is established, a fluid challenge of 10-20 mL/kg should be administered over 1-2 hours to exclude prerenal AKI. Consideration should be given to use of vasopressor support such as dopamine to ensure that the infant has a mean arterial pressure adequate to provide renal perfusion. A lack of improvement in urine output and serum creatinine following adequate bladder drainage, fluid resuscitation, and establishment of an adequate mean arterial pressure suggests intrinsic AKI.

The goal of medical management of intrinsic AKI is to provide supportive care until there is spontaneous improvement in renal function. After adequate resuscitation, intake

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should be restricted to insensible losses (500 mL/m^2 per day, or 30 mL/kg per day) plus urine output and other measured losses (see Chapter 92) to prevent symptomatic fluid overload. Daily to twice daily weights and careful intake and output measurements are essential to follow volume status. Nephrotoxic drugs should be discontinued to reduce the risk of additional renal injury. Medications should be adjusted by dose, interval, or both according to the degree of renal dysfunction. Potassium and phosphorus should be restricted in those neonates with hyperkalemia, hyperphosphatemia, oliguria, and/or rapidly worsening renal function. Metabolic acidosis may require treatment with intravenous or oral sodium bicarbonate. Loop diuretics may prove helpful in augmenting the urinary flow rate but should be withheld if there is no response or in the case of anuria.

Renal Replacement Therapy

Renal replacement therapy is rarely needed in neonates with AKI but should be considered if maximum medical management fails to maintain acceptable fluid and electrolyte levels. The indications for the initiation of renal replacement therapy include hyperkalemia, hyponatremia with symptomatic volume overload, acidosis, hypocalcemia, hyperphosphatemia, uremic symptoms, and an inability to provide adequate nutrition because of the need for fluid restriction in the face of oliguria (Box 93.3). The two purposes of renal replacement therapy are ultrafiltration (removal of water) and dialysis (removal of solutes). In general, only neonates greater than 1.5-2 kg in size may be considered for renal replacement therapies because of limited ability to place and maintain dialysis access in smaller infants.

Peritoneal dialysis is the most commonly used renal replacement modality in the neonatal population, because it is technically less difficult and does not require vascular access or anticoagulation. For this procedure, hyperosmolar dialysate is repeatedly infused into and drained out of the peritoneal cavity through a surgically placed catheter, accomplishing ultrafiltration and dialysis. Cycle length, volume of dialysate infused ("dwell volume"), and the osmolar concentration of the dialysate can be varied to accomplish the goals of therapy. Contraindications to peritoneal dialysis include recent abdominal surgery, necrotizing enterocolitis, pleuroperitoneal leakage, and ventriculoperitoneal shunting.

• BOX 93.3 Indications for Dialysis

- Hyperkalemia
- Hyponatremia
- Acidosis
- Hypocalcemia
- Hyperphosphatemia
- Volume overload
- Uremic symptoms
- Inability to provide adequate nutrition

Continuous renal replacement therapy (CRRT) is becoming a more frequently used therapeutic modality in neonates and infants with AKI.[9] For this procedure, the patient's blood is continuously circulated through a pump-driven extracorporeal circuit containing a highly permeable hemofilter. In continuous venovenous hemofiltration (CVVH), an ultrafiltrate of plasma is removed, a portion of which is returned to the patient in the form of a physiologic replacement fluid. In continuous venovenous hemodialysis (CVVH-D), countercurrent dialysate is used rather than replacement fluid to achieve solute removal. CRRT can be employed in conjunction with extracorporeal membrane oxygenation (ECMO) by putting the CRRT circuit in line with the ECMO circuit. The chief advantage of CRRT is the ability to carefully control fluid removal, which makes this modality especially useful in the neonate with hemodynamic instability. The main disadvantages are the need to achieve and maintain central vascular access and the need for continuous anticoagulation.

Intermittent hemodialysis is a less commonly used but technically feasible mode of renal replacement therapy in the neonatal population. Hemodialysis involves intermittent 3- to 4-hour treatments in which fluid and solutes are rapidly removed from the infant using an extracorporeal dialyzer, with clearance achieved by the use of countercurrent dialysate. The chief advantage of hemodialysis is the ability to rapidly remove solutes and fluid, a characteristic that makes this modality the therapy of choice in neonatal hyperammonemia. The main disadvantages are the requirement for central vascular access, usually a double lumen 7 French catheter, and the hemodynamic instability and osmolar shifts that may occur with rapid solute and fluid shifts.

Providing adequate renal replacement therapy may be limited by the challenges in placing and/or maintaining intravascular or peritoneal dialysis access in the very small premature neonate. If dialysis access cannot be established, care of the infant with AKI is limited to maximal supportive medical management, with meticulous attention to fluid, electrolyte, and acid–base balance.

Prognosis

Research has demonstrated that AKI is not just a marker of severity of illness in neonates but is also independently associated with poor outcomes. A recent large multicenter retrospective study demonstrated that the presence of AKI was independently associated with increased mortality in neonates (10% vs 1%), as well as increased length of hospital stay (median 23 vs 19 days).[37] Infants with higher stages of AKI had higher mortality rates and lengths of hospitalization when compared to infants with lower stages of AKI.

In the past, AKI was felt to be a completely reversible syndrome in neonates, with the idea that kidney function returning to baseline indicated no further renal risk. However, observational studies have demonstrated high rates of chronic kidney disease (CKD) in survivors of neonatal AKI.[18] The risk of CKD in survivors of neonatal

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AKI may be compounded by the risks of prematurity and low birth weight, both of which are associated with CKD because of associated inadequate nephron development.[2] Long-term nephrology follow-up care is important to monitor for evidence of CKD over time. All neonates with an identified episode of AKI should be referred to nephrology for outpatient follow-up to assess for microalbuminuria, proteinuria, hypertension, and rise in serum creatinine over time indicative of CKD. Special attention should be given to those infants with a history of AKI stages 2 and 3 or treatment with dialysis, significant prematurity, IUGR, or underlying renal anomalies. Early identification of CKD allows implementation of strategies to slow the loss of kidney function, including healthy lifestyle, careful management of BP, reduction of proteinuria, hydration, and avoidance of nephrotoxin exposure.

Hypertension

Incidence and Definition

The incidence of hypertension in neonates is estimated to be approximately 1%-2%.[24] Hypertension is most often seen in infants with a concurrent condition such as chronic lung disease, renal disease, or a history of umbilical arterial catheterization. The definition of neonatal hypertension is sustained blood pressure above the 95th percentile for infants of similar size, gestational age, and postnatal age. Identification of elevated blood pressure in neonates can be difficult because of variations in blood pressure measurement techniques, normal changes in blood pressure with gestational age and weight, and other factors that affect blood pressure readings, including level of wakefulness, feeding, crying, and pain.

Useful data on normal infant blood pressures were published by Zubrow and colleagues, who prospectively measured blood pressure in nearly 700 infants, showing that blood pressure increased with gestational age, postconceptual age, and birth weight.[74] Based on these data and synthesis of several other studies, a practical table of systolic, diastolic, and mean arterial blood pressure values was created and may be useful in defining normal and elevated blood pressures in neonates greater than 2 weeks of age from 26-44 weeks' postconceptual age (Table 93.6).[24]

Causes

The causes of neonatal hypertension are varied and are outlined in Box 93.4. Renovascular hypertension is the most frequent cause of neonatal hypertension and accounts for up to 80%-90% of all cases. The most common cause of renovascular hypertension is renal arterial thromboembolism related to umbilical artery catheterization. Risk factors for complications from umbilical artery catheters include maternal diabetes, sepsis, dehydration, birth trauma, perinatal asphyxia, patent ductus arteriosus, and cocaine exposure.

TABLE 93.6 Estimated Blood Pressure Values after 2 Weeks of Age in Infants from 26-44 Weeks' Postconceptional Age

Postconceptional Age	50th %	95th %	99th %	Postconceptional Age	50th %	95th %	99th %
44 Weeks				**34 Weeks**			
SBP	88	105	110	SBP	70	85	90
DBP	50	68	73	DBP	40	55	60
MAP	63	80	85	MAP	50	65	70
42 Weeks				**32 Weeks**			
SBP	85	98	102	SBP	68	83	88
DBP	50	65	70	DBP	40	55	60
MAP	62	76	81	MAP	58	62	69
40 Weeks				**30 Weeks**			
SBP	80	95	100	SBP	64	80	85
DBP	50	65	70	DBP	40	55	60
MAP	60	75	80	MAP	48	65	68
38 Weeks				**28 Weeks**			
SBP	77	92	97	SBP	60	75	80
DBP	50	65	70	DBP	38	50	54
MAP	59	74	79	MAP	45	58	63
36 Weeks				**26 Weeks**			
SBP	72	87	92	SBP	55	72	77
DBP	50	65	70	DBP	30	50	56
MAP	57	72	71	MAP	38	57	63

DBP, Diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.
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• BOX 93.4 Causes of Neonatal Hypertension

- Renovascular Disease
  - Renal arterial thrombosis
  - Renal arterial stenosis
  - Renal venous thrombosis
- Obstructive Uropathy
  - Hydronephrosis
- Renal Parenchymal Disease/Malformations
  - Acute tubular necrosis
  - Polycystic kidney disease
  - Renal dysplasia
- Coarctation of the Aorta
- Neurologic Disorders
  - Pain
  - Seizures
  - Intracranial hypertension
  - Drug withdrawal
- Miscellaneous Causes
  - Bronchopulmonary dysplasia
  - Drug exposure (e.g., corticosteroids, catecholamines)
  - Abdominal wall closure
  - Extracorporeal membrane oxygenation

Less common causes of neonatal renovascular hypertension include congenital renal artery stenosis, fibromuscular dysplasia, midaortic coarctation, and renovascular compression by tumors.

Other causes of neonatal hypertension include renal disorders such as AKI, autosomal recessive polycystic kidney disease, and obstructive uropathy. The most significant nonrenal cause of neonatal hypertension is bronchopulmonary dysplasia (BPD). Although the mechanism by which BPD is associated with hypertension is not clearly defined, the severity of the blood pressure elevation appears to correlate with the severity of the lung disease.[4] Less common causes of neonatal hypertension include endocrine disorders, coarctation of the aorta, intraventricular hemorrhage, history of abdominal wall closure, tumors, treatment with ECMO, seizures, pain, and drug withdrawal. Medications such as corticosteroids, vasopressors, caffeine, theophylline, and bronchodilators have been associated with elevated blood pressures in neonates.

Clinical Presentation

The majority of neonates with hypertension are asymptomatic, as elevated blood pressures are typically noted on routine monitoring. If present, symptoms of neonatal hypertension are often nonspecific, including poor feeding, irritability, and lethargy. Marked blood pressure elevation may lead to cardiopulmonary symptoms, including tachypnea, cyanosis, apnea, impaired perfusion, vasomotor instability, congestive heart failure, and hepatosplenomegaly. Neurologic symptoms such as tremors, hypertonicity, hypotonicity, opisthotonos, asymmetric reflexes, hemiparesis, seizures, apnea, or coma may also occur. The renal effects of hypertension may include AKI and sodium wasting related to pressure natriuresis.

• BOX 93.5 Standardized Protocol for Blood Pressure Measurement in Neonates

- Measured by oscillometric device
- 1.5 hours after a feed or medical intervention
- Infant lying prone or supine
- Appropriately sized blood pressure cuff
- Right upper arm
- After cuff placement, infant is left undisturbed for 15 minutes
- Infant asleep or in quiet awake state
- Three successive blood pressure readings at 2-minute intervals

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Evaluation

The first step is to determine whether the elevated blood pressure persists when the infant is quiet and relaxed. A standardized protocol for accurate blood pressure measurement in neonates is shown in Box 93.5.[24] Blood pressures are preferably measured in the upper arm, as leg blood pressure measurements tend to overestimate the true blood pressure. History should focus on prenatal medication exposures, presence or history of an umbilical artery catheter, and treatment with medications that raise blood pressure. Blood pressure trends since birth should be reviewed to establish the onset and severity of hypertension. A complete physical examination is imperative, including four-extremity blood pressure measurements to diagnose or rule out aortic coarctation. The infant should be examined carefully for signs of volume overload, including peripheral edema, cardiac gallop, or rales. The abdomen should be carefully inspected for presence of abdominal or flank masses or renal bruits. Ambiguous genitalia in a hypertensive infant should raise the suspicion of congenital adrenal hyperplasia. Initial laboratory studies should include a urinalysis and determinations of serum electrolytes, blood urea nitrogen, serum creatinine, and serum calcium. Other diagnostic studies, including renin, aldosterone, cortisol, thyroid function tests, and catecholamines, can be considered based on the clinical scenario and results of screening studies.

Ultrasonography of the kidneys with a Doppler flow study of the aorta and renal arteries should be performed to exclude a renal arterial or aortic thrombus or structural anomalies of the urinary tract. Absence of a defined thrombus does not, however, rule out renovascular hypertension as the majority of thrombi are very small and not detectable by ultrasonography. Computed tomography, magnetic resonance angiography, and angiography may be considered in more difficult cases, although their use may be limited in the very small infant. Echocardiography should be performed to exclude aortic coarctation and evaluate the left ventricular mass.

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Treatment

The first approach to the treatment of neonatal hypertension is to correct all iatrogenic causes of blood pressure elevation, including improper measurement technique, vasopressor administration, volume overload, narcotic withdrawal, or inadequately controlled pain. If blood pressures remain elevated above the 99th percentile, experts advocate antihypertensive treatment with an intravenous or oral antihypertensive agent to prevent adverse effects on the kidneys, heart, and central nervous system (Tables 93.7 and 93.8).

Neonates with signs and symptoms of a hypertensive emergency such as cardiopulmonary failure, acute neurologic dysfunction, and AKI are best treated with a continuous intravenous infusion of an antihypertensive agent such as nicardipine, esmolol, or labetalol. Careful monitoring using an arterial line is recommended. The chief advantage of a continuous infusion is the ability to quickly increase or decrease the rate of infusion to achieve the desired blood pressure. The goal of therapy is a gradual decrease in blood pressure to minimize injury to the brain, heart, and kidneys. Blood pressure should not be lowered below the 95th percentile for at least 24-48 hours to avoid the possibility of cerebral and optic disc ischemia.

Oral antihypertensive agents are best used in infants with less severe hypertension or in those whose acute hypertension has been controlled with intravenous infusions and who are ready to switch to chronic oral therapy. Calcium channel blockers, such as isradipine and amlodipine, are first-choice agents. ACE inhibitors such as captopril may be useful but are not recommended for infants less than 44 weeks' postconceptional age, because they may impair the final stages of renal maturation. If ACE inhibitors are used, careful attention to urine output and the levels of serum creatinine and potassium is recommended, as neonates may be extremely sensitive to the reduction in renal blood flow associated with the administration of these agents. Diuretics such as chlorothiazide may be useful agents in infants with chronic lung disease. Intermittent administration of intravenous agents, such as hydralazine or labetalol, may be considered in hypertensive infants with mild to moderate hypertension in whom oral agents cannot be used because of gastrointestinal dysfunction.

In infants with suspected renovascular hypertension, the umbilical artery catheter should be removed as soon as

TABLE 93.7 Intravenous Antihypertensive Medications

Drug	Dose	Interval	Action
Esmolol	100-500 mcg/kg/min	Continuous infusion	Beta blocker
Hydralazine	0.15-0.6 mg/kg/dose	Every 4-6 hr	Vasodilator
Labetalol	0.2-1.0 mg/kg/dose 0.25-3.0 mg/kg/hr	Every 4-6 hr Continuous infusion	Alpha and beta blocker
Nicardipine	1-4 mcg/kg/min	Continuous infusion	Calcium channel blocker
Sodium nitroprusside	0.5-10.0 mcg/kg/min	Continuous infusion	Vasodilator

TABLE 93.8 Oral Antihypertensive Medications

Drug	Dose	Interval	Class
Amlodipine	0.05-0.3 mg/kg/dose	Daily to BID	Calcium channel blocker
Captopril	0.01-0.5 mg/kg/dose	TID	Angiotensin-converting enzyme inhibitor
Chlorothiazide	5-15 mg/kg/dose	BID	Distal tubule diuretic
Clonidine	5-10 mcg/kg/day (in 3 divided doses)	TID	Alpha-agonist
Enalapril	0.04-0.3 mg/kg/dose	Daily to BID	Angiotensin-converting enzyme inhibitor
Furosemide	1-2 mg/kg/dose	Daily to TID	Loop diuretic
Isradipine	0.05-0.15 mg/kg/dose	QID	Calcium channel blocker
Labetalol	0.05-1.0 mg/kg/dose	BID to TID	Alpha and beta blocker
Propranolol	0.5-1.0 mg/kg/dose	TID	Beta blocker

BID, Twice daily; QID, four times daily; TID, three times daily.

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possible. If a large thrombus is identified, systemic heparinization may be considered to prevent extension of the clot. If the hypertension cannot be controlled medically or massive aortic thrombosis results in major complications, thrombolysis with urokinase, streptokinase, or tissue plasminogen activator may be considered. If severe hypertension persists, surgical thrombectomy or nephrectomy may be contemplated.

Prognosis

Most neonates with hypertension presumed to be caused by umbilical artery catheters or bronchopulmonary dysplasia experience improvement in their blood pressures and do not typically require antihypertensive medications beyond 12 months of age. Infants may require periodic increases in their antihypertensive medications following discharge from the hospital because of rapid growth, but over time antihypertensive agents may be weaned by maintaining a stable medication dose as the infant grows in size. On the other hand, infants with hypertension related to renal disease or another secondary cause will most likely have hypertension that persists into childhood.

Long-term studies of children and adolescents with a history of neonatal hypertension are needed. There is growing evidence that neonates born prior to completion of nephrogenesis at 34-36 weeks' gestation may be at increased risk for development of hypertension and chronic kidney disease in adolescence or adulthood.[2]

Nephrocalcinosis

Nephrocalcinosis, defined as calcium salt deposition in the renal interstitium, is a well-known complication in the neonatal population, occurring in 7%-41% of hospitalized premature infants.[59] Infants at highest risk appear to be those with lower gestational age and birth weight, often in combination with severe respiratory disease. Nephrocalcinosis is usually discovered incidentally on abdominal imaging studies, although infants with nephrocalcinosis may present with microscopic or gross hematuria, granular material in the diaper, or urinary tract infection.

Neonatal nephrocalcinosis is multifactorial in etiology and develops as the consequence of an imbalance between stone-promoting and stone-inhibiting factors.[59] The immature renal tubular cells of the preterm infant are more susceptible to crystal formation and aggregation. Furthermore, the low GFR of the preterm infant results in a low tubular fluid flow rate that promotes crystal formation. Hypercalciuria (excessive urinary calcium excretion) is a common risk factor and may result from chronic treatment with loop diuretics, increased calcium intake from TPN, or vitamin D supplementation. Subcutaneous fat necrosis following birth trauma is a rare but serious cause of hypercalciuria. Other risk factors for nephrocalcinosis include hypocitraturia (low urinary citrate excretion); this is a common finding in patients with persistent metabolic acidosis, which often occurs in ill preterm infants. Less common genetic conditions in which there is an increased risk of nephrocalcinosis include primary hyperoxaluria, distal renal tubular acidosis, Bartter syndrome, Williams syndrome, and idiopathic infantile hypercalcemia.

Routine ultrasonographic screening should be considered for all infants who receive long-term loop diuretics for chronic lung or heart disease. In those with documented nephrocalcinosis, loop diuretics should be discontinued, if possible. Thiazide diuretics, such as chlorothiazide, may be substituted as they tend to reduce urinary calcium excretion, although serum calcium must be monitored closely to avoid hypercalcemia. Agents that may increase urinary calcium excretion, including glucocorticoids, xanthine derivatives, and any sodium-containing supplements should be minimized or discontinued if possible. Administration of calcium and phosphorus in TPN as well as vitamin D supplementation should be reduced if excessive. A high urinary flow rate should be maintained to reduce the probability of urinary crystallization. Metabolic acidosis, if present, should be treated with potassium citrate. The goal of therapy should be the maintenance of the spot urinary calcium-to-creatinine ratio at less than 0.8 for infants less than 7 months of age.[59]

The usual outcome for infants with neonatal nephrocalcinosis without an underlying genetic defect is spontaneous resolution over the first 2 years of life. Serial renal ultrasonography is needed to confirm resolution of nephrocalcinosis. There is concern that neonatal nephrocalcinosis may increase risk for impairment in kidney function later in life, particularly in premature infants who are inherently at increased risk of chronic kidney disease. Although results are conflicting whether nephrocalcinosis affects renal growth and function, one case series demonstrated evidence of tubular dysfunction and shorter kidney length in the first year of life of infants with nephrocalcinosis.[29] Long-term nephrology follow-up care of premature infants with nephrocalcinosis is recommended.

Renal Vascular Thrombosis

Thromboembolic complications are rare but serious events in the NICU. The neonatal kidney is particularly vulnerable to thrombosis because of its relatively low blood flow, small vessel diameter, enhanced renal vasoconstriction, and intervening events including hypoxia, volume depletion, hypotension, and infection that disturb the delicate balance between procoagulant and anticoagulant factors. Both venous and arterial thrombosis may occur in the neonate, although renal venous thromboses (RVT) are more common. Risk factors for RVT include prematurity, maternal diabetes mellitus, congenital heart disease, polycythemia, hypertonic dehydration, acute blood loss, perinatal asphyxia, in utero death of a twin, sepsis, RDS, and prolonged central venous cannulation.[58] A subset of neonates with RVT have an inherited thrombophilia, including deficiencies of protein C, protein S or antithrombin, Factor V Leiden mutation, or the prothrombin gene mutation.

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Thrombosis begins in the small renal veins and propagates toward the main renal vein, ultimately reaching the inferior vena cava. Thrombosis is usually unilateral (70%) but may be bilateral or extend into the inferior vena cava and is associated with adrenal infarction in a minority of patients.

The classic clinical triad of symptoms in RVT includes a flank mass, macroscopic hematuria, and thrombocytopenia, although all elements of the triad are present in fewer than 25% of infants with RVT. Additional signs may include oliguric AKI, hypertension, vomiting, lethargy, anorexia, fever, and shock. Ultrasonography in the acute phase reveals enlarged and echogenic kidneys with loss of corticomedullary differentiation. A Doppler study may reveal resistance or absence of blood flow in the main renal vein and collateral vessels. Uptake may be absent or severely diminished on a radionuclide scan. Ultrasonography following the acute phase may show gradual decrease in kidney size with renal atrophy.

Initial evaluation after identification of a thrombosis should include baseline testing, including a CBC, prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen concentration. Maternal blood may be tested for lupus anticoagulant and anticardiolipin antibody. Testing for an inherited prothrombotic state should be conducted in neonates with thrombosis, which is clinically significant, recurrent, or spontaneous. Testing is best deferred until after resolution of the acute event.

There are no evidence-based guidelines for management of neonatal RVT, although expert opinion guidelines suggest the need for a multidisciplinary team including neonatology, nephrology, radiology, and hematology. If the thrombosis appears to be catheter-associated, the catheter should be removed. Supportive medical treatment consists of correction of fluid and electrolyte imbalances as well as supportive treatment of AKI, possibly including dialysis. Anticoagulation (unfractionated heparin or low molecular weight heparin) may be employed to prevent the extension of thrombosis, although the benefits of anticoagulation should be weighed against the risks of hemorrhagic events, including intraventricular hemorrhage. Thrombolytic therapies such as recombinant tissue plasminogen activator or urokinase should be reserved for cases of critical compromise of kidney function, as seen in bilateral renal vein thrombosis. Surgical thrombectomy is considered in patients with thrombosis of the inferior vena cava, and nephrectomy may be necessary in infants with severe refractory hypertension.

Although the perinatal mortality rate in infants with RVT has decreased progressively during the past decades, the prognosis for the affected kidney is poor, with progressive atrophy in up to 70% of kidneys.[58] Long-term complications include hypertension in 20% of patients, chronic kidney disease, and end-stage kidney disease in the minority of patients with a history of bilateral thrombosis.

Congenital Anomalies of Kidneys and Urinary Tract

Many of the disorders of the kidney and urinary tract that present in utero or in the neonatal period are the result of congenital malformations or inherited disorders (Box 93.6; see also Table 93.1). Most of the congenital abnormalities of the kidney and urinary tract disorders occur sporadically, and the pathogenesis is not well defined. As mentioned above, studies have begun to elucidate the genetic basis for some of these disorders, such as Eagle-Barrett ("prune belly") syndrome, renal hypoplasia, and renal dysplasia.[63,70] The following section will review some of the more common congenital renal anomalies that present in neonates and infants. Because of the rapidly changing nature of molecular genetics, it is suggested that the reader consult the OMIM (Online Mendelian Inheritance in

• BOX 93.6 Overview of Congenital and Inherited Disorders of the Kidney and Urinary Tract that Present in Infancy

Urologic Anomalies

- Ureteropelvic junction or ureterovesical junction obstruction
- Posterior urethral valves
- Eagle-Barrett syndrome
- Vesicoureteral reflux

Cystic and Dysplastic Disorders

- Renal hypoplasia
- Renal dysplasia (including multicystic dysplastic kidney)
- Unilateral or bilateral renal agenesis
- Polycystic kidney disease
- Autosomal recessive polycystic kidney disease
- Autosomal dominant polycystic kidney disease
- Glomerulocystic kidney disease
- Other cystic disorders
- Infantile nephronophthisis
- Diffuse cystic dysplasia associated with congenital abnormalities

Tubular Transport Disorders

- Renal tubular acidosis
- Fanconi syndrome
- Bartter syndrome
- Nephrogenic diabetes insipidus
- Tubular disorders associated with syndromes (e.g. Lowe syndrome, cystinosis, and galactosemia)
- Pseudohypoaldosteronism

Miscellaneous Disorders

- Congenital nephrotic syndrome
- Teratogen fetopathies (e.g., ACEIs, ARBs, mycophenolate mofetil)
- Tumors (e.g., Wilms tumor, neuroblastoma, congenital mesoblastic nephroma)

ACEIs, Angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers.

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Man) database at http://www.omim.org (accessed March 4, 2019) for the most up-to-date information about the genetic basis for these disorders.

Renal Agenesis

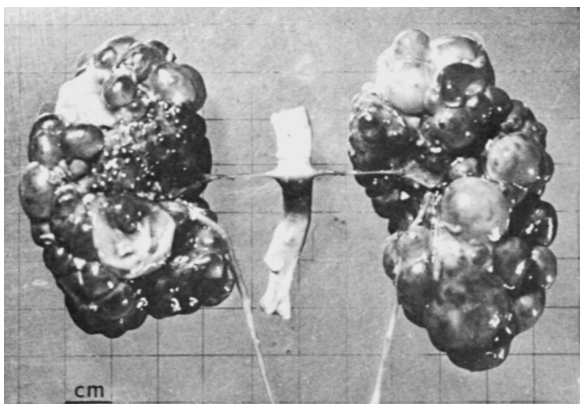
Unilateral renal agenesis (URA; congenital absence of the kidney) occurs in 1 of 2000-2500 births, and bilateral renal agenesis occurs in 1 of 4,000-10,000.[42,68] Renal agenesis occurs when the ureteric bud fails to induce proper differentiation of the metanephric blastema, an event that may be related to both genetic and environmental factors. In a review of birth registry data, about 30% of infants with URA had extra-renal anomalies, cardiac in 60% and skeletal in 30%, and only 7% had contralateral CAKUT.[42] Syndromic URA may be seen in infants with the VACTERL association (i.e., *v*ertebral abnormalities, *a*nal atresia, *c*ardiac abnormalities, *t*racheoesophageal fistula or *e*sophageal atresia, *r*enal agenesis and dysplasia, and *l*imb defects), caudal regression syndrome, branchio-oto-renal syndrome, and multiple chromosomal defects, but it may also occur in otherwise healthy infants. In isolated renal agenesis, compensatory hypertrophy of the remaining solitary kidney is usually evident in utero and may begin as early as 20 weeks' gestation, with the contralateral kidney growing at about the 97th percentile for gestational age.[55] The presence of hypertrophy in a solitary kidney is an important clinical indicator in terms of prognosis for good long-term renal function. VCUG may be considered for neonates with unilateral renal agenesis who have hydronephrosis, bladder abnormality, or small or echogenic solitary kidney. Unilateral renal agenesis is also associated with developmental defects of the Müllerian ducts in about 10% of females,[68] such as Mayer-Rokitansky or Herlyn-Werner-Wunderlich syndromes.[35] These disorders, however, may not be clinically evident until adolescence, when patients present with amenorrhea or dysmenorrhea. In males, cases of congenital absence of the vas deferens along with URA have been reported.[41]

Renal Dysplasia

Renal dysplasia is characterized by abnormal renal development in the fetus, leading to replacement of the renal parenchyma by cartilage and disorganized epithelial structures. The pathogenesis of renal dysplasia may involve mutations in developmental genes (Table 93.1), urinary tract obstruction, or in utero toxin/medication exposure.[19,48] Renal dysplasia occurs frequently in infants with obstructive uropathy and a variety of congenital disorders, such as VACTERL association; CHARGE syndrome; brachio-oto-renal syndrome; Jeune syndrome; and trisomies 13, 18, and 21. Most forms of "polycystic kidneys" that are reported in association with syndromes, in fact, represent bilateral cystic dysplasia. Renal dysplasia may also occur as an isolated finding. The function of dysplastic kidneys is quite variable, and infants with bilateral dysplasia may exhibit signs of renal insufficiency as early as the first few days of life. Concentration and acidification defects may also be present, but hematuria, proteinuria, and hypertension are unusual findings. Children with bilateral renal dysplasia generally develop progressive renal insufficiency during childhood and adolescence.

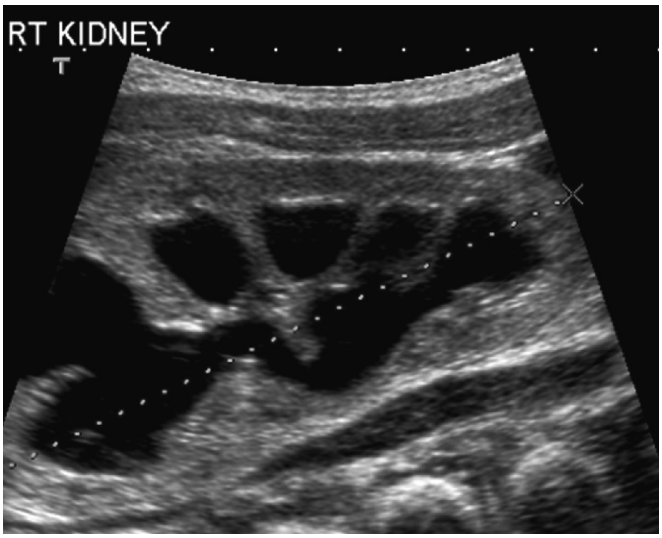
Multicystic Dysplastic Kidney

Multicystic dysplastic kidney (MCDK) represents the most severe form of renal dysplasia and is characterized by a nonfunctioning kidney that is devoid of normal renal architecture and composed of multiple large cysts that resemble a cluster of grapes (Fig. 93.4).[69] In a recent review of European registry data, the incidence of MCDK was 1 in 2400 total births and 1 in 3200 live births.[69] MCDK is slightly more prevalent in males and occurs twice as often on the left side as the right side. The pathogenesis is poorly understood but may involve failure of the ureteric bud to integrate and branch appropriately into the metanephros.[32] Multiple different genetic abnormalities may be linked to MCDK (Table 93.1), and 4% of infants will have an abnormal karyotype while 17% have pathogenic copy number variation.[28] With the widespread use of prenatal ultrasonography, 90% of cases of MCDK are identified in utero.[69] Eighty-four percent of infants with unilateral MCDK will have an isolated renal anomaly and overall, these infants do well in the perinatal period.[69] Bilateral MCDK is usually fatal and associated with extra-renal anomalies in about half of cases. About 20% of children with unilateral MCDK will have vesicoureteral reflux into the contralateral kidney, which is grades I-III in 96%.[26] Historically, a full evaluation of the urinary tract, including a VCUG, was advised for all infants with MCDK to rule out abnormalities of the contralateral urinary tract, including vesicoureteral reflux (VUR). However, contralateral abnormalities are uncommon and most VUR in children with MCDK is insignificant, so most infants can be managed conservatively with watchful waiting.[26] The majority of MCDKs undergo partial or



• **Fig. 93.4** Bilateral multicystic dysplastic kidneys in a newborn infant. Gross pathology demonstrates enlarged, irregularly cystic kidneys; the usual reniform configuration is barely apparent. Both ureters are atretic, and the renal arteries are extremely small. This condition results in total absence of renal function and is one of the multiple causes of oligohydramnios sequence (Potter syndrome).

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• **Fig. 93.5** Neonatal hydronephrosis. Sonogram of the right kidney in a 1-day-old neonate with a history of prenatal hydronephrosis demonstrates severe dilation of the collecting system.

complete spontaneous involution over time, with close to 60% involution by 10 years.[26] The contralateral kidney, if unaffected by other urologic malformations, generally shows compensatory hypertrophy, allowing the child to maintain normal renal function. It is common practice to follow patients with MCDKs using serial ultrasonography to ensure involution and appropriate compensatory growth of the contralateral kidney over time. Hypertension does not appear to occur at increased frequency in isolated MCDK, and the risk for malignancy is extremely low and may not be higher than the general population. Surgical removal, therefore, is reserved for children in whom the MCDK grows larger over time.[26]

Hydronephrosis

Hydronephrosis, defined as significant dilation of the upper urinary tract (Fig. 93.5), is one of the most common congenital conditions detected by prenatal ultrasonography.[71] The differential diagnosis of hydronephrosis (in order of frequency) includes physiologic hydronephrosis (50%-70% of cases), ureteropelvic junction obstruction (10%-30%), vesicoureteral reflux (10%-40%), ureterovesical junction obstruction (5%-15%), multicystic dysplastic kidney (2%-5%), posterior urethral valves (1%-5%), ureterocele (1%-3%), and Eagle-Barrett syndrome (<1%).[71] The grading system for prenatal and postnatal hydronephrosis proposed by the Society of Fetal Urology has become widely accepted.[52] This system is dependent on the measurement of anterior–posterior renal pelvis dilation (APRPD) taken at the maximal diameter of intrarenal pelvis dilation. Normal APRPD is less than 4 mm at 16-28 weeks' gestation, less than 7 mm after 28 weeks, and less than 10 mm at 2 days of life.[52] In addition, the parenchymal thickness, echogenicity, and differentiation of the kidneys should be delineated, and the ureters and bladder should be examined for abnormalities. Finally, the presence or absence of oligohydramnios should be commented on prenatally. The APRPD on prenatal US can inform diagnosis and postnatal outcomes and, therefore, the postnatal management.[15]

Physiologic Hydronephrosis

At least 80% of all prenatally detected mild hydronephrosis (APRPD 7-10 mm at 30 weeks' gestational age) resolves spontaneously and is not associated with an anatomic abnormality of the urinary tract. Hydronephrosis, which improves or resolves during the pregnancy, is unlikely to have any postnatal implications.[53] Physiologic hydronephrosis may be caused by a delay in the maturation of the ureter, which leads to transient urinary flow obstruction. The hydronephrosis in these patients generally resolves within the first 2 years of life.[15]

Ureteropelvic Junction Obstruction

Ureteropelvic junction (UPJ) obstruction is the most common cause of moderate to severe congenital hydronephrosis and may be the result of incomplete recanalization of the proximal ureter, abnormal development of the ureteral musculature, abnormal peristalsis, or polyps. UPJ obstruction is more common in boys and may be associated with other congenital anomalies (including other genitourinary malformations) or syndromes. The diagnosis is confirmed by an obstructive pattern observed on a diuretic-enhanced radionuclide scan, which is typically deferred until several weeks of age owing to limitation in testing related to low newborn GFRs. Many clinicians advocate antibiotic prophylaxis to prevent urinary tract infection, which was shown to be effective in preventing infection in patients with high-grade hydronephrosis.[16,72,73] Temporary relief of obstruction may be necessary and is often achieved by placement of a percutaneous nephrostomy drain. Definitive treatment often involves surgical repair. The indication for surgery varies by center and provider, and children with more severe hydronephrosis are more likely to receive intervention. About 20%-25% of children with UPJ obstruction will have surgery for decreased renal function or progression of hydronephrosis.[53] Early consultation with an experienced pediatric urologist is recommended.

Ureterovesical Junction Obstruction

Ureterovesical junction (UVJ) obstruction is another cause of congenital hydronephrosis and is characterized by hydronephrosis with associated ureteral dilatation. This disorder may be related to the deficient development of the distal ureter or the presence of a ureterocele and is likely to spontaneously resolve in 70% of patients.[53] The diagnosis is confirmed by a radionuclide scan and VCUG. UVJ obstruction is usually not associated with other congenital malformations. A ureteral dilation greater than 1 cm is associated with higher risk of urinary tract infection so antibiotic prophylaxis may be indicated.[34] Temporary or permanent surgical interventions may be required, based on the clinical situation.

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Vesicoureteral Reflux

Vesicoureteral reflux (VUR) accounts for 10%-40% of neonatal hydronephrosis. It is defined as the retrograde propulsion of urine into the upper urinary tract during bladder contraction. The underlying cause of VUR is believed to be ectopic insertion of the ureter into the bladder wall, resulting in a shorter intravesicular ureter, which acts as an incompetent valve during urination. Vesicoureteral reflux is graded from I to V, with grade I indicating the lowest and grade V the highest. In infants and children evaluated for their first urinary tract infection, at least one-third have VUR identified on a VCUG. Although the exact genetic basis of this condition has not been determined, there appears to be a genetic component, because the incidence of VUR is approximately 30% in first-degree relatives, including siblings.[66] Table 93.1 lists a number of mutations, which have been associated with VUR.

Primary VUR tends to resolve over time as the intravesical segment of the ureter elongates with growth. VUR itself is not thought to cause renal damage. Instead, VUR may be associated with CKD if there is either primary renal dysplasia or with secondary scarring acquired as the result of febrile urinary tract infection.[56] Clinicians should be aware that ultrasonography is a poor screening tool for VUR, even in young children with documented urinary tract infection and high-grade reflux.[46]

Management of VUR depends on its extent and severity as well as the presence or absence of associated renal parenchymal abnormalities (e.g., renal dysplasia). In the past, antibiotic prophylaxis was recommended for patients with all grades of VUR. This practice is also the subject of controversy, and patients with low grade (I–II) VUR probably do not require prophylaxis. Antibiotic prophylaxis does appear to decrease the rate of urinary tract infections in patients with high-grade VUR.[34] Surgical repair is considered in children with high-grade VUR or breakthrough urinary tract infections despite antibiotic prophylaxis. Long-term complications of VUR in conjunction with infections include hypertension, renal scarring, and chronic kidney disease ("reflux nephropathy").

Posterior Urethral Valves

Posterior urethral valves (PUV) represent the most common cause of lower urinary tract obstruction, with an incidence of 1 in 5000-8000 live male births. A posterior urethral valve is composed of a congenital membrane that obstructs or partially obstructs the posterior urethra and is formed when the mesonephric duct fails to adequately regress. Findings on prenatal ultrasound may include hydronephrosis; dilated ureters; a thickened, trabeculated bladder; dilated proximal urethra; and oligohydramnios. The antenatal presentation may include a palpable, distended bladder, poor urinary stream, and signs and symptoms of renal and pulmonary insufficiency. The VCUG is diagnostic for PUV and reveals associated VUR in 30% of patients.

Prenatal therapy with laser valve ablation or insertion of vesico-amniotic shunt has been attempted, but the benefits of prenatal intervention for postnatal and long-term outcomes are still unclear.[45,49] Postnatal treatment is centered on securing adequate drainage of the urinary tract, initially by placement of a urinary catheter and later by primary ablation of the valves. Vesicostomy may be required in infants who show persistent obstruction and impaired urinary drainage despite ablation. Upper tract diversion is less commonly required but may be attempted in patients with markedly dilated, tortuous ureters and worsening renal function despite placement of a bladder catheter. The long-term outcome for infants with PUV depends on the degree of associated renal dysplasia, as postnatal correction of the obstruction often does not result in normalization of renal function.[21,54] Approximately 15%-20% of boys with PUV who present in infancy will progress to end-stage renal disease by adolescence.[6,7] Reported risk factors for progression to end-stage renal disease include a nadir serum creatinine of greater than 1 mg/dL, bladder dysfunction, and urinary tract infections.[6,7] A more recent analysis, however, demonstrated that while a creatinine greater than 1 mg/dL has good specificity for the development of chronic kidney insufficiency in infants with PUV, it has poor sensitivity,[21] so infants should be referred to a pediatric nephrologist for ongoing care.

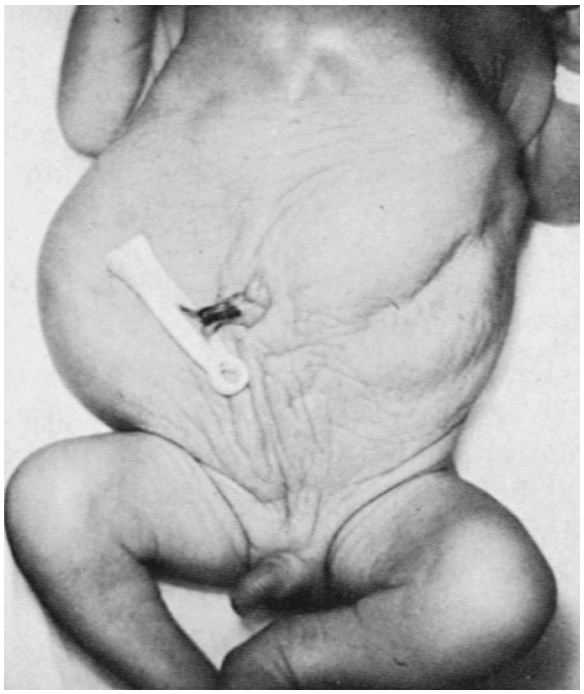
Eagle-Barrett Syndrome

Eagle-Barrett ("prune belly") syndrome (EBS) is characterized by a triad of genitourinary abnormalities (markedly enlarged bladder with poor contractility without urethral obstruction, megaureters, and renal dysplasia), deficiency of abdominal wall musculature, and cryptorchidism (Fig. 93.6). Not all patients display all three components, and the severity of findings may be variable. The estimated incidence is 1 in 35,000-50,000 live births, with more than 95% of the cases occurring in boys. Although most cases occur sporadically, several reports of familial inheritance led to the identification of at least two potential causative genes, CHRM3/acetylcholine receptor and ACTA2/alpha-smooth muscle actin2, and whole gene deletion of HNF1-ß as well as trisomy 21 have also been associated with EBS.[70] Cardiac, pulmonary, gastrointestinal, and orthopedic anomalies are present in a large percentage of EBS patients, some of which may be attributable to oligohydramnios sequence. Treatment in the neonatal period involves optimization of urinary tract drainage, management of renal insufficiency, and antibiotic prophylaxis. Management later in childhood may include the surgical repair of reflux, orchiopexy, reconstruction of the abdominal wall, and dialysis and/or renal transplantation.

Bladder Exstrophy-Epispadias Complex

The bladder exstrophy-epispadias complex includes a spectrum of malformations that ranges from the mildest form, epispadias, through classic bladder exstrophy, to the most severe form, cloacal exstrophy, which may encompass

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• **Fig. 93.6** Eagle-Barrett ("prune-belly") syndrome. Photomicrograph illustrates the characteristic appearance of a wrinkled abdomen, indicative of absent or deficient abdominal musculature.

omphalocele, bladder exstrophy, imperforate anus, and spinal defects.[70] The incidence of bladder exstrophy-epispadias complex is estimated at 1 in 10,000 births with a male predisposition.[70]

Enlargement or mechanical disruption of the cloacal membrane (the bladder portion of the cloaca and the overlying ectoderm) prevents the invasion of mesodermal cells along the infraumbilical midline, resulting in exstrophy. The nature of the specific abnormality is dependent, in large part, on the timing of the rupture of the cloacal membrane. If rupture occurs before the fourth week of gestation, cloacal exstrophy develops, whereas if rupture occurs after 6 weeks of gestation, epispadias or classic bladder exstrophy occurs. As with other congenital structural urogenital anomalies, many cases of bladder exstrophy-epispadias complex are sporadic. However, there are some reports of occurrence within families, suggesting a genetic component for this multifactorial disorder.[44]

The clinical presentation of classic bladder exstrophy is characterized by an evaginated bladder plate with urine dripping from the ureteric orifices on the bladder surface. Bilateral inguinal hernias are usually present as well. Pubic bones can be felt on both sides of the bladder. The penis appears shorter and the epispadic urethra covers the dorsum of the penis. Testes are usually descended. In females, the clitoris is completely split next to the open urethra.[25] Epispadias is categorized by three degrees of severity, with severe forms involving the entire urethra and bladder.[25] Cloacal exstrophy is the more severe form and can easily involve different organs that require immediate surgical attention.

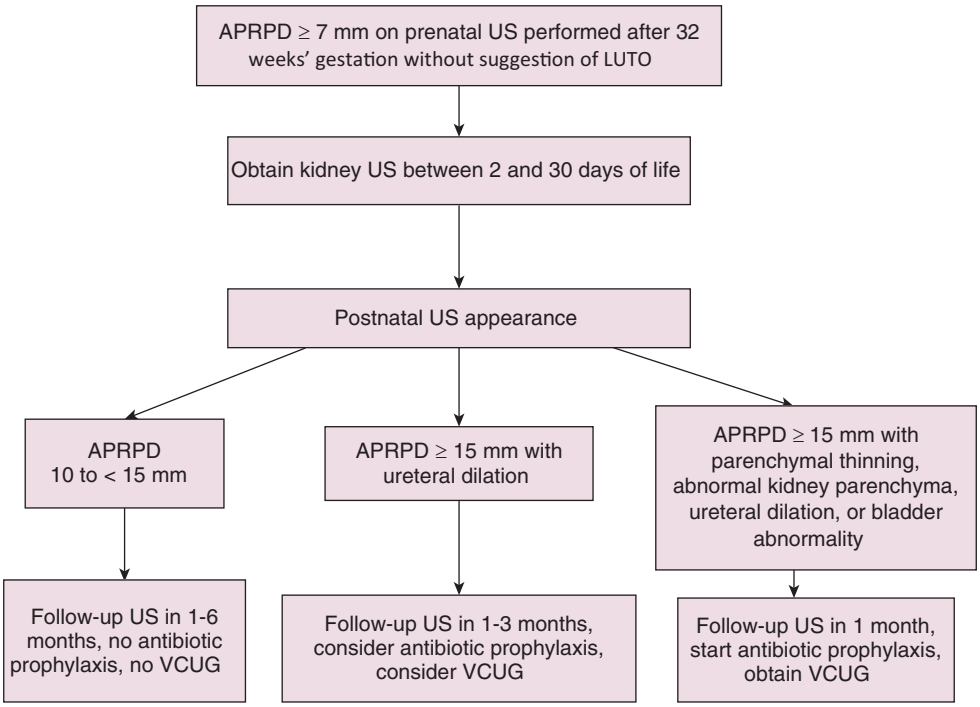
A renal sonogram is mandatory for every infant with bladder exstrophy-epispadias complex to obtain a baseline examination of both kidneys before repair. Spine ultrasound and radiographs are required to define individual abnormalities. Hip radiographs and possibly magnetic resonance imaging of the pelvis help estimate the symphysis gap and hip localization.[25] Treatment is surgical, and patients require long-term follow-up and a multidisciplinary team that includes a pediatric urologist, pediatric orthopedic surgeon, pediatric nephrologist (if renal dysplasia is present), and appropriate support team.[25]

Management of Antenatal Hydronephrosis

The postnatal management of infants with history of antenatal hydronephrosis is dependent on the degree of dilation seen on third-trimester ultrasound and on the suspicion for lower urinary tract obstruction. A thick-walled bladder, usually defined as wall thickness of 5 mm or greater, that fails to empty and a dilated urethra, with or without bilateral hydronephrosis, should raise the suspicion of lower tract obstruction, and those infants should be evaluated by a pediatric urologist and/or nephrologist in the immediate postnatal period.[53] In the presence of oligohydramnios, the infant should be delivered in a setting capable of providing high acuity care, and immediate respiratory support as these infants are more likely to have significant renal dysfunction.[53]

Several grading systems for antenatal hydronephrosis have been recommended, but the most commonly cited is the one proposed by the Society of Fetal Urology.[52] This system has shown some ability to predict which infants will go on to need surgical intervention versus which ones can be monitored because their degree of hydronephrosis is likely to self-resolve. Grading of antenatal hydronephrosis is based on the anterior–posterior renal pelvis dilation (APRPD) of the renal pelvis when it is visualized in the transverse plane. In the third trimester, an APRPD less than 7 mm is considered normal, while mild, moderate, and severe hydronephrosis are defined as APRPD 7-9 mm, 10-15 mm, and greater than 15 mm respectively.[53] Mild hydronephrosis (APRPD 7 to <10 mm) is more likely to be a transient dilation that will self-resolve. Only about 3% of these infants will have VUR or develop urinary tract infections, and most will not require surgical intervention.[62] Therefore, they do not require antibiotic prophylaxis, and the first postnatal ultrasound may be delayed for 1-2 weeks. Of infants with severe hydronephrosis, about 20% will have VUR and 10%-35% will develop UTIs mostly in the first year of life.[73] Even in the absence of VUR, children with severe hydronephrosis are at high risk of urinary tract infection, especially in the setting of ureteral obstruction or dilation. There is mixed evidence for the benefit of antibiotic prophylaxis for infants with moderate to severe hydronephrosis; however, many practitioners will recommend prophylactic antibiotics, as some studies have shown a decreased risk for infection with prophylactic antibiotics.[14,34,72,73] The need for VCUG in these patients is controversial and may be

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• **Fig. 93.7** Suggested postnatal management of antenatal hydronephrosis.[49] APRPD, anterior posterior renal pelvic dilation; LUTO, lower urinary tract obstruction; US, ultrasound; VCUG, voiding cystourethrogram.

dependent on provider preference.[53] Fig. 93.7 demonstrates one suggested approach to the management of antenatal hydronephrosis.

Oligohydramnios of Renal Origin

Severe congenital renal malformation (see also Chapters 13 and 24) may lead to oligohydramnios of renal origin with resultant pulmonary hypoplasia and Potter sequence. In general, oligohydramnios of renal origin portends a poor prognosis, especially when diagnosed during the second trimester.[47] Renal anomalies or obstruction of both kidneys may lead to low amniotic fluid. Cases of serial amnioinfusion with successful delivery of live infants who survived with subsequent dialysis have been reported.[12] Randomized trials testing the effectiveness of vesico-amniotic shunting have failed to show benefit but were also underpowered.[64] Therefore, to date, no prenatal intervention for oligohydramnios of renal origin is considered standard of care, although it may be attempted depending on center expertise or in research settings.

Inherited Renal Disorders

Inherited renal disorders include a spectrum of abnormalities involving the glomeruli or renal tubules. Monogenic diseases (those with single gene defects) that may present in the newborn period include congenital nephrotic syndrome, polycystic kidney diseases, and several disorders of tubular transport.

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome (CNS) is a rare condition that is defined as the development of nephrotic syndrome within the first 3 months of life. As in other forms of nephrotic syndrome, the clinical characteristics include heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema.[36] Most of the cases of primary CNS occur in infants with Finnish ancestry (CNF). CNF is a well-characterized autosomal recessive disorder with an estimated incidence of 1 in 8200 live births in the Finnish population.[67] However, primary CNS has also been described in infants of non-Finnish ancestry and in infants with other genetic defects that affect the structure or function of the glomerular slit diaphragm (e.g., Denys-Drash or Pierson syndromes). Secondary CNS can occur in infants with congenital infections or a history of maternal systemic lupus erythematosis.[67]

A prenatal diagnosis of CNS should be suspected in mothers with a high serum or amniotic fluid alpha-fetoprotein concentration, which results from massive fetal urinary protein losses. The ultrasonographic detection of placental edema, ascites, or fetal hydrops should also raise the suspicion of this disorder.

Infants with CNF typically have full-blown nephrotic syndrome at birth, with massive proteinuria, profound hypoalbuminemia, hyperlipidemia, and edema. Forty-two percent of the infants with CNF are delivered prematurely; the mean gestational age is 36.6 weeks. Many

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infants, particularly those born after 37 weeks, are small for their gestational age. The placenta is always large, weighing greater than 25% of the infant's birth weight.

CNF, also called CNS type I, is caused by mutations in *NPHS1*, located on chromosome 19. *NPHS1* encodes nephrin, a key component of the glomerular slit diaphragm. Alterations in nephrin cause disruption of the filtration barrier, leading to massive urinary protein loss and the clinical characteristics of nephrotic syndrome. The renal histopathology of CNF includes mesangial hypercellularity, tubular microcysts, and variably sized glomeruli with a characteristic fetal appearance, demonstrating prominent cuboidal epithelial cells. Although *NPHS1* mutations account for the majority of patients with CNS, other genetic forms of CNS have been identified, including disorders associated with mutations in *NPHS2* (podocin), *WT-1* (Wilms tumor suppressor gene), and *LAMB2* (laminin beta-2 gene).[67]

The treatment of congenital nephrotic syndrome is complex.[36] The clinician should first exclude congenital infections such as syphilis, HIV, CMV, hepatitis B, rubella, and toxoplasmosis, all of which have been associated with treatable forms of nephrotic syndrome in neonates. Unlike other forms of nephrotic syndrome occurring later in life, primary CNS is resistant to therapy with corticosteroids and immunosuppressive agents. Current treatment includes intravenous albumin infusions, aggressive nutritional support, correction of associated hypothyroidism, and prompt treatment of infectious and thromboembolic complications. Bilateral nephrectomy is typically required for the management of massive protein loss, followed by peritoneal dialysis support and early renal transplantation.

Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) is an inherited disorder characterized by polycystic kidneys and a developmental bile duct disorder called congenital hepatic fibrosis. ARPKD is rare and is estimated to occur in approximately 1 in 40,000 live births.[33] The majority of patients with ARPKD present in the newborn period, although rare presentations in later childhood are described. Prenatal ultrasonography shows enlarged, echogenic kidneys. Although the amniotic fluid volume is initially normal, oligohydramnios is often noted in the late second trimester. The newborn infant with ARPKD may present with palpable abdominal masses, severe hypertension, and renal insufficiency. Respiratory failure related to pulmonary hypoplasia and marked abdominal distention from the massively enlarged kidneys is common in neonates with ARPKD.

ARPKD is caused by mutations in *PKHD1*, located on chromosome 6p21. *PKHD1* encodes fibrocystin, a very large, novel protein with receptor-like properties for which the exact function is unknown. Renal histopathology reveals that the principal site of subsequent cyst formation in ARPKD is the collecting tubule. Progressive interstitial fibrosis is an additional histopathologic feature of ARPKD. In addition, although virtually all infants with ARPKD have histologic evidence of congenital hepatic fibrosis at birth, clinical evidence of hepatic involvement is present in only 40% of affected newborns.

The diagnosis of ARPKD is typically made based on characteristic clinical features, including enlarged echogenic kidneys, oligohydramnios, and hypertension. However, other cystic disorders, including diffuse cystic dysplasia and ADPKD, can be clinically indistinguishable from ARPKD in the newborn period. Although initial management is similar for all of the disorders, establishing a definitive diagnosis may be helpful for future family planning, and consultation with a geneticist is recommended. Genetic testing, through direct sequencing, is available for ARPKD but may detect only 80% of cases.[31]

The management of the neonate with ARPKD is largely supportive. Ventilatory support is critical in neonates with pulmonary hypoplasia or respiratory embarrassment. Hypertension is often a primary concern and may require the administration of continuous intravenous infusions of several antihypertensive agents. Patients may require correction of electrolyte imbalances, notably hyponatremia. Optimizing nutrition may be challenging owing to massively enlarged kidneys causing feeding difficulties. Unilateral nephrectomies have not been shown to improve the respiratory status but may improve feeding issues. Hepatic complications, such as portal hypertension, are typically absent in the newborn period, and synthetic function is intact.

In the era of modern neonatal care, survival in the neonatal period is estimated to be about 70%. Most mortality is the result of respiratory distress caused by severe pulmonary hypoplasia and inability to achieve adequate oxygenation and ventilation despite aggressive ventilator support. With improved care of pediatric chronic kidney disease, long-term survival has improved as well. Approximately 80% of neonatal survivors are alive at 10 years of life. Morbidity is significant, however, and complications include chronic kidney disease, growth failure, hepatic complications (portal hypertension, bleeding varices, and ascending cholangitis), and chronic lung disease.[31] Progression to end-stage renal disease occurs in 50% of patients in the first decade of life. With the long-term survival afforded by dialysis and renal transplantation, the hepatic complications have emerged as an important cause of morbidity and mortality, particularly as patients enter adulthood.

The clinical presentation of neonatal autosomal dominant polycystic kidney disease (ADPKD) is similar to that of ARPKD, ranging from asymptomatic cysts seen on renal ultrasonography to severe neonatal manifestations.[23] Because the two conditions can be very similar, renal ultrasonography of the patient's parents is important in establishing the correct diagnosis. Historically, the prognosis for an infant with ADPKD presenting in the neonatal period was thought to be poor. Data, however, suggest that over 90% of these patients maintain intact renal function during childhood.[23] Although ADPKD is a systemic disease that can affect the liver, gastrointestinal tract, aorta,

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and cerebral vessels, extra-renal manifestations in children are rare.

Neonatal Bartter Syndrome

Neonatal Bartter syndrome is one of the inherited hypokalemic tubulopathies that also include classic Bartter syndrome and Gitelman syndrome. Bartter syndrome is inherited as an autosomal recessive trait; the incidence of neonatal Bartter syndrome is 1 in 50,000-100,000 live births. Newborn infants with neonatal Bartter syndrome typically present with profound salt wasting, polyuria, hypokalemia, and hypercalciuria (see also Chapter 92).

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is caused by a defect in the reabsorption of bicarbonate or in the secretion of hydrogen ions that is not related to a decrease in GFR. RTA should be suspected in infants with persistent hyperchloremic (i.e., nonanion gap) metabolic acidosis. There are three forms of RTA: proximal (type II), distal (type I), and hyperkalemic (type IV). RTA may be sporadic or inherited as a classic Mendelian trait. RTA is discussed in detail in Chapter 92.

Tumors of the Kidney

Renal tumors in the newborn infant are uncommon. Interestingly, despite the widespread use of antenatal ultrasound, only 15% are detected prenatally.[57] The more typical clinical presentation of renal tumors in the neonatal period is abdominal swelling or a palpable mass. Other symptoms may include hypertension, hematuria, fever, and feeding intolerance.

The more common types of neonatal renal tumors include congenital mesoblastic nephroma, multilocular cystic nephroma, and Wilms tumor (nephroblastoma).[57] Malignant rhabdoid tumor is a very rare but aggressive renal malignancy that presents in newborns and young infants and carries an extremely poor prognosis. Other renal neoplasms, such as renal cell carcinoma or lymphoma, are exceedingly rare in neonates.

Congenital mesoblastic nephroma is the most common renal neoplasm in the first year of life.[57] Approximately 60% of all congenital mesoblastic nephromas are diagnosed before 6 months of age; the clinical presentation is an abdominal mass. Congestive heart failure and hypertension are less common manifestations. Nephrectomy is curative, with the exception of infrequent local recurrences and rare pulmonary metastases.

Multilocular cystic nephroma is a benign renal tumor that consists of large cysts separated by fibrous septae. This tumor arises from metanephric blastema and has features of immature blastema, tubules, and skeletal muscle on histopathologic examination. The prognosis is excellent with surgical removal alone.

Wilms tumor accounts for 90% of all renal tumors diagnosed in the pediatric population. However, 80% of Wilms tumors are diagnosed in patients between the ages of 1 and 5 years, making its appearance uncommon in the first year of life and rare in the neonatal period. Most Wilms tumors occur sporadically, but 15% are associated with congenital anomalies or syndromes, including congenital aniridia, hemihypertrophy, WAGR (Wilms, aniridia, genitourinary anomalies, mental retardation) syndrome, Denys-Drash syndrome, and Beckwith-Wiedemann syndrome.[57]

Definitive therapy for a localized renal mass begins with surgical exploration, and in most cases the primary treatment is nephrectomy. Infants with multilocular cystic nephromas or congenital mesoblastic nephromas require no postoperative therapy. Infants with malignant tumors such as Wilms tumor are treated according to well-established oncologic protocols. The prognosis for most infants with neonatal renal tumors is good, although an infant with aggressive Wilms tumor, atypical congenital mesoblastic nephroma, malignant rhabdoid, or renal sarcoma may have a poor prognosis.

Key Points

- Acute kidney injury (AKI) occurs in 30% of critically ill neonates and is independently associated with increased mortality and length of hospital stay.
- Providers should monitor for chronic kidney disease (CKD) in survivors of neonatal AKI, as well as neonates with a history of nephrocalcinosis, prematurity, and/or low birth weight.
- Hypertension occurs in 1%-2% of neonates and is most commonly associated with renovascular thromboembolism related to umbilical arterial catheterization.
- Neonatal nephrocalcinosis is multifactorial in origin and usually resolves spontaneously within the first 2 years of life.
- If mild, antenatal hydronephrosis is most likely to be physiologic and benign, resolving spontaneously over time. Moderate to severe hydronephrosis, especially if associated with oligohydramnios, or small/echogenic/cystic kidneys, is more likely to represent significant urinary tract pathology.
- Congenital anomalies of the kidney and urinary tract (CAKUT) encompass a wide spectrum of conditions associated with genetic and/or environmental risk factors. CAKUT includes disorders such as renal dysplasia, posterior urethral valves, UPJ obstruction, renal agenesis, and multicystic dysplastic kidney.

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94

The Skin of the Neonate

VIVEK NARENDRAN

This chapter provides an overview of the principles of newborn skin care followed by a summary of the many diseases of the newborn presenting with primary or secondary cutaneous manifestations. A basic understanding of the structural development of the skin as well as the multiple functions subserved by the skin during transition to extrauterine life will be highlighted. The caregiver will be able to distinguish benign and transient lesions of newborn skin, such as erythema toxicum, from potential life-threatening diseases such as herpes simplex neonatorum. In addition, the chapter highlights the fact that many common cutaneous findings in the newborn, such as sebaceous gland hyperplasia and neonatal pustular melanosis, have an intrauterine etiology. The advantage of the accessibility of the skin to physical examination is counterbalanced by the extreme structural and functional diversity of this organ.

The skin is a critical interface between the body and environment. This layer differentiates between "self" and "nonself." At birth, the first response in resuscitation includes drying the baby to prevent heat loss and an assessment of skin color, perfusion, and integrity. Pathologic processes visible on the skin surface range from general signs of systemic dysfunction (cyanosis, pallor, jaundice) to clinical evidence of specific diseases (vesicles, petechiae). Cutaneous characteristics are routinely used as determinants of gestational age (breast buds, plantar creases, desquamation). The definitive organ of mammals, the mammary gland, similar to the epidermis, is an ectodermally derived cutaneous structure.[51] Maternal–infant bonding is, in large part, a complex dynamic interaction between skin surfaces.

At birth, the skin of the term infant must perform multiple functions critical for survival in an extrauterine environment (Box 94.1).[11] Many of these functions depend on structural development of the skin during the last trimester of pregnancy. The development of a competent epidermal barrier, for example, is essential for temperature regulation, maintenance of fluid homeostasis, infection control, and prevention of penetration of environmental toxins and drugs. Similarly, the acquisition of the skin microbiome is important in regulating keratinocyte homeostasis to locally produce hormones, neurotransmitters, and cytokines, which in turn maintain epidermal integrity, enhance innate immunity, and inhibit pathogenic bacteria.[54]

The epidermal permeability barrier primarily resides in the outermost layer of the epidermis, the stratum corneum. This layer, approximately one-fourth the thickness of a sheet of paper, develops in utero during the third trimester of pregnancy in conjunction with a protective mantle of vernix caseosa. Extremely low birth weight preterm infants (<1000 g birth weight) lack a well-developed stratum corneum, which poses special problems for newborn care. The stratum corneum is necessary for the adherence of thermistors, cardiorespiratory monitors, and endotracheal tubes, and forms the primary environmental interface with caregivers and parents. Box 94.2 gives a summary and consensus of general principles of skin care.[11]

The Structural Biology of Fetal and Neonatal Skin

Development of the Epidermis

Human skin has two distinct but interdependent components—the epidermis and the dermis (Fig. 94.1). The epidermis has marked regional variations in thickness, color, permeability, and surface chemical components. It consists of a highly ordered, compact layering of keratinocytes and melanocytes. Traditionally, the epidermis is segmented into distinct structural and functional compartments called the stratum germinativum (basale), stratum spinosum, stratum granulosum, and stratum corneum (see Fig. 94.1). Intermixed is a third distinct cell type, the Langerhans cell, which is derived from bone marrow precursors and migrates into the primitive epidermis.

The process of cutaneous morphogenesis can be divided into embryonic and fetal periods (Fig. 94.2).[30] This transition, which occurs at approximately 2 months, is an important time in skin development, because many critical morphogenetic events occur during this transitional period. Between 30 and 40 days of development, the embryonic skin consists of a two-layered epidermis: the basal layer, associated with the basal lamina, and the periderm, which serves as a cover and a presumptive nutritional interface with

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Abstract

This chapter provides an overview of the importance of newborn skin in neonatal adaptation and reviews common neonatal skin conditions. The anatomy and function of the skin along with fetal skin development is discussed in depth. The basic primary and secondary skin lesions are characterized and associated with common skin diagnosis to facilitate clinical diagnosis. Common benign and transient skin conditions are differentiated from the pathologic skin lesions. The immaturity of the preterm epidermal barrier and its consequences are highlighted. The role of vernix caseosa, a cheesy material that coats the fetus and serves multiple functions in the newborn, is detailed.

Keywords

epidermal barrier
vernix caseosa
vascular anomalies
preterm skin
cornification disorders
infections

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• BOX 94.1 Multiple Physiologic Roles of the Skin at Birth

- Barrier to water loss
- Thermoregulation
- Infection control
- Immunosurveillance
- Acid mantle formation
- Antioxidant function
- Ultraviolet light photoprotection
- Barrier to chemicals
- Tactile discrimination
- Attraction to caregiver

• BOX 94.2 Principles of Newborn Skin Care

Delivery Room

- Provide immediate drying and tactile stimulation.
- Remove blood and meconium.
- Leave vernix intact and spread to allow absorption.

Bathing

- Limit frequency.
- Use neutral pH cleansers.
- Use only water for infants weighing less than 1000 g.
- Avoid antibacterial soaps.

Emollients

- Avoid petrolatum-based ointments in infants with very low birth weight during the first week of life.
- Use emollients as needed for dryness in older infants.

Disinfectants

- Use chlorhexidine, and remove excess after procedure.
- Use of isopropyl alcohol and alcohol-based disinfectants is discouraged in infants with very low birth weight until the stratum corneum has formed.

Adhesives

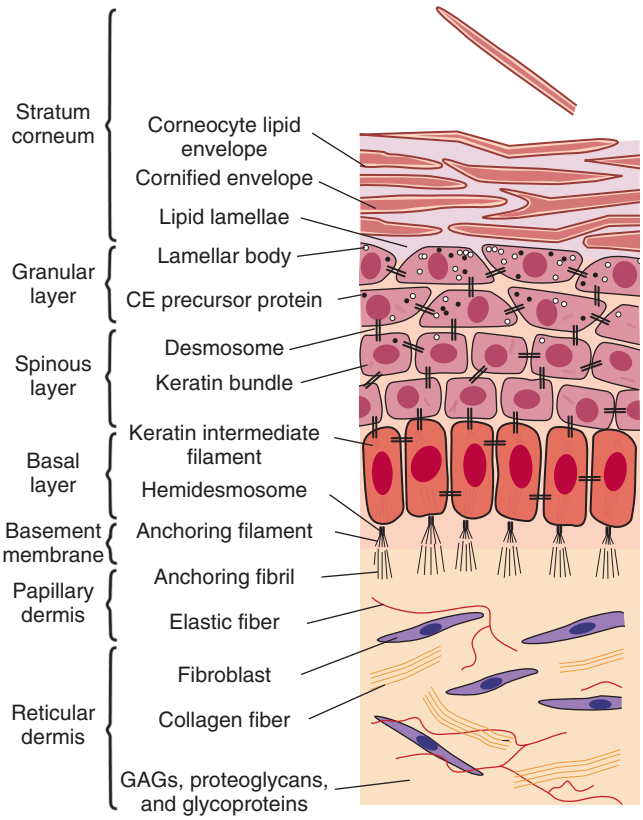
- Minimize use of adhesives.
- Use hydrogel electrodes.
- Avoid solvents and bonding agents.
- Counsel patience during tape removal.

Transepidermal Water Loss

- For infants younger than 30 weeks' gestation, select high incubator humidity (>60%) and transparent, semipermeable dressings to reduce evaporative water and heat loss.
- Use incubators and supplemental conductive heat to avoid drying effects of radiant warmers.
- Measure humidity routinely.

Cord Care

- Allow natural drying.
- Avoid the routine use of isopropyl alcohol.



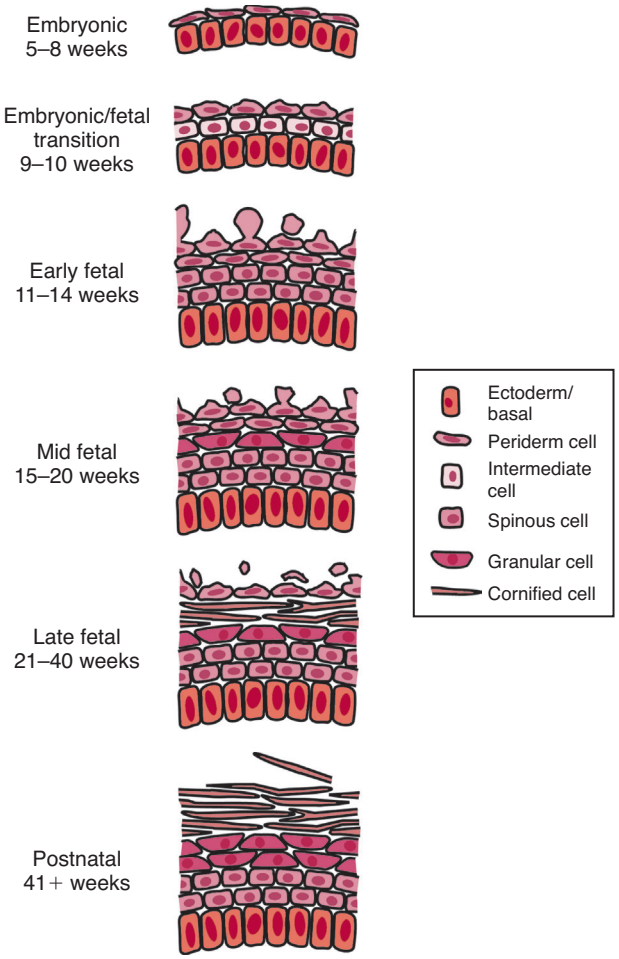
• **Fig. 94.1** Structure of skin. The normal term infant's skin is composed of three separate layers: dermis, basement membrane, and epidermis. The epidermis can be subdivided into four further strata (basal, spinous, granular, corneum), each representing a specific stage in terminal differentiation. (From Hardman MJ, Byrne C. Skin structural development. In: Hoath SB, Maibach HI, eds. *Neonatal skin: structure and function.* New York: Marcel Dekker; 2003:1-19.)

the amniotic fluid. The basal layer includes cells that give rise to the future definitive epidermis, whereas the periderm is a transient layer that covers the embryo and fetus until the epidermis keratinizes at the end of the second trimester. Basal cells join with each other and peridermal cells by a relatively few desmosomes but do not yet form hemidesmosomes with the basement membrane. Small numbers of keratin intermediate filaments are associated with these junctions. Matrix adhesion of the embryonic epidermis is likely mediated by actin-associated α6β4 integrin.[30]

Langerhans cells and melanocytes migrate into the embryonic epidermis and are identifiable at 40 and 50 days of gestation, respectively. At this stage, the Langerhans cells do not express CD1 antigen on their cell surfaces, nor are Langerhans cell granules identifiable. Likewise, at this time, the melanocyte lacks the characteristic cytoplasmic organelle, the melanosome. A third immigrant cell, the Merkel cell, does not appear to be present in embryonic epidermis and may differentiate at a later stage from keratinocytes in situ.

At the time of embryonic–fetal transition (60 days' gestation), the epidermis begins to stratify, forming an intermediate layer of cells. These young keratinocytes still contain a high volume of glycogen in their cytoplasm and produce large amounts of intermediate filaments in association with the desmosomes. At this time, new keratins are identifiable as markers of differentiation, as is the pemphigus antigen, which is detectable on the cell surface. These cells, unlike

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• **Fig. 94.2** Schematic diagram of the six key stages of epidermal differentiation and development. The epidermis develops from a single layer of undifferentiated ectoderm (5-8 weeks) to a multilayered, stratified, differentiated epithelium with a competent epidermal barrier (40 weeks). The periderm undergoes intense proliferation (11-14 weeks) and forms characteristic blebs and microvilli thought to be functionally important. Regression and disaggregation of the periderm occur concomitant with formation of the vernix caseosa (not shown). (From Hardman MJ, Byrne C. Skin structural development. In: Hoath SB, Maibach HI, eds. *Neonatal skin: structure and function.* New York: Marcel Dekker; 2003:1-19.)

adult spinous cells, remain proliferative and continue to express epidermal growth factor receptors on their surfaces. Two to three additional layers of intermediate cells are added during the second trimester. These cells show a progressive increase in the number of keratin filaments but do not further differentiate until the onset of keratinization in the interappendageal epidermis around 22-24 weeks' gestation.

The Langerhans cells in the embryonic epidermis begin to express CD1 antigen and contain Langerhans granules after the embryonic–fetal transition.[12] The numbers of Langerhans cells increase significantly during the third trimester; however, the function of these cells in fetal skin remains unknown. Between 80 and 90 days' gestation, melanocytes also increase in density at a time when keratinocytes in the epidermis are forming appendages, and melanin synthesis begins at the end of the first trimester. Transfer of melanosomes to keratinocytes occurs in the 5th month of gestation.

Melanin production is low in the newborn, who is not as pigmented as the older child and is more sensitive to sunlight, but there is no significant difference in the number of melanocytes in light, medium, or deeply pigmented skin or in infant or adult skin. Difference in color is the result of the shape, size, chemical structure, and distribution of melanosomes and the activity of individual melanocytes.

Development of the Appendages

The appendages derive from embryonic invaginations of epidermal germinative buds into the dermis. They include hair, sebaceous glands, apocrine glands, eccrine glands, and nails. The arrector pili muscle is attached to the hair follicle. Lanugo (i.e., fine, soft, immature hair) frequently covers the scalp and brow of the premature infant. The scalp line may be poorly demarcated, and lanugo also may cover the face. Scalp hair is usually somewhat coarser and matures earlier in dark-haired infants.

The growth phases of the hair follicle are usually synchronous at birth. Eighty percent of the follicles are in the resting state.[58] During the first few months of life, the synchrony between hair loss and regrowth is altered so that 20% of scalp hairs are growing in the same phase at the same time. Hair may become coarse and thick, acquiring an adult distribution, or there may be temporary alopecia.

There are sex differences in hair growth; boys' hair grows faster than girls' hair. In both sexes, scalp hair growth is slower at the crown. The normal pattern of hair growth is disturbed in many chromosomal disorders. Evidence supports a genetic link between the formation of clockwise posterior parietal hair whorls and specific (right) handedness of the individual. This finding supports an unexpected association between gene-based hair patterning and human brain development that warrants further substantiation. Supporting the significance of the skin–brain connection, evidence has shown the human hair follicle can synthesize cortisol de novo and is a functional equivalent of the hypothalamic-pituitary-adrenal axis.

The eccrine sweat glands are coiled structures that form during the first trimester as a downgrowth from epidermal cellular clones. No new glands are formed after birth. They are distributed over the entire body surface and are innervated by sympathetic cholinergic nerves. During the first 24 hours of life, term infants usually do not sweat; on approximately the 3rd day, sweating begins on the face. Palmar sweating begins later. Thermal sweating as a function of body or environmental temperature should be distinguished from emotional sweating associated with crying or pain. The latter is best assessed on the palms and soles.

The sebaceous glands differentiate primarily from the epithelial portion of the hair follicle at approximately 13-15 weeks of life and almost immediately produce sebum in all hairy areas. The glands develop as solid outpouchings from the upper third of the hair follicle. These solid buds become filled with liquid centrally where the cells disintegrate; acini

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and ducts develop, opening most frequently into the canals between the hair follicle wall and hair shaft.[50] Ectopic glands occur occasionally on the lips, buccal mucosa, esophagus, and vagina.

Surprisingly little is known about the regulation of the rapid growth and activity of sebaceous glands up to and immediately after birth. Hypothetically, secretion by the fetal adrenal gland of weak androgens such as dehydroepiandrosterone (DHEA) is followed by intra-sebocyte conversion to testosterone and production of products of the pilosebaceous unit such as vernix caseosa. This hypothesis remains to be fully tested, but it has the singular advantage of functionally integrating two disparate and unexplained facts; that is, the mutual hyperplasia of the sebaceous gland and the adrenal cortex during the latter half of gestation in the human fetus. Androgens are the only hormones that unequivocally have a stimulating effect on the sebaceous glands; estrogens depress their growth. Between 2 months and 2 years, the sebaceous glands of the normal infant begin a period of quiescence that lasts until puberty.

The apocrine glands are relatively large organs that originate from and empty into a hair follicle. Embryologically, they develop somewhat later than the eccrine glands. Apocrine development is advanced by 7 or 8 fetal months, when the glands begin to produce a milky-white fluid containing water, lipids, protein, reducing sugars, ferric iron, and ammonia. In the newborn, the acini are well formed. The biologic function of the gland is unknown in infants, but it is related to pheromone production in other animal species.

Vernix Biology

Vernix caseosa, a unique material that coats the fetal skin surface during the last trimester of pregnancy, contains lipids of sebaceous origin as well as numerous water-laden fetal corneocytes. A growing body of evidence supports the hypothesis that vernix caseosa participates in regionally "waterproofing" the skin surface, thereby allowing cornification to occur, initially around the hair follicles and then over the interfollicular skin.[71] A better understanding of vernix caseosa and fetal sebaceous gland physiology is biologically relevant and may be applicable to care of the very low birth weight infant and to clinical situations in which the epidermal surface is inadequately developed, burned, or traumatized.

Physiologically, vernix is a hydrophobic material containing wax esters, cholesterol, ceramides, and squalene in addition to other minor lipid components. Vernix has high water content (≈80%), with the water primarily distributed within flat, polygonal, cornified squames. As term approaches, vernix detaches from the fetal skin surface under the influence of pulmonary surfactant and is swallowed by the fetus. In close analogy to breast milk, vernix contains multiple molecules associated with the innate immune system, including lysozyme, lactoferrin, and defensins, as well as antioxidants such as alpha tocopherol.[28] Vernix possesses both emollient (moisturizing) and cleansing functions. Thus, at birth, the human infant is covered with a complex material possessing endogenous anti-infective, antioxidative, moisturizing, and cleansing capabilities. Extreme prematurity, as well as postmaturity, is associated with diminished vernix on the skin surface at birth.

Development of the Dermis

The fetal dermis acquires some of the characteristics of adult dermis around 20 weeks' gestation. However, it is only in the more mature fetus that the true structural and biochemical qualities of the newborn dermis are detectable. The dermis contains three identifiable zones: the region adjacent to the basement membrane, the papillary dermis, and the reticular dermis (see Fig. 94.1). The superficial dermis has finer collagen fibers and is biochemically more active than the deeper zone. The papillary dermis also is more susceptible to light injury and elastic tissue degeneration than the reticular dermis. The dermis has a symbiotic relationship with, and may exert a controlling influence on, the epidermis. It is a metabolically active tissue that contains fibrous elements, amorphous ground substance, free cells, nerves, blood vessels, and lymphatics.

The fibrous elements are collagen and elastic tissue. Collagen types I, III, V, and VI comprise the dermal collagens, whereas type IV is present in the basement membrane of the dermal–epidermal junction and dermal vessels, and type VII occurs in anchoring fibrils and basal keratinocytes. With increasing age, collagen becomes progressively less soluble, and thicker bundles predominate. The morphologic characteristics and chemical properties of cutaneous elastic fibers differ from those of collagen. Elastic fibers are first detectable in the skin by histochemical means and electron microscopy at around 20 weeks' gestation.

The fibroblasts are the most numerous cells in the dermis. They produce collagen and the glycosaminoglycans of the ground substance. Mast cells (which produce heparin and histamine), histiocytes, macrophages, lymphocytes, neutrophils, and an occasional plasma cell and eosinophil are also present in the dermis. The major glycosaminoglycans in the ground substance of skin are hyaluronic acid and dermatan sulfate (i.e., chondroitin sulfate B). An increase in age brings a shift from hyaluronic acid toward dermatan sulfate and a decrease in water content of the dermis.

Blood and Lymphatic Vessel Development

The vascular network supplying the skin develops in early embryonic life from the mesoderm. In 60- to 70-day-old fetuses, there are two vascular networks: a superficial one that appears to correspond to the subpapillary plexus of adult skin and a deeper network that represents the deep reticular vascular network of adult skin. New capillary beds organize to supply the developing epidermal appendages from the 5th month of gestation. These two networks persist into the newborn period; however, the arrangement of vessels remains unstable for the first year of

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life, and further organization of the vascular network occurs postnatally.

Vasomotor tone is controlled by a delicate and complex series of neural and pharmacologic mechanisms that involve the sympathetic nervous system, norepinephrine, acetylcholine, and histamine, and may involve serotonin, vasoactive polypeptides, corticosteroids, and prostaglandins. The physiologic requirements of skin vary considerably; skin blood flow ranges from 0.1-150 mL/mm^2 of tissue per minute.

Development of Cutaneous Innervation

The nerve networks in the dermis develop at a very early embryologic age and appear to be distributed in a random fashion. The most superficial nerves have the smallest diameter and are the least myelinated. In addition to the dermal nerve network, which may show considerable regional variation, nerve fibers may serve particular regions or structures such as hair follicles, eccrine glands, arrector pili muscles, and the subepidermal zone. Superficial nerves conduct mechanosensory stimuli from the specialized Merkel cells within the epidermis. The sebaceous glands are not innervated.

Special neurologic structures include a dense perifollicular nerve network with exquisite tactile sensory properties and mucocutaneous end organs highly concentrated in erogenous zones. Meissner tactile organs are found in newborn skin as undeveloped structures that mature after birth. Merkel corpuscles probably govern two-point tactile discrimination on palms and fingertips; they are disk-shaped terminals that are seen during the 28th week of fetal life. After birth, these receptors undergo little alteration. Vater-Pacini corpuscles are found around the digits, palms, and genitals; they are fully formed and numerous at birth.[29]

The arrector pili muscles are innervated by sympathetic nerves, and norepinephrine acts as the neurotransmitter. The eccrine glands are innervated by sympathetic fibers, but acetylcholine acts as the neurotransmitter. Parasympathetic fibers may accompany the sensory nerves in the vessel walls and cause vasodilation. The axon reflex is poorly developed in the newborn; in the neonate of low birth weight, axon reflex sweating may be difficult to elicit.

Disorders and Diseases of Fetal and Neonatal Skin

This section provides a cursory synopsis of normal and abnormal aspects of newborn skin. An accurate description of primary and secondary skin lesions forms the basis for the diagnosis of skin pathology. Tables 94.1 and 94.2 describe the basic lesional morphology of infant skin with specific examples. More definitive treatises on normal skin

TABLE 94.1 Primary Cutaneous Lesions*

Type	Description	Clinical Examples
Macule	A circumscribed, flat lesion with color change, up to 1 cm in size; by definition, they are not palpable	Ash leaf macules, café-au-lait spots, capillary ectasias
Patch	Same as macule but >1 cm in size	Nevus depigmentosus, nevus simplex, mongolian spots
Papule	A circumscribed, elevated, solid lesion, up to 1 cm in size; elevation may be accentuated with oblique lighting	Verrucae, milia, juvenile xanthogranuloma
Plaque	A circumscribed, elevated, plateau-like, solid lesion, >1 cm in size	Mastocytoma, nevus sebaceous
Nodule	A circumscribed, elevated, solid lesion with depth, up to 2 cm in size	Dermoid cysts, neuroblastoma
Tumor	Same as a nodule but >2 cm in size	Hemangioma, lipoma, rhabdomyosarcoma
Vesicle	A circumscribed, elevated, fluid-filled lesion up to 1 cm in size	Herpes simplex, varicella, miliaria crystalline
Bulla	Same as a vesicle but >1 cm in size	Sucking blisters, epidermolysis bullosa, bullous impetigo
Wheal	A circumscribed, elevated, edematous, often evanescent lesion, caused by accumulation of fluid within the dermis	Urticaria, bite reactions, drug eruptions
Pustule	A circumscribed, elevated lesion filled within purulent fluid, <1 cm in size	Neonatal pustular melanosis, erythema toxicum neonatorum, infantile acropustulosis
Abscess	Same as a pustule but >1 cm in size	Pyodermas

*Lesions arise de novo and are therefore most characteristic of the disease process.
Modified from Yan AC, et al. Lesional morphology and assessment. In: Eichenfeld LF, et al., eds. *Neonatal and infant dermatology.* 3rd ed. Philadelphia: Elsevier Saunders; 2015 [chapter 3].

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TABLE 94.2 Secondary Cutaneous Lesions*

Type	Description	Clinical Examples
Crust	Results from dried exudates overlying an impaired epidermis. Can be composed of serum, blood, or pus.	Epidermolysis bullosa, impetigo
Scale	Results from increased shedding or accumulation of stratum corneum as a result of abnormal keratinization and exfoliation. Can be subdivided further into pityriasiform (branny, delicate), psoriasiform (thick, white, and adherent), and ichthyosiform (fish scalelike).	Ichthyoses, postmaturity desquamation, seborrheic dermatitis
Erosion	Intraepithelial loss of epidermis. Heals without scarring.	Herpes simplex, certain types of epidermolysis bullosa
Ulcer	Full thickness loss of the epidermis with damage into the dermis. Will heal with scarring.	Ulcerated hemangiomas, aplasia cutis congenita
Fissure	Linear, often painful break within the skin surface, as a result of excessive xerosis.	Inherited keratodermas, hand and foot eczema
Lichenification	Thickening of the epidermis with exaggeration of normal skin markings caused by chronic scratching or rubbing.	Sucking callus, atopic dermatitis
Atrophy	Localized diminution of skin. *Epidermal atrophy* results in a translucent epidermis with increased wrinkling, whereas *dermal atrophy* results in depression of the skin with retained skin markings. Use of topical steroids can result in epidermal atrophy, whereas intralesional steroids may result in dermal atrophy.	Aplasia cutis congenita, intrauterine scarring, and focal dermal hypoplasia
Scar	Permanent fibrotic skin changes that develop as a consequence of tissue injury. In utero scarring can occur as a result of certain infections or amniocentesis or postnatally from a variety of external factors.	Congenital varicella, aplasia cutis congenita

*Lesions arise as characteristic modifications of primary lesions through environmental interaction (e.g., drying) or subject interaction (e.g., scratching).
Modified from Yan AC, et al. Lesional morphology and assessment. In: Eichenfeld LF, et al., eds. *Neonatal and infant dermatology*. 3rd ed. Philadelphia: Elsevier Saunders; 2015 [chapter 3].

structure, function, development, and specific disease states are available.[49] The remainder of this chapter delineates specific conditions of newborn skin ranging from transient lesions to definitive cutaneous diseases and diagnostic categories.

Transient Cutaneous Lesions

A number of benign and transient lesions of the skin are commonly observed in a normal nursery population.[34] It is important for the infant caregiver to distinguish such ephemeral lesions from significant life-threatening diseases with cutaneous manifestations.

Sebaceous Gland Hyperplasia and Milia

Approximately 8% of infants have multiple, white, 1-mm cysts (i.e., milia) scattered over the cheeks, forehead, nose, and nasolabial folds. These milia may be few or numerous, but they frequently occur in clusters. Milia are often confused with the more common condition of sebaceous gland hyperplasia (43% of infants), which manifests as smaller, flatter, more yellow dots seen on the midface as well (Fig. 94.3). Histologically, milia are keratogenous cysts similar to Epstein pearls, which are distributed along the midpalatal raphe. Bohn nodules are cysts that occur on the palate and the buccal and lingual aspects of the dental ridges and represent remnants of mucous gland tissue. Intraoral lesions are found in 75%-80% of newborns. Because all these cysts exfoliate or involute spontaneously within the first few weeks of life, no treatment is required.

Pigmentary Lesions

The most frequently encountered pigmented lesion is the mongolian spot (dermal melanosis), which occurs frequently in African-American, Asian, and Native-American infants and infrequently in white infants. Although most of these lesions are found in the lumbosacral area, occurrence at other sites is not uncommon. The pigmentation is macular and gray-blue, lacks a sharp border, and may cover an area 10 cm or larger in diameter. Pigmentary lesions result from delayed disappearance of dermal melanocytes.

Most of these lesions gradually disappear during the first few years of life, but aberrant lesions in unusual sites are more likely to persist. Because of their distinctive color and morphology, mongolian spots are not easily confused with congenital pigmented melanocytic nevi or café au lait spots,

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which often have their onset later in infancy or in early childhood, although they may be present at birth.

Rarely, extensive mongolian spots may be associated with inborn errors of metabolism (Hurler syndrome, GM1 gangliosidosis, mucolipidosis) and neurocristopathies.[24]

Nevus Simplex or Salmon Patch

The nevus simplex is the most common neonatal cutaneous lesion and is present in up to 80% of normal newborns (Fig. 94.4).[34] These lesions blanch when compressed and are usually centrally located and symmetric, appearing on the nape, the eyelids, and the glabella. In a prospective study of affected infants, most of the facial lesions had faded by 1 year of age, but those on the neck were more persistent. Surveys of adult populations confirm the persistence of the nuchal lesions in approximately one-fourth of the population.

Harlequin Color Change

Harlequin color change is a transient phenomenon observed in the immediate neonatal period and common in the low birth weight infant. The dependent side of the body becomes intensely red, and the upper side pales, with a sharp midline demarcation. The peak frequency of attacks in one series occurred on the 2nd, 3rd, and 4th days, but episodes were observed during the first 3 weeks of life. These episodes are of no pathologic significance. They have been attributed to a temporary imbalance in the autonomic regulatory mechanism of the cutaneous vessels; there are no accompanying vital sign changes.



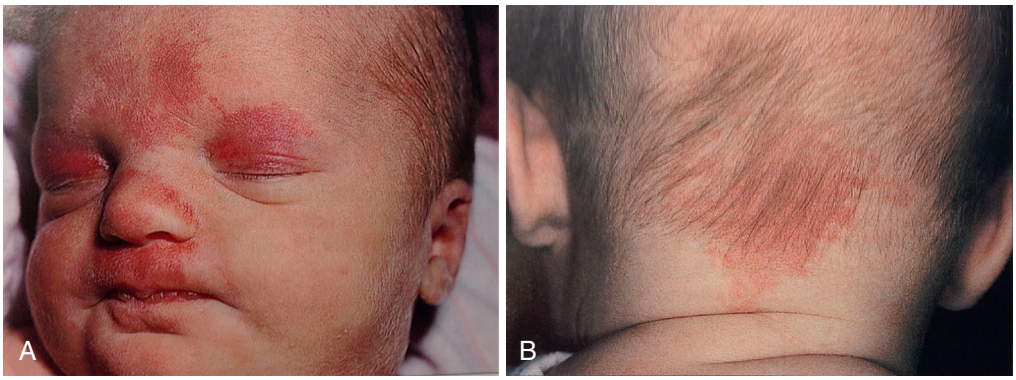
• **Fig. 94.3** Sebaceous gland hyperplasia is manifested by tiny yellow-white follicular papules without inflammation over the nose and surrounding area. (From Lucky AW. Transient benign cutaneous lesions in the newborn. In: Eichenfield LF, et al., eds. *Neonatal and infant dermatology.* 3rd ed. Philadelphia: Elsevier Saunders; 2015, Chapter 7.)

Erythema Toxicum

Erythema toxicum is a benign and self-limited eruption that usually develops at 24-72 hours of age, but new lesions may appear until 2-3 weeks of age.[46] The disorder is more common in term than premature infants, which suggests that it may represent an inflammatory reaction requiring mature skin. These lesions may vary considerably in character and number; they may be firm, 1-3 mm, pale yellow to white papules or pustules on an erythematous base resembling flea bites or erythematous macules as large as 3 cm in diameter. Individual lesions are evanescent, often lasting only a matter of hours. They may be found on any area of the body but occur only rarely on the palms and soles. They are asymptomatic with no related systemic involvement and the cause is unknown, although a variety of specific cytokines have been implicated in the pathogenesis. A microscopic examination of a Wright- or Giemsa-stained smear of the pustule contents demonstrates numerous eosinophils; Gram stains are negative for bacteria and cultures are sterile. No treatment is necessary because spontaneous resolution occurs in 6 days to 2 weeks.

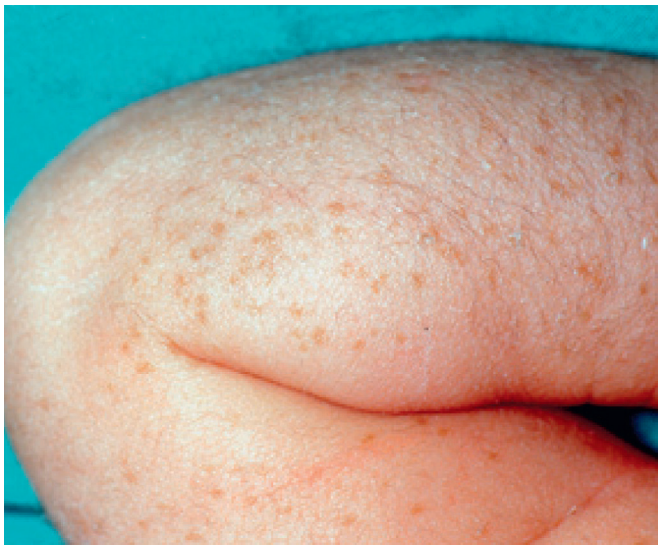
Transient Neonatal Pustular Melanosis

Transient neonatal pustular melanosis is a distinctive eruption that heals with brown pigmented macules. It consists of three types of lesions: first-stage lesions are small superficial vesiculopustules with little or no surrounding erythema. These rapidly progress to the second stage, which consists of collarettes of scale or scale crust surrounding a



• **Fig. 94.4** Capillary ectasias or transient macular stains (salmon patches). **A,** Also called a nevus simplex, these lesions appear on the glabella, eyelids, nose, and upper lip. **B**, The most common location for a nevus simplex is the nape of the neck. (From Lucky AW. Transient benign cutaneous lesions in the newborn. In: Eichenfield LF, et al, eds. *Neonatal and infant dermatology.* 3rd ed. Philadelphia: Elsevier Saunders; 2015 [chapter 7].)

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• **Fig. 94.5** Transient neonatal pustular melanosis begins in utero with superficial pustules, followed by rupture, leaving a collarette of scale and subsequent postinflammatory hyperpigmentation. (From O'Connor NR, McLaughlin MR, Ham P. Newborn skin: part I. Common rashes. *Am Fam Physician*. 2008;77:47-52.)



• **Fig. 94.6** Miliaria crystallina. (From Antaya RJ, Robinson DM. Blisters and pustules in the newborn. *Pediatr Ann*. 2010;39:635-645.)

hyperpigmented macule (third stage) (Fig. 94.5). All three types of lesions may be present at birth, but the macules are observed more frequently. The lesions may be profuse or sparse and occur on any body surface, including the palms, soles, and scalp. Sites of predilection are the forehead, submental area and anterior neck, and lower back. When intact pustules rupture, a pigmented macule often is discernible central to the collarette of scale, which represents the margin of the unroofed pustule. Presumably, the macules result from postinflammatory hyperpigmentation, and those present at birth may be the sequelae of in utero pustular lesions.

Pustular melanosis may be confused with erythema toxicum, congenital cutaneous candidiasis, or staphylococcal pyoderma. Cultures and Gram stains of smears prepared from intact pustules are devoid of organisms; Wright stains of intralesional contents demonstrate cellular debris, polymorphonuclear leukocytes, and a few or no eosinophils, in contrast to those of erythema toxicum. Although the pustules disappear in 48 hours, the hyperpigmented macules may persist for as long as 3 months. These lesions require no therapy as the disorder is benign and transient.

Miliaria

Miliaria is an eruption characterized by crops of superficial vesicles resulting from eccrine sweat gland duct obstruction leading to sweat retention. The three types of lesions are superficial thin-walled vesicles without inflammation (i.e., miliaria crystallina, Fig. 94.6); small, erythematous, grouped papules (i.e., miliaria rubra); and nonerythematous pustules (i.e., miliaria pustulosis or profunda). The eruption most frequently develops in the intertriginous areas and over the face and scalp. It is exacerbated by exposure to a warm and humid environment. Miliaria sometimes can be confused with erythema toxicum; rapid resolution of the lesions when the infant is placed in a cooler environment differentiates them from other causes of infectious pustulosis. A Wright-stained smear of vesicular lesions demonstrates only sparse squamous cells or lymphocytes, permitting exclusion of infectious vesicular eruptions. No topical therapy is indicated.

Neonatal Acne and Infantile Acne

Neonatal acne occurs in up to 20% of newborns and is more commonly seen in boys. Increased sebaceous secretions secondary to maternal and neonatal androgens and colonization of the sebaceous glands by the yeast *Malassezia furfur* are implicated in its pathogenesis[20] and are characterized by small red papules and pustules on the face during the first weeks of life. Unlike in adolescents, comedones and cysts are usually absent. The lesions are asymptomatic and resolve spontaneously without scarring over several weeks. The clinical significance lies in differentiating this rash from infections, excluding virilization as its underlying cause and potential implication of severe acne in adolescence.

Infantile Acropustulosis

Infantile acropustulosis is characterized by recurrent crops of pruritic, sterile vesiculopustules with a predilection for the palms and soles. The lesions appear in crops every 2-3 weeks and last 7-10 days. They involve the hands and feet primarily, but occasionally may involve the limbs as well. Because of the distribution, it is often confused with scabies. It is more common in African-American and male infants. The condition resolves spontaneously. A subcorneal pustule filled with neutrophils is seen on skin biopsy. Traditional therapy consists of topical steroids and antihistamines, although one report indicates successful treatment with topical maxacalcitol, an active form of vitamin D3.[37] A recessive mutation in the gene coding interleukin 1 receptor antagonist has been described in a case of infantile pustulosis treated successfully with recombinant human interleukin 1 receptor antagonist anakinra.[44]

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Disorders of Cornification: The Scaly Baby

The most common and benign causes of excessive scaling are due to physiologic desquamation (normal term infants) and dysmaturity (post-mature and small for gestational age infants), neither of which have long-term sequelae. Less common causes include the congenital ichthyoses and the ectodermal dysplasias (particularly hypohidrotic ectodermal dysplasia), all of which are chronic, heritable disorders.[13,19]

Physiologic Desquamation and Dysmaturity

The gestational age of a newborn with accentuated physiologic desquamation usually is 40-42 weeks; peak shedding occurs near the 8th day of life. These infants are otherwise normal in physical appearance and behavior. In contrast, the dysmature infant (see Chapter 22) has distinctive characteristics. The body is lean with thin extremities and decreased subcutaneous fat. The ponderal index is low with diminished body weight in relation to length. The skin is often scaly with parchment-like desquamation, especially of the distal extremities. There is often meconium staining of the skin as well as the nails and umbilical cord. The hair is abundant and the nails are abnormally long. In the normal infant with accentuated physiologic scaling and the dysmature infant, desquamation is a transient phenomenon, and the integument continues to serve its intended protective function. In contrast, the infant with congenital ichthyosis may have serious difficulties early in life because of impaired barrier function and the subsequent risks of secondary infection.

Ichthyoses

The term *ichthyosis* derives from the similarity of the skin condition to the scales of a fish. It refers to a complex and often confusing plethora of conditions characterized by disorders of cornification with or without systemic symptoms.[13,19] In 2010, a consensus conference of experts developed a new classification that was clinically based and easily comprehensible by clinicians.[52] It was broadly divided into nonsyndromic (restricted to skin) and syndromic (skin plus other organs). Ichthyosis in the newborn period may manifest as scaling only, scaling and erythroderma, a collodion membrane, or the thickened plates of harlequin ichthyosis. Although rare, it is important for the neonatal caregiver to recognize the patient with ichthyosis as the barrier function of the skin is often compromised. Prompt management and diagnosis can be lifesaving. Selected conditions with particular relevance to the newborn are highlighted below, followed by a general overview of treatment strategies. Table 94.3 lists the major clinical phenotypes of the ichthyoses in the newborn period.

X-Linked Ichthyosis

X-linked ichthyosis is the most common form of ichthyosis in the newborn period, affecting approximately 1 in 2500 male babies. Genetic mutations of the *STS* gene lead to deficiency of steroid sulfatase. Female carriers of the gene for X-linked ichthyosis, when pregnant with an affected male fetus, have a deficiency of placental steroid sulfatase reflected by low maternal urinary estriol excretion and a difficult or prolonged labor that often requires intervention. Clinical manifestations of X-linked ichthyosis in males include alterations in the skin, eye, and testes of affected infants. Most patients have cutaneous findings at birth, and 80%-90% show scaling by 3 months of age. Rarely, a collodion membrane may be present. The hyperkeratosis is variable, but the scales typically are large, thick, and dark and are prominent over the scalp, neck, anterior trunk, and extensor extremities. Sparing of palms and soles and partial sparing of the flexures are helpful diagnostic features. Systemic manifestations are generally absent, and complications are rare. Skin biopsy is helpful (although the histologic pattern resembles that of lamellar ichthyosis), showing hyperkeratosis, a well-developed granular layer, hypertrophic epidermis, and a perivascular lymphocytic infiltrate. This form of ichthyosis is clinically apparent in affected

TABLE 94.3 Clinical Presentation of Ichthyoses in the Newborn

Phenotype	Type of Ichthyosis
Erythroderma	Netherton syndrome, KID syndrome, CIE Also consider: Omenn syndrome, SCID, ectodermal dysplasia, erythrodermic psoriasis
Generalized scaling	XLI, Netherton syndrome, Sjögren-Larsson syndrome, trichothiodystrophy, neutral lipid storage disease
Collodion baby	Lamellar ichthyosis, CIE, self-healing collodion baby, harlequin ichthyosis (mild), Sjögren-Larsson syndrome, trichothiodystrophy, neutral lipid storage disease Also consider: ectodermal dysplasias, Gaucher disease
Vernix-like hyperkeratosis	Harlequin ichthyosis, KID syndrome
Constrictive scales with deformities	Harlequin ichthyosis
Blisters/erosions	Epidermolytic ichthyosis, ichthyosis bullosa of Siemens Also consider: epidermolysis bullosa, TEN, SSSS, immunobullous disease, mastocytosis

CIE, Congenital ichthyosiform erythroderma; KID, keratitis-ichthyosis-deafness; SCID, severe combined immunodeficiency; SSSS, staphylococcal scalded skin syndrome; TEN, toxic epidermal necrolysis; XLI, X-linked ichthyosis.
Different clinical presentations of ichthyosis in the newborn and the most likely underlying clinical conditions.
Adapted from Craiglow BG. Ichthyosis in the newborn. *Semin Perinatol.* 2013;37:26-31.

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homozygous males and not in heterozygous females. Cryptorchidism is seen in approximately 25% of affected males; these patients may be at increased risk for testicular cancer. Deep stromal corneal opacities have also been found in about 50% of male infants with the disorder and in a smaller percentage of female carriers, but they do not affect vision.

Harlequin Ichthyosis

Harlequin ichthyosis and harlequin fetus are rare, very severe disorders of keratinization inherited as an autosomal recessive trait in most families owing to mutations in the *ABCA12* gene. The skin of affected infants is markedly thickened, hard (armor-like), and hyperkeratotic, with deep crevices running transversely and vertically. The fissures are most prominent over areas of flexion. Rigidity of the skin around the eyes results in marked ectropion, although the globe is usually normal. The ears and nose are underdeveloped, flattened, and distorted, and the lips are everted and gaping, producing a "fish-mouth" deformity. The nails and hair may be hypoplastic or absent. Extreme inelasticity of the skin is associated with flexion deformity of all joints. The hands and feet are ischemic, hard, and waxy in appearance, with poorly developed distal digits.

Most harlequin fetuses are born prematurely, usually between 32 and 36 weeks' gestation, adding to their morbidity and mortality. Complications relate to an impaired skin barrier with associated hypernatremic dehydration, altered thermoregulation, increased metabolic demands, and increased risk of respiratory failure and sepsis. Although the disease still has a high mortality, therapeutic trials of oral retinoids combined with multidisciplinary intensive care have resulted in dramatic survival of several of these infants.[21] All surviving infants develop chronic, severe ichthyosis.

Collodion Baby

The collodion baby is less severely affected than the infant with harlequin ichthyosis and may represent a phenotypic expression of several genotypes. The infant is covered with a cellophane-like membrane, which by its tautness may distort the facial features and the digits. The membrane is shiny and brownish yellow, resembling an envelope of collodion or oiled parchment, and may be perforated by hair. This condition eventuates in lamellar ichthyosis or congenital ichthyosiform erythroderma in approximately 60% of patients. Sjögren-Larsson syndrome, Conradi-Hünermann syndrome, trichothiodystrophy, dominant lamellar ichthyosis, and neonatal Gaucher disease account for the remainder of the infants born with a collodion membrane. Rarely, shedding of the collodion membrane results in a normal underlying integument (i.e., lamellar exfoliation of the newborn). Collodion babies often are born prematurely. The presence of ectropion, eclabium, and crumpled ears causes these infants to resemble one another for the first few days of life. Fissuring and peeling begin shortly after birth, and large sheets may desquamate, revealing erythema of variable intensity. These infants have an abnormal epidermal barrier, which leads to complications such as dehydration, electrolyte imbalance, temperature instability, and cutaneous and systemic infection. Complete shedding of the collodion membrane may take several weeks. Pedigree information and histopathologic examination of a skin biopsy are additional aids in the delineation of the specific type of ichthyosis.

Management of Ichthyosis

Management of ichthyotic patients in the newborn period varies from managing mild cosmetic problems with excessive dryness and scaling to treatment of potentially life-threatening illness because of deficits in the epidermal barrier and subsequent infection. Table 94.4 lists the primary complications that form the primary targets of therapy for ichthyosis. Severely affected infants require aggressive topical care, oral systemic retinoids (Acitretin), liberal use of bland emollients, and careful monitoring of electrolyte needs. The infant should be placed in an environment with increased humidity and every effort taken to prevent infections. Keratolytic agents if necessary can be used with caution in the neonatal period. The long-term goal of ichthyotic therapy is to eliminate scaling owing to excessive cornification and reduce dryness (xerosis) of the skin without inducing irritation. Although the stratum corneum is often thick and scaly, the barrier is compromised, and there are significant risks of systemic absorption of potentially toxic substances applied topically. Avoidance of corneal desiccation and ulceration is critical if ectropion is present.

Future Prospects

At present, there is no definitive cure for ichthyosis, and current therapies are generally palliative. Over the past decade, however, the molecular basis of many of these predominantly monogenetic disorders has been elucidated.[13,19] Identification of the affected genes opens the door for prenatal diagnosis and genetic counseling for these potentially lethal conditions. Rapid progress in this field is anticipated, including the possibility of cutaneous gene therapy. Parents are referred to an extensive online support group for families of infants with cornification disorders, the Foundation for Ichthyosis and Related Skin Types (FIRST) (www.firstskinfoundation.org).

Vesicobullous Eruptions

Blistering eruptions in the neonatal period are relatively common (Table 94.5) and may be caused by infections, congenital diseases, or infiltrative processes or may be of unknown origin.[1,22,32] The management of such infants depends on knowledge of the cause of the disease or, when this is not possible, on an understanding of the pathogenesis of the type of blister encountered. Establishing the pathogenesis often depends on determining at which level (plane) within the skin the blister has occurred.

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TABLE 94.4 Clinical Complications of Ichthyosis and Therapeutic Management

Complications with Ichthyosis	Therapeutic Management Strategies
Restricted chest movement, contractures of limbs and soft tissues, sucking and feeding problems, compartment syndromes	Respiratory support, nasogastric feeding, liberal emollients with daily bathing and/or retinoids to thin and remove scale, monitor tissue perfusion and compartment pressure, orthopedic and plastic surgery evaluation of contractures, ophthalmology consult for ectropion and avoidance of corneal desiccation
Risk for bacterial infections and sepsis caused by impaired epidermal barrier	Watch for clinical signs of localized infection and/or sepsis with institution of aggressive culturing and treatment, topical antibiotics to fissures, reverse isolation
Risk of dehydration and electrolyte imbalance	Monitor fluid balance and electrolytes, humidified incubator to decrease evaporative water loss, intravenous hydration and/or alimentation
Fragile, easily traumatized skin; risk of absorption of topical preparations	Minimal handling; avoid aggressive adhesives; use self-adherent wraps or gauze; use bland emollients; avoid silver sulfadiazine, lactic acid, and salicylic acid preparations; antibacterial soaps

TABLE 94.5 Clinical Conditions of the Newborn Presenting with Cutaneous Vesicles, Bullae, Pustules, and Erosions

Differential Category	Specific Conditions
Noninfectious transient conditions	Sucking blister, superficial trauma, miliaria, neonatal acne, erythema toxicum neonatorum, transient neonatal pustular melanosis, eosinophilic pustular folliculitis, acropustulosis of infancy
Nontransient bullous dermatoses	Epidermolysis bullosa, Langerhans cell histiocytosis, incontinentia pigmenti, epidermolytic hyperkeratosis, pemphigus vulgaris, mastocytosis, hyper-IgE syndrome, herpes gestationis
Infectious vesiculopustular dermatoses	Viral infections: Herpes simplex, varicella, cytomegalovirus; Bacterial infection: Group B streptococcus, Group A streptococcus, *Haemophilus influenza* type B, *Staphylococcus aureus*, Listeria, *Pseudomonas*; Other: *Treponema pallidum*, *scabies*, *Candida*, *Aspergillus*

Adapted from Antaya RJ, Robinson DM. Blisters and pustules in the newborn. *Pediatr Ann.* 2010;39:635-645; Avram MM, Gobel V, Sepehr A. Case records of the Massachusetts General Hospital. Case 30-2007. A newborn girl with skin lesions. *N Engl J Med.* 2007;357:1327-1335.

Blister sites may be intraepidermal or subepidermal. In the epidermis, the blister can be very high (subcorneal), midepidermal, or basal. The midepidermal blister may be formed by primary separation of intercellular contacts (e.g., acantholysis), by secondary edematous disruption of intercellular contacts (e.g., spongiosis), or by intracellular injury as seen in patients with viral infections. The diagnosis of a blistering disease usually requires a family history, an immediate past history of the infant and mother, laboratory studies to exclude infectious agents, evaluation of the infant's general state of health, consideration of the morphologic characteristics of the eruption, and often a biopsy of the involved skin. The biopsy should be obtained from a fresh, typical, small lesion and should include some surrounding skin.

Sepsis

Bacterial sepsis in the neonate can present with vesicles, pustules, or bullae. The most common cause of sepsis presenting with pustules is *S. aureus.* Group B *Streptococcus* (GBS) *agalactiae* is a leading cause of neonatal sepsis, pneumonia, and meningitis, but it rarely manifests in the neonate at birth with vesicles, pustules, or bullae. Other occasional causes of pustules and sepsis in neonates include *Listeria monocytogenes*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae.*

Staphylococcal Infection and Impetigo

Superficial skin infections caused by *Staphylococcus aureus* range from localized bullous impetigo to generalized cutaneous involvement with systemic illness.[4] In contrast to congenital blistering diseases, which are often present at birth, skin infections with *S. aureus* usually develop after the first few days of life. They may be bullous, crusted, or pustular. Typical lesions are small vesicles or pustules or large, fragile bullae filled with clear, turbid, or purulent fluid. They rupture easily, leaving red, moist, denuded areas often with a superficial varnish-like crust. Although they may develop anywhere on the body, the blisters and pustules commonly occur on the diaper area, axillae, and periumbilical skin. The diagnosis is made by Gram stain and culture of the blister fluid, which can distinguish this eruption from streptococcal impetigo and other bullous disorders of the neonatal period. Blood cultures should be obtained from affected infants before initiating systemic antibiotic therapy,

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even if the infants are usually otherwise well. Contacts and nursery personnel should be investigated for a source of the infectious organism. The infant should be placed in isolation and observed carefully for early signs of sepsis. A high index of suspicion during examination of other infants in the nursery is the most effective means of preventing epidemic spread of this infection.

Compresses of physiologic saline solution and systemic antibiotics to cover the principal etiologic possibilities are indicated until culture results are available. Fluid and electrolyte replacement therapy may be required if the disease is extensive. Recovery is usually complete in several days with no residual scarring.

Staphylococcal Scalded Skin Syndrome

The staphylococcal scalded skin syndrome is a severe bullous eruption heralded by a bright erythema that resembles a scald. The erythema begins on the face and gradually spreads downward to involve the remainder of the skin, with accentuation in the flexural areas. The level of cleavage is superficial, occurring in the granular layer of the epidermis, and the bullae, therefore, are flaccid, easily ruptured, and rapidly progress into areas of denudation. The infant is febrile, irritable, and has marked cutaneous tenderness. The face, neck, and flexural areas are the first to be eroded. The entire upper epidermis may be shed from the limb like a glove. Crusting around the mouth and eyes results in a typical facies. Conjunctivitis is common, as is hyperemia of the mucous membranes, but oral ulcerations do not occur. Infants with a milder form of the disease display a scarlatiniform eruption with perioral and flexural desquamation but without bullae or denudation. Like staphylococcal pyoderma, staphylococcal scalded skin syndrome is rarely seen at birth, with most neonatal cases presenting between 3 and 7 days of life.

The infecting organism in scalded skin syndrome is *S. aureus*, usually a group 2 phage type, although other phage types occasionally have been incriminated. These organisms produce an exotoxin (i.e., exfoliatin) that has proteolytic activity on desmoglein-1, a molecule found within the desmosomes of keratinocytes that is responsible for the cutaneous manifestations.[26] Two major serotypes of the toxin, A and B, cause bullous impetigo and scalded skin syndrome. In cases of the former, the toxin produces exfoliation and blisters locally, whereas in the latter, the toxin circulates systemically with widespread epidermal necrolysis. Histologic examination of the skin demonstrates separation at the level of the granular layer with cell death and acantholysis; there is a striking absence of inflammatory infiltrate. Because intact bullae are sterile, cultures should be obtained from the nasopharynx, conjunctival sac, umbilicus, abnormal skin, blood, urine, and any other suspected focus of infection that might have provided a portal of entry for the organism.

Treatment consists of prompt systemic administration of penicillinase-resistant semisynthetic penicillin and pain management. Fluid and electrolyte replacement is warranted if necessary, and reports indicate successful use of skin-substitute dressings. Flaky desquamation occurs during the healing phase. Scarring never occurs because the blister cleavage plane is intraepidermal.

Streptococcal Infection

Infection with group B beta-hemolytic streptococci rarely produces skin lesions, but vesicles, bullae, and erosions have been reported. Epidemics of group A streptococcal infection may occur primarily as omphalitis or rarely as isolated pustules. These infants should be treated aggressively with parenteral antibiotics, because sepsis, cellulitis, meningitis, and pneumonia have been documented.

Miscellaneous Bacterial and Spirochete Infections

Listeria and *Haemophilus* may also be the cause of cutaneous vesicles or pustules in the newborn. *Pseudomonas aeruginosa* may cause large hemorrhagic bullae in the neonatal period. This is usually a nosocomial infection seen primarily in infants with low birth weights. The skin lesions result from septicemia and hematogenous spread to the skin. In older children, the pustules and bullae are in the perineal region, but in the newborn, they may occur anywhere. The lesions rapidly ulcerate, leaving "punched-out" erosions. Diagnosis can be made by performing a Gram stain or culture of the bullae or the base of the ulcer. Parenteral antibiotics should be administered immediately, and the prognosis is usually poor. Although previously rare, congenital syphilis is increasing in incidence and mirrors the increase in pregnant women.[69] Sixty percent of infants with congenital syphilis are asymptomatic at birth. Vesicles or bullae with erythema on a polished base may form on the palms and soles and are pathognomonic. (Fig. 94.7).[1] This rash is accompanied by hepatosplenomegaly, periostitis of long bones, snuffles, and iritis. The diagnosis is made by using a combination of nontreponemal and treponemal antibody tests as recommended by the CDC. More recently, the reverse syphilis testing algorithm has outperformed the traditional testing and has been widely accepted.[67] The main stay of treatment remains systemic procaine and benzathine penicillin.

Viral Lesions

One of the most important causes of vesicular rash in the neonatal period is herpes simplex infection.[32] Frequently, an inconspicuous cutaneous lesion heralds severe systemic infection. The infection may be acquired in utero or perinatally. Intrauterine herpes simplex infection typically presents with vesicles at birth or within 24 hours. The vesicular eruption may be widespread or even bullous, resembling epidermolysis bullosa. Rarely, congenital scars may be present when infection was early in gestation, in which case additional findings may include low birth weight, microcephaly, chorioretinitis, and neurologic changes. Perinatally acquired herpes simplex may be limited to the skin, eyes, and mouth or may be disseminated with multiple organ involvement. The cutaneous lesions usually develop in the second week

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• **Fig. 94.7 A,** Congenital syphilis with erythema and widespread plantar desquamation of the foot. **B,** Erythematous rash on palmar surface. (From Ferreira ST, et al. Skin rash: a manifestation of early congenital syphilis. *BMJ Case Rep.* Published online: doi: 10.1136/bcr-2016-216148).

of life, concurrent with or after nonspecific systemic signs and symptoms. Typically the lesions are 1- to 3-mm vesicles, usually occurring on the scalp or face. Vesicles may be present on the torso or buttocks, especially in a breech delivery. Rarely, pustules, erosions, or oral ulcerations may be the only cutaneous findings. In infants with cutaneous lesions suggestive of herpes simplex infection, antiviral therapy should be administered immediately, and the diagnosis can be confirmed by PCR of HSV antigens in blood or CSF. Isolation of HSV by culture of vesicle scrapings or "surface" culture of mouth, nasopharynx, rectum, or conjunctivae is the traditional diagnostic method.[36] Current recommendations for prevention of herpes simplex infections include cesarean section for women with active lesions or prodromal symptoms consistent with herpes. Vaccines against HSV2 have been of low efficacy. High-dose, prolonged acyclovir therapy remains the treatment of choice for neonatal herpes simplex infections.

Primary varicella may occur in the newborn if the mother has a primary varicella infection in the last 3 weeks of pregnancy. The onset of this diffuse vesicular disease is 5-10 days of age, and the lesions may be numerous and monomorphic given the infant's impaired ability to mount an immune response. Varicella zoster has also been reported in the neonatal period in infants of mothers who have had primary varicella during pregnancy. These vesicles are unilateral and occur in a dermatomal distribution. The vesicles of varicella, herpes zoster, and herpes simplex have a similar histologic pattern, with cleavage in the mid-epidermis. Acantholysis and marked destruction of individual cells result in the ballooning type of degeneration characteristic of viral vesicles.

Candidiasis

See Chapter 49. *Candida* species are commensal organisms commonly found in the gastrointestinal and female genital tracts. Roughly one-third of health care workers in neonatal intensive care units test positive for candida on routine surveillance cultures, and up to 40% of women are culture positive for *Candida* at the time of delivery. Candidiasis in the first 4 weeks of life is usually benign and is localized most often to the oral cavity (thrush) or the diaper area. If maternal vaginal organisms are acquired during the birth process, the infant may manifest symptomatic mouth lesions or become an intestinal carrier. Fecal contamination is the usual source of the organism in candidal dermatitis. Paronychial lesions also may occur, particularly in thumb-sucking infants. The lesions of thrush are detectable as creamy white patches of friable material on the buccal mucosa, gums, palate, and tongue. Early cutaneous lesions consist of erythematous papules and vesicopustules that become confluent, forming a moist, erosive, scaly dermatitis surrounded by satellite pustules.

Rarely, cutaneous candidiasis may be congenital as a result of ascending infection from a vaginal or cervical focus. Risk factors for this type of candidiasis include a foreign body in the uterus or cervix, premature birth, and a history of vaginal candidiasis. Affected infants usually have a widespread eruption with pustules on the palms and soles, and occasionally, nail dystrophy. In contrast to acquired cutaneous candidiasis, congenital candidiasis has lesions at nonflexural sites.[9] Distinctive yellow-white papules on the umbilical cord and placenta represent *Candida* granulomas. *C. albicans* may be demonstrable on histologic examination

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of these tissues and may be cultured from the amniotic fluid.

Although candidal infection is usually localized to skin, infants who weigh less than 1500 g are also at risk for systemic infections. In addition to birth weight less than 1500 g, risk factors for disseminated candidiasis include central line placement, being on a ventilator, broad spectrum antibiotic use, and parenteral nutrition.

In the chronic mucocutaneous or granulomatous forms of candidiasis (rare in the neonatal period), the scalp, lips, hands, and nails may be sites of chronically scaling, heaped-up lesions. These two forms of infection often are associated with a defect in the immune response, multiple endocrinopathies, or both.

The diagnosis is usually clinical or aided by identification of budding yeast spores on Gram stain or of spores and pseudohyphae on a potassium hydroxide preparation. Growth of the organism is rapid on Sabouraud dextrose or Mycosel agar.

Treatment depends on the extent of involvement. Topical antifungal agents from the imidazole group are the most effective for disease limited to the skin. Systemic administration of amphotericin B, 5-fluorocytosine, or an imidazole should be reserved for patients with evidence of disseminated disease.[66] Fluconazole or itraconazole for disseminated candidiasis in the very low birth weight infant has been used for prophylaxis or an alternative to systemic amphotericin B and 5-fluorocytosine. Recent clinical trials have shown that probiotics reduce oral, vaginal, and enteric colonization of Candida and may reduce the incidence of invasive candidiasis.[42]

Hereditary Blistering Diseases

Epidermolysis Bullosa

Epidermolysis bullosa (EB) refers to a group of heterogeneous diseases that are characterized by simplex (intraepidermal), junctional (lucidolytic), or dystrophic (subepidermal) subtypes with blisters produced by minor degrees of trauma and heat.[6] These disorders are the result of a variety of inherited defects of the proteins that maintain skin integrity. In 2008, EB was reclassified into four major subtypes based on the region within the skin that the defective or missing protein is expressed and at what depth the resultant blister occurs.[17] Table 94.6 lists the major clinical EB subtypes, the ultrastructural features (i.e., depth of blister), the affected proteins, and the inheritance patterns. Recent advances have made molecular analysis of the defect available as well. At present, 14 distinct structural genes representing more than 1000 different mutations are linked etiologically to EB subtypes.[6,18] First trimester prenatal diagnosis is available and preimplantation genetic testing is possible in select centers.

The clinical features may be quite variable in the newborn period, making it difficult to identify the specific subtype of EB and the expected prognosis. Some subtypes of EB are severe, life-threatening diseases, and others are mild and do not manifest until adolescence. In all forms of EB, blisters may be readily elicited (Nikolsky sign) by gentle rubbing (Fig. 94.8). If there is friction in utero, the baby may be



• **Fig. 94.8** Denudation and erosion as a result of blistering in an infant with epidermolysis bullosa. (From Antaya RJ, Robinson DM. Blisters and pustules in the newborn. *Pediatr Ann.* 2010;39:635-645.)

TABLE 94.6 Epidermolysis Bullosa: Major Subtypes with Corresponding Level of Skin Cleavage, Affected Proteins, and Mode of Inheritance in the Newborn

	EB Simplex (Epidermolytic)	Junctional EB (Lucidolytic)	Dystrophic EB (Dermolytic)	Mixed EB Type
Level of skin cleavage	Within the epidermis	Within the lamina lucida (basement membrane)	Within the dermis	Multiple cleavage points
Affected proteins	Keratins 5 and 14, plectin, dystonin, plakophillin-1, desmoplakin	Laminin-332, collagen XVII, α6β64 integrin	Collagen VII	Kindlin-1
Inheritance pattern	Most are autosomal dominant except for suprabasilar types and forms with muscular dystrophy or pyloric atresia	Autosomal recessive	Both autosomal dominant and recessive	Autosomal recessive (Kindler syndrome)

EB, Epidermolysis bullosa.
Adapted from Gonzalez ME. Evaluation and treatment of the newborn with epidermolysis bullosa. *Semin Perinatol.* 2013;37:32-39.

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born with large areas of denuded skin. In the past, this was referred to as Bart syndrome, but further delineation of the molecular defects has shown that several subtypes of EB can result in this clinical picture (Table 94.6). More frequently, the birth process or minor perinatal trauma causes blistering of the skin. The more severe, dystrophic, recessive forms of EB are associated with low birth weight.

Junctional EB is further subtyped into generalized severe (Herlitz type) and generalized intermediate (non-Herlitz type) based on the absence or decrease of laminin-332 respectively. JEB deserves special mention because it is almost always present at birth and is a very severe form of EB. The mean age of death in the generalized severe form is 5 months secondary to sepsis, respiratory failure, or failure to thrive. The epidermis loosens after minimal trauma, and bullae of various sizes are formed anywhere on the body. The nails are frequently involved. Oral and anal lesions also occur. Many lesions heal spontaneously, but large bullae may fail to heal and result in moist, chronic vegetative lesions consisting of exuberant granulation tissue. There may be significant loss of electrolytes and protein through these erosions.

Blisters and erosions may also be severe and widespread in the epidermolytic subtype of EB simplex. This subtype may be distinguished clinically by the characteristic grouping of the blisters and the formation of milia. In all forms of EB, blisters may be readily elicited by gentle rubbing (Nikolsky sign). Mild trauma can result in a blister within a few minutes to hours, and the resulting fresh lesions may be used for histopathologic examination. Treatment is aimed at protecting the skin from trauma and secondary infection.

Scarring or dystrophic EB has recessive and dominant forms. In contrast to the simplex and junctional groups (except the Dowling-Meara type), milia may mark the site of healed blisters. In the severe form of recessive dystrophic EB, hemorrhagic erosions and blisters may be present at birth, especially on the feet. The toe and finger lesions may heal with fusion of digits and loss of nails, resulting in a characteristic mitten-like envelope of the hands. As the fingers fuse (this usually takes several years), the hands and arms become fixed in a flexed position and contractures develop. Repeated episodes of blistering, infection, and scar formation lead to severe deformities, loss of hair, mucosal scarring, dysphagia, anemia, and retarded physical and sexual development. Visceral amyloidosis, hyperglobulinemic purpura, clotting abnormalities, and squamous cell carcinoma are associated with this severe, life-limiting disease.

The dominant forms of scarring EB usually are less severe than the major recessive type. Lesions may be generalized or localized at birth, or they may appear later and may be limited to the elbows, knees, hands, feet, and sacrum. Oral involvement is common but is usually not severe. Nails may be lost, but deforming scars and contractures occur infrequently. Red plaques rather than blisters may result from injury. The lesions heal with soft, wrinkled scars. Pigmentary change and milia may be formed at old blister sites. General health is usually unimpaired.

The initial diagnosis of EB is a clinical one, and other disorders that cause blistering, particularly infections, should be excluded. Clinical differentiation of EB subtypes is difficult or impossible; for this reason, all infants with the diagnosis should undergo skin biopsy to obtain a more precise diagnosis. Light microscopy may be helpful in determining the level of cleavage, but results can often be difficult to interpret. Immunofluorescence mapping of biopsied EB skin specimens is the currently recommended primary laboratory method of diagnosing EB subtypes.[17] If available, electron microscopy, immunofluorescence mapping, and DNA mutational analysis are used simultaneously to confirm the diagnosis.

Unfortunately, there is no effective treatment for infants with EB. Treatment is aimed at protecting the skin from trauma, providing wound healing dressings, maximizing nutrition, and preventing secondary infection. Management strategies for treating neonatal EB are given in Box 94.3. Gene and cell-based molecular therapies hold hope for future approaches that may cure or ameliorate specific EB subtypes.

Incontinentia Pigmenti

Incontinentia pigmenti (IP) is a rare, X-linked, dominant genodermatosis that affects the skin, skeletal system, eyes, and central nervous system (CNS). Incontinentia pigmenti results from mutations in the *IKBKG* (formerly known as *NEMO*) gene on chromosome Xq28 that inhibits expression of NF-kappa B, an essential modulator. The common IP deletion is at exons 4 through 10, found in 80% of known cases. This protein is required for activation of a transcription factor important in apoptotic, inflammatory, and immune pathways. Molecular analysis of the *IKBKG* gene is commercially available; however, the diagnosis of IP is typically based on characteristic clinical findings.[23] Almost all patients are female, but affected male patients have been reported and are thought to represent genetic mosaicism or Klinefelter syndrome.

The cutaneous lesions usually are present at birth and have four morphologic stages. Stage 1 is known as vesicular or inflammatory stage, characterized by vesicles and pustules distributed in a linear pattern, along Blaschko lines on the extremities and less often on the head, trunk, and face (Fig. 94.9). In the majority the lesions are either present at birth or appear within the first 2 weeks. Stage 2 is the verrucous stage, wherein warty papules or plaques are distributed in a linear fashion along the Blaschko lines, not necessarily along the same lines occupied by the vesicular lesions. This occurs between 2-6 weeks and may overlap with stage 1. In stage 3, linear or whorled lesions with a brownish pigmentation develop along Blaschko lines during early infancy and disappear during adolescence. Stage 4 is the hypopigmented or atrophic stage, where hypopigmented lesions occur along Blaschko lines mainly in the

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• BOX 94.3 Management of Epidermolysis Bullosa in the Neonatal Period

Minimize Trauma to Skin and Promote Comfort

- Use gentle handling and reduce friction.
- When possible, use wrapping or suturing instead of taping when applying instruments or monitors; if taping is necessary, leave probes in place.
- Use oral sucrose with dressing changes.
- Administer acetaminophen or opiate agonist for extreme discomfort.

Provide Ideal (Moist) Wound-Healing Environment

- Open and drain tense vesicles with sterile needle.
- Perform gentle daily debridement of crust in bathtub.
- Apply emollients and nonstick primary dressing.
- Protect wound and secure primary dressing with secondary dressing such as gauze wrap and stockinette or Coban tape.
- Tape dressing to itself and not to skin.

Prevent Sepsis and Bacterial Superinfection of Wounds

- Observe wounds for purulence and foul smell.
- Monitor colonization with weekly surveillance cultures.
- Apply topical antibiotics combined with emollient on open erosions to control colonization.
- Cover Gram-positive organisms with intravenous antibiotics if there are signs or symptoms of sepsis.

Maximize Nutrition with Minimal Trauma for Optimal Wound Healing and Growth

- Breastfeed if there is mild oral involvement and the infant can feed through pain.
- If not, have mother pump breast milk and bottle feed with high-flow nipple or drip feeds.
- Add breast milk fortifier to maximize caloric intake.
- For formula-fed baby, use high-calorie formulas.
- Obtain dietary consultation and follow up to ascertain energy needs and how to meet them.

Monitor for Extracutaneous Complications

- Eye: Request ophthalmology consultation for redness or photophobia.
- Gastrointestinal: If oral involvement, watch for feeding intolerance.
- Genitourinary: Look for gross hematuria, meatal narrowing in boys; consider urinary source if infant is febrile.
- Polyhydramnios: Look for pyloric atresia.
- Respiratory: Monitor airway for hoarse cry or stridor as a sign of laryngeal involvement.

Provide Psychosocial Support

- Provide counseling regarding prognosis once diagnosis is known. Emphasize unpredictability of course even when subtype is known.
- Discuss usual short-term complications in general terms.
- Provide access to peer counseling through Internet sites and local chapters of national patient advocacy groups.

Expanded from Bruckner AL, et al. Inherited and Acquired Blistering Diseases. In: Eichenfield LF, et al., eds. *Neonatal and infant dermatology*. 3rd ed. Philadelphia: Elsevier Saunders; 2015 [chapter 7].

lower extremities. This develops during adolescence and persists into adulthood.[23] Nail hypoplasia, areas of alopecia, and ocular and skeletal abnormalities also may be detected. There is often peripheral eosinophilia during the vesicular phase of the disease. The diagnosis should be considered when inflammatory vesicles arranged in lines are seen in a newborn female infant. Delayed dentition, partial anodontia, and abnormalities of the CNS can occur but may not be apparent during the neonatal period. Biopsy of a small blister demonstrates a subcorneal vesicle filled with eosinophils. The differential diagnosis includes herpes simplex infection and other blistering diseases. The clinical evolution of the cutaneous process, the demonstration of a large number of eosinophils in the skin lesions and peripheral blood, and the presence of pigment-laden macrophages in the upper dermis of end-stage lesions establish the diagnosis. No specific therapy is required for the skin lesions; if inflammation becomes excessive during the vesicular phase, treatment with cold compresses, oatmeal baths, and topical steroids may be helpful. Ophthalmologic and neurologic examinations are indicated for all infants with this disorder. Parents can be directed to the IP International Foundation (www.ipif.org) for information on latest research articles and treatment protocols.

Zinc Deficiency

Zinc deficiency occurs in the genetic disorder acrodermatitis enteropathica (AE) and is an acquired condition attributable to inadequate zinc intake. Acrodermatitis enteropathica, a rare disorder, is inherited as an autosomal recessive trait. The AE gene (*SLC39A4*) has been localized to chromosomal region 8q24.3 and encodes for a member of the ZIP family of metal transporters.[38] Alopecia, dermatitis, and diarrhea form the clinical triad of AE. Cutaneous manifestations are typically flexural, anogenital, and periorifacial. There is typical sparing of upper lip, resulting in a "horseshoe-shaped" lesion (Fig. 94.10). Secondary infection with *C. albicans* is a common complication. The onset may be as early as the 3rd week of life, but more frequently it occurs later in infancy. The disease is caused by a defect in zinc absorption or transport, and plasma zinc levels should be checked when the diagnosis of AE is suspected. Low levels of alkaline phosphatase, a zinc-dependent enzyme, may aid in diagnosis. The clinical presentation is later in breastfed infants because of higher bioavailability of zinc in breast milk. Oral zinc sulfate (3 mg/kg per day) is the treatment of choice. Maternal blood and breast milk zinc levels should be assessed to support maternal supplementation and continuation of exclusive breastfeeding.

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• **Fig. 94.9** Incontinentia pigmenti. Erythematous vesicopapular lesions following the lines of Blaschko in a V-shaped configuration over the dorsal skin. Lesions typically evolve through verrucous, hyperpigmented stages to finally manifest hypopigmentation and dermal atrophy. (Courtesy of Dr. Taeun Chang.)



• **Fig. 94.10** Recalcitrant perioral eruption caused by zinc deficiency in an infant with acrodermatitis enteropathica. Note the "horseshoe-like" involvement with relative sparing of the upper lip.

A similar eruption has been observed in premature infants maintained on total parenteral nutrition inadequately supplemented with zinc. These infants suffer from relative zinc deficiency caused by high metabolic demands. Premature and term infants receiving breast milk with low levels of zinc and infants with malabsorption syndrome or cystic fibrosis also have developed symptomatic zinc deficiency. Maternal zinc deficiency in pregnancy may result in fetal malformation, growth restriction, prematurity, postmaturity, and perinatal death.

Pigmentary Abnormalities

The melanocyte system of the newborn skin is not mature at birth. As a result, all babies regardless of racial pigmentation may look lighter than their parents at birth. Within the first few weeks, pigmentation becomes more evident because melanin production has been stimulated by exposure to the postnatal environment.

Diffuse Hyperpigmentation

The intensity of pigmentation must be considered in light of the infant's genetic and racial background. Diffuse hyperpigmentation in the newborn is unusual. It may be caused by a gene whose main effect is on the melanocyte, by a hereditary disease that has secondary pigmentary consequences, by endocrinopathy, by a nutritional disorder, or by hepatic disease. Although in such cases, hyperpigmentation may be described as diffuse; it may be accentuated in certain areas such as the face, over bony prominences, or in the flexural creases.

Localized Hyperpigmentation

Cafe au Lait Macules

Café au lait spots are flat, pigmented macules with distinct borders that may be present in the newborn infant and are light brown in whites and dark brown in blacks.[60] Whereas lesions are seen in 24%-36% of older children, most commonly on the trunk, they are present in 0.3%-18% of newborns, usually over the buttocks.[55] Lesions vary with ethnicity and race; they are seen over the buttocks in newborns. Lesions that are larger than 0.5 cm in diameter and more than six in number, especially when accompanied by "freckling" in the flexures, strongly suggest neurofibromatosis. The axillary freckles really represent tiny café au lait macules. Café au lait spots are usually the first cutaneous lesions to appear in a patient with neurofibromatosis, but additional genetic and clinical investigations may be required to establish a diagnosis. For example, small, pigmented spots (i.e., Lisch nodules) may be detected on the iris by slit-lamp examination in most patients older than 6 years with classic neurofibromatosis. Patients with tuberous sclerosis also may have café au lait spots that are identical in appearance to those of neurofibromatosis, but they are usually accompanied by white macules, which are called ash leaf macules.

McCune-Albright Syndrome

In a patient with McCune-Albright syndrome (i.e., polyostotic bone dysplasia, café au lait spots, and multiple endocrine disorders), the pigmented patches may be solitary or multiple, unilateral, elongated, and large (>10 cm), and often have a ragged, irregular border. These manifestations are caused by somatic activating mutations in the *GNAS* gene, which codes for the alpha subunit of the stimulatory G-protein (protein Gsα) that is involved in intracellular cyclic adenosinemonophosphate (cAMP) production.[39]

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Congenital Melanocytic Nevi

Congenital nevi represent nested proliferations of melanocytes that are present at birth or appear in the first months of life. Small nevi (<1.5 cm) are seen in 1%-2% of newborns, intermediate nevi (1.5-20 cm) in 0.6%, and large nevi in less than 0.02%.[55] Small lesions (as opposed to giant pigmented nevi) are flat and light to dark brown, often with variegated color or speckling and an accentuated epidermal surface ridge pattern. These lesions vary in site, size, and number, but most often are solitary. Histologically, they are characterized by the presence of nevus cells in the dermis, and most have nevus cells extending into the deeper dermis; fat; and perivascular, periappendageal, and perineural sites. There is no clear-cut evidence that the small congenital nevus is a premalignant lesion, and conservative management consisting of serial observation with photographic documentation may be appropriate.[55] Individualized approaches about surgical excision include the location and appearance of the lesion, ease of excision, and expected cosmetic result. Laser treatment may lighten small nevi but does not completely remove the melanocytes, and its use for this indication is controversial.

Large Congenital Melanocytic Nevi

The giant (>20 cm) nevus (Fig. 94.11) is the most important of the congenital melanocytic (pigmented) nevi (CMN). A somatic mutation in codon 61 of the tyrosine kinase gene *NRAS* accounts for 80% of large CMN. The lifetime risk of malignant transformation and melanoma is estimated to be 6%-8%.[55] The onset of melanoma in utero has been reported. These nevi may occupy 15%-35% of the body surface, most commonly involving the trunk. The pigmentation often is variegated from light brown to black. The affected skin may be smooth, nodular, or leathery in consistency. Prominent hypertrichosis is often present. Almost invariably, numerous satellite nevi coexist elsewhere on the body. Leptomeningeal melanocytosis has been documented in some of these patients, and this complication may manifest as seizures.



• **Fig. 94.11** Giant congenital melanocytic nevus involving the bathing trunk area with sparing of the genitalia. Note the thickening of the skin and hypertrichosis. This infant had a similar lesion on the scalp.

Because of the significant incidence of malignant transformation, the hideous deformity, and the intense pruritus that may accompany them, it is desirable, when feasible, to excise these lesions surgically as soon as possible. Lasers, dermabrasion, and tissue expansion techniques have been used in conjunction with surgical excision for removal and cosmesis of large lesions. Recently, NRAS inhibitor trametinib has been used to treat large CMN in patients with *NRAS* gene mutations.[65]

Peutz-Jeghers Syndrome

The cutaneous lesions of the Peutz-Jeghers syndrome may be present at birth or develop soon thereafter. They consist of brown to blue-black macules, somewhat darker than freckles, which develop around the nose and mouth. The lips and oral mucosa often are involved, as are the hands, fingertips, and toes. Macular hyperpigmentation is the only visible sign of this autosomal dominant disorder until adolescence, when the patient begins to suffer from attacks of intussusception, bleeding, and subsequent anemia secondary to coexisting small bowel polyposis.

Xeroderma Pigmentosum

Xeroderma pigmentosum is transmitted by an autosomal recessive gene and results in marked hypersensitivity to ultraviolet light. The skin is normal at birth but changes develop soon thereafter depending on the degree of UV exposure. The infant develops erythema, speckled hyperpigmentation, atrophy, actinic keratoses, and all known types of cutaneous premalignant and malignant lesions. The outcome is often fatal by the second decade of life as a result of metastatic disease. The underlying abnormality in most cases is a deficiency in an endonuclease that is responsible for the repair of DNA damaged by ultraviolet light. Approximately 20% of patients have neurologic problems. Protection from ultraviolet light exposure is mandatory to prevent skin damage and tumor development. Prenatal diagnosis of xeroderma pigmentosum is possible using PCR-based genetic diagnosis combined with measurement of DNA repair of amniotic fluid cells or chorionic villi fibroblasts.[47]

Postinflammatory Hyperpigmentation

Hyperpigmentation may result secondarily from any inflammatory process in the skin and may have many causes, including primary irritant dermatitis, infectious processes, panniculitis, and hereditary diseases such as EB. The hyperpigmentation may result from enhanced melanosome production, larger melanin deposits in basal cells, greater numbers of keratinocytes, an increase in the thickness of the stratum corneum, or deposits of melanin in dermal melanophages. Hyperpigmentation usually fades gradually over weeks to months without treatment, although a low-potency topical steroid may decrease residual inflammation.

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Blue Nevus

Occasionally, a blue nevus (so called because of its Prussian blue color), or dermal melanocytoma, may be present at birth. It usually is a 1- to 3-cm, oval, dome-shaped, black-blue tumor found on the upper half of the body. It grows very slowly and has little tendency to become malignant but may be difficult to differentiate clinically from vascular tumors. Excisional biopsy is diagnostic and curative.

Hypopigmentation

Diffuse or localized reduction or absence of cutaneous pigment in the neonate may be caused by a heritable or developmental disorder or may result from a nutritional disease or postinflammatory change.[8] Decrease in cutaneous melanin may be caused by an absence or destruction of melanocytes or by a defect in one of four biologic processes: formation of melanosomes, formation of melanin, transfer of melanosomes to keratinocytes, and transport of melanosomes by keratinocytes.

Albinism

Albinism (e.g., complete albinism, oculocutaneous albinism), which occurs in all races, has an incidence of 1 case per 17,000 persons in the United States; the phenotypic picture is caused by an autosomal recessive gene. Several forms of this disorder have been delineated. The affected infant usually has markedly reduced skin pigment, yellow or white hair, pink pupils, gray irides, photophobia, and cutaneous photosensitivity. Melanocytic nevi can be present in patients with albinism, and the nevi may or may not be pigmented. In blacks, the skin may be tan, the hair may have a yellow or orange color, and freckles can appear on exposure to light. The usual eye findings are photophobia, nystagmus, and a central scotoma with reduced visual acuity. Other associated abnormalities reported in certain types of albinism are small stature and coagulation disorders.

The biochemical defect responsible for oculocutaneous albinism type 1 is a deficiency of tyrosinase, the enzyme responsible for converting tyrosine to dopa, an early step in the formation of melanin. The range of tyrosinase deficiency correlates well with the spectrum of color seen in affected individuals. Structurally, the melanosomes appear to be normal. In oculocutaneous albinism type 2, however, mutations in the *P* gene affect function of a melanosomal protein. Molecular analyses of the tyrosinase and *P* genes are necessary for precise diagnosis. Treatment in all cases is aimed at protection from ultraviolet light, because early actinic keratoses and squamous cell carcinoma are common occurrences in these patients.

Partial Albinism (Piebaldism)

Partial albinism is an inherited disease caused by mutations of the autosomal dominant *KIT* gene coding for the tyrosine kinase transmembrane cellular receptor for mast/stem cell growth factor, a critical factor for melanoblast migration and function. This leads to defective cell proliferation and melanocyte migration during embryogenesis.[8] This condition is present at birth but may not be evident in fair-skinned infants because of a lack of contrast in skin color. In piebaldism, the hair and skin are affected. The amelanotic areas usually involve the midline frontal scalp (i.e., widow's peak), resulting in the characteristic white forelock, forehead to the base of the nose, chin, thorax, trunk, back midarm, and midleg. There are normal islands of pigment within the amelanotic areas, and the distribution pattern is fairly constant. Examination of an affected area by electron microscopy shows an absence of melanocytes or melanocytes with markedly deformed melanosomes. Repigmentation does not take place. The differential diagnosis may include vitiligo, achromic nevus, nevus anemicus, and the hypomelanotic macules of tuberous sclerosis. A combination of dermabrasion and grafting of pigmented skin into depigmented areas, with or without phototherapy, has been tried with variable results.

Phenylketonuria

Phenylketonuria, caused by an absence of phenylalanine hydroxylase, results in a variety of neurologic and cutaneous abnormalities, which include mental retardation, seizures, diffuse hypopigmentation, eczema, and photosensitivity (see Chapter 90).

Chédiak-Higashi Syndrome

The Chédiak-Higashi syndrome is a rare, fatal disorder resulting from mutations in the autosomal recessive lysosomal trafficking regulator (*LYST*) gene. Clinical features include diffuse to moderate reduction in cutaneous and ocular pigment; photophobia; hepatosplenomegaly; and recalcitrant, recurrent infections. Seizures and progressive neurologic deficits have occurred in some patients in early childhood. The leukocytes and other cells contain the pathognomonic giant azurophilic granules, and this finding has its parallel in the melanocyte, which produces giant melanosomes. These abnormal granules are unable to discharge their lysosomal and peroxidative enzymes into phagocytic vacuoles. The diagnosis can be made by the characteristic family history, physical findings, laboratory demonstration of abnormal leukocytes and melanosomes, and the usual course, which leads to death in childhood. Death results from a lymphoma-like process (accelerated phase or hemophagocytic lymphohistiocytosis) or infection. Treatment is palliative, but bone marrow transplantation has been used successfully to reverse the immunologic defects.[40]

Waardenburg Syndrome

Waardenburg syndrome is an auditory-pigmentary syndrome inherited as an autosomal dominant condition secondary to mutations in the *PAX3* gene controlling neural crest differentiation.[8] The most constant features are lateral displacement of the inner canthi, a prominently broad nasal root, confluent eyebrows, variegation of pigment in the iris (i.e., heterochromia iridis) and fundus, congenital deafness, a white forelock, and cutaneous hypochromia. The

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clinical picture is quite striking, and the diagnosis usually is not difficult. Although usually limited to small areas, the hypopigmentation may be severe and extensive enough to resemble that of piebaldism.

Nevus Anemicus

Nevus anemicus is a congenital vascular anomaly that appears as a permanently pale, mottled lesion that occurs most often on the trunk. The lesions appear hypopigmented but contain normal amounts of pigment. The nevus is best characterized as a pharmacologic abnormality rather than an anatomic one. Pallor results from increased local reactivity to catecholamines, which results in vasoconstriction and subsequent pallor. When rubbed, the lesion does not redden like the surrounding skin. There is no effective treatment.

Nevus Achromicus

Present at birth but often not visible until 1-2 years of age, nevus achromicus is usually a unilateral, hypopigmented, irregularly shaped lesion. The hypopigmented area is quite uniform in color, and in contrast to nevus anemicus, the vessels within it react normally to rubbing. The melanocytes in the affected epidermis seem to function poorly or not at all.

White Macules in Tuberous Sclerosis

Tuberous sclerosis is a condition with multisystem involvement characterized by hamartomas, often in association with mental retardation and seizures. Mutations in the tumor suppressor gene *TSC1* (hamartin) or more commonly *TSC2* (tuberin) are implicated in the pathogenesis of tuberous sclerosis. Between 50% and 90% of infants with tuberous sclerosis have white macules that become apparent at birth or soon thereafter. These hypomelanotic macules are referred to as "ash leaf" macules, as they resemble the leaf of an ash tree. More commonly, these lesions are polygonal thumbprint-like and smaller than the ash leaf macules. In fair-skinned infants, the hypopigmented areas may be demonstrated more easily by examining the skin with a Wood lamp. These lesions are often leaflet shaped, are variable in number, and occur more frequently on the trunk and buttocks. The melanocytes within areas of macular hypopigmentation contain poorly pigmented melanosomes. A single, hypopigmented macule in an infant without other features of tuberous sclerosis does not warrant extensive investigation. These macules in general do not require treatment. Severe forms of cutaneous manifestations of tuberous sclerosis have been successfully treated with either systemic or topical sirolimus (rapamycin) or everolimus.[7]

Vascular Anomalies: Vascular Malformations and Vascular Tumors

Vascular anomalies are a common problem in the neonate.[25,41,57] They were divided into two major categories—vascular malformations and vascular tumors—by the International Society for the Study of Vascular Anomalies (ISSVA) in 1997 and were updated in 2014 to be more clinically relevant and incorporate new knowledge.[72] The updated increasing list of genetic causes associated with vascular anomalies is freely available on ISSVA website (www.issva.org). The vascular tumors are subdivided into benign, locally aggressive, and malignant. Similarly, the malformations are categorized further as simple, combined, involving major named vessels, and associated with other anomalies. Malformations are developmental defects derived from the capillary, venous, arterial, or lymphatic vessels. These lesions remain relatively static, and growth is commensurate with growth of the child. Hemangiomas are benign tumors of the vascular endothelium characterized by a proliferative and an involutional phase.

Simple Malformations: Capillary

See Nevus Simplex or Salmon Patch. Port-wine stains (i.e., nevus flammeus) are capillary malformations that are almost always present at birth and should be considered permanent developmental defects.[41] These lesions may be only a few millimeters in diameter or may cover extensive areas with facial lesions being the most common. They do not proliferate after birth but may appear to increase in size with the growth of the child. Port-wine stains usually are sharply demarcated and flat in infancy but with time develop a pebbly or slightly thickened surface. Color ranges from pale pink to purple.

The most successful treatment modality is the pulsed dye laser, which is effective in fading these lesions, although only 15%-20% will clear completely.[53] Some studies report treatment is more effective if undertaken in infancy, whereas others have found no difference.

Most port-wine stains occur as isolated defects and do not indicate involvement of other organs, but they occasionally may be a clue to the presence of defects in the eye or certain vascular malformation syndromes. Children with facial port-wine stains involving skin innervated by the V1 or V2 branches of the trigeminal nerve should have a thorough ophthalmologic examination in infancy.

Simple Malformations: Venous and Common Associated Syndromes

Venous malformations are typically composed of ectatic venous channels with slow blood flow. They present as soft, compressible masses that tend to increase in volume with an increase in venous pressure during exercise or when the affected segment is dependent. They tend to persist and often dilate with secondary venous congestion, pain, and thrombosis.

Sturge-Weber syndrome (i.e., encephalofacial angiomatosis) consists of a facial port-wine stain, usually in the cutaneous distribution of the first branch of the trigeminal nerve, a leptomeningeal venous malformation, mental retardation, seizures, hemiparesis contralateral to the facial lesions, and ipsilateral intracortical calcification.[41] Ocular manifestations are frequent and include buphthalmos, glaucoma, angioma of the choroid, hemianoptic defects, and optic atrophy. Roentgenograms of the skull of the older child show pathognomonic "tramline," double-contoured calcifications in the

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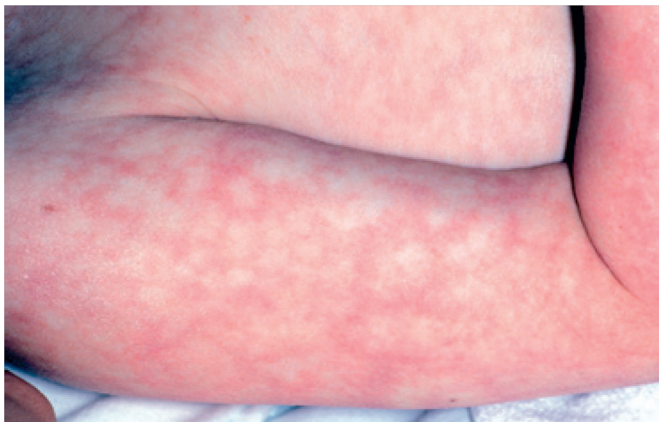
cerebral cortex on the same side as the port-wine stain. Magnetic resonance imaging is the diagnostic modality of choice. Electroencephalography may demonstrate unilateral depression of cortical activity, with or without spike discharges. The prognosis depends on the extent of cerebral involvement, rapidity of progression, and response to treatment. Anticonvulsant therapy and neurosurgical procedures have been of value in treating some patients.

Klippel-Trénaunay-Weber syndrome is characterized by a cutaneous vascular malformation (usually a port-wine stain), venous varicosities, and overgrowth of the bony structures and soft tissues of the involved part.[41] The vascular lesions are apparent at birth. Some of these patients also have venous malformations, lymphatic anomalies, and arteriovenous shunts. Complications include severe edema, phlebitis, thrombosis, ulceration of the affected area, and vascular malformations involving the viscera. The prognosis depends on the extent of involvement, which can be assessed by peripheral vascular studies and scans. Management includes careful orthopedic assessment of limb growth. Surgery may be effective in treating severe limb hypertrophy in some patients. Compressive clothing (Jobst garments) may be helpful, but proper fitting is difficult in infants with rapid growth.

Port-wine stains also occur with moderate frequency in Beckwith-Wiedemann syndrome (i.e., macroglossia, omphalocele, macrosomia, and cytomegaly of the fetal adrenal gland) (see Chapter 86), Robert syndrome, and Cobb syndrome (i.e., cutaneomeningospinal angiomatosis).

The blue-rubber bleb nevus syndrome is a rare disorder consisting of multiple venous malformations of the skin and bowel.[41] Cutaneous lesions sometimes are present at birth, and their appearance is characteristic as the descriptive name of this syndrome suggests. The lesions are blue to purple, rubbery, compressible protuberances that vary from a few millimeters to 3-4 cm in diameter. They are diffusely distributed over the body surface and may be sparse or number in the hundreds. Gastrointestinal lesions are common in the small bowel but also may involve the colon. Occasionally, lesions in the liver, spleen, and central nervous system have been observed. Severe anemia may result from recurrent episodes of gastrointestinal bleeding. Neither the skin nor the bowel lesions regress spontaneously. Surgery is sometimes palliative, but it is frequently impossible to resect the entire affected bowel.

Vascular malformations also have been reported as a congenital feature of Bannayan-Riley-Ruvalcaba syndrome. Maffucci syndrome (i.e., vascular malformations and dyschondroplasia) and Gorham disease (i.e., vascular malformations and disappearing bones) usually are not apparent in the neonatal period. Cutis marmorata telangiectatica congenita is a vascular malformation that may persist for years in large, well-defined patches. This lesion should not be confused with the more common and transient lesion of cutis marmorata caused by cutaneous vasomotor instability that is seen commonly in premature infants in response to cold exposure (Fig. 94.12).



• **Fig. 94.12** Cutis marmorata on the upper arm showing normal reticulated mottling of the skin. (From O'Connor NR, McLaughlin MR, Ham P. Newborn skin: part I. Common rashes. *Am Fam Physician.* 2008;77:47-52.)

Malformations: Lymphatic

Lymphangiomas are hamartomatous malformations composed of dilated lymph channels that are lined by normal lymphatic endothelium.[41] They may be superficial or deep and often are associated with anomalies of the regional lymphatic vessels. In addition to surgery, trials using intralesional injection of sclerosing agents have proven effective.

Milroy primary congenital lymphedema is present at birth and often affects the dorsal aspects of the feet. This autosomal dominant condition arises from a congenital dysgenesis of the lymphatic microvessels secondary to mutation in the *FLT4* (VEGFR3) gene. This condition is rarely associated with significant complications.

Lymphangioma circumscriptum is probably the most common type of lymphangioma and may be present at birth or may appear in early childhood. Areas of predilection are the oral mucosa, the proximal limbs, and the flexures. This malformation consists of clustered, small, thick-walled vesicles resembling frog spawn; it is often skin colored but may have a red or purple cast because of the presence of blood mixed with lymph in the vesicles. Treatment is excision, with attention to removal of the deep component of the lesion. Large lesions may require full-thickness skin grafting. Recurrence has been observed even with full-thickness grafts.

Simple lymphangioma appears in infancy as a solitary, skin-colored, dermal, or subcutaneous nodule. After trauma, it may exude serous fluid. Occasionally it has been associated with more extensive lymphatic involvement. Uncomplicated lesions can be removed by simple excision.

Deep lymphangiomas are more diffuse and consist of large, cystic dilations of lymphatics in the dermis, subcutaneous tissue, and intermuscular septa. Surgery is impractical in most cases.

Cystic hygroma is a benign, multilocular tumor usually found in the neck region. The tumors tend to increase in size and should be treated by surgical excision.

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Simple Malformations: Arteriovenous

Arteriovenous malformations (AVMs) are more aggressive types of simple malformations. They are composed of malformed arteries, veins, and capillaries, with direct arteriovenous communications resulting in arteriovenous shunting.[72] They may be misdiagnosed and mimic other vascular lesions such as an involuting hemangioma or other simple malformations. They present as an enlarging red, warm, painful lesion with pulsation, thrill, or bruit. Rarely, it can present as an ulcerated and bleeding lesion or in high output congestive cardiac failure. Arteriovenous malformations may remain quiescent for years followed by sudden growth at puberty or following local trauma. Arteriovenous malformations are the most difficult vascular anomaly to manage and exhibit high recurrence rates following treatment. Magnetic resonance imaging and angiographic imaging are essential to delimit the lesions. Treatment of AVMs may consist of surgical excision and/or embolization.

Vascular Tumors: Hemangiomas

Hemangiomas are the most common soft tissue tumors of infancy, occurring in approximately 1%-3% of newborns and up to 12% in infants. They are clinically heterogeneous and present as solitary cutaneous lesions, with their appearance dictated by the depth, location, and stage of evolution. Infantile hemangiomas (IHs) are characterized by a growth phase, marked by endothelial proliferation and hypercellularity followed by an involutional phase. As the tumor proliferates, it assumes its most recognizable form, a bright red, slightly elevated, noncompressible plaque (Fig. 94.13). IHs are subclassified as focal, multifocal, segmental, and indeterminate depending on their morphology, extent, or distribution.[72] The endothelial cells contain a unique immunohistochemical marker called glucose transporter 1 (GLUT1), which is used for diagnosis. A negative GLUT1 renders a diagnosis of IH unlikely.[70]

Hemangiomas that lie deeper in the skin are soft, warm masses with a slightly bluish discoloration. Frequently IHs have superficial and deep components. Female gender, prematurity, and multiple gestation pregnancy have been documented to increase the incidence of IHs. They range from a few millimeters to several centimeters in diameter and usually are solitary, but up to 20% of infants have multiple lesions. Increased numbers of superficial IHs have an increased likelihood of visceral involvement (diffuse neonatal hemangiomatosis). Generally, superficial hemangiomas have reached their maximal size by 6-8 months, but deep hemangiomas may proliferate for 12-14 months or, rarely, up to 2 years.

Despite the benign nature of most cutaneous hemangiomas, a significant number cause functional compromise or permanent disfigurement. Approximately 20%-40% of patients have residual skin changes; nasal tip, lip, and parotid hemangiomas are notorious for slow involution, and very large superficial facial hemangiomas often leave disfiguring scarring. Ulceration, the most frequent complication, can be excruciatingly painful and carries the risk of infection, hemorrhage, and scarring. Occasionally, hemangiomas manifest as congenital ulcerations with only a very small rim of the typical hemangioma, making the diagnosis difficult.



• **Fig. 94.13** **A**, Infant with midfacial hemangioma. **B**, Same infant after treatment with oral propranolol. (From: Blei F, Guarini A. Current workup and therapy of infantile hemangiomas. *Clin Dermatol* 2014:32;459-470.)

Periorbital hemangiomas and hemangiomas that involve the ear pose considerable risk to vision, hearing, and speech. Multiple cutaneous (i.e., diffuse hemangiomatosis) and large facial hemangiomas may be associated with visceral hemangiomas. Subglottic hemangiomas manifest with hoarseness and stridor, and progression to respiratory failure may be rapid. Approximately 50% of these infants have associated cutaneous hemangiomas, and "noisy breathing" by an infant with a cutaneous hemangioma involving the chin,

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lips, mandibular region, and neck warrants direct visualization of the airway. Sixty percent of young infants with extensive facial hemangiomas in the "beard" distribution develop symptomatic airway hemangiomas.

Extensive cervicofacial hemangiomas may be associated with multiple anomalies, including vascular malformations (i.e., PHACE [*p*osterior fossa, *h*emangioma, *a*rterial lesions, *c*ardiac abnormalities, *e*ye abnormalities] syndrome). This syndrome has a marked female predominance (9:1) and is thought to represent a developmental field defect that occurs during the 8th-10th weeks of gestation. Lumbosacral hemangiomas may be markers for occult spinal dysraphism and anorectal and urogenital anomalies. Imaging of the spine is indicated in all patients with midline hemangiomas in this region.

Congenital hemangiomas are relatively uncommon, present fully grown at birth, and either undergo rapid involution (RICH: rapidly involuting congenital hemangioma) or persist into adulthood (NICH: noninvoluting congenital hemangioma). Cellular proliferation in both RICH and NICH occurs prenatally with no further growth after birth. The endothelial cells do not express GLUT1. Congenital hemangiomas that resolve rapidly often leave pronounced atrophic skin changes in their wake (Fig. 94.14).

Most hemangiomas require "active nonintervention" coupled with a careful discussion of the natural history of the lesions and photographic documentation of involution.[5,10,41] Studies have shown, however, that up to 40% of children develop complications requiring intervention. Ulceration is the most common complication, but other problems include bleeding, airway or visual axis obstruction, cosmetic disfigurement, and high-output cardiac failure. Since 2008, propranolol has become the first-line treatment, eclipsing systemic steroids and interventional radiology. A list of medical and surgical treatment options along with their safety concerns are given in Table 94.7.

Kaposiform hemangioendothelioma (Kasabach-Merritt phenomenon), a complication of a rapidly enlarging vascular lesion, is characterized by hemolytic anemia, thrombocytopenia, and coagulopathy. These massive tumors are usually a deep red-blue color, are firm, grow rapidly, have no sex predilection, tend to proliferate for a longer period (2-5 years), and have a different histologic pattern. These lesions express lymphatic endothelial markers (podoplanin, prox-1) but do not express GLUT1. Most patients with Kasabach-Merritt phenomenon do not have typical hemangiomas but rather have other proliferative vascular tumors, usually kaposiform hemangioendotheliomas or tufted angiomas.[41] The Kasabach-Merritt phenomenon requires aggressive, often multimodality treatment such as transcutaneous arterial embolization and carries a significant mortality rate.



• **Fig. 94.14** **A**, Rapidly involuting congenital hemangioma, a large bulky lesion on scalp at birth. **B**, Same lesion at age 9 months with no treatment. (From Wassef M, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics* 2015:136(1);e203. Copyright © 2015 by the AAP.)

Epidermal Nevi

Epidermal nevi are a group of lesions that are found commonly in the neonatal period. Most of them consist of an overgrowth of keratinocytes and often have an identifiable differentiation toward one of the appendages normally found in skin. They vary considerably in their size, clinical appearance, histologic characteristics, and evolution, depending on their topographic location. Lesions occurring in sites normally rich in sebaceous glands (e.g., the scalp) may look like sebaceous nevi, whereas others found in areas where the epidermis is thick (e.g., the elbow) look primarily warty.

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TABLE 94.7 Management Options for Infantile Hemangiomas

Clinical Strategy	Dosage	Safety Concerns
Active nonintervention	Adjust scheduled visits based on rapidity of growth and family concern	Monitor for functional or life-threatening complications during proliferative phase
Systemic Treatment		
• Propranolol	1-3 mg/kg per day after meals*	Hypotension, hypoglycemia, bronchial hyperreactivity, seizure, restless sleep, constipation, cold extremities
• Corticosteroids	1-3 mg/kg per day	High blood pressure, increased appetite, stomach irritation, cardiomyopathy, growth suppression, increased risk of systemic infection, aseptic necrosis of bones
• Vincristine†	Recommended dosages vary	Strong vesicant; irritates vessels, mixed sensory-motor neurotoxicity, loss of deep tendon reflexes, constipation
• Interferon†	Recommended dosages vary	Flulike reactions, transammonitis, neutropenia, skin necrosis, spastic diplegia (up to 20%)
Topical Treatment		
• Timolol 0.5% gel	1 drop twice daily	Theoretical risks similar to those for propranolol but not yet well documented in patients treated with timolol for infantile hemangiomas
• Laser	Standard: pulsed dye laser 585-595 nm; use every 2-4 weeks as needed; particularly useful for ulcerating lesions, residual erythema, telangiectasia	May lead to ulceration in some patients, particularly in lip area
	Refractory lesions: ND:Yag or alexandrite laser Residual scar: fractionated CO_2 laser	ND:Yag, alexandrite, and CO_2 lasers—higher risk of scarring
• Topical corticosteroids	Applied twice daily	Cutaneous atrophy and telangiectasia

ND:Yag, Neodymium-doped yttrium aluminum garnet.
*Dosing guidelines have not been fully elucidated.
†Dosing recommendations vary; consult those with experience in administering these agents.
Adapted from Chen TS, Eichenfield LF, Friedlander SF. Infantile hemangiomas: an update on pathogenesis and therapy. *Pediatrics.* 2013;131:99-108.

The most common type of epidermal nevus in the newborn infant is the sebaceous nevus, a hairless, papillomatous, yellow or pink, slightly elevated plaque on the scalp, forehead, or face. These lesions have a characteristic oval or lancet shape. Because there is a slight increase in malignant transformation (basal cell carcinoma) in these lesions after puberty, prophylactic surgical excision is recommended.[33]

The treatment of large, verrucous epidermal nevi is generally unsatisfactory. The only effective treatment is removal of the lesion together with its underlying dermis. This is only possible in localized lesions, and treatment should be delayed beyond the neonatal period, because these lesions may extend over a period of years.

Patients with epidermal nevi may have associated abnormalities, but there are three well-defined entities: Proteus syndrome, CHILD syndrome (i.e., congenital hemidysplasia with ichthyosiform nevus and limb defects), and nevus sebaceous syndrome.

Inflammatory Diseases of the Skin

Several inflammatory skin conditions may occur in the neonate. Irritant contact dermatitis, atopic dermatitis, and seborrheic dermatitis are the most frequently encountered. They may be difficult to distinguish because their clinical features have a significant degree of overlap. There are four phases of cutaneous inflammation, any one of which may persist as the dominant feature depending on the age of the patient, the local physiologic characteristics of the skin involved, and the persistence of the underlying cause. The initial stage is erythema, which proceeds to microvesicle formation, weeping, or oozing. The epidermal response to the injurious process then causes a burst of rapid epidermal mitotic activity that leads to scaling. Lichenification (i.e., thickening of the skin) and pigmentary disturbances supervene. In the young infant, the first three stages predominate; lichenification, which results from scratching or rubbing, is not seen. The enumeration of the complex cellular and

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• **Fig. 94.15** Neonate with irritant diaper dermatitis. (From Atherton D. Understanding irritant napkin dermatitis. *Int J Dermatol.* 2016;55(1);7-9.)

molecular components of the inflammatory network in the skin has led to better understanding of the different symptomatology and offers potential targets for therapy.[64]

Irritant Contact Dermatitis

Primary irritant contact dermatitis (as opposed to allergic contact dermatitis) is probably the most common exogenous cause of dermatitis in the newborn. The distribution of the eruption varies somewhat, depending on the precipitating agent. Saliva may be irritating to the face and fecal excretions to the buttocks (diaper dermatitis). Detergent bubble bath, antiseptic proprietary agents, and soap zealously used to clean the perianal area may cause acute eczematous diaper dermatitis, which may become generalized (Fig. 94.15). Obtaining precise information about what has been applied to the skin and how it has been applied is imperative in making an accurate diagnosis. The principal irritants in diaper dermatitis are fecal enzymes, skin maceration, friction, high pH, and prolonged contact with urine and feces.[2] Its proper management should include obtaining a culture for bacteria and yeast, the discontinuance of all ointments containing irritants, the use of barrier cream, and conservative treatment for 1 or 2 weeks. If no improvement follows, a skin biopsy may be indicated.

Seborrheic Dermatitis

Seborrheic dermatitis is characterized by greasy, non-pruritic scaling associated with patchy redness, fissuring, and occasional weeping, usually involving the scalp, ears, axillary, and perineal folds. There is controversy about whether seborrheic dermatitis is a distinct entity or presages the advent of atopic dermatitis. Some infants never progress beyond the seborrheic phase of the dermatitis, which in its classic form rarely is seen in the first month. Cradle cap is a minor variant of seborrheic dermatitis. Treatment of seborrheic dermatitis consists of a mild shampoo containing selenium zinc with gentle brushing to remove scales. A low-potency topical corticosteroid or antifungal shampoo such as ketoconazole may be efficacious. The usual course of seborrheic dermatitis is one of rapid regression after 1 or 2 weeks of therapy. Occasionally, a seborrheic-like process may involve the entire body, resulting in full-blown exfoliative dermatitis, which has been called Leiner disease when associated with failure to thrive and chronic diarrhea.

Atopic Dermatitis

Atopic dermatitis generally does not present in the newborn period; however, 90% of cases present before 4 years of age.[15] Atopic dermatitis is characterized by red, scaling patches and plaques on the face, particularly the cheeks and on the extensor surfaces of the extremities. Like seborrheic dermatitis, the eruption may be generalized. These infants are often agitated because of the severe pruritus. Clear diagnostic criteria have been established for the diagnosis of atopic dermatitis and include pruritus, chronicity, typical family history, and distribution. Skin barrier dysfunction is prominent in atopic dermatitis, with an abnormal stratum corneum, increased turnover time, and elevated transepidermal water loss with immune dysregulation of both innate and adaptive immune systems. Increased levels of IgE correlate with increased atopic symptoms during early childhood.[59] Several studies have demonstrated that certain dietary and environmental interventions in the first months of life may decrease the incidence of atopic dermatitis in babies at risk for the disease. These include elimination of house dust mites and passive smoking, probiotics/prebiotics supplementation, exclusive breastfeeding for 3 months, and delayed weaning beyond 6 months.

Dermatitis resembling atopic dermatitis may be a feature of a number of systemic conditions, including ataxia-telangiectasia, X-linked agammaglobulinemia, phenylketonuria, gluten-sensitive enteropathy, and long-arm 18 deletion syndrome.[68] Many patients with hypohidrotic ectodermal dysplasia have an eczematous eruption identical to that of atopic dermatitis. Purpura is a frequent additional component of eczema, particularly in Langerhans cell histiocytosis and Wiskott-Aldrich syndrome.

Children with atopic dermatitis have a much higher prevalence of staphylococcal colonization and substantial loss of biodiversity than nonatopic children.[73] Staphylococcal exoproteins and superantigens evoke inflammatory reactions in the host. When bacterial or fungal infection exists, appropriate antibacterial or antifungal therapy is indicated based on the results of culture and sensitivity studies. Weeping lesions should be treated with compresses or bathing in tepid water, protective ointments such as simple zinc oxide paste should be applied after each diaper change, and soiled ointments and pastes should be removed with mineral oil. A more extensive eruption may be treated for short periods with a 1%-2.5% hydrocortisone ointment. A scaly eruption in the scalp may be treated by frequent shampooing with a zinc pyrithione- or salicylic acid–containing shampoo. Bathing should be done in tepid water containing water-dispersible oil. Infants with diffuse dermatitis lose heat readily and are intolerant of even mild changes in environmental temperature or humidity. Humidification of

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• **Fig. 94.16** Giant congenital juvenile xanthogranuloma. Note the yellowish color of the plaque with an erythematous rim and peau d'orange surface. (From Berti S, Coronella G, Galeone M, et al. Giant congenital juvenile xanthogranuloma. *Arch Dis Child.* 2013;98:317.)



• **Fig. 94.17** Congenital mastocytoma. This firm, solitary tumor is composed of aggregates of mast cells and exhibits a typical ovoid shape and pink-tan color. When rubbed, it will become erythematous and form wheals (Darier sign) and in the newborn will develop overlying blisters. (Courtesy of Kara Shah, Cincinnati.)

the bedroom in winter and air conditioning in summer is desirable. The efficacy of dietary management and probiotic supplementation for atopic eczema in older children remains controversial.

Subcutaneous and Infiltrative Dermatoses

Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) is a benign, non-Langerhans cell histiocytosis characterized by solitary or multiple yellow-red cutaneous papules that may enlarge to become nodules or plaques (Fig. 94.16).[35] One-fifth of infants with JXG are affected at birth, and two-thirds have onset of lesions before 6 months of age. There is no predilection for race or sex, and no familial predisposition has been observed for this self-limited disorder, which usually remains confined to the skin. The skin lesions often are restricted to the head, neck, and upper trunk. Involution occasionally leaves a flat atrophic pigmented scar. Serum lipid levels are normal, but histologically, the lesions result from an infiltrate of fat-laden histiocytes, giant cells, and mixed inflammatory cells. Ocular lesions are the most frequent complication (although involvement of other organs may occur rarely) and may result in tumors, unilateral glaucoma, hyphema, uveitis, heterochromia iridis, and proptosis. Ophthalmologic consultation is required for management of the ocular lesions, but the best treatment for the skin lesions is expectant observation.

Several unusual variants may occur, such as giant juvenile xanthogranuloma or bony involvement. There is an increased incidence of juvenile xanthogranulomas among patients with neurofibromatosis type I in which they may be markers for acute granulocytic leukemia.

Mastocytosis

Mast cell disease refers to a spectrum of conditions characterized by mast cell infiltration of the skin or other organs.[56] Pediatric mastocytosis presents before 2 years in 90% of cases and includes three forms: a disseminated maculopapular or nodular eruption (formerly urticaria pigmentosa, 75%), a solitary mast cell tumor (mastocytoma, 20%), and diffuse cutaneous mastocytosis (5%).[43] The diagnosis is usually clinical, but demonstration of excessive numbers of mast cells on skin biopsy is definitive.

The most common form seen at birth is the firm, solitary mast cell tumor (mastocytoma, Fig. 94.17). These tumors usually are ovoid, are pink or tan, and rarely exceed 6 cm in diameter. The lesions are conspicuous by their tendency to form wheals when rubbed (Darier sign) and, in the newborn, to develop overlying blisters. Solitary lesions involute spontaneously within months to years. Maculopapular mastocytosis manifests as numerous pink-brown, 1-2 cm oval macules and papules. The lesions are usually located centrally and often develop later in infancy. Treatment is usually unnecessary, but in symptomatic patients, distressing cutaneous symptoms such as dermatographism and pruritus may be helped with oral antihistamines. Hot water bathing and vigorous toweling must be avoided, as must histamine releasers such as codeine, morphine and its derivatives, aspirin, alcohol-containing elixirs, and certain anesthetics. The patient support website http://www.mastokids.org includes a comprehensive list of degranulating triggers and practical tips for parents. Pediatric mastocytosis was previously considered to be benign and a spontaneously regressing disease; however, recent systematic review suggests that clinical regression (partial or complete) occurs in 67% of cases, stabilization in 27%, and fatality in 2.9%.[43] The genetics of this condition are unclear. Roughly one-third of the cases have *KIT* D816V mutations.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a rare nonmalignant proliferative disorder with skin involvement. The Reclassification Working Group of the Histiocytic Society stratified

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LCH into (a) single system (S-S-LCH) and (b) multisystem (M-S-LCH) to differentiate involvement of one organ versus two-or-more organ dysfunction. Skin manifestations are seen in 12% of single system LCH, while more than 50% have cutaneous involvement in multisystem LCH.[48] Langerhans cell histiocytosis is characterized by accumulation of clonal dendritic cells immunologically resembling normal epidermal Langerhans cells.[45] Langerhans cell histiocytosis can present at any time from birth to adulthood. Unlike normal Langerhans cells, LCH cells can infiltrate almost any body site accompanied by lymphocytes, neutrophils, eosinophils, and multinucleated giant cells forming characteristic granulomas. Commonly involved areas include the scalp, followed by the skin flexures, including the perineum. The appearance of skin LCH is very diverse, with crusted or scaly papules, vesicles, nodules, eroded nodules, and purple plaques.[62] The majority of infants with LCH show multisystem involvement. Single or multifocal bone lesions with lymph node involvement are common, and intracranial disease may present with exophthalmos or diabetes insipidus. Definitive diagnosis is made on skin biopsy. CD1a-positive Langerhans cells are seen infiltrating the skin. Langerhans granules (Birbeck granules) within the cells on electron microscopy are also a common finding. Langerhans cell histiocytosis with multisystem organ involvement is most often a rapidly fatal disease. The somatic BRAF (V600E) mutation in children with LCH is associated with severe features, permanent injury, and poor short-term response to chemotherapy.[27] Various chemotherapeutic regimens and systemic corticosteroids have been used for treatment.

In 1973, Hashimoto and Pritzker described a pure cutaneous form of LCH, which occurs only in the neonate or infant. The characteristic features of this congenital, self-healing reticulosis are skin lesions in an otherwise well infant, a histopathology demonstrating Langerhans cell infiltrate, and spontaneous involution of the skin lesions. The pathology is said to be typical with histiocytic infiltration limited to the dermis, sparing of the epidermis, and so-called myelin-dense bodies seen on electron microscopy. This entity is considered a mild form of LCH, as progression to severe LCH has now been reported in children who initially met the above criteria. The diagnosis of purely cutaneous LCH should be made only after several years of follow-up.

Sclerema Neonatorum, Scleredema, and Subcutaneous Fat Necrosis

Sclerema neonatorum, scleredema, and subcutaneous fat necrosis (SFN) are disorders of the subcutaneous tissues that are commonly seen in the first 1-2 weeks of life. Of the three conditions, sclerema neonatorum has the worst prognosis and usually affects the severely ill preterm or debilitated newborn. It manifests by diffuse hardening of the subcutaneous tissue, resulting in a tight, smooth skin that feels bound to the underlying structures. The skin is nonpitting, cold, and waxy hard. The joints become immobile and the face masklike. Histologically, the epidermis and dermis are normal, the subcutaneous tissue may exhibit a sparse inflammatory infiltrate without fat necrosis, and there may be radially arranged needle-shaped crystals with adipocytes. The etiology is unclear, presumed to be an underlying fulminant sepsis. Management includes broad-spectrum antibiotics, intravenous immunoglobulin, exchange transfusion, and systemic steroids.[61] Prognosis remains poor despite aggressive interventions. Scleredema is often confused with sclerema neonatorum and typically is seen in premature infants in the first week of life. Unlike sclerema, this condition manifests a pitting edema that is firm and often most prominent in the lower extremities. Histologically, there is often lobular panniculitis without vasculitis associated with marked skin edema. Infections and hypothermic injury have been linked to scleredema, but the exact etiology remains unclear. Treatment is supportive, and the condition often heals spontaneously as the infant improves clinically.

The lesions of subcutaneous fat necrosis, in contrast to the previous conditions, are more common in postmature infants and typically manifest in a localized and sharply circumscribed form. They appear 1-4 weeks after delivery as small nodules or large plaques and are found on the cheeks, buttocks, back, arms, and thighs. The affected fat is firm, and the overlying skin may appear reddish or violaceous and occasionally has the texture of orange peel. Histologically, there is a granulomatous reaction in the fat, with formation of needle-shaped crystals, foreign body giant cells, fibroblasts, lymphocytes, and histiocytes. Resolution of the lesion results in fibrosis. Possible precipitating causes of fat necrosis include cold exposure, trauma, asphyxia, therapeutic hypothermia, and peripheral circulatory collapse. The lesions usually resolve in several weeks or months without complications. Hypercalcemia has been associated in 60% of patients in a 20-year retrospective cohort study of 30 newborns.[14]

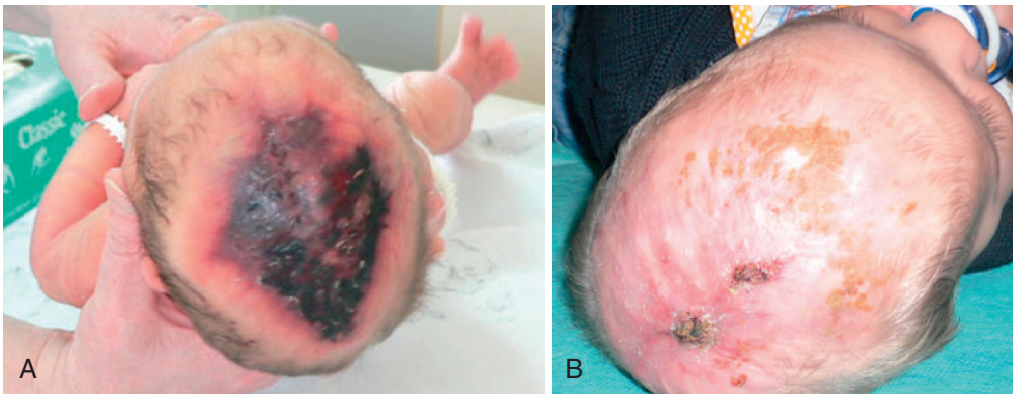
Miscellaneous Congenital Diseases Affecting the Skin

A multitude of hereditary diseases affect the skin. Some of the congenital diseases with prominent cutaneous findings are reviewed here.

Aplasia Cutis Congenita

Aplasia cutis congenita (ACC) is a rare group of disorders of varying etiology characterized by the focal absence of skin at birth.[16] Most frequently, the lesions are on the scalp in the midline, but other areas of the body may be affected, including the trunk and extremities (Fig. 94.18). Approximately 80% of patients have the defect confined to the skin and often less than 2 cm in diameter; however, some patients present large cutaneous defects along with aplasia of the underlying skull. Several theories have been proposed to explain the pathogenesis of this disorder, but a single unifying mechanism seems unlikely. Possible etiologies include

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• **Fig. 94.18** Aplasia cutis congenita. The large full-thickness scalp defect in this 3-day-old infant (**A**) was accompanied by a bony defect in the cranium. Conservative management without surgery led to complete bony recovery of the skull at 8 months of age (**B**) with residual scar alopecia and epithelialization of the skin defect. (From Starcevic M, Sepec MP, Zah V. A case of extensive aplasia cutis congenita: a conservative approach. *Pediatr Dermatol.* 2010;27:540-542.)

incomplete closure of the neural tube, localized vascular insufficiency, amniotic membrane adhesions, teratogenic agents, and intrauterine infections. Large scalp defects are associated with trisomy 13. The diagnosis is usually based on clinical findings. Increased levels of acetylcholinesterase and α-fetoprotein have been reported in the amniotic fluid of mothers with children with aplasia cutis. Prognosis and management should be individualized based on the size, location, and presence or absence of ulceration or underlying bony defect. Management strategies include simple observation, prevention of infection in the case of ulceration, and surgical excision or skin grafting in the case of large defects.

Cutis Laxa

Cutis laxa (i.e., generalized elastolysis) is a heterogeneous group of congenital and acquired disorders and is a feature of several malformation syndromes.[16] There are three major forms of congenital cutis laxa, one inherited as an autosomal dominant trait, and two inherited in an autosomal recessive fashion. In all forms of the disease, affected infants have diminished resilience of the skin, which hangs in folds, resulting in a bloodhound appearance. The joints are not hypermobile, and there is no tendency to increased bruising as in Ehlers-Danlos syndrome. Elastic tissue may be greatly diminished in the dermis and is of poor quality. The collagen has normal tensile properties. In the autosomal dominant form, there are few complications, and the life span is usually normal. In the generalized recessive type of cutis laxa, elastic fibers elsewhere in the body are defective, resulting in inguinal, diaphragmatic, and ventral hernias; rectal prolapse; diverticula of the gastrointestinal and genitourinary tracts; pulmonary emphysema; and aortic aneurysms. Cardiorespiratory complications may cause death during childhood. The other recessive form of cutis laxa, with retarded growth and skeletal dysplasia, is typified by intrauterine growth restriction, congenital dislocation of the hips, and a peculiar facies with frontal bossing, antimongoloid slanting of the palpebral fissures, and widening of the fontanelles. Unlike other loose-skin syndromes, persons with cutis laxa have almost normal wound healing. These children are good candidates for cosmetic plastic surgery and its attendant psychological benefits.[16]

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders with the common features of hyperextensible skin, joint laxity, and soft tissue fragility.[63] Bleeding episodes and cardiovascular complications are characteristic of some forms of the disorder. The skin of patients with EDS is hyperextensible when stretched but snaps back with normal resiliency, in contrast to the skin of patients with cutis laxa, which hangs in redundant folds. In some forms of EDS, the skin also is excessively fragile. Associated findings may include short stature, scoliosis, soft tissue contractures, multiple dislocations, periodontosis, and eye defects. Involvement of the gastrointestinal tract may lead to episodes of acute blood loss or megacolon. Aortic aneurysms also may develop. The underlying genetic defect is unique to different subtypes. This led to the widely used Villefranche classification of EDS, which has six subtypes.[63] Identified gene mutations include various collagens; collagen-processing genes; and tenascin-X, a connective tissue protein. Forty percent of newborns with EDS are delivered prematurely.[62]

Ectodermal Dysplasias

The term ectodermal dysplasias describes a group of more than 100 rare congenital disorders with abnormal development of two or more structures derived from embryonic ectoderm. Such structures include nails, teeth, hair, the lens of the eye, and sweat glands. Information on specific syndromes, clinical management, and the availability of support programs can be found through the National Foundation for Ectodermal Dysplasia (www.nfed.org).

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The most commonly encountered form of ectodermal dysplasia is the hypohidrotic type.[62] Diminution or absence of sweating, hypotrichosis, and defective dentition are the most striking features of hypohidrotic ectodermal dysplasia, which is inherited in an X-linked recessive (*EDA* gene) fashion in two-thirds of the cases. The facies are distinctive because of frontal bossing and depression of the bridge of the nose. Eyebrows and lashes are absent or sparse. The skin around the eyes is wrinkled and frequently hyperpigmented. The skin elsewhere is thin, dry, peeling (like postmature babies), and hypopigmented, and the cutaneous vasculature is more visible. The scalp and body hair is sparse and the ears and chin prominent. The lips are thick and everted and may show pseudo rhagades. Dental anomalies range from total anodontia to hypodontia with peg-shaped teeth.

The most striking physiologic abnormality is the diminution or absence of sweating. Sweat pores usually are decreased to absent on the fingertips. Absence or hypoplasia of eccrine glands can be confirmed by skin biopsy. Other glandular structures also may be absent or hypoplastic. Less constant ancillary findings include conductive hearing loss, gonadal abnormalities, stenotic lacrimal puncta, corneal dysplasia, and cataracts. Mental development is normal. Marked heat intolerance is caused by an inability to regulate the body temperature adequately by sweating. Because the respiratory mucosa also may be deficient in mucus-secreting glands, viral respiratory tract infections in these patients tend to linger and become complicated by secondary bacterial infections in the bronchial tree. It is imperative to diagnose these children in infancy.

Every effort should be made to moderate extreme environmental temperatures by using air conditioning. Deficient lacrimation can be palliated by the regular use of artificial tears. The nasal mucosa also must be protected by intermittent saline solution irrigations and application of petrolatum. It is imperative that these children have a thorough dental evaluation during the first years of life, and dental prostheses should be provided even for toddlers so that adequate nutrition is maintained. Reconstructive procedures can be performed later in life to improve the facial configuration. A wig may be required for patients with scant scalp hair.

The incidence of atopic diseases—asthma, allergic rhinitis, and atopic dermatitis—is increased significantly among patients with anhidrotic ectodermal dysplasia. Atopic manifestations should be managed as they would be in otherwise healthy infants and children. Accurate carrier detection and early neonatal and prenatal diagnoses are feasible using molecular genetic testing.

Numerous other types of ectodermal dysplasia have been defined, including hidrotic ectodermal dysplasia, ectrodactyly ectodermal dysplasia cleft palate (EEC) syndrome, ankyloblepharon ectodermal dysplasia cleft palate (AEC) syndrome, ectodermal dysplasia cleft palate midfacial hypoplasia (Rapp-Hodgkin) syndrome, and chondroectodermal dysplasia (Ellis-van Creveld) syndrome. Some of these conditions may manifest with scalp erosions or impetiginous lesions in the neonate. Isolated lack of sweat glands occurs in congenital familial anhidrosis.

Porphyrias

The inherited porphyrias are a diverse group of inborn errors of heme biosynthesis, resulting from the deficient activity of a specific enzyme in the pathway. They are classified as hepatic or erythropoietic according to the organ site in which the underlying heme synthetic defect is predominantly expressed. The erythropoietic porphyrias include congenital erythropoietic porphyria (CEP) and erythropoietic protoporphyria (EPP). The erythropoietic porphyrias present at birth, infancy, or early childhood, whereas the hepatic porphyrias present after puberty or in adulthood.

Erythropoietic protoporphyria is the most common childhood porphyria, caused by a deficient activity of ferrochelatase (<30% of normal), and usually presents by age 2 years. EPP is inherited as an autosomal recessive condition. Clinical diagnosis is made with a history of crying or skin pain following sun exposure. Some patients are photosensitive to fluorescent lighting. Hemolytic anemia is absent. The diagnosis is made by the markedly elevated levels of protoporphyrin in erythrocytes and/or by the identification of biallelic pathogenic variants in FECH (ferrochelatase) on molecular genetic testing. The treatment includes sun avoidance; oral administration of β-carotene, cysteine, and antihistamines to increase tolerance to sunlight; vitamin D supplementation; and liver transplantation. Recently, Afamelanotide (Scenesse®), a synthetic melanocyte stimulating hormone analog, has been approved in Europe to improve quality of life by its ability to increase pain-free sun exposure.[3]

Congenital erythropoietic porphyria, also called Gunther disease, is a rare autosomal recessive disorder caused by deficient activity of uroporphyrinogen III synthase. The *CEP* gene has been mapped to chromosome 10, allowing prenatal diagnosis to be made with chorionic villus sampling. Diagnosis is also suspected when a reddish-brown amniotic fluid is noticed at amniocentesis. Clinical presentation includes severe photosensitivity from birth or early infancy with formation of vesicles and bullae on areas exposed to sun, phototherapy, or fluorescent lighting. There is also marked skin fragility. Diagnosis is made by elevated levels of uroporphyrin I in urine and erythrocytes and increased levels of coproporphyrin I in feces. Treatment modalities include oral superactivated charcoal, hypertransfusion, splenectomy, and bone marrow transplantation.

Transient porphyrinemias have been described in newborns with hemolytic disease with unclear etiology. These infants present with erythema, violaceous discoloration, purpura, erosions, and blisters on areas exposed to phototherapy. The elevated levels of porphyrins normalize spontaneously after the first few months.

Neonatal Lupus Erythematosus

Neonatal lupus erythematosus (NLE) is an acquired autoimmune disease caused by transplacental passage of

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• **Fig. 94.19** Cutaneous neonatal lupus erythematosus. Note the "raccoon" eye over the right periorbital area and the typical erythematous annular plaques over the glabella with central atrophy. (From Jaka A, et al. Cutaneous neonatal lupus erythematosus. *Indian J Dermatol Venereol Leprol.* 2012;78:775.)

maternal autoantibodies. It occurs in 1 of every 20,000 live births in the United States.[31] Pregnant women whose sera contain antibodies against Ro/SSA or La/SSB are at risk of having a child with NLE. Permanent congenital heart block and transient skin lesions are the hallmark of this condition. Mean age at the onset of skin rash is 6 weeks but may be present at birth.

Clinically, the skin lesions are primarily annular and papulosquamous and are widespread, but most commonly seen on the face and scalp, predominantly affecting the periorbital and malar areas, and often cause a "raccoon eyes" appearance (Fig. 94.19). Sun exposure precipitates or aggravates these lesions. Telangiectasia may be a presenting sign and a more permanent sequela. Between 30% and 50% of mothers of infants with NLE have a connective tissue disease, most commonly SLE or Sjögren syndrome. The presence of anti-SSA/Ro antibodies, with or without anti-La, rather than the type of maternal autoimmune disease, is the risk factor for the development of neonatal lupus.[74]

Many questions regarding pathogenesis remain unanswered. Serologic studies for autoantibodies are confirmatory for diagnosis. It is unclear why less than 5% of mothers with anti-Ro and anti-La antibodies give birth to affected children and why mothers of affected infants are often asymptomatic despite having the same antibodies. Approximately 40%-60% of mothers with NLE infants are asymptomatic.[31] Diagnosis of NLE in the infant, therefore, may lead to diagnosis of lupus in the mother. Treatment of skin lesions is primarily aimed at sun protection along with topical steroids. A triple therapy combining plasmapheresis, IVIG, and glucocorticoids may potentially stop the evolution of fetal cardiac disease in positive anti-SSA/Ro antibody patients. Development of rheumatic disease later in childhood can occur and warrants long-term follow-up. The risk of a subsequent child having any manifestation of NLE is roughly 25%.

Principles of Newborn Skin Care

It is reported that nearly 80% of normal newborns develop a skin problem, for example, a "rash," during the first month of life. Despite the desire of parents and caregivers to promote good skin care and the ubiquity of skin problems, particularly in the preterm infant, there is a surprising lack of evidence upon which to base infant skin care recommendations. Common skin care practices are still based on tradition, experience, and cultural factors. Ideal skin care guidelines should preserve skin integrity, allow physiologic adaptation to a changing environment, prevent toxicity, and avoid potential sensitivity from topical medications. Basic principles of skin care were cited earlier in Box 94.2.

The gross appearance of the skin at birth is related in part to the maturity of the infant. The premature infant's skin may be readily distinguished from the term infant's skin. At birth, it is more transparent and gelatinous and tends to be free of wrinkles. The premature infant may be covered with fine lanugo hair. Sexual hormonal effects are less conspicuous in the premature infant; the scrotum is less rugose and pigmented, the labia majora are less prominent and not approximated, the nipples and areolas are less pigmented, and breast tissue is less palpable.

The extremely premature infant (<750 g) is at particular risk secondary to a poorly developed epidermal permeability barrier. The stratum corneum becomes multilayered during the third trimester. Transepidermal water losses (TEWL) may be 10- to 15-fold higher in extremely low birth weight preterm infants compared with term infants. At 23 weeks' gestation, the stratum corneum is nearly absent with transepidermal water loss of ~75 g/m^2/hour; at 26 weeks the TEWL is ~45 g/m^2/hour. By 29 weeks, the TEWL is ~17 g/m^2/hour and remains higher than the values of 4-6 observed in full-term infants.[71] Around weeks 34 and 35, the barrier is relatively well formed. Each milliliter of water lost via

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evaporation expends 0.58 kilocalories. Epidermal permeability is highest in the premature infant immediately after birth. Heat and water loss can be a significant source of morbidity in the preterm infant and should be prevented beginning in the delivery room. The difference between cutaneous permeability in premature infants and term infants decreases with each postnatal day. At 2 weeks after birth, however, the epidermal barrier of the very low birth weight infant still has markedly increased transepidermal water loss compared to infants born at the same corrected gestational age.

An immature permeability barrier can lead to increased absorption of environmental toxins and infections (Table 94.8). The normal acid mantle of the skin develops more slowly in preterm infants, and the expression of cationic antimicrobial peptides, such as those associated with the protective coating of vernix caseosa at birth, may be diminished. The dermis is deficient in structural proteins leading to poor mechanical properties and easy tearing of the skin.

Strategies for improving epidermal barrier function in VLBW preterm infants are listed in Box 94.4. Studies have shown that postnatal massage of moderately preterm infants with traditional oils reduces infection and mortality. As might be expected from an organ situated at the body surface, there is a continuing and complicated interplay between genotype and environment in their effects upon skin condition. This interaction is illustrated in the etiology of common skin disorders such as diaper dermatitis. It is anticipated that increasing understanding of the molecular basis of the skin disorders and diseases covered in this chapter will shed new light on the mechanisms of more common and less serious skin problems in the newborn.

• BOX 94.4 Strategies to Improve Epidermal Barrier Function in Preterm Infants

- Topical application of one or more nonphysiologic lipids (e.g., petrolatum)
- Topical application of natural oils (e.g., sunflower oil) or mixtures of physiologic lipids (ceramides, cholesterol, free fatty acids)
- Topical dressings
- Vapor-permeable: allow metabolic (repair) processes to continue in the underlying epidermis
- Vapor-impermeable (occlusive): delay metabolic responses in the underlying epidermis
- Xeric stress: postnatal transition to low-humidity (~60%) environment accelerates barrier development

Adapted from Hoath SB, et al. Physiologic development of the skin. In: Polin RA, et al., eds. *Fetal and neonatal physiology*. 5th ed., vol. 1. Philadelphia: Elsevier Saunders; 2017:498-514.e4.

TABLE 94.8 Potential Untoward Effects from Application of Topical Products in Neonates

Compound	Function	Toxicity
Adhesive remover solvents	Skin preparations to aid in adhesive removal	Epidermal injury, hemorrhage, and necrosis
Alcohols	Skin antiseptic	Cutaneous hemorrhagic necrosis, elevated blood alcohol levels
Aluminum	Metal containers for topical ointments	Neurotoxicity
Ammonium lactate	Keratolytic emollient	Possible lactic acidosis
Aniline	Dye used as a laundry marker	Methemoglobinemia
Benzethonium chloride	Skin cleansers	Poisoning by ingestion, carcinogenesis
Benzocaine	Mucosal anesthetic (teething products)	Methemoglobinemia
Benzyl benzoate	Scabicide	Neurotoxicity
Bicarbonate	Baking soda for diaper dermatitis	Metabolic alkalosis
Boric acid	Baby powder, diaper paste	Vomiting, diarrhea, erythroderma, seizures, death
Calcipotriol	Topical vitamin D3 analogue	Hypercalcemia, hypercalcemic crisis
Camphor	Topical antipruritic and camphorated oils	Gastrointestinal toxin and neurotoxicity
Chlorhexidine	Topical antiseptic	Systemic absorption but no toxic effects
Coal tar	Shampoos, anti-inflammatory ointment	Excessive use of polycyclic aromatic hydrocarbons is associated with an increased risk of cancer

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TABLE 94.8 Potential Untoward Effects from Application of Topical Products in Neonates—cont'd

Compound	Function	Toxicity
Corticosteroids	Topical anti-inflammatory	Skin atrophy, striae, adrenal suppression
Diphenhydramine	Topical antipruritic	Central anticholinergic syndrome
Gentian violet	Antimicrobial	Possibly carcinogenic
Glycerin	Emollients, cleansing agents (Aquanil)	Hyperosmolality, seizures
Hexachlorophene	Antiseptic soaps	Neurotoxicity
Imidazoles	Topical antifungals	Drug interactions secondary to p450 inhibition
Iodochlorhydroxyquin	Topical antibiotic	Optical neuritis
Isopropyl alcohol	Topical antiseptic	Skin necrosis and neurotoxicity
Lactic acid	Topical keratolytics	Metabolic acidosis
Lidocaine	Topical anesthetic	Petechiae, seizures
Lindane	Scabicide (Kwell)	Neurotoxicity
Mercuric chloride	Diaper rinses, teething powders	Acrodynia, hypotonia
Methylene blue	Amniotic fluid leak diagnosis	Methemoglobinemia
Neomycin	Topical antibiotic (Neosporin)	Neural deafness
N,N-dimethyl-m-toluamide (DEET)	Insect repellant	Neurotoxicity
Nystatin	Topical antifungal	Nephrotoxicity
Phenolic compounds (pentachlorophenol, hexachlorophene, resorcinol)	Laundry disinfectant, topical antiseptic (PHisoHex)	Neurotoxicity, tachycardia, metabolic acidosis, methemoglobinemia, death
Phenylephrine	Ophthalmic drops	Vasoconstriction, periorbital pallor
Povidone-iodine	Topical antiseptic (Betadine)	Hypothyroidism
Prilocaine	Topical anesthetic (EMLA)	Methemoglobinemia
Propylene glycol	Topical vehicles, emollients, cleansing agents (Cetaphil)	Hyperosmolality, neurotoxicity, seizures
Resorcinol	Topical antiseptic	Methemoglobinemia
Salicylic acid	Keratolytic emollient	Metabolic acidosis, salicylism
Silver sulfadiazine	Topical antibiotic (Silvadene)	Kernicterus (sulfa component), agranulocytosis, argyria (silver component)
Sulfur	Scabicide	Paralysis, death
Tacrolimus	Topical immunomodulator	Elevated blood levels of immunosuppressive drugs
Triclosan	Deodorant and antibacterial soaps	Toxicities seen with other phenolic products
Triple dye (brilliant green, gentian violet, proflavine hemisulfate)	Topical antiseptic for umbilical cord	Ulceration of mucous membranes, skin necrosis, vomiting, diarrhea
Urea	Keratolytic emollient	Uremia

Compiled from Mathis EF, Williams ML. *Skin of the premature infant,* and Danby SG, Bedwell C, Cork MJ. Neonatal skin care and toxicology. Both in Eichenfield LF, et al., eds. *Neonatal and infant dermatology*. 3rd ed. Philadelphia: Elsevier Saunders; 2015.

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Key Points

- The skin of the term infant serves multiple functions critical for survival in an extrauterine environment.
- An accurate description of primary and secondary skin lesions forms the basis for the diagnosis of skin pathology.
- There are benign and transient neonatal skin lesions that need to be differentiated from pathologic lesions.
- Vernix caseosa provides a hydrophobic barrier to the developing skin and contains multiple anti-infective peptides that are associated with the innate immune system.
- Preterm infants have an immature epidermal barrier leading to heat and water loss and increased absorption of environmental toxins, which predisposes them to infections.
- Etiology of skin pathology varies widely from an intrauterine origin, infection, allergic reaction, malformation, and tumors, to being genetically inherited.
- Identification of affected genes is leading to prenatal diagnosis, genetic counseling, and potential gene replacement therapies in certain skin conditions.

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95

Examination and Common Problems in the Neonatal Eye

FARUK H. ÖRGE

"The eye is the light of the body; therefore, if the eye is good, then the whole body will be full of light, but if the eye is bad, then the whole body will be full of darkness."

Clinicians should develop the ability to recognize the signs and symptoms of serious eye diseases or complications of diseases early in their course to prevent visual loss and, in some cases, preserve life. For example, early detection and treatment of congenital cataracts and congenital glaucoma are critical for visual rehabilitation. Malignant orbital tumors and intraocular tumors such as retinoblastoma are life threatening.

Ocular findings can also assist in the diagnosis of a systemic illness such as type 1 neurofibromatosis (NF1) and CHARGE syndrome (*c*oloboma, *h*eart anomaly, *a*tresia choanae, *r*etardation, *g*enital anomaly, *e*ar anomaly).[97]

The visual system is not completely developed at birth but progressively matures during the neonatal period.[27] The neonatologist must recognize normal ocular findings during different stages of the infant's growth to understand what is abnormal. Some ocular and visual milestones are shown in Table 95.1.

A screening eye examination should be performed during the newborn physical examination and during routine well-baby checkups.[4] The screening examination should include the assessments[24] listed in Box 95.1. Fortunately, the screening examination identifies most problems such as glaucoma, cataract, infection, or tumor. However, if abnormalities are suspected because of the history, presence of systemic anomalies, or abnormal result of the screening examination, a more detailed ocular evaluation is mandatory, preferably by a pediatric ophthalmologist.[34]

Neonatal Eye Examination

A screening ocular examination begins with a careful history, especially of ocular diseases in the family.[24] For example, a family history of retinoblastoma necessitates a comprehensive ocular examination of the fundus shortly after birth. Information about maternal diseases (e.g., rubella), injuries, medications, or use of drugs or alcohol during the prenatal period should be obtained. It is also important to document the duration and abnormalities of pregnancy, labor, and delivery. Premature birth suggests potential retinopathy of prematurity (ROP), and difficult delivery with obstetric forceps can result in direct ocular trauma.

The examination should be done under comfortable circumstances and with the proper equipment (Fig. 95.1). Much can be learned if the examiner takes a few moments initially to observe the infant for facial anomalies, the external ocular appearance, and ocular motility while taking the history. The examination is most easily performed with the baby in a parent's arms; the more difficult parts of an examination often can be accomplished while a baby is nursing or sucking on a bottle or pacifier. It is well documented that an oral sucrose solution can calm the baby significantly for them to allow easier examination. The screening eye examination should include an evaluation of visual function, preferably one eye at a time. For infants less than 4-6 weeks of age, visual function is assessed by withdrawal or blinking to light, or pupil constriction to light.[24]

Maintenance of the eyes on an object is called fixation. The infant's ability to fixate and follow a target can be an approximate guide to the amount of visual function present. Beyond 4-6 weeks of age, visual function is assessed in terms of the quality of the fixation and following. By experience, the clinician must develop an age-appropriate scale that assesses this quality of fixation and following, paying attention to the intensiveness, steadiness, and maintenance of the fixation and the smoothness and duration of the following.

Visual acuity refers to the subjective response from the patient of the ability to discern images of set sizes, such as the tumbling "E" or Snellen letters. Most normally developing children can participate in some form of visual acuity testing by the age of 30 months. If additional information regarding visual function is desired, some ancillary visual tests are available and used in indicated situations. (1) Optokinetic nystagmus describes a reflex ocular response to a moving target. As a target moves across the visual field, a pursuit motion occurs, followed by a rapid return motion in

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Abstract

Clinicians should develop the ability to recognize the signs and symptoms of serious eye diseases or complications of diseases early in their course to prevent visual loss and, in some cases, preserve life. For example, early detection and treatment of congenital cataracts and congenital glaucoma are critical for visual rehabilitation. Malignant orbital tumors and intraocular tumors such as retinoblastoma are life threatening. Ocular findings can also assist in the diagnosis of a systemic illness such as type 1 neurofibromatosis (NF1) and CHARGE syndrome (coloboma, heart anomaly, choanal atresia, retardation, genital anomaly, ear anomaly). The visual system is not completely developed at birth but progressively matures during the neonatal period. The neonatologist must recognize normal ocular findings during different stages of the infant's growth to understand what is abnormal. A screening eye examination should be performed during the newborn physical examination and during routine well-baby checkups. Fortunately, the screening examination identifies most problems such as glaucoma, cataract, infection, or tumor. However, if abnormalities are suspected because of the history, presence of systemic anomalies, or abnormal result of the screening examination, a more detailed ocular evaluation is mandatory, preferably by a pediatric ophthalmologist.

Keywords

eye
ophthalmology
vision screening
eye exam
eye sight
ophthalmoscopy
red reflex

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TABLE 95.1 Visual System Milestones

Description	Age
Pupillary light reaction present	30 weeks' gestation
Pupillary light reaction well developed	1 month
Lid closure in response to bright light	30 weeks' gestation
Blink response to visual threat	2-5 months
Visual fixation present	Birth
Fixation well developed	2 months
Visual following well developed	3 months
Accommodation well developed	4 months
Visual evoked potential acuity at adult level	6 months
Grating acuity preferential looking at adult level	2 years
Snellen letter acuity at adult level	2 years
Color vision present	2 months
Color vision at adult level	6 months
Stereopsis developed	6 months
Stereoacuity at adult level	7 years
End of critical period for monocular visual deprivation	10 years
Conjugate horizontal gaze well developed	Birth
Conjugate vertical gaze well developed	2 months
Vestibular (doll's eye) rotations well developed	34 weeks' gestation
Optokinetic nystagmus well developed	Birth
Ocular alignment stable	4 months
Fusional convergence well developed	6 months
Eyeball 70% of adult diameter	Birth
Eyeball 95% of adult diameter	3 years
Cornea 80% of adult diameter	Birth
Cornea 95% of adult diameter	1 year
Differentiation of fovea completed	4 months
Myelination of optic nerve completed	7 months-2 years
Iris stromal pigmentation well developed	6 months

From Edward DP, Kaufman LM. Anatomy, development, and physiology of the visual system. *Pediatr Clin N Am.* 2003;50:1.

• BOX 95.1 Screening Assessments

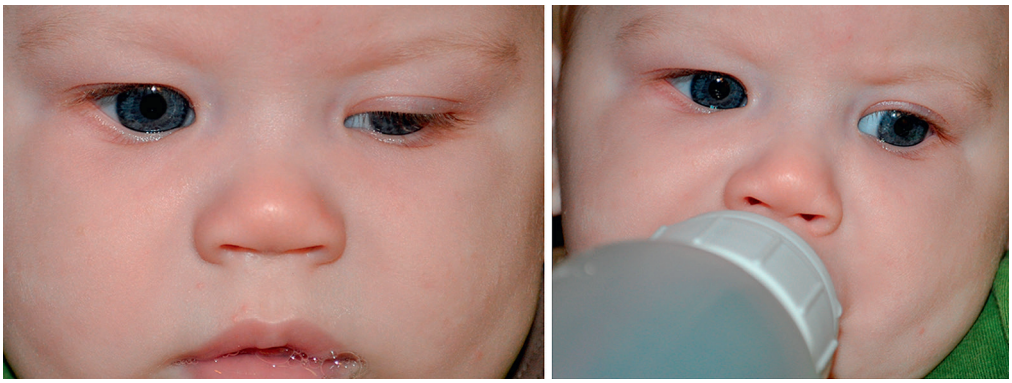
- Reaction to light or visual stimuli to estimate visual function
- Craniofacial dysmorphism
- Orbits
- Eyelids
- Lashes
- Ocular motility
- Globes
- Conjunctiva
- Sclera
- Cornea
- Iris
- Pupils
- Red reflex test



• **Fig. 95.1** Basic equipment for ocular examination: Various types of eyelid specula to keep the eyelids open, scleral depressor to gently move the eye around, cyclomydril eye drops for dilation (1.25% phenylephrine [ophthalmic], 0.25% cyclopentolate [ophthalmic]), and a 20 or 28 diopter magnifying lens.

the opposite direction to regain fixation. We experience this response when telephone poles or fence posts are watched from a fast-moving vehicle. With an optokinetic drum, which consists of black and white stripes on a spinning cylinder, if the examiner can elicit optokinetic nystagmus in the infant, this establishes that the child has enough visual function to discern the stripes. The stripe widths can be calibrated so as to yield a visual acuity equivalent. Optokinetic nystagmus can be evident in term newborns.[73] (2) Another quantitative technique to measure a visual acuity equivalent in the infant older than 3 months is forced preferential looking.[108] An infant prefers to look at black and white stripes instead of a uniformly gray target. For the

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• **Fig. 95.2** Marcus Gunn jaw wink phenomenon: Left upper lid ptosis seen in the first picture while the left lid raises up as patient sucks from the bottle.

test, infants are quickly shown a card that has stripes on one end and a gray target on the opposite end. The examiner watches the infant's eyes to see whether the baby looks right or left to find the stripes. If the infant's visual function is high enough to distinguish the stripes from the gray target, the infant will look consistently toward the stripes. If the infant's visual function is less than the ability to distinguish the stripes from the gray target, the infant will look randomly right or left. By varying the size of the stripes, the examiner can grade the visual acuity equivalent. The disadvantages of this procedure include the number of people necessary to administer the test, the time involved, and the need for the cooperation of an alert infant. (3) Unfortunately, most estimations of an acuity equivalent in the infant rely heavily on adequate motor responses as part of the visual evaluation. Immature or underdeveloped motor systems can reduce or interfere with eye or head movements and decrease the estimation of the visual acuity equivalent. Visual evoked potentials, which measure the electrical cortical responses to a visual stimulus, eliminate the need for patient cooperation or motor control.[35] Electrodes are placed over the occipital cortex to monitor activity in the brain as the eyes are visually stimulated with graded stripes or checkerboard patterns, and a computer-averaged tracing is made.

Continuing with the screening eye examination, the general facial configuration and the structure of the orbits are inspected next. Note any facial dysmorphism that could affect ocular health or be part of an ocular syndrome, such as clefts or abnormal head shape. The orbits should be proportional and symmetric compared with the overall craniofacial configuration. Palpation is performed to examine the orbital margin, the contents of the upper and lower lids, and the round contour of the globes. The orbital rims should be sharply outlined. In the newborn infant, the rims are initially round and increase in vertical diameter with normal growth. The area of the lacrimal sac is palpated for abnormal masses or increased size by pressing the sac against the bones of the nose and medial orbital wall. Mucopurulent material expressed from the lacrimal puncta is a symptom of obstruction of the nasolacrimal system. The eyelids are examined grossly and are compared for symmetry of horizontal and vertical placement. Spontaneous opening and closing of the lids should be observed. The lid margins should be inspected for regularity of contour, apposition to the globe, and the presence of lacrimal puncta. The punctum, the proximal opening into the nasolacrimal drainage system, is a minute hole in each lid margin a short distance from the inner corner of the eye. A rapid up-and-down movement of the lid during nursing indicates a jaw-winking phenomenon[61] (Fig. 95.2).

The examiner should view the lashes, which normally are directed outward in an orderly row. Abnormalities include distichiasis and trichiasis and are discussed later in this chapter. Lid position abnormalities should be checked (i.e., epiblepharon).

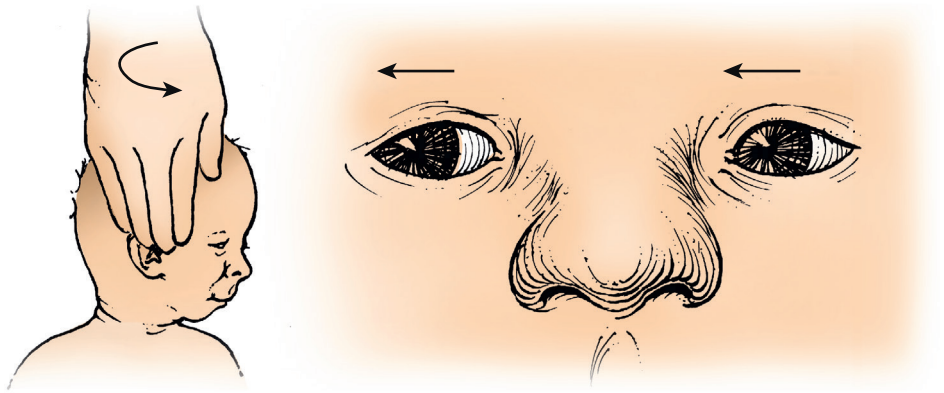
The ocular motor system is evaluated with a motility examination. This includes ocular alignment, conjugate ocular movements, and range of movement. Infants younger than 4 months may show small physiologic misalignments of the eyes. Misaligned eyes beyond the age of 4 months should be considered pathologic.[34]

Alignment is tested with the corneal reflex test (Hirschberg test). The examiner shines a well-focused light at the patient's eyes and notes the spot on the cornea where the light is reflected back. If the patient is properly fixating, the light reflex should appear in the same location on each cornea, slightly nasal to the anatomic center of the cornea. If the light reflex is centered in one eye and deviated laterally in the fellow eye, esotropia is present. If the light reflex is centered in one eye and deviated nasally in the fellow eye, exotropia is present.

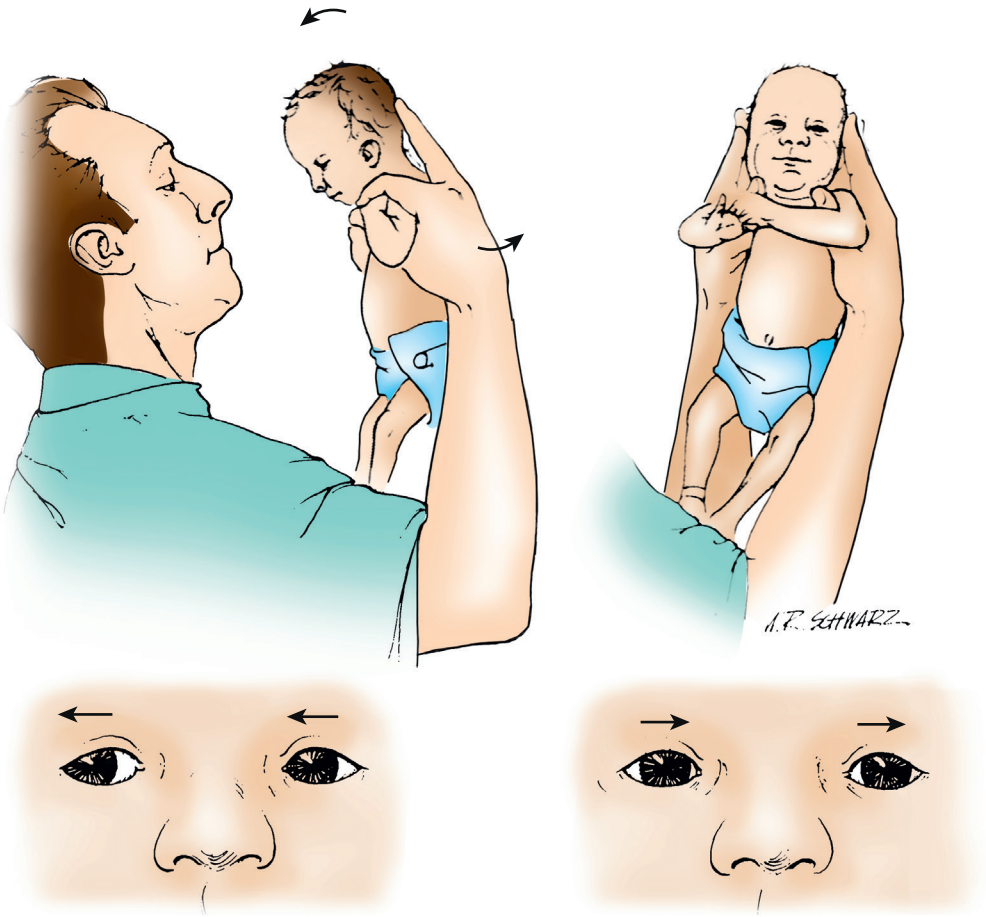
A positive cover-uncover test will support the impression of strabismus. If the patient does not appear to move the eyes well enough into the periphery, either spontaneously or by following an object, these movements can be driven by the doll's head maneuver (vestibulo-ocular reflex [VOR]). The reflex is tested by turning the infant's head to one shoulder, producing an opposite movement of the eyes (Fig. 95.3). The eyes appear stationary as the head turns. This reflex may be reduced in severely brain damaged infants but normal in blind infants.[19]

Another rotational reflex is elicited by holding the infant vertically and rotating the infant in an arc around the

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• **Fig. 95.3** Doll's head rotation: As the head is turned toward the shoulder, a tonic neck muscle reflex produces corresponding ocular rotation in the opposite direction as though the eyes were remaining in their original position as the head moves.



• **Fig. 95.4** Rotational nystagmus: The infant's head is inclined slightly forward with eyes open. With rotation, the eyes move in the opposite direction as in a doll's eye rotation. When rotation stops, the recovery movement occurs in the reverse direction.

examiner (Fig. 95.4). The infant's eyes will then tonically rotate in the direction of the spin, with short quick movements (saccades) in the direction opposite the spin. This ocular reflex may be a form of optokinetic nystagmus and is reduced in infants with major defects of the vestibular system, lower motor pathways to the extraocular muscles, visual system, or central nervous system.[19]

Examination of the globes may be difficult owing to the inability of the examiner to open the neonates' eyelids sufficiently. Various pediatric eye speculums, such as an Alfonso speculum (Bausch and Lomb, STORZ, San Dimas, CA), can be used to maintain the lids open and allow for adequate inspection of the ocular surface, anterior segment, or posterior segment. Before placing the eye speculum, topical

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ocular anesthesia can be achieved with a drop of tetracaine 0.5% eye drops. Oral sucrose can also relieve some of the discomfort of an ocular speculum.[36] The conjunctiva is inspected after the lids are separated, with the use of a pediatric ocular speculum or fingers. The bulbar and palpebral conjunctivae are normally moist and pinkish. Redness or exudate is abnormal and can indicate infection. The conjunctivae of the lids overlying the tarsal plates should be examined after the lids are everted. Eversion is usually simple to perform with the examiner's fingers, particularly if the infant is attempting to squeeze the lids shut. The normally white sclera is evaluated for changes of color. A bluish coloration, however, is present in premature infants and in other small babies because of their very thin sclera.

The cornea is inspected with a penlight, paying attention to corneal size, shape, clarity, and luster. Magnification with loupes or an ophthalmoscope with the 20-diopter lens in place may be used. During the first few days of life, premature and term infants might demonstrate a slightly hazy cornea, which is thought to be the result of corneal edema. Thereafter, the surface of the cornea should have good luster and be absolutely transparent even to the extreme periphery. Any opacity or translucency is abnormal after the first few days of life, and referral to an ophthalmologist is indicated. Changes in transparency or opacification in the peripheral cornea may be associated with a local mesenchymal abnormality or glaucoma (Fig. 95.5).

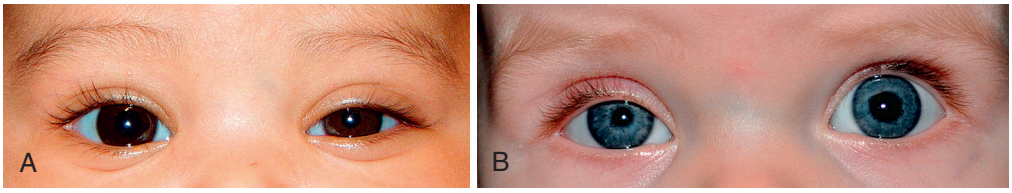
The irides are usually similar in appearance. Although normally incomplete for the first 6 months of life, pigmentation of both irides develop simultaneously. In a normal infant, the iris is often blue or blue-gray for the first few weeks or months of life. However, darkly pigmented babies can show pigmentation at birth or within the first week. Heterochromia (dissimilarity in pigmentation between the two eyes or within one eye) can indicate a normal hereditary pattern, congenital Horner syndrome (Fig. 95.6*A, B*), or one of several syndromes (e.g., Waardenburg) discussed later in this chapter. These syndromes might not become apparent until the end of the neonatal period or even later in life when the iris is fully pigmented.



• **Fig. 95.5** Congenital glaucoma: Left eye larger than the right eye with grayish discoloration secondary to corneal edema in the left eye.

The pupils should be central, round, and equal in diameter. The pupillary space should be uniformly black. Any amount of a white reflection is abnormal and could indicate an abnormality within the lens, vitreous, or retina. The neonate's pupils are typically miotic in ambient light, perhaps related to prolonged sleep.[55] A penlight or a transilluminator is used to shine a light at each pupil. Beyond a corrected gestational age of 30 weeks, pupils should constrict to both direct and contralateral stimulation.[55] First, the reaction of the illuminated pupil is observed. It should constrict briskly (although the response in the neonate may be slower than in an older child) and should remain constricted as long as the illumination is maintained. If a poor response is observed, the contralateral pupil's reaction is studied. If the contralateral pupil constricts, the directly illuminated eye must have intact photoreceptors and optic nerve pathways. Failure of constriction in the directly illuminated eye in this instance could result from abnormalities in the iris. If neither pupil constricts on direct illumination to one eye, the first eye may be severely deficient in vision. The swinging flashlight test is used to check for a relative afferent pupillary defect. Normally, if the light is quickly shifted from one eye to the other, the newly illuminated eye's pupil should show an initial small constriction movement. If illumination is maintained on the eye, small rhythmic constriction and dilation movements may follow—called hippus, a normal phenomenon. If, however, the shift of light is followed by dilation of the newly stimulated eye, a Marcus Gunn (or relative afferent pupillary defect) is present. This result indicates decreased vision in the eye that inappropriately dilated. Pupillary reflexes should be completely normal in patients with central (cortical) visual impairment.

The red reflex test is an essential part of the infant screening eye examination.[3,111] Examination starts with a "0" diopter setting in the direct ophthalmoscope, and the child is examined at arm's length, with both pupils illuminated (Fig. 95.7). The red reflex of each eye should be clearly



• **Fig. 95.6** **A,** Congenital Horner syndrome affecting the left side: Note the smaller left pupil, the mild left upper lid ptosis, the left lower lid reverse ptosis and heterochromia (left eye lighter brown while right eye dark brown). **B,** Horner syndrome affecting right side: Note right pupil smaller than the left and mildly droopy right upper lid.

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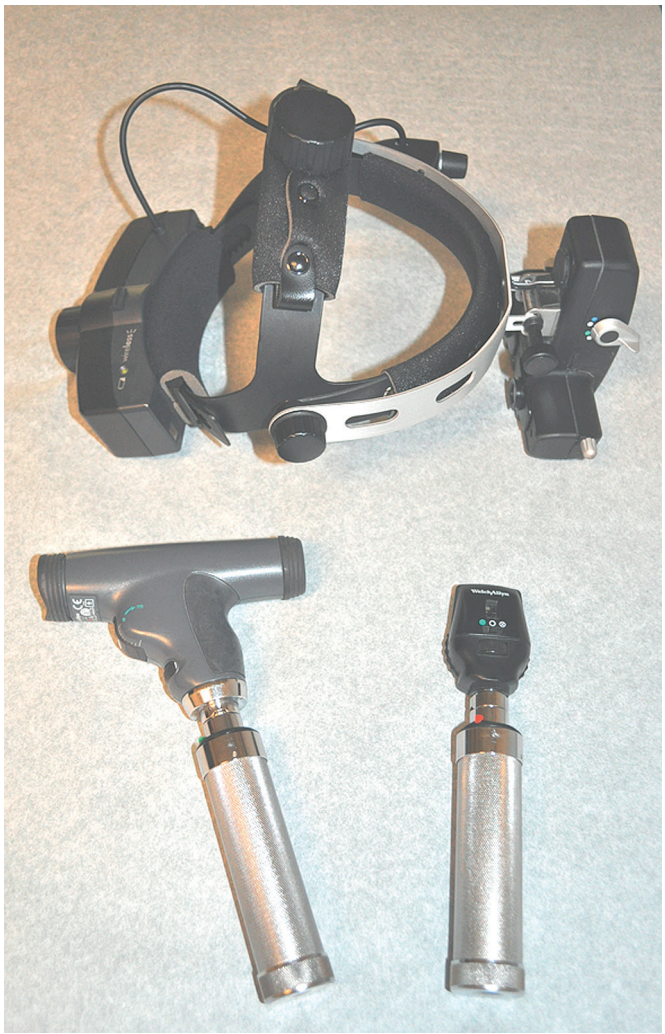
• **Fig. 95.7** Red reflex: Normal red reflex in the left eye and a white reflex in the right eye. This patient was later diagnosed with retinoblastoma in the right eye.

distinct, with no shadows or alterations. Look for any asymmetry of the intensity of the red reflex within each pupil and between the two pupils. If a red reflex cannot be seen, the pupils can be dilated with cyclomydril eye drops[89] (Alcon Laboratories), and if a clear and equal red reflex is still not seen, the baby should be referred to an ophthalmologist.[34] Precise viewing of the anterior chamber and crystalline lens requires a slit-lamp examination, instrumentation that is usually not available to the neonatologist or primary care physician. An indirect assessment of the clarity of the cornea, anterior chamber, lens, and vitreous is performed during the red reflex test, which measures the ability of light to enter the eye and reflect back out of the eye off the retina. Similarly, the red reflex test indirectly assesses the intactness of the retina. The adventurous neonatologist or primary care physician can attempt direct viewing of the infant's retina with a direct ophthalmoscope or a panoptic (Fig. 95.8). Viewing the retina of the infant's undilated eye with a direct ophthalmoscope is a challenge, even to the pediatric ophthalmologist, but a panfundoscope can provide adequate examination with more ease. If a view of the retina is required, such as for retinopathy of prematurity screening, the consulting ophthalmologist would dilate the infant's eyes and use more sophisticated examination instrumentation such as the indirect ophthalmoscope.

Certainly, the use of the direct ophthalmoscope to directly view the retina is not considered part of the screening eye examination in the infant.[81] However, if a direct ophthalmoscope examination is attempted, attention should be directed to the clarity of the vitreous cavity and the appearance of the optic disc, major retinal vessels, the macula, and the surrounding retina.

Normal Ocular Findings

The eye of the newborn infant differs from the adult eye primarily in function, although structural differences also exist. The growth of the eye, which parallels that of the brain, continues at a rapid rate for the first 3 years of life, especially during the first year. The anteroposterior dimension of the eye at birth is about 16.5 mm and grows to about 23 mm in adulthood. Normal values in the neonate fall within a very wide range. Suspected abnormalities in size often are substantiated only by comparison with measured values



• **Fig. 95.8** Panoptic, indirect, and direct ophthalmoscope.

in the fellow eye or by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). The horizontal and vertical diameters of the cornea of the newborn are about 9-10 mm. Enlarged corneas suggest the diagnosis of congenital glaucoma.

The lid fissures of the term infant are usually narrow and often widely separated horizontally by prominent epicanthal folds. Normal horizontal measurement of the lid fissures in the newborn can range from 17-27 mm (Table 95.2). These measurements should be symmetric. The term telecanthus indicates a disproportionate increase in the distance between the medial canthal angles. It is particularly noticeable in fetal alcohol syndrome and Waardenburg syndrome. Measurements between the two medial canthi in the term newborn vary from 18-22 mm. Hypertelorism is defined as an increase in distance between the orbits, observed clinically as a large interpupillary distance, which is often seen in many craniofacial syndromes. A secondary telecanthus is observed in patients with hypertelorism.

Reflex tearing to irritants is evident shortly after birth. However, emotional tearing begins at about 3 weeks of age and is developed at 2-3 months. The newborn infant

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TABLE 95.2 Normal Ocular Measurements

	Term Neonate	Premature*
Intermediate canthal distance, mm	18-22	12-16
Medial canthus to lateral canthus, mm	17-27	12-16
Anteroposterior diameter of eye at birth, mm	16	10-16
Horizontal diameter of cornea, mm	10 (average), 9 (lower limits)	7.5-8 (lower limits)

*Neonates weighing 1000-1300 g.

possesses a strong blink reflex in response to light and to stimulation of the lids, lashes, or cornea. The reflex response to a threatening gesture does not appear until 7 or 8 weeks of age in the term infant. Repetitive eye opening is evident at birth.[45]

After birth, the eyes should appear straight for the most part, although erratic, purposeless, and independent movements can be observed during the first few months of life. Any constant strabismus beyond the age of 4 months requires further evaluation.[6] Conjugate horizontal gaze should be evident in the newborn; vertical conjugate gaze develops by 2 months of age. Convergence spasms are a normal transient phenomenon of infancy.

The ability to maintain a steady gaze or to fixate and follow an object is only weakly initiated at 4-6 weeks of age. At first, the eyes pursue a moving visual stimulus with short saccades. By 3 months of age, the infant can fixate and follow in both vertical and horizontal directions. At about 4 months of age, central fixation is associated with the motor activity of grasping. Binocular vision is present at about 6 months of age.

Prematurity

The ocular findings of the premature infant differ from those of the term neonate. At 28 weeks of gestation, the globe is only 10-14 mm in diameter. The anterior and posterior hyaloid vascular systems are usually present to some degree, although their involution continues for the next several months. Remnants of this system may be seen in the form of persistent blood vessels or fibrous strands anterior and posterior to the lens. The main hyaloid artery coursing from the optic disc to the posterior lens surface may be patent or appears as a white strand in the vitreous. A moderate amount of vitreous haze is often present at this time, interfering with visualization of the fundus. Vascularization of the retina begins with the ophthalmic artery entering the eye through the posterior edge of the eye's embryonic fissure at 4 months of gestation. Retinal vessels then grow anteriorly to vascularize the peripheral retina, a process that is not complete until near term. Thus premature infants have incomplete retinal vascularization, creating the basis for retinopathy of prematurity (see also Chapter 96).

Pupil constriction to light is not seen until 30 weeks of gestational age.[55] Lack of pupil response to light should not be considered abnormal until at least 32 weeks after conception. Premature infants have a higher incidence of myopia, amblyopia, and strabismus in childhood. Careful follow-up of all children born prematurely is advisable to ensure early detection of these ocular conditions.

Requesting Ophthalmologic Consultations

Routine ophthalmologic consultation for all infants in the nursery is not warranted.[34] Pathologic ocular findings in normal neonates are sufficiently unusual that evaluation should be requested only after a screening ocular examination indicates the presence of an abnormality or for patients who for some reason are at increased risk for ocular problems. Indications for ophthalmologic consultation include a family history of congenital cataracts, retinoblastoma, congenital glaucoma, or other serious ocular diseases. Intrauterine infectious disease such as rubella, toxoplasmosis, or cytomegalovirus necessitates a thorough eye evaluation. For preterm infants, ophthalmologic consultation is necessary to exclude retinopathy of prematurity.

Orbital Abnormalities

The contents of the orbit are confined to a conical shape by its bony walls. At the posterior apex of the orbit, the extraocular muscles originate, and the vascular and nerve structures enter the orbit. The bone structures of the lateral wall do not protect the orbital contents as far anteriorly as do the remaining sides of the orbit, which leaves the eye more susceptible to trauma on its lateral side. In the neonate, the orbital rims form a circular outline at the anterior base of the cone.

Box 95.2 lists systemic syndromes associated with abnormal orbits.

The terms proptosis, exophthalmos, and exorbitism are often used interchangeably to describe forwardly displaced eyes. In the strictest sense, proptosis results from an increase in orbital contents within a normal bony orbit, exophthalmos from Graves disease, and exorbitism from shallow bony orbits.

Proptosis

The diagnosis of proptosis can be confirmed if the examiner observes the infant's eyes and lids from above, over the prominence of the eyebrows. A more anterior protrusion of the orbital content is observed in comparison with the opposite side. In proptosis, the eye frequently also has a widened palpebral fissure.

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• BOX 95.2 Syndromes Associated With Abnormal Orbits

Hypotelorism

- Cebocephaly
- Oculodentodigital dysplasia
- Trisomy 13
- Scaphocephaly

Hypertelorism

- Cerebral gigantism
- Cerebrohepatorenal syndrome
- Chromosome deletions
- Craniosynostosis
- Frontonasal dysplasia and median cleft face syndrome
- Infantile hypercalcemia
- Smith-Lemli-Opitz syndrome
- Isolated finding

Masses within the orbital cavity can expand most easily anteriorly, producing proptosis. Those located within the cone of extraocular muscles produce a symmetric anterior displacement, whereas tumors located outside the cone of extraocular muscles displace the eye outward and away from the area of origin of the tumor. A tumor in the inferior portion of the orbit displaces the eye upward and forward, whereas one located medially displaces the eye laterally and forward. A diffuse, extensive tumor can produce sufficient changes to affect the eye's movement, whereas a localized tumor often does not interfere with rotation of the eye. If a tumor is located anterior to the equator of the globe, it can extend anteriorly into the lids without producing proptosis.

An orbital encephalocele or meningocele producing proptosis may be evident at birth or may be delayed until later years. This abnormality results from a defect in the wall between the cranial cavity and the orbit, usually located at the suture lines. Pressure within the cranium causes herniation of brain tissue, meninges, or both into the orbit, most often at the inner angle of the orbit at the root of the nose.

Diagnosis is made by identifying the bone defect in association with the area of the orbital cyst. Clinically, an encephalocele is suggested by the presence of a pulsating, fluctuant cyst that can be reduced somewhat with digital pressure or that increases with coughing or crying. Excessive manipulation of the encephalocele can cause pulse and respirations to slow or can cause convulsions. Neurosurgical consultation and intervention are necessary.

Proptosis also can occur from venous engorgement of the orbital cavity such as that produced by a carotid-cavernous fistula. A cephalic bruit is often heard in the infant but is not pathognomonic of a carotid-cavernous sinus fistula. A false diagnosis of proptosis might be made when there is a slight ptosis of one eye, which gives the opposite, normal eye an appearance of a wide palpebral fissure. Marked enlargement of the eye, as in congenital glaucoma or high myopia, makes the eye appear proptotic because of the increased size of the globe. Facial abnormalities that produce shallow orbits, as in Crouzon disease, simulate proptosis because the normal amount of orbital structure appears to protrude in an abnormally shallow orbit.

Hyperthyroid Exophthalmos

Hyperthyroid exophthalmos, a rare neonatal sequela of hyperthyroidism, can occur as the result of maternal Graves disease during the last trimester of pregnancy. The infant is born with classic hyperthyroidism, including exophthalmos, upper lid retraction, and extraocular muscle involvement. Symptoms usually subside during the first 2 months of life.[41]

Enophthalmos

Enophthalmos refers to eyes that look sunken into the orbit. Causes in infants include orbital asymmetry, microphthalmos, trauma resulting in an orbital blow-out fracture, congenital fibrosis of the extraocular muscles, and congenital Horner syndrome.[23] Numerous syndromes, and many infants with unclassifiable facial dysmorphisms, feature deep-set eyes, such as Lowe syndrome, Cockayne syndrome, and Cornelia de Lange syndrome.

Ocular Hypotelorism or Hypertelorism

Abnormal spatial relationships between the two orbits create excessively wide or excessively narrow intraorbital distances.[71] These abnormalities are caused by a variety of related cranial abnormalities involving the disproportionate growth or lack of development of the body and lesser wing of the sphenoid and ethmoid sinuses and of the maxillary processes. Hypotelorism (narrowing of the intraorbital distance) may be associated with central nervous system malformation.

Ocular hypertelorism is a term indicating increased separation between the bony orbits, usually greater than two standard deviations above the mean. It is an anatomic description rather than a diagnostic entity and is noted with varying severity in many syndromes such as the craniosynostosis syndromes. One condition with marked hypertelorism is frontonasal dysplasia (median facial cleft syndrome), which may be the result of morphokinetic arrest during embryogenesis.

Characteristic findings of frontonasal dysplasia are medial cleft nose, lip, and palate; widow's peak; and cranium bifidum occultum. Common other ocular abnormalities include exotropia, dacryostenosis, epibulbar dermoids, palpebral fissure changes, and optic atrophy.[95] A phenotypically similar but probably distinct clinical entity within the frontonasal dysplasia spectrum has been reported with the features of facial midline defects, basal encephalocele, callosal agenesis, endocrine dwarfism, and morning glory disc anomaly.[93]

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Eyelid Abnormalities

Colobomas

Colobomas of the lids are partial-thickness or complete defects that can range from a small notching of the lid borders to involvement of the entire length of the lid. Most lid colobomas occur in the medial aspect of the upper lid. When the lower lid is involved, the defect is more often in its lateral aspects. The cause of lid colobomas is often unknown unless associated with a craniofacial syndrome. It has been suggested that these isolated colobomas arise from the localized failure of adhesion of the lid folds that results in a lag of growth or from mechanical effects of amniotic bands. Syndromes with associated lower lid colobomas are mandibulofacial dysostosis (Treacher Collins syndrome), Goldenhar syndrome (more often upper lid), amniotic band syndrome, and Burn-McKeown syndrome.[123]

The treatment of lid colobomas is important when the lid defect prevents adequate lid closure and allows exposure of the cornea. Subsequent thickening, opacification, infection, ulceration, or perforation of the unprotected cornea can occur. Vision can be degraded by the amblyopia that develops. Early surgical correction is often required when the coloboma is greater than one-third of the eyelid margin.[100]

Congenital Blepharophimosis

The term blepharophimosis describes eyelids that are too narrow horizontally and vertically. There is usually an associated ptosis, and strabismus is frequently present. Lid fissure measurements commonly are reduced to about two-thirds of normal, whereas the space between the medial canthi is considerably widened. Surgical repair to widen the medial and lateral canthal angles, elevate the upper lid, and correct the strabismus is available.

Blepharophimosis can occur in isolation, as a feature of BPES (blepharophimosis, ptosis, and epicanthus inversus syndrome), or in multiple systemic syndromes such as fetal alcohol syndrome, Saethre-Chotzen syndrome, and van den Ende-Gupta syndrome. BPES has been mapped to the FOXL2 gene encoding a fork head transcription factor. BPES is divided into type 1 and type 2, with and without premature ovarian failure, respectively.[11]

Epicanthus

Epicanthus is the most commonly encountered lid abnormality. A skinfold originating in the upper lid extends over the medial end of the upper lid, the medial canthus, and the caruncle, and ends in the skin of the lower lid. It gradually disappears with the growth of the bridge of the nose as the child loses its baby face. Epicanthal folds can give a false appearance of crossed eyes (pseudostrabismus). Epicanthus inversus is similar except that the predominance of the skinfold arises in the lower lid and runs diagonally upward toward the root of the nose to overlie the medial canthus. These folds are benign and generally do not require treatment.

Congenital Ectropion, Entropion, and Epiblepharon

Congenital ectropion is an eversion of the lid margin, most commonly of the lower lid. It may be associated with other eye abnormalities or syndromes such as Duane syndrome. If the ectropion is mild, no treatment is necessary. A more severely everted lid might require surgical correction. The integrity of the cornea requires monitoring and will determine the treatment.

Often associated with other lid or ocular abnormalities, congenital entropion is an in-turning of the lid margin, most often of the lower lid. If the lashes on the lid margin rub the cornea and cause corneal abrasions, surgery is necessary.

Epiblepharon is an extra fold of skin along the lower lid that can cause lashes to turn inward. This condition usually requires no treatment and is most often seen in infants of Asian ancestry. This condition usually improves spontaneously during the first 2 years of life, but if it persists, consideration should be given to surgical correction. As the lashes are soft when the child is younger, lashes rubbing against the cornea tend not to produce symptoms. But beyond age one, as the lashes get thicker and harder, corneal irritation leading to abrasion and even ulceration not controlled with simple lubrication with ointments warrants earlier surgical intervention.[151]

Blepharoptosis

Ptosis is asymmetry in upper lid height or symmetrical lowering of both upper lids. Although both upper and lower eyelids may be ptotic, the terms blepharoptosis or ptosis generally refer to the upper lids unless otherwise specified (Fig. 95.9). The condition could be idiopathic or inherited, unilateral or bilateral, congenital or acquired. When looking straight ahead, the normal lid should elevate to a point at least midway between the pupil and the upper margin of the cornea. Neonates may have a transient self-limited droopy or closed lid as a result of facial edema or lid trauma during normal vaginal delivery. A temporary, simulated ptosis (protective ptosis or guarding) can result from irritation or infection of the cornea or conjunctiva.



• **Fig. 95.9** Congenital ptosis of the left upper lid.

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Congenital ptosis most often results from the dysfunction of the levator palpebrae muscle, mostly seen as an idiopathic or familial disorder. Although occlusion of the pupil is rare, the ptotic lid can induce a corneal astigmatism and refractive amblyopia. Occlusive patching and glasses may be needed. Mild, unilateral ptosis should prompt a comparison of pupil size to evaluate for Horner syndrome. Congenital Horner syndrome (ipsilateral ptosis, miosis, anhydrosis [see Fig. 95.6*A, B*]) is often a result of trauma at birth, although it may be associated with mediastinal disease or neuroblastoma. The involved iris may be hypopigmented.

Ptosis also may be associated with a Marcus-Gunn jaw-winking phenomenon. This syndrome is caused by anomalous motor innervation of the levator palpebrae muscle from nerve twigs to the pterygoid, masseter, or lingual muscles. The affected patient has an up-and-down rhythmic movement of the upper lid during nursing activity (see Fig. 95.2). The jaw-winking portion of the syndrome is thought to decrease or disappear in early adulthood, but the ptosis remains. Many surgical procedures have been designed to mitigate the ptosis.

Two forms of myasthenia gravis can produce ptosis in the neonatal period. In about 15% of neonates born to mothers with myasthenia gravis, a transient form of myasthenia occurs shortly after birth.[44] Affected children have a weak cry and poor suck and can develop weakness in all muscle groups. Ocular symptoms are rare and most commonly involve ptosis. A variety of congenital myasthenia syndromes linked to genetic disorders of the neuromuscular junction or acetylcholine production can display ptosis and ophthalmoparesis, which are often variable and related to the level of fatigue. Pseudoptosis, or false ptosis, may be apparent when the globes are of different sizes or if enophthalmos or proptosis is present.

Microphthalmia (small eye) is a common congenital defect that can be mildly expressed. In such situations, the lid will look drooped even if it is functioning properly (Fig. 95.10). A unilateral large globe caused by monocular myopia can produce a relative ptosis in the contralateral normal eye.



• **Fig. 95.10** Microphthalmus: Patient with microphthalmic right eye also has significant choroidal coloboma in the same eye.



• **Fig. 95.11** Ankyloblepharon: Persistent adhesion between upper and lower lid.

Ankyloblepharon

The upper and the lower lids may be fused at birth or through an inflammatory process (Fig. 95.11). The term ankyloblepharon is used to designate this condition, which may be dominantly inherited. Simple excision of the bridging tissues between the eyelids is all that is required to separate the lids.

Eyelid Lesions

Nevi

Nevi may occur anywhere on the lid margin, skin, or conjunctiva. Often a congenital nevus will not be noticed until puberty, when pigment begins to accumulate and the lesion is thought to be growing (Fig. 95.12). Observation for change in size, shape, depth, or pigmentation is recommended.

Dermoid Cysts

Dermoid cysts are tumors that appear at the suture lines, most commonly at the superotemporal brow or in the superior medial central area of the brow (Fig. 95.13). Occasionally they appear to be free in the orbit or lid without demonstrable direct connection to a suture line. They are benign choristomata that grow slowly but will thin out the adjacent bone. They should be removed surgically without rupturing the cyst (Fig. 95.14). If a dermoid cyst is ruptured by accidental trauma or surgery, severe local inflammation can result if the extruded contents are not irrigated from the wound.

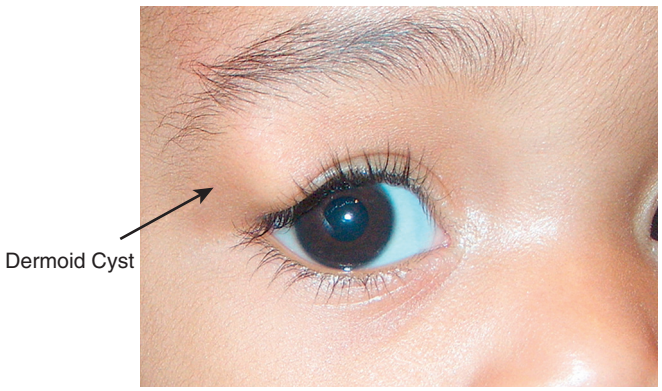
Hemangioma

Hemangiomata are quite common and occur in up to 10% of newborns.[118] They may virtually occur in any body location including the upper or lower lids and orbit. In infants, the hemangioma usually is not well encapsulated and frequently periorbital, and orbital lesions will occur in association with similar lesions elsewhere on the body.

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• **Fig. 95.12** Nevus of Ota: Hyper-pigmented nevus affecting the left temple, forehead, and periorbital; also associated with scleral melanosis.



• **Fig. 95.13** Dermoid cyst in right temporal anterior orbit: Firm, non-tender, oval mass palpated.

Although observation of lid involvement assists in making the diagnosis, a biopsy might be required to exclude other orbital tumors if the hemangioma lacks a superficial component. Crying or straining by the infant often causes the mass to increase in size and assume a bluish coloration. Digital pressure on the superficial portion of the tumor is rapidly reversed, demonstrating the high flow of capillary hemangioma. When a hemangioma involves the eyelids, amblyopia can develop. Amblyopia may be secondary to the hemangioma's obstruction of the visual axis or from pressure on the cornea that subsequently induces astigmatism and anisometropic amblyopia.

Congenital capillary hemangiomata are inconsequential at birth but grow rapidly during the first 6 months of life.



• **Fig. 95.14** Dermoid cyst removed in total; pathology confirmed diagnosis of dermoid cyst.

Spontaneous involution occurs at about age 2-4 years. The natural history of hemangiomas is that they will regress over several years even without treatment, but local soft tissue and occasional bone deformities may remain and are common around the eye.

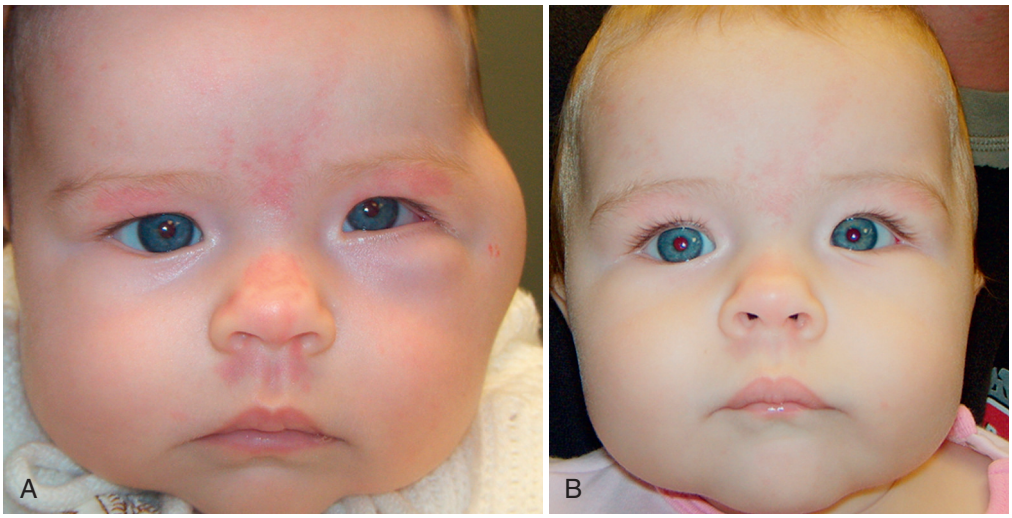
When threatening the sight via amblyopiogenic properties, treatment is warranted. Until recently, treatment was oral use or intralesional injections of steroids, subcutaneous interferon, or excision of the lesion. Although these modalities are still valid, they are not free of side effects. Oral propranolol or topical timolol are effective ways of treating these tumors[22,67] (Figs. 95.15*A*, *B*). In the past, treatment involved systemic, injectable, or topical corticosteroids with potential side effects over months of treatment. Central artery occlusion is a rare but well-described complication of steroid injection with permanent vision loss.[104] Occasionally, surgery is indicated for well-defined, easily accessible tumors to avoid side effects of medical treatment.[109] Oral use of propranolol (2 mg/kg/day) is found to be very effective in the hemangioma treatment. However, its use, although relatively uncommon, necessitates that side effects such as hypotension and hypoglycemia have to be monitored closely. Also, an MRI of the brain to rule out associated intracranial vascular abnormalities will prevent cerebrovascular injuries secondary to the blood flow and tension changes caused by this medication.

Other eyelid lesions include, but are not limited to, plexiform neuromas secondary to neurofibromatosis type-1, amyloid depositions, and juvenile xanthogranuloma.

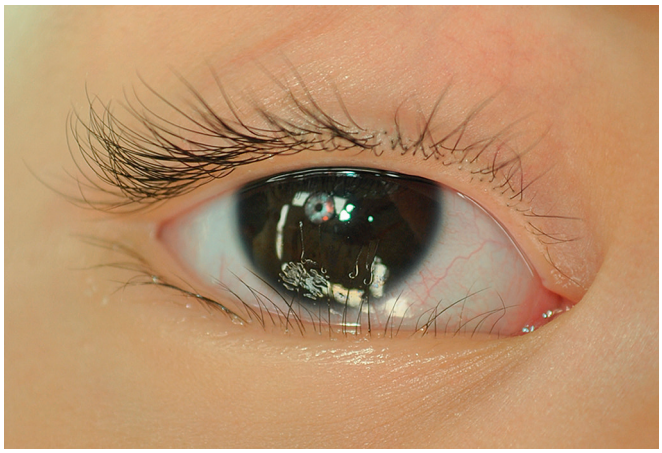
Eyelash Abnormalities

Lashes may be redundant, absent, misdirected, or discolored. The condition may be inherited or acquired through mucous membrane diseases of the conjunctival sacs, infectious process, or trauma. *Trichiasis* is a lash that grows from

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• **Fig. 95.15 A,** Diffuse capillary hemangioma affecting the left side of the face and orbit. **B,** Resolved hemangioma with oral propranolol treatment.



• **Fig. 95.16** Epiblepharon: Right lower lid lashes turned in toward the cornea, abrading the front surface of the eye.

a normal location but is misdirected toward the ocular surface. *Congenital trichiasis* patients should be examined for Down syndrome or signs of ectodermal dysplasia. If a second row of lashes is present in the area of the meibomian glands (metaplasia), the condition is referred as *distichiasis*. This condition usually results in contact of the lashes with the cornea, producing corneal irritation and abrasions. True distichiasis is rare but can easily be distinguished from trichiasis, entropion, and epiblepharon (Fig. 95.16), all of which may be seen together. Excessive eyelash growth can result as a side effect from multiple medications, including topical prostaglandin analogues and epidermal growth factor receptor inhibitors.[29]

Hypertrichosis

Excessive hair on the lids and forehead can occur as a dominant characteristic in male infants and, on occasion, may be extreme. Hypertrichosis involving the eyebrows, forehead, and upper lid appears in *Cornelia de Lange syndrome*, a pathologic dwarfism associated with multiple congenital anomalies. Hypertrichosis lanuginosa is transmitted as an autosomal dominant condition. The fetal lanugo persists into adult life, creating an abundant covering of hair on the eyebrows, forehead, eyelids, and other areas of the body.

Lacrimal Abnormalities

Watery Eye

Epiphora (excess tearing) usually does not occur until after the first 3 weeks of life, when the major portion of the lacrimal gland has become functional. Although the usual cause of epiphora is a blockage of the nasolacrimal ducts (dacryostenosis), the possibility of congenital glaucoma is the most important consideration in the differential diagnosis. Less commonly, tearing can result from an obstruction of the common canaliculus, from congenital absence of the lid puncta, or from dacryocystitis. Congenital absence of the entire lacrimal drainage apparatus is extremely rare. Reflex tearing may be produced by any stimulation of the fifth cranial nerve. Epiphora can occur as the result of corneal abrasion, corneal foreign body, or nasal and facial lesions that irritate the fifth cranial nerve. Chronic nasal congestion also may produce epiphora by mechanically blocking the nasolacrimal duct. Dacryostenosis may be present in up to 7% of neonates and creates a stagnant pooling of tears in the lacrimal sac that contributes to chronic or recurrent dacryocystitis. The inflammation is marked by a purulent exudate in the medial canthal area of the conjunctiva. Severe dacryocystitis can produce swelling and induration of the lacrimal sac medial and inferior to the medial canthus. Treatment of mild nasolacrimal infection consists of topical antibiotic drops or ointment. If surrounding cellulitis is suspected, systemic administration of medication and locally applied

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heat may be required. Repeated massage of the lacrimal sac at the medial canthal area serves to flush out the stagnant tears, decrease the risk for infection, and "pop" open the nasolacrimal obstruction. If the epiphora continues, a lacrimal probe passed through the nasolacrimal duct to the nose usually creates an adequate opening. Probing between 6 and 12 months of age is sometimes performed in an office setting under topical anesthesia with the baby swaddled in a sheet. In more than 90% of children with congenital dacryostenosis, the obstructions spontaneously correct during the first year of life. If persistent, treatment is then offered but requires general anesthesia because these children are too large to swaddle for an office probing. Surgical options include simple probing, silicone tube intubation, or balloon dilation of the lacrimal system.[70]

Dacryocystocele

A congenital dacryocystocele presents within the first week of life as a bluish mass adjacent to but lower than the medial canthus. Similar lesions found higher than the medial canthus should be suspected to be encephalocele. The distended lacrimal sac is filled with clear fluid, feels firm or fluctuant to palpation, and does not pulsate like a frontal encephalocele.[125] Initiating oral antibiotics is recommended as soon as a dacryocystocele is identified to prevent infection of the dacryocystocele, which can occur in up to two-thirds of these patients. If the patient presents with signs of a dacryocele infection, admission to a pediatric intensive care unit for intravenous antibiotics is required. Surgical treatment with a nasolacrimal probing should be considered within the next 2-4 days (Figs. 95.17*A, B*).

Dry Eye

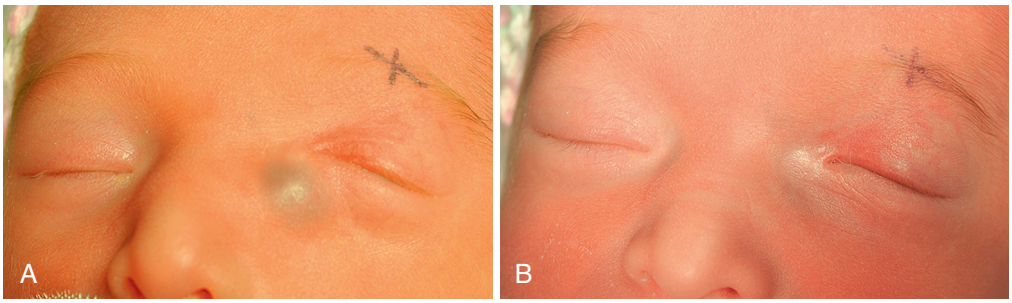
The normal newborn will have moist eyes from basal secretion of tears. Reflex tearing from ocular irritation or psychogenic (emotional) tearing may not develop for weeks to months after birth. Infants do not usually have symptoms from dry eyes unless in rare conditions such as *alacrima* from a congenital lack of tear glands or Riley-Day syndrome. Recognition of alacrima in the infant is important in preventing corneal abrasions, infections, and perforations, the inevitable sequelae of dry eye. During the first month of life, an infant with alacrima from any cause might not appear different from the normal infant, because tear production is minimal during this period. The usual time of discovery is at 6-12 months of age after the lack of tears has produced changes such as scarring or ulceration of the cornea. At 1-2 months of age, early symptoms of dry eye are conjunctival hyperemia and photophobia. Instead of the ample tears expected with conjunctival irritation, a sticky mucoid secretion is produced, and the cornea shows punctuate staining with fluorescein solution application. Treatment includes frequent use of artificial tears (as often as every 15-30 minutes), punctal occlusion, or tarsorrhaphy (partial or complete temporary or permanent suturing of the upper and the lower lid together to decrease the exposed ocular surface area).

Isolated congenital lack of tears, usually bilateral, is a rare anomaly. The cause is unknown, but it has been suggested to result from hypoplasia of the lacrimal gland or from an absence of innervation of the lacrimal gland structures. The ocular findings in familial dysautonomia (Riley-Day syndrome) are characteristic and can produce the initial criteria for diagnosis. They include alacrima and corneal anesthesia. These ocular changes and constriction of the pupil by instillation of 0.125% pilocarpine should establish the diagnosis. The onset of major systemic symptoms occurs when the child is about 2 years old. An abnormal swallowing mechanism, inappropriate blood pressure and respiratory control, decreased sensitivity to pain, deficient taste perception, and abnormal ocular findings in this syndrome are the result of sympathetic, parasympathetic, and sensory neuronal abnormalities. Additional ocular findings are myopia, anisometropia (significantly different refractive error in the two eyes), exotropia, tortuosity of the retinal vessels, and occasionally ptosis. Familial dysautonomia results from a mutation in the *IKBKAP* gene encoding elongation protein 1, resulting in defective splicing.[84]

Globe Abnormalities

Anophthalmia

Anophthalmia is a rare sporadic phenomenon in which there is total absence or a minute rudiment of the globe, and it can present either unilaterally or bilaterally (Fig. 95.18).



• **Fig. 95.17 A,** Dacryocystocele: Bluish-colored, firm, nonmobile cyst seen below the medial canthal tendon. **B,** Dacryocystocele: After decompression with tear duct probing.

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• **Fig. 95.18** Anophthalmia: Goldenhar syndrome, with maldeveloped right side of the face and anophthalmia.

It occurs as a developmental failure of the optic vesicle. It is often accompanied by other congenital anomalies, such as central nervous system defects and mental retardation, and has been observed in isolation, in genetic defects (e.g., *SOX2*, *STRA6*, *PAX6* genes), and in chromosomal syndromes (e.g., trisomy 13).[119] Because lid formation does not depend on ocular formation, the lids are fully formed. However, the lids remain closed and can be partially fused, and they are smaller and sunken without the support of the eye. Treatment involves reconstruction of the orbit to improve the appearance of the face. Plastic molds of the conjunctival sac of gradually enlarging sizes are used to stretch the lids and sac sufficiently to hold an ocular prosthesis. In unilateral situations, orbital reconstruction using tissue expanders can dramatically improve the overall facial appearance.

Cryptophthalmia

In cryptophthalmia, the eyelids fail to cleave, and uninterrupted skin runs from the forehead to the malar area. The eyelids and eyelashes usually are absent; however, the eye can be palpated beneath the skin and might even be observed to move with the stimulation of a strong light.

The anterior segment of the eye is invariably disorganized into fibrovascular tissue adherent to the subcuticular tissue of the lids. Because the conjunctival sac is absent or small, attempts to separate the lids from the ocular structures are usually unsuccessful, and surgical correction is not advisable in most circumstances. Although a globe is present, only rarely is vision obtainable.

Cryptophthalmia is frequently associated with systemic abnormalities such as urogenital malformations (Fraser syndrome) linked to defects of the *FRAS1* and *FREM2* genes, and a thorough genetic evaluation is indicated.[54,118]

Microphthalmia

Microphthalmia describes a variety of conditions in which the axial length of the neonatal eye is less than two-thirds of the normal 16 mm. Causes include familial, syndromic, and chromosomal abnormalities and environmental influences during gestation. Simple microphthalmia is a condition in which there is an abnormally small eye but with intact internal organization. It may be associated with other ocular features of importance: a high degree of hypermetropia, retinal folds, a tendency for choroidal effusions, and the late occurrence of glaucoma.[122]

Complex microphthalmia describes small eyes with internal disorganization, such as anterior segment dysgenesis, cataract, coloboma, or persistent fetal vasculature.[121] Colobomatous microphthalmia occurs when the embryonic cleft of the optic vesicle fails to close. Typically, this form is associated with other ocular anomalies such as colobomas of the iris, ciliary body, fundus, or optic nerve, or colobomatous orbital cysts (see Fig. 95.21).

Microphthalmia can also be associated with other ocular and systemic syndromes, including intrauterine infections such as rubella and cytomegalovirus, craniofacial anomalies, anterior segment dysgenesis syndromes, or chromosomal abnormalities. Because of the heterogenicity of associated findings, infants with microphthalmia should be evaluated by both an ophthalmologist and geneticist.

Large Eye

An abnormally enlarged eye in the neonatal period is rare but is extremely important to recognize. An apparently enlarged eye may be caused by colobomatous microphthalmia with an associated large cyst, congenital megalocornea (see later), or congenital glaucoma (see later). Colobomatous microphthalmia results when the embryonic optic vesicle fails to close. Tissue that originally should have become intraocular is encased in a cystic structure outside the eye in the orbit. If the cyst becomes sufficiently large that proptosis occurs, the microphthalmic eye simulates an enlarged eye.

Scleral Abnormalities

The normal term neonate has a glistening white sclera. The overlying conjunctiva and the conjunctival vessels superimpose a filmy, vascular pattern. A generalized bluish discoloration of the underdeveloped sclera is normal in premature infants. Rarely, a congenital weakness in a small area of the sclera produces a bluish bulge called a staphyloma. The light blue color is caused by thinness of the sclera that transmits the darker color of the underlying uveal tissue. Osteogenesis imperfecta may be associated with a similar bluish discoloration of the sclera in the term neonate because of inadequately developed scleral collagen. Blue sclera may also be seen in other systemic diseases such as Marfan syndrome, Ehlers-Danlos syndrome, and Crouzon syndrome.

Pigmentation of the conjunctiva and sclera is common in darkly pigmented people. Intrascleral nerve loops appear as darkly pigmented dots about 3-4 mm from the limbus. Congenital ocular melanosis and oculodermal melanosis (nevus of Ota [see Fig. 95.12]) occur as a unilateral slate-blue pigmentation in infancy.

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Corneal Abnormalities

Cloudy Cornea

The normal premature infant might have a slightly hazy cornea for the first few weeks of life, caused by temporary excess hydration of the cornea. In the normal term infant, a similar appearance may be seen for the first 48 hours after delivery.

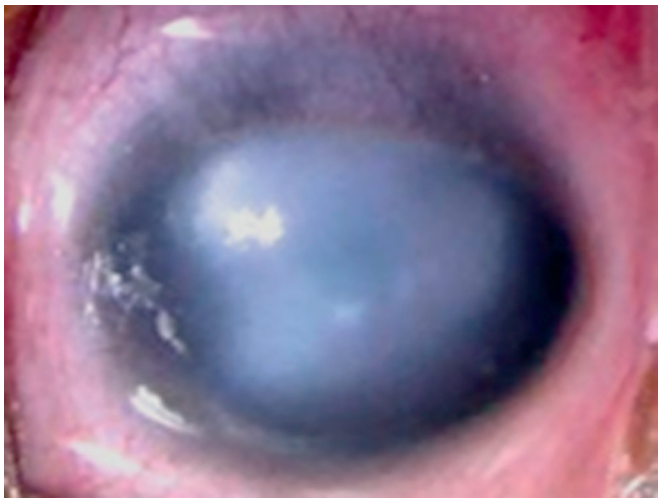
A persistently hazy or cloudy cornea suggests congenital glaucoma or birth injury. Anterior segment dysgenesis syndromes, corneal dystrophies, infection, or systemic disease should also be considered (Fig. 95.19).

Enlarged Cornea

Most newborn infants have a corneal diameter of about 9-10 mm. If this measurement exceeds 12 mm, congenital glaucoma must be considered, especially if corneal haze, tearing, and photophobia are present. Megalocornea is an enlarged cornea exceeding 13 mm in diameter. The cornea is usually clear, with distinct margins and thin iris stroma. There are no other features of congenital glaucoma, such as elevated intraocular pressure, tearing, photophobia, or conjunctival injection. Megalocornea as an isolated finding is usually inherited in an autosomal dominant manner. Megalophthalmia, which is commonly inherited as an X-linked recessive trait, is characterized by deep anterior chambers, subluxation of the lens, hypoplastic iris, and cataract formation in early adult life. A corneal diameter of less than 10 mm may be an isolated finding or may be associated with other ocular anomalies. Cases of autosomal dominant and recessive inheritance of microcornea have been described.

Anterior Segment Dysgenesis Syndromes

A wide spectrum of clinical findings is observed in the anterior segment dysgenesis syndromes, including abnormalities of the cornea, anterior chamber, iris, and lens. Corneal opacities, adhesions of the iris, and glaucoma can occur. Although a continuous spectrum of findings can be evident in a family pedigree, or between the two eyes of one patient, eyes are often assigned into the distinct subgroups of posterior embryotoxon, Axenfeld anomaly, Rieger anomaly, or Peter anomaly.



• **Fig. 95.19** Cloudy cornea: This patient is a 30-week-gestation premature child with Peters anomaly.

Corneal Dystrophies

Most corneal dystrophies become apparent in adolescence or early adult life. However, congenital hereditary endothelial dystrophy may be present at birth. This condition is characterized by bilateral cloudy corneas, normal corneal diameter, and normal intraocular pressure. Early cornea transplantation may be helpful, but the prognosis is guarded.

Corneal Manifestations of Systemic Disease

Corneal opacities and haze can occur because of inborn errors of metabolism. Most are not associated with corneal opacities in the neonatal period. Systemic diseases that cause corneal opacities include the mucopolysaccharidoses, mucolipidoses, Fabry disease, hypophosphatasia, cystinosis, and Wilson disease.

Congenital Glaucoma

Although congenital glaucoma is uncommon, the devastating effects of uncontrolled ocular pressure are sufficiently important to keep this disease uppermost in the mind of the examining physician. The classic symptoms of congenital glaucoma include tearing, light sensitivity, and blepharospasm. As the disease progresses, the increased intraocular pressure produces stretching of the eye, creating an increased corneal diameter greater than 12 mm (buphthalmos, Fig. 95.5), cloudy cornea, progressive myopia, and loss of vision. Symptoms can be apparent at birth or weeks to months later.

Congenital glaucoma can occur as a primary disease or secondary to numerous other ocular conditions or systemic syndromes. A list of diseases associated with congenital glaucoma is shown in Box 95.3. In addition to visual impairment from glaucomatous damage, amblyopia from visual deprivation or anisometropia can prevent a successful visual outcome. The prognosis depends on the age of onset, time to diagnosis, and associated ocular and systemic conditions. Unlike the glaucoma in adults, the treatment is surgical in vast majority of cases, and medical management is only used for temporizing the condition or better visualization for various surgical procedures.

Iris Abnormalities

Aniridia

Aniridia (absence of the iris) is a rare congenital anomaly, usually bilateral, that is almost invariably associated with

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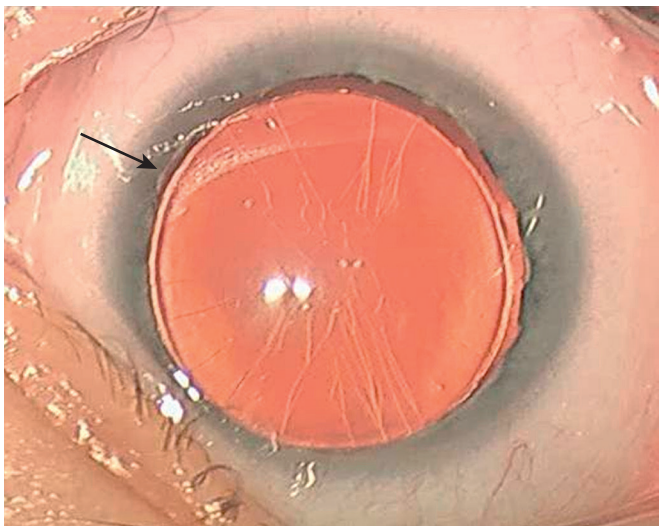
• BOX 95.3 Conditions Associated With Glaucoma

Seen in Isolated (Congenital) Conditions

- Aniridia
- Rubella syndrome
- Hallermann-Streiff syndrome
- Lowe syndrome
- Axenfeld or Rieger syndrome
- Sturge-Weber syndrome

Uncommonly Seen in These Conditions

- Chromosome abnormalities
- Down syndrome
- Homocystinuria
- Marfan syndrome
- Neurofibromatosis
- Ocular-dental-digital syndrome
- Persistent hyperplastic primary vitreous
- Rubinstein-Taybi syndrome
- Weill-Marchesani syndrome



• Fig. 95.20 Aniridia: This patient has a remnant of the iris tissue that appears like a significantly dilated pupil. Sometimes the iris remnant cannot be visualized with direct observation.

poor vision and nystagmus. A small rudimentary cuff of peripheral iris can be observed grossly or microscopically (Fig. 95.20). Associated ocular findings include glaucoma, corneal pannus, cataract, abnormal optic discs, and foveal hypoplasia. Because the fovea sub serves our best vision, its maldevelopment causes the nystagmus and poor visual acuity.

Aniridia is caused by a defect in the *PAX6* gene on chromosome 11 at 11p13.[47] WAGR syndrome, a contiguous gene syndrome, results from a larger deletion in the area that involves the Wilms tumor gene (*WT1*) and includes Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation.[31] All infants with nonfamilial aniridia should undergo chromosomal analysis to detect small deletions; if a deletion exists, the infant should be carefully monitored for early detection of Wilms tumor.[68]

• BOX 95.4 Syndromes Associated With Iris Colobomas

- Congenital colobomatous microphthalmia
- CHARGE association
- Trisomy 13
- Trisomy 18
- Rieger syndrome
- Iris coloboma and anal atresia syndrome
- Lowe syndrome (infrequent)
- Rubinstein-Taybi syndrome (uncommon)
- Multiple chromosome anomalies

CHARGE, *c*oloboma, *h*eart anomaly, choanal *a*tresia, *r*etardation, *g*enital anomaly, *e*ar anomaly.

Coloboma

Iris coloboma is one of the most common congenital abnormalities of the eye. It can occur as a single ocular finding, have a Mendelian mode of inheritance, be associated with a chromosomal abnormality, or be associated with other malformation syndromes (Box 95.4). Typical colobomas occur in the inferonasal quadrant, where the embryonic fissure closes. Because typical iris colobomas result from an abnormal closure of the embryonic fissure, they also may be associated with a coloboma of the ciliary body, fundus, or optic nerve. Associated microphthalmia is common. When the optic nerve or macula is involved in the coloboma, visual difficulty occurs. It is always wise to evaluate the fundus for a pathologic condition when an iris coloboma is detected. Atypical iris colobomas occur away from the inferonasal quadrant. Atypical colobomas, which vary from a small notch in the pupil to the absence of an entire segment of the iris, are not usually associated with visual difficulties. Coloboma of the iris, uvea, or retina, with or without microphthalmia, is a feature of CHARGE association (Fig. 95.21).

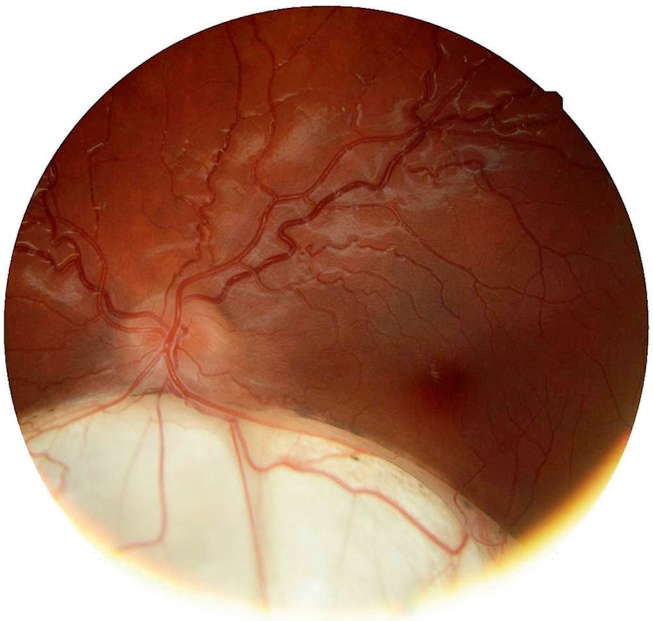
Persistent Pupillary Membrane

Persistent pupillary membranes are common in the neonate, particularly in the premature infant. The membranes are remnants of the anterior fetal vascular supply of the lens that failed to atrophy in the 7th month of gestation. If these persistent vessels adhere to the lens, a localized cataract can form.

Iris Heterochromia

Heterochromia indicates a difference in pigmentation in the irides. For example, one eye may have a blue iris, and the other iris may be brown; or one iris may have a wedge of lighter or darker pigmentation. The heterochromia itself

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• **Fig. 95.21** Choroidal coloboma.

does not affect ocular health or vision but may secondarily result from other pathologic ocular conditions, such as trauma or inflammations. Heterochromia can occur as an isolated autosomal dominant trait. It also is associated with several syndromes such as Waardenburg syndrome. Congenital Horner syndrome produces heterochromia, usually after the neonatal period, resulting from the failure of normal pigmentation to develop in the iris on the sympathetically denervated side. Aganglionic megacolon (Hirschsprung disease) can also be associated with iris heterochromia.

Abnormal Red Reflex

This is one of the most important abnormalities that requires immediate evaluation. The term leukocoria is used to describe a white pupil seen by the naked eye or during the red reflex test. Leukocoria is not a diagnosis but rather a description of an observation. Because the infant sleeps much of the time and because the pupils are small, a white pupil often is not noticed until the infant becomes more alert and active. False positive red reflex test results are commonly due to small pupils, shifting gaze, limited patient cooperation, poor illumination from the ophthalmoscope, and examiner inexperience. Regardless, these patients should be over-referred to the ophthalmologist to ascertain the true-positive results.

Causes of leukocoria in infants include opacities of the cornea, lens, and vitreous, as well as retinal diseases such as retinoblastoma, chorioretinal coloboma, persistent hyperplastic primary vitreous, endophthalmitis, Coats disease, congenital retinal fold, retinoschisis, or scarring from ROP. Abnormal red reflexes can also result from misaligned eye or from high or asymmetric refractive errors.

Lens Abnormalities

Cataract

The lens helps images focus on the retina and is designed to be transparent. The lens grows continuously during life, laying down new lens fibers on its external surface much as an onion does. The lens is preserved in capsules (anterior and posterior) and has a nuclear core and surrounding cortical portion. Any opacity or abnormality within these structures is defined as cataract. Childhood cataracts can be classified as congenital, infantile, or juvenile depending on the age of onset. Congenital cataracts are present at birth but may go unnoticed until an effect on the child's visual function is noticed or a white pupil reflex develops. Congenital and infantile cataracts are responsible for about 10% of all blindness worldwide.[7]

It is important to consider the origin of a cataract. The etiology of pediatric cataracts can be broadly classified and summarized as hereditary, metabolic (galactosemia, Fabry disease, hemolytic jaundice, etc.), traumatic, secondary (maternal infection, inflammation, steroid use, etc.), seen with chromosomal abnormalities (Lowe, Alport, Marfan, Hallerman Strieff, and other syndromes), iatrogenic, and idiopathic. Furthermore, cataracts can be classified according to their morphology as diffuse/total, anterior polar, lamellar, nuclear, posterior polar, posterior lentiglobus, posterior (and anterior) subcapsular, persistent hyperplastic primary vitreous, and traumatic.

The size and shape of a cataract depends on the area of the lens that is being formed at the time the damage or developmental defects occur. Damage that occurs in the early embryonic period produces opacifications in the center of the lens. Such nuclear cataracts have clear layers in the periphery of the lens. Later periods of damage produce ringlike opacifications surrounded by central and peripheral clear areas (zonular cataracts). Recent damage produces peripheral opacifications near the surface of the lens (cortical cataracts). Dense opacities near the central axis cause greater visual disturbance, especially if they are located in the central visual axis.

However, most congenital cataracts are genetic or isolated and idiopathic. A list of causes of neonatal cataracts is shown in Table 95.3.

Genetically determined cataracts often are isolated abnormalities and bilateral. Many genetic loci have been mapped.[99] The primary mode of transmission is autosomal dominant. Recessive transmission and X-linked transmission have been recorded. Because there is variable expressivity, parents should be examined for mild cataracts.

The rubella embryopathy syndrome is rare in the era of rubella vaccination but is still seen in developing countries. The syndrome comprises multiple congenital anomalies that result from maternal viremia during the first trimester of pregnancy. Cataracts are present in about 20% of children with the congenital rubella syndrome (Fig. 95.22). The rubella virus may remain dormant in lens material in the

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TABLE 95.3 Neonatal Cataracts

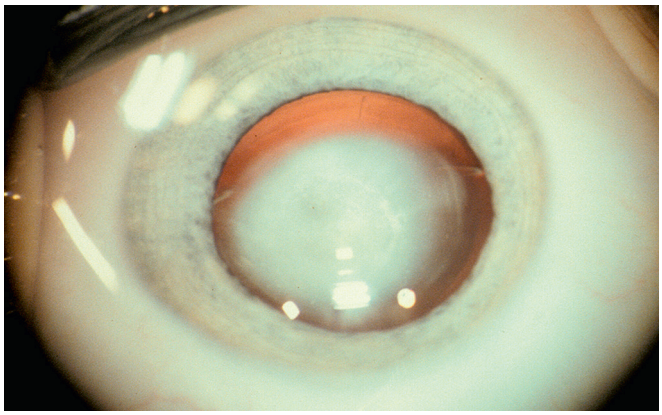
Type	Incidence
Genetic	
Dominant	N/A
Recessive	N/A
X-linked recessive	N/A
Sporadic	1/3 of all congenital cataracts
Viral	
Rubella	Frequent
Toxoplasmosis, varicella, herpes simplex, measles, mumps, vaccinia, cytomegalovirus	Infrequent
Inborn Errors of Metabolism	
Galactosemia	Frequent
Galactokinase deficiency	Frequent
Hypocalcemia	Infrequent
Congenital hemolytic jaundice	Infrequent
Mannosidosis	Frequent
Refsum disease	Infrequent
Fabry disease	Frequent
Myotonic dystrophy	Frequent
Hereditary spherocytosis	Infrequent
Lowe syndrome	Frequent
Trauma	
Birth trauma	Infrequent
Blunt trauma	Frequent
Perforating injuries	Frequent
High-voltage electric-shock	Frequent
Battered child syndrome	Infrequent
Endocrine	
Congenital hypoparathyroidism	Frequent
Albright hereditary osteodystrophy	Infrequent
Neurologic	
Marinesco-Sjögren syndrome	Infrequent
Smith-Lemli-Opitz syndrome	Rare
Sjögren syndrome	Infrequent
Laurence-Moon-Bardet-Biedel syndrome	Frequent
Miscellaneous	
Aniridia (sporadic or associated with Wilms tumor)	Infrequent
Treacher Collins syndrome	Infrequent
Pierre Robin syndrome	Infrequent
Rubinstein-Taybi syndrome	Infrequent
Hallermann-Streiff syndrome	Frequent
Conradi syndrome	Presence of cataract indicates worse prognosis
Chromosome Anomalies	
Trisomy 13	Infrequent
Trisomy 18	Infrequent
Trisomy 21	Infrequent
Patau syndrome	Infrequent
Turner syndrome	Infrequent
Associated With Other Eye Malformations	
Microphthalmia	Frequent
Rieger anomaly	Infrequent
Persistence of fetal vasculature	Frequent
Retinitis pigmentosa	Infrequent
Norrie disease	Infrequent
Colobomas	Frequent
Lenticonus	Frequent

N/A, not available.
Modified from Arkin M, Azar D, Fraioli A. Infantile cataracts. *Int Ophthalmol Clin.* 1992;32(1):110-111.

offspring for as long as several years. Microphthalmia, pupil abnormalities, congenital glaucoma, and anterior uveitis also may result. A cloudy, edematous, or white cornea may be found with normal intraocular pressure as part of the rubella embryopathy. Rubella retinopathy is a pigmentary disturbance of the retina without demonstrable effect on visual function. A TORCH (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex) titer should be obtained from all infants with nongenetic congenital cataracts.

Galactosemia is a hereditary inborn error of metabolism with deficiency of the enzymes responsible for galactose metabolism: galactose-1-phosphate uridyltransferase, galactokinase, or uridine diphosphategalactose-4-epimerase. The affected neonate may appear normal at birth. Cataracts usually develop during the first 2 months of life. The cataracts may be zonular or may appear as vacuoles (classically described as "drop of oil") in the center of the lens owing to an accumulation of galactose and galactitol. Early diagnosis and a regimen of a galactose-free diet

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• **Fig. 95.22** Infantile cataract: White opacification seen in the center of the visual axis. This is a posterior lenticonus type cataract.

can prevent development or further progression of cataracts. All congenital forms of infantile cataracts require a prompt evaluation by an ophthalmologist. Dense cataracts are treated surgically to prevent irreversible amblyopia and strabismus. Removal of the lens, followed by optical correction and amblyopia therapy, provides the best hope of restoring vision.

The prognosis for vision is poorer in the involved eye when the cataract is monocular. Intraocular lens implantation, especially in older infants, is often used to restore the focusing ability of the eye.[106] Long-term follow-up is necessary to monitor vision development, treat strabismus and amblyopia, and detect glaucoma.

Subluxed Lens

The discovery of a subluxed lens (ectopia lentis) in an eye helps in identifying systemic disease processes associated with this abnormality. Although lens dislocation may be present during the neonatal period, it typically develops in the first or second decade of life. Therefore, other causes such as blunt trauma should be suspected, especially if it is seen with other signs of ocular, peri-ocular, and/or systemic signs of trauma (i.e., shaken baby syndrome). Marfan syndrome is the most common cause, but homocystinuria, sulfite oxidase deficiency, hyperlysinemia, Ehlers-Danlos syndrome, Weill-Marchesani syndrome, and trauma can also produce this finding. There is also an isolated genetic form. The dislocation results from a laxity, absence, or defect of the zonular attachments that suspend the lens from the ciliary body. A subluxed lens usually is not treated during the neonatal period unless there is the complication of cataract formation or glaucoma.

By dilating the pupil, the examiner can visualize the edge of a dislocated lens in the pupillary space. Ectopia lentis may also be suggested by iridodonesis (shaking of the iris), which occurs when the posterior surface of the iris lacks the normal support of the lens. A dislocated lens is one of the toughest surgical problems in pediatric ophthalmology.

Retina and Vitreus Diseases

During the neonatal period, nonvascular structures of the fundus are nearly transparent because uveal pigmentation is not fully developed. The neonatal retina does have sheen to its inner surface, but the macular region appears flattened. Retinal transparency is disturbed when abnormalities are present. The retina resembles a pale, ghostlike sheet when it is detached. Retinal edema gives a slightly raised, opalescent appearance. Infection obscures the underlying structures with a fuzzy, white thickening of the retinal tissue. In pathologic processes characterized by a lack or an excess of pigment, retinal abnormalities may become evident only after the first few months of life. The choroid is the deepest layer normally visible with the ophthalmoscope. Pathologic processes that prevent its development or that destroy areas of choroid expose areas of bare sclera, which appear glistening white.

Retinal Dysplasia

Many of the heritable retinal disorders tend to be noticed far beyond the neonatal period. Although these are genetic problems obviously present at birth, it takes years or sometimes decades to manifest its affects and debilitating visual effects. Retinal dysplasia is rare and is a usually bilateral, congenital anomaly of term infants showing congenital retinal folds and retinal detachments. Histopathologically, the retina shows disorganization and dysplasia. The retinal detachments may clinically resemble a mass and should be considered in the differential diagnosis of retinoblastoma. Rather than a distinct clinical entity, retinal dysplasia may represent a common final pathway of many different developmental disorders of retinal differentiation and organization. Retinal dysplasia can occur as part of a group of congenital anomalies—including defects of the central nervous system, cardiovascular system, and skeletal system—that are sufficiently severe to produce early death of the infant. Specific conditions that result in retinal dysplasia include trisomy 13, Norrie disease, and Walker-Warburg syndrome.

Norrie Disease

A rare genetic disorder transmitted as an X-linked recessive trait, Norrie disease is characterized by the presence of bilateral total retinal detachments that result in a white pupil. Organization of the retinal detachment can disrupt the lens, producing cataract, or can affect the anterior chamber angle, producing congenital glaucoma. The usual result is atrophy of the globe. Norrie disease maps to the *NDP* gene on chromosome Xp11.4, most commonly caused by mutations of the cysteine-knot motif.[127] Patients with Norrie disease may also develop progressive mental disorders often with psychotic features, and about one-third of patients develop sensorineural deafness.

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Mutations of the *NDP* gene away from the cysteine-knot motif often result not in Norrie disease but in a clinically distinct entity termed familial exudative vitreoretinopathy (FEVR). FEVR is characterized by avascularity of the peripheral retina, abnormal retinal neovascularization, retinal traction, and detachment.[28] FEVR is actually a genetically diverse disorder, having been also mapped to the *FZD4* and *LRP5* genes, both of which encode for receptors for the *NDP* gene product.[12]

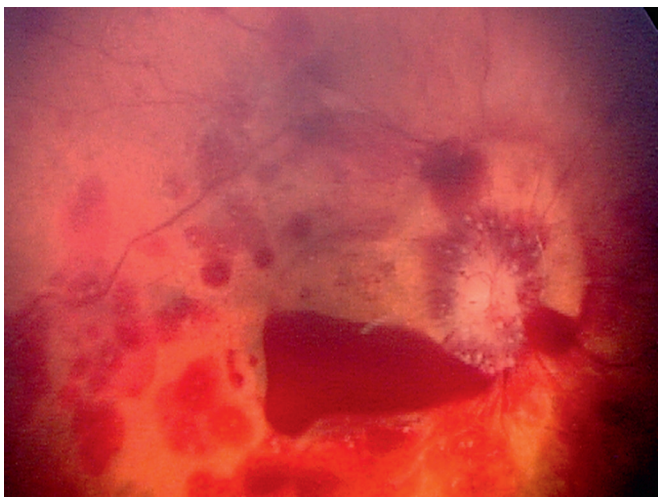
X-Linked Juvenile Retinoschisis

Juvenile X-linked retinoschisis is transmitted as an X-linked recessive trait, occurring almost exclusively in males, and invariably bilateral. It is a progressive, degenerative disorder. Although relatively rare worldwide, it is the most common X chromosome disorder in Finland. Retinoschisis is a splitting of the nerve fiber layer (the most superficial layer of the retina) with ballooning of the inner layer into the vitreus. This splitting creates a veil like appearance in front of the retina. Visual function is absent in the affected tissue. Macular changes and vitreous hemorrhages can occur as associated findings. Both lead to loss of vision. Early diagnosis offers a better chance in improving prognosis. It has no known systemic manifestations.

Retinoschisis can also be seen in trauma, and especially is pathognomonic for shaken baby syndrome when seen with retinal hemorrhages affecting multiple layers of the retina (Fig. 95.23).

Leber Congenital Amaurosis (LCA)

LCA, first described by Theodore Leber in 1869, is an autosomal recessive condition that presents before age 1 year with severely affected vision (majority light perception), nystagmus, and poor papillary reactions. Although retinal examination can be normal, nonrecordable electroretinography (ERG)—a diagnostic test that measures the electrical responses of the photoreceptors to light stimulation—is associated with this condition. Children with this disorder sometimes rub or poke their eyes excessively, called "blindism behavior." Nystagmus usually appears after a few months. LCA that has no other associated systemic manifestations is termed uncomplicated LCA. Today, LCA is recognized as a heterogeneous group of disorders that together are estimated to account for approximately 5% of all retinal dystrophies and approximately 10%-18% of all cases of congenital blindness. To date, seven genes have been implicated in the pathophysiology of LCA and together account for almost 40% of patients presenting with this condition. Ground-breaking gene therapy work has made significant advancement in potential cure of these diseases.[43]



• **Fig. 95.23** Shaken baby syndrome.

Albinism

Albinism refers to the absence or reduction in the amount of melanin in the skin, eye, or both. Diseases featuring albinism are genetically determined and involve defects of melanogenesis. Ocular albinism is X-linked recessive. It is the leading cause of nystagmus in male infants and children. The diagnosis of albinism in the neonatal period is difficult to substantiate, because the uveal pigment is underdeveloped during this period. The diagnosis may be suggested when pigmentation of the skin, hair, and irises fails to progress during the first several months in comparison with that of parents and siblings. Lack of pigmentation is more apparent earlier in darker races. The fundus remains blonde, and choroidal vessels are prominent. Photophobia, nystagmus, and abnormal transillumination of the irides are characteristic features of albinism. Moderately to severely reduced vision is characteristic as a result of foveal hypoplasia and the consequent nystagmus.

Abnormal Macula

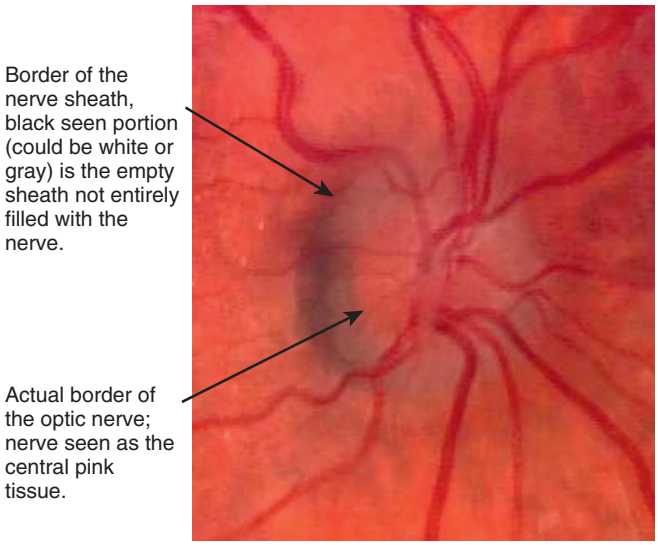
Several of the lysosomal storage diseases alter the appearance of the macula, a fact that may be useful in detecting these disorders (Table 95.4). The stored material accumulates in the ganglion cells of the retina, which decreases the transparency of the retina except at the very center of the macula, where no ganglion cells exist. The center of the macula retains its normal cherry-red appearance, in sharp contrast to the surrounding grayish involved fundus.

Sphingolipidoses that may produce a cherry-red spot are Tay-Sachs disease, in which a cherry-red spot may be present shortly after birth or may develop during the first year, and Niemann-Pick disease (infantile), in which about 50% of patients have a cherry-red spot in the macula during the neonatal period. Of the lipidoses, Farber disease shows a grayish discoloration of the macula at 6-8 weeks of age, and GM1-gangliosidosis demonstrates a cherry-red spot in the macula in about 30% of patients before 2 months of

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TABLE 95.4 Neonatal Macular Changes

Condition	Defect
Tay-Sachs disease	Cherry-red spot
Niemann-Pick disease	Cherry-red spot
GM1 gangliosidosis	Cherry-red spot
Neuraminidase deficiency	Cherry-red spot and corneal clouding
Farber disease	Gray macula
Best vitelliform degeneration	Cystic macula (rare)
Toxoplasmosis	Chorioretinal scar
Coloboma	Absence of retina and choroids



• **Fig. 95.24** Optic nerve hypoplasia: "Double ring sign"; first ring shows the border of the nerve sheath, and the second ring is formed by the actual border of the optic nerve tissue edge.

age. The mucopolysaccharidoses are characterized by the abnormal deposition of mucopolysaccharides in the cornea, but the macula appears normal.

Congenital Disc Anomalies

Optic Nerve Hypoplasia

Optic nerve hypoplasia is the most common congenital disc anomaly and is a common cause of congenital blindness. It can be associated with alcohol and drug abuse of the mother. It may be unilateral or bilateral, and may occur with or without any associated neurologic or ocular abnormalities.[65]

It is an abnormally small optic nerve head that may appear gray or pale because of a decreased number of optic nerve axons with normal glial tissue. A yellowish peripapillary ring of sclera and an outer concentric ring of hyper- or hypopigmentation, known as the "double ring" sign, surround the optic disc. The surrounding large retinal veins are usually tortuous[49,112] (Fig. 95.24).

The diagnosis of optic nerve hypoplasia is based upon small optic discs, decreased or normal vision, and visual field defects with corresponding nerve fiber bundle defects. Visual acuity ranges from 20/20 to no light perception. Localized defects with peripheral constriction are common. Visual acuity is determined mainly by the integrity of the papillomacular bundle and does not correlate with the size of the optic disc.[37,90]

Unilateral or bilateral optic nerve hypoplasia may be associated with central nervous system malformations,[13] especially forebrain malformations and endocrinologic abnormalities,[52] as in septo-optic dysplasia (de Morsier syndrome). Focal thinning or absence of the side of the chiasm corresponding to the hypoplastic optic disc can be seen on magnetic resonance imaging (MRI). In bilateral optic nerve hypoplasia, the optic chiasm is atrophied. The prechiasmatic intracranial optic nerve corresponding to the hypoplastic disc is thinned. The diagnosis of optic nerve hypoplasia may be presumed based upon diminished intracranial optic nerves with other neuroradiologic features of septo-optic dysplasia.[14]

Other CNS malformations associated with optic nerve hypoplasia include abnormalities in the cerebral hemispheres and the pituitary infundibulum.[13,37,49,52,65,90,112] Hemispheric migration abnormalities, such as schizencephaly and cortical heterotopia, and hemispheric injury, such as periventricular leukomalacia and encephalomalacia, may occur in 45% of patients with optic nerve hypoplasia.[52] Fifteen percent of patients with optic nerve hypoplasia may have perinatal injury of the pituitary infundibulum leading to necrosis. This brain abnormality is seen as posterior pituitary ectopia on MRI. This is associated with antidiuretic hormone deficiency. Growth hormone deficiency is most often associated with optic nerve hypoplasia. Hypothyroidism, hypocortisolism, panhypopituitarism, diabetes insipidus, and hyperprolactinemia may also occur.[8] Cerebral hemispheric abnormalities that are often associated with thinning or agenesis of the corpus collosum are predictive of neurodevelopmental defects.[13]

Optic Disc Atrophy

Optic atrophy indicates loss of nerve fiber layers forming the optic disc. Clinically it is subjectively graded on the scale of 1-4 (grade 1 atrophy mild pallor of the disc, grade 4 severe atrophy as the optic nerve appears white), but newer technology such as optical coherence tomography allows to objectively quantify the actual nerve fiber amount and consecutive loss. Causes of childhood optic atrophy are listed in Box 95.5.

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• BOX 95.5 Causes of Childhood Optic Atrophy

Compressive intracranial lesions
Compressive bony disorders
- Craniosynostosis
- Fibrous dysplasia

Hydrocephalus
Post-papilledema optic atrophy
Infectious
Hereditary
- Leber hereditary optic neuropathy
- Dominant optic atrophy (Kjer)
- Recessive optic atrophy
- Behr optic atrophy
- DIDMOAD (diabetes insipidis, diabetes mellitus, optic atrophy, deafness) (Wolfram) optic atrophy

Toxic or nutritional optic neuropathy
Hypoxia
Trauma
Postoptic neuritis
Radiation optic neuropathy
Paraneoplastic syndromes
Neurodegenerative disorders with optic atrophy
- Krabbe disease
- Canavan disease
- Leigh disease
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like (MELAS) episodes
- Neonatal adrenoleukodystrophy
- Metachromic leukodystrophy
- Riley-Day syndrome
- Lactic acidosis
- Spinocerebellar degeneration
- Mucopolysaccharidosis

Ocular disorders
- Glaucoma
- Retinal disease
- Vascular disease
- Uveitis
- Optic nerve hypoplasia

Segmental Optic Nerve Hypoplasia

Superior segmental optic nerve hypoplasia may occur in children of insulin-dependent diabetic mothers. These children have no other systemic anomalies and may be found via incidental inferior visual field defects.[59,90]

Megalopapilla

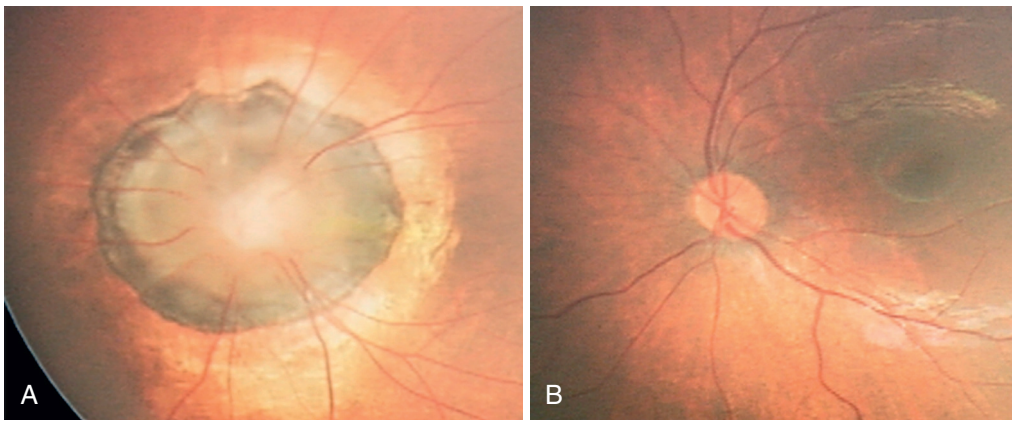
Megalopapilla refers to an enlarged optic disc with no other structural abnormalities. More commonly, it is bilateral. Visual acuity is generally normal. Differential diagnosis should include glaucoma, optic disc coloboma, and orbital optic glioma.[40]

Morning Glory Disc Anomaly

This condition consists of an optic nerve coloboma associated with retinal vascular abnormalities, glial proliferation, metaplasia, and pigment changes around the head of the nerve. The embryologic origin and hereditary factors are unclear. It usually occurs unilaterally in females and rarely in African Americans.[91]

The enlarged optic disc is orange-pink and is located centrally within a funnel-shaped excavation around the nerve head. White glial proliferative tissue lies over the center. Anomalous blood vessels emanate radially from the disc (Figs. 95.25*A, B*). The macula may occasionally be incorporated into the excavation.[91]

Visual acuity is often poor, ranging from 20/200 to a finger counting. The most common complication is retinal detachment, which can lead to further vision loss.[113] Systemically, it can be associated with transphenoidal encephalocele, hypoplasia of the ipsilateral intracranial vasculature, Moyamoya syndrome,[74] and PHACES (*p*osterior fossa malformations, large facial *h*emangioma, *a*rterial anomalies, *c*ardiac anomalies and aortic *c*oarctation; *e*ye anomalies; and *s*ternal abnormalities). MRI and MR angiography should be performed to rule out these conditions.



• Fig. 95.25 A, Morning glory disc anomaly: The defect looks like a fully opened morning glory flower. **B,** Normal appearance of scaled fundus photography.

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Optic Disc and Choroidal Coloboma

Coloboma may occur in one or both eyes with equal frequency. The inheritance pattern may be sporadic or autosomal dominant.[32] It has been linked to a mutation of the *PAX6* gene.

A coloboma of the fundus is visible as a defect in the retinal and choroidal layers through which the underlying sclera is visible (see Fig. 95.21). Leukocoria may result. Typical coloboma occur inferonasally, which is the site of the closure of the embryonic fissure. The fissure usually begins to close at the globe's equator and then extends posteriorly toward the optic disc and anteriorly toward the periphery. Any part or this entire region may be involved in the colobomatous defect. The visual prognosis depends on how much of the macula or optic disc is involved. If the defect extends inferiorly to involve the adjacent retina and choroid, then microphthalmia and iris and ciliary colobomas may form.[32]

Colobomas may be associated with other multisystemic congenital syndromes such as CHARGE, Walker-Warburg syndrome, Goltz focal dermal hypoplasia, Aicardi syndrome, Goldenhar syndrome, and linear sebaceous nevus syndrome.[82] Orbital cysts may also be rarely seen with optic disc colobomas.[97] Table 95.5 lists systemic abnormalities that may be associated with optic disc changes.

In CHARGE syndrome, at least three of the following features must be present for the condition: heart defect, choanal atresia, restricted growth, genital anomalies, and ear anomalies or deafness.

TABLE 95.5 Systemic Abnormalities That May Be Associated With Optic Disc Changes

With CNS Abnormalities

Dandy Walker cyst
Arhinencephaly
Anencephaly
Agenesis of corpus callosum
Sphenoidal encephalocele

With Chromosomal Abnormalities

Trisomy 13 (Patau syndrome)
Trisomy 18 (Edward syndrome)

With Congenital Syndromes

Meckel-Gruber syndrome (autosomal recessive)
Goltz syndrome (X-linked dominant)
Lenz microphthalmia syndrome (X-linked recessive)

CHARGE Association: With at Least Three of the Following Features

Coloboma
Heart defects
Atresia of the choanae
Retardation of growth and development
Genital hypoplasia
Ear abnormalities and/or hearing loss

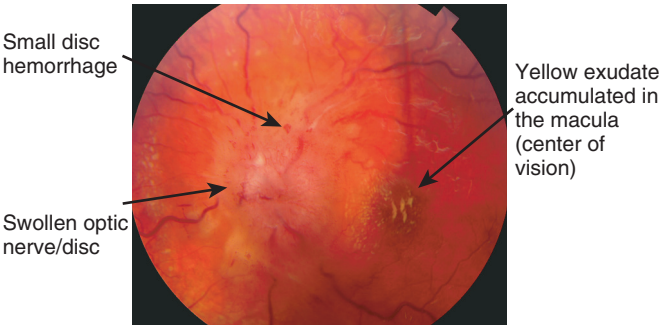
Optic Disc Pit

Optic disc pit is a congenital oval or round depression in the optic nerve head. Its incidence is 1 in 11,000, and it usually occurs sporadically. Most occur unilaterally. In unilateral cases, the affected disc is slightly larger than the normal one. Optic pits may appear gray, white, or yellowish. They average about 0.3 disc-diameters in width and are often located temporally. Visual acuity is usually normal, but approximately 50% of patients with optic disc pits have visual field defects. This condition may lead to retinal detachment and macular edema or hole.[16,38]

Optic Disc Drusen

Drusen are an accumulation of substances (calcium, mucopolysaccarides, amino acid, ribonucleic acids, deoxyribonucleic acid, and iron)[101] buried within the optic disc, causing disc elevation. It is important to distinguish this relatively common (3.4-24/1000 population) condition from other causes of disc elevation, primarily papilledema (Fig. 95.26). The vast majority is seen bilaterally. It is inherited as an irregularly autosomal dominant disorder. Most are asymptomatic. Although very rare, significant visual field defects and visual acuity decrease may be seen.[10] These changes are generally slowly progressive.

The accumulated substances can be buried in the disc (the most common appearance in newborns), or may be visible when they are superficial. Therefore, direct visualization could be diagnostic, but when in doubt, B-scan ultrasonography is the most reliable method to detect the calcium in the drusen. Although visual evoked potential (VEP) is also abnormal in 41%-97% of patients, it is not a reliable diagnostic modality for drusen.[63] Treatment is often not needed, but monitoring for elevated intraocular pressure and vascular complications along with other possible associated disorders (retinitis pigmentosa, pseudoxanthoma elasticum)[20] is recommended.



• **Fig. 95.26** Papilledema: Left optic nerve significantly swollen with no visible distinct disc margins, tortuous veins, macular exudate accumulation, and small hemorrhages at disc margins.

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Hyaloid System Remnants

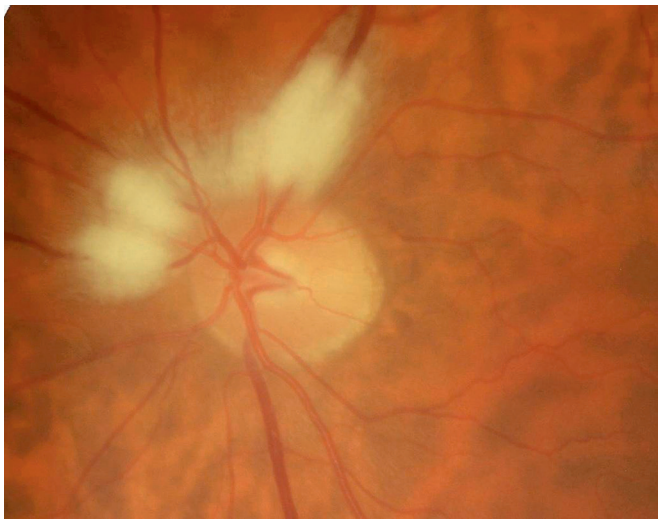
The hyaloid vascular system and the glial sheath of Bergmeister should normally atrophy spontaneously by the end of the gestation. The embryonic vitreous system develops as a complex network of vessels that grows anteriorly from the disc to surround the developing lens and normally involutes during the third trimester. The persistence and proliferation of these normally transient vessels of the primary vitreus, especially the posterior tunica vasculosa lentis (vascular remnant behind the lens), leads to the formation of persistent hyperplastic primary vitreus (PHPV), also known as primary fetal vasculature (PFV). PFV causes a white pupillary reflex that must be distinguished from retinoblastoma. Disc abnormalities are determined by the extent of persistence of glial and/or vascular components.

At birth, PFV may appear as a strand or plaque of white tissue immediately behind a clear lens. Vessels are frequently seen to radiate from the plaque's center, and the retrolental mass may, therefore, be pinkish white. When the pupil is dilated, the ciliary processes are often drawn centrally along the posterior surface of the lens toward the central mass. Almost always unilateral, PFV occurs in term infants without a history of oxygen therapy. The involved eye is commonly microphthalmic. PFV should be suspected in the neonate with a rapidly progressive unilateral cataract. Differentiation of PFV from ROP is usually possible because of the unilateral involvement and occurrence of PFV in a term infant. Differentiation from retinoblastoma is important. The absence of calcification within the eye, as occurs in retinoblastoma, is a critical finding. A persistent embryonic iris vessel or one that notches the pupil suggests the presence of PFV, even when an opaque lens obscures its presence. Ophthalmic ultrasonography can help in the diagnosis of difficult cases. Surgical removal of the lens and vitreous with optical correction and amblyopia treatment must be attempted very early to achieve any degree of success in recovering vision.

Myelinated Nerve Fibers

During fetal development at 5 months' gestation, myelination progresses from the lateral geniculate body to the optic tracts, then the optic chiasm, and last to the optic nerve by 8 months of gestation.[72] Anomalous myelinated nerve fibers occur when myelination extends beyond the posterior portion and into the disc and peripapillary areas. The myelinated areas have a whitish, feathery appearance and are usually continuous with the disc at the upper or lower poles (Fig. 95.27). The process may progress after birth but does not usually extend into the macula. Visual acuity is not affected.

In the general population, it is seen at a frequency of 0.3%-1%.[72] It is inherited as an autosomal dominant disorder and occurs unilaterally in 80% of patients.[72] It may be associated with systemic disorders such Gorlin syndrome[25] (multiple basal cell nevi), which is an autosomal dominant disorder that may present in children with cutaneous lesions (small pits in the hands and feet, jaw cysts, and other bony abnormalities).



• **Fig. 95.27** Myelinated nerve fiber layer: Just above and nasal to the optic nerve head, the white, feathery appearance of the myelinated nerve fibers is seen. These myelinations will be above the vessels. These are benign findings and rarely progress.

Intraocular Tumors

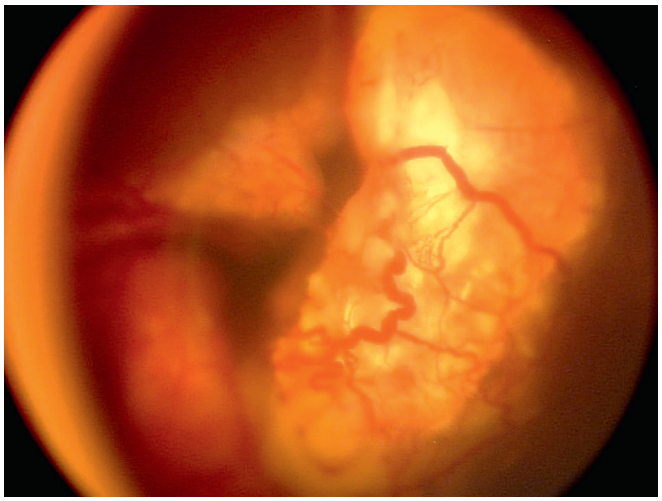
Retinoblastoma

Retinoblastoma is the most frequent malignant intraocular tumor in the pediatric population, including neonates. The tumor arises sporadically or may be hereditary. Retinoblastoma occurs in about 1 in 15,000-18,000 live births, with no predilection for sex. The predilection for race is yet to be defined. Up to 30% of cases are bilateral. Bilateral cases are transmitted in an autosomal dominant manner with incomplete penetrance. Only 10%-15% of unilateral cases are hereditary. The average age of presentation in bilateral cases is about 10 months, and 21 months in unilateral cases.[103] About 75% of cases of retinoblastoma include calcium deposits, which can be detected with B-scan ultrasonography and computerized tomography. Magnetic resonance imaging of the brain may detect a pinealoblastoma[46] (trilateral disease).

In the United States, clinical presentation is leukocoria in 60% or strabismus in 20% with other presentations (red eye, glaucoma, and screening by pediatrician or ophthalmologist) in the minority (Fig. 95.28). Leukocoria is detected more often by a parent or family member (80%) than a medical professional despite the routine screening with red reflex.[124] The eye with leukocoria has relatively advanced disease. Screening the red reflex after dilation might be a way to detect retinoblastoma in an early stage with improved visual prognosis and ocular survival.

The genetic basis for retinoblastoma has been widely studied. The gene, located on the q14 band of chromosome

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• **Fig. 95.28** Retinoblastoma: White calcific retinoblastoma filling the eye, the retinal vessels seen over the lesion; the retina has detached completely secondary to the tumor.

13, is a tumor suppressor gene. Mutation or inactivation of both alleles in a vulnerable retina cell results in transformation of the cell into retinoblastoma.[21] The tumor originates in the retina and grows anteriorly into the vitreous or posteriorly into the choroid. If the tumor disrupts vision, a sensory strabismus may result. Hence, all infants with strabismus require a fundus examination with dilated pupils to exclude retinoblastoma. With further enlargement, the tumor produces secondary glaucoma, which may be associated with pain and photophobia or symptoms identical to those of congenital glaucoma. With extension into the anterior chamber, an opaque layer of leukocytes (pseudohypopyon) or spontaneous bleeding (hyphema) can occur. With exophytic growth, retinal detachment can be the presenting sign. Proptosis is a late finding. Massive necrosis of the tumor can cause a picture mistaken for orbital cellulitis. Hence, a fundus examination should be part of any work-up of orbital cellulitis. The diagnosis of retinoblastoma is made noninvasively by exam under anesthesia with ophthalmoscopy, orbital ultrasound, and fluorescein angiography. Calcification identified within the eye on CT scan, ultrasound, and MRI findings helps to confirm the diagnosis.[103] The differential diagnosis may be exceedingly difficult if the tumor is advanced or atypical, and enucleation may be required for histologic study and positive identification. Other lesions that rarely can simulate retinoblastoma in neonates are coloboma of the fundus, congenital retinal fold, retinal dysplasia, persistent hyperplastic primary vitreous, retinoschisis, retinal detachment, organized vitreous hemorrhage, or scarring from ROP.

The treatment of retinoblastoma is determined by its size and location. Treatment of retinoblastoma involves a team approach between pediatric oncologists, radiologists, and ophthalmologists. The most significant factor in the prognosis is the stage of disease when treatment is instituted. When retinoblastoma is limited to the eye, 98% of patients can expect a 5-year, disease-free survival.[2] If the retinoblastoma remains in the optic nerve anterior to the lamina scleralis, the prognosis is good. Hematogenous spread to the bone and liver,[80] along with direct spread to the brain, indicates very poor prognosis.

Local treatment modalities for early, small tumors include photocoagulation, plaque radiotherapy, trans-pupillary thermotherapy, and cryotherapy. For more advanced tumors, primary systemic chemotherapy is followed by local consolidation with the same treatment modalities as above (photocoagulation, etc.). Enucleation continues to be a treatment modality that is often used in unilateral advanced retinoblastoma in order to avoid chemotherapy. Selective intra-arterial chemotherapy is also being investigated as an enucleation-sparing procedure.[1,102] With extension beyond the globe, the cure rate is reduced. Chemotherapy is used in this case to prevent metastatic disease. Patients with the familial form of retinoblastoma also are at risk for developing secondary malignancies.[80] The most common secondary malignancy is osteogenic sarcoma, usually occurring in the teen years. Pinealoblastoma forms the third part of what is called trilateral retinoblastoma. This malignancy usually occurs during the first 4 years of life.

Astrocytic Hamartoma

Astrocytic hamartoma can be found infiltrating the optic nerve or in the retina. They occur bilaterally in 50% of patients with tuberous sclerosis complex.[64] The most common type appears as a smooth, flat, salmon-colored lesion that is either round or oval shaped. It is semitransparent and located in the superficial posterior pole of the retina. Astrocytic hamartomas consist of astrocyets, calcium, and amorphous material. They may demonstrate auto-fluorescence in angiography. Visual function is often normal unless the optic disc or the macula is affected. As they typically do not grow or affect vision, treatment is not needed. It may be an isolated phenomenon in 30% of cases. Calcified hamartomas may be seen in the basal ganglia and ventricles on MRI. Larger tubers may be seen in the cortical gray matter. The diagnosis of tuberous sclerosis is based on clinical criteria and can be confirmed with molecular gene testing for chromosome 9q34 and chromosome 16p13.[96] Astrocytic hamartomas can also be associated with neurofibromatosis type 1.[94]

Racemose Hemangioma

Racemose hemangiomas are rare arteriovenous anastomoses consisting of engorged retinal vessels entering the optic disc, then into the peripheral retina, and finally out of the optic disc. They are thought to be congenital abnormalities, but remodeling may occur over the years.[5] About one-third are associated with Wyburn-Mason syndrome (arteriovenous malformations in the midbrain that are ipsilateral to a separate retinal lesion). Growth into the orbit can cause diplopia, proptosis that is usually nonpulsatile, orbital bruit, and conjunctival vascular dilatation[128]. They are usually stable.

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• **Fig. 95.29** Exotropia. The patient is fixing with the left eye while the right eye is drifting outward. It can also be easily identified via the corneal reflex, which is seen in the center of the pupil in the left eye while also seen in the nasal aspect of the iris in the right eye.

Neuromuscular Abnormalities

Strabismus

Strabismus or misalignment of the eyes is approached based on etiology.[51,126] Horizontal deviations are the most frequent type of strabismus and can be further classified in esodeviations, eye deviated inward, and exodeviations (Fig. 95.29), eye deviated outward. Vertical deviations are rare in infancy similar to other stages of life. Both horizontal and vertical deviations could be comitant or incomitant. Comitant strabismus has the same amount of deviation in all gazes. In infancy, infantile exotropia and early intermittent exotropia are the most frequent types of comitant exodeviation. Congenital/infantile esotropia, early accommodative esotropia, esotropia associated with neurologic conditions or prematurity, and sensory esotropia are frequent forms of comitant esodeviation in infancy. Accommodative esotropia is secondary to exaggerated accommodative efforts in significant hyperopia or with vision directed at a near target. Sensory strabismus can occur because the oculomotor system requires a certain level of vision in both eyes to maintain ocular alignment. If vision is lost in one or both eyes, an ocular misalignment may follow. Unilateral vision loss results more often in esodeviation, unlike older ages when it results more in exodeviation. It is paramount, therefore, to visualize macula in evaluation of esotropia in infants. Retinoblastoma can manifest with sensory esotropia.

Incomitant deviations are variable on various gaze positions and result from impairment of the globe movements secondary to muscular restrictions or muscular weaknesses. Fractures with entrapment of muscles or orbital tumors can cause restrictive strabismus. Cranial nerve palsies and congenital myasthenia gravis are the main causes for nonrestrictive incomitant strabismus in infants. In 4th cranial nerve palsy, compensatory head position to the opposite side along with incomitant vertical strabismus can be noticed as early as a few months of life. This condition needs to be differentiated from more common muscular torticollis, as strabismus surgery done in timely fashion is the correct treatment in 4th cranial nerve palsy and resolves compensatory head tilt. Other forms of incomitant strabismus—alphabet patterns, Duane syndrome, or Brown syndrome—are likely present at this age group but hard to diagnose given the low degree of cooperation.

To further complicate the evaluation of strabismus in infancy, there are two conditions that can be confused with true strabismus. Early in infancy, there could be small angle misalignments of variable magnitude before the establishment of firm foveal fixation. This condition resolves with development of foveal fixation and binocularity and establishment of firm control of the eye movements; this type of misalignment leaves no long-term consequences. Another condition is pseudostrabismus that can present in two types: pseudoesotropia and pseudoexotropia. In pseudoesotropia, the large nasal bridge, prominent epicanthal folds, or other configurations of face in the infant can create an appearance of inward deviation of one or both eyes. Symmetric red reflexes and corneal light reflexes with no eye shift at the cover–uncover test differentiate pseudoesotropia from true esotropia. It is important to remember that epicanthal folds may exist with true esotropia, and if there is an intermittent esotropia, the eye may be straight on one examination. Infants with severe ROP causing a dragging of the macula may appear to have strabismus when the dystopic maculae are aligned. Again, there is no shift with cover–uncover tests.

Treatment of strabismus is done by pediatric ophthalmologist specialist after a complete eye examination, including careful cycloplegic refraction and dilated fundus exam. Surgery is the main treatment in infantile esotropia and is performed after correction of significant refractive errors and treatment of associated amblyopia. This approach maximizes the chance of stable surgical alignments of the eye. Surgery should be undertaken early to increase chance of binocular cooperation (between 4 and 6 months in healthy infants).

Nystagmus

Nystagmus consists of rhythmic oscillations of the eyes. Nystagmus can be unilateral or bilateral; it can be horizontal, vertical, torsional, or a combination of the above. Jerk nystagmus has one direction faster; pendular nystagmus has both directions of equal speed. Nystagmus is said to be infantile (infantile nystagmus syndrome, INS) if onset is before 6 months of age and acquired after that. Documenting the direction (horizontal, vertical, and torsional), frequency (mild, moderate, or fast), amplitude (small, moderate, or large), laterality (one or both eyes), associated head positioning is useful to help guide the possible underlying cause of the nystagmus. In infancy, nystagmus can be divided into nystagmus secondary to poor vision, nystagmus associated with neurologic anomalies, and various types of congenital/infantile nystagmus. Optic nerve atrophy, hypoplasia, or severe optic nerve anomalies along with early-onset retinal dystrophies or macular scars are the main causes for nystagmus associated with poor

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vision in infancy and generally pendular type nystagmus is seen with these conditions. Electroretinography or brain imaging using MRI are required for further characterization of these conditions. Brain imaging is also necessary in nystagmus associated with neurologic findings. Infantile nystagmus syndrome (INS) is diagnosed based on clinical characteristics, seemingly unaffected vision, and absence of other neurologic signs. No brain imaging is necessary if diagnosis of INS is established. However, in spasmus nutans (triad of unilateral nystagmus, head nodding, and torticollis) brain imaging is mandatory. Fine and rapid, asymmetric nystagmus seen in spasmus nutans can resemble nystagmus seen in chiasmal glioma. Hence, the benign nature of spasmus nutans can be demonstrated only retrospectively after disappearance (usually within 2 years).[17]

Opsoclonus

Opsoclonus is a striking ocular motility disorder characterized by involuntary, chaotic bursts of multidirectional, high-amplitude saccades without an inter-saccadic interval. When the oscillations are clinically horizontal, they are termed ocular flutter. Hoyt et al. have reported that opsoclonus may occur as a transient phenomenon in healthy neonates.[50] In this case, this phenomenon disappears by 6 months of age.

The major diagnostic consideration for opsoclonus in the first several years of life is a neural crest tumor such as neuroblastoma. Neuroblastoma is found in approximately half of cases with opsoclonus in this age range.[117] Opsoclonus also occurs commonly as a part of a "benign" encephalitis (Kinsbourne myoclonic encephalopathy, dancing eyes, and dancing feet).[62]

Amblyopia

Amblyopia represents an uncorrectable-with-glasses decrease in vision in one or both eyes with no apparent structural abnormality of the eye to explain it. It is a consequence of various organic processes that interfere with development of vision during a critical young age. Amblyopia can develop at any time during the "sensitive period" of visual development, usually during the first 7 years in humans, and can be treated if discovered within this same time frame of plasticity. When a diagnosis of amblyopia is made, other organic causes need to be excluded. Even if organic causes are present, the amblyopia might still be partially responsive for the decrease in vision and is important to treat in a timely manner for a better success rate. The main causes are strabismus, refraction, occlusion, and visual deprivation.

Strabismic amblyopia occurs in children who first develop strabismus and then favor one eye. The constantly deviated eye will then develop amblyopia; hence, strabismic amblyopia is always unilateral. Refractive amblyopia results from large refractive errors that create significant blurry vision. This can be a bilateral or unilateral process.

Deprivation amblyopia is caused by opacities in the visual axes, such as cataracts or corneal scars or macular and optic nerve conditions. If the visual obstruction is not cleared by 3 or 4 months of age, the amblyopia becomes very dense and unresponsive to treatment—hence the urgency to identify and treat congenital cataracts.

Treatment of underlying causes of amblyopia is important for the success of therapy. Various methods of visual penalization are applied to the good-seeing eye in the treatment of monocular amblyopia. Patching is the oldest and most often used method in all forms of monocular amblyopia. Atropine daily can be used as first-line therapy in monocular moderate amblyopia or as a second line in patch failure. Other methods of penalization are described and available. If bilateral amblyopia is present because of high refractive error, glasses are prescribed.

The Blind Infant

The definitions of blindness that are used in literate children (legal blindness: Snellen visual acuity less than 20/200 or visual field less than 20 degrees) are not applicable to infants. Also, vision in this age is normally very low and changing rapidly. The majority of tests used to estimate vision in infants give, at the most, 20/400 vision at birth and vision less than 20/40 by 1 year of age. For these reasons, a more appropriate term at this age is apparent blindness. This is suggested by history and examination clues: absence of any light reaction including no pupillary reaction, absent eye movements, nystagmus early in life, searching eye movements, oculodigital sign, paradoxical pupillary reaction (dilation with light), staring at bright lights, and waving of hands between the eyes and a light source. Important medical history details include history of prematurity, perinatal hypoxia, and family history of blindness at young age. Three major causes for blindness at this young age are: obvious eye malformations, anterior visual pathways disease (retina, optic nerve, chiasm) that can be subtle, and cerebral visual impairment. An external abnormal eye is occasionally a quick diagnosis when microphthalmos, bilateral white cataract, corneal opacities, advanced ROP, persistent fetal vasculature, or retinoblastoma are present. For the subtler cases of anterior visual pathway disease versus cerebral visual impairment, nystagmus can be the distinguishing factor, as it is normally present in the former and absent in the latter. Optic nerve conditions require further MRI of the brain to characterize. Nystagmus and no optic nerve pathology indicate electroretinogram (ERG) to demonstrate the presence of retinal dystrophy. The possibility of cerebral visual impairment suggested by normal structure of the eye and no nystagmus can be confirmed with normal vestibulo-ocular response (VOR) with prolonged "after" nystagmus. History of prematurity in this scenario suggests a form of cerebral visual impairment, namely periventricular leukomalacia that can be confirmed with MRI of the brain. Absence of VOR and nystagmus suggests the presence of congenital motor apraxia, bilateral Duane syndrome, or Möbius syndrome,

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when the baby cannot move the eye but vision may still be good. Likewise, after a generalized seizure, the movements of the eye or reaction to visual stimuli can be suppressed and simulate blindness with recovery after the postictal period.[15]

Eye Findings in Chromosomal Syndromes

Chromosomal anomalies involve significant alteration of genetic materials with multiple genes being affected simultaneously. However, genes that control the development and function of the eye are spread on multiple chromosomes. Therefore, it is not surprising that the majority of chromosomal anomalies involve the eye in some form. Following is a selection of eye features that are important, given the frequency or severity.

Trisomy 21

Ocular findings associated with Down syndrome are extensive. Because of this, children with Down syndrome should be examined by an ophthalmologist during infancy and periodically after that. From front to back, the eye findings are as follows: significant refractive errors, amblyopia, nystagmus, strabismus, nasolacrimal duct obstruction, epicanthus, telecanthus, upward slant of palpebral fissures, blepharitis, keratoconus, glaucoma, iris nodules (Brushfield spots), cataract, and optic nerve swelling. Caution should be exercised when using dilating drops in these children, as they can have an exaggerated systemic reaction to atropine, and atlanto-axial instability can induce a risk in case of neck hyperextension.

Trisomy 13

Ocular findings are present in 90% of Patau syndrome subjects.[105] Intraocular cartilage found at histopathology is virtually pathognomonic for trisomy 13.[56] Typical inferonasal iris coloboma with sectoral cataract in the same location is highly suggestive of this syndrome. Other eye features in this syndrome are microphthalmia, cyclopia, short/slanted palpebral fissures, ptosis, hypertelorism, corneal opacities, luxation of the lens, coloboma of the lens, persistent tunica vasculosalentis, persistent fetal vasculature (formerly known as persistent hyperplastic primary vitreous), typical coloboma of the choroid, and retinal dysplasia.[56,105]

Trisomy 18

The most common eye anomalies in Edwards syndrome include epicanthus, hypertelorism, and hypoplastic supraorbital ridges. Ankyloblepharon filiforme adnatum (strands joining the upper and lower lids together) is very suggestive of trisomy 18. Less frequently, strabismus, cyclopia, colobomatous microphthalmia, microcornea, corneal opacities, congenital glaucoma, posterior subcapsular cataract, and retinal depigmentation are present in this syndrome.

11p Abnormalities

Infants with a deletion of the short arm of chromosome 11 involving the *PAX6* gene and the adjacent *WT1* gene on the 11p13 band have the WAGR syndrome of aniridia, genito-urinary abnormalities, and mental retardation.[31] Wilms tumor has been diagnosed in a significant percentage of children with this chromosomal deletion and must be evaluated with periodic ultrasounds of the abdomen for a number of years.

13q Abnormalities

The most important possible finding that requires a comprehensive retinal examination is retinoblastoma. The retinoblastoma gene is a tumor suppressor gene that is lost in 13q deletion. That creates a situation when cells throughout the body have only one copy of the tumor suppressor gene and are vulnerable to lose that copy and start developing tumors, among them retinoblastoma, which tends to be bilateral and start at a young age. Other ocular abnormalities are almost always present and severe, including microphthalmia, iris and choroidal colobomas, ptosis, cataracts, and down-slanting palpebral apertures and epicanthus.

Turner Syndrome

Strabismus, ptosis, congenital cataracts, and occasionally corneal nebulae and blue sclerae in the neonatal period have been described as being associated with Turner syndrome.

Eye Findings in Craniofacial Syndromes

Eye abnormalities can be associated with congenital anomalies of the face, skull, or head in both craniosynostotic and nonsynostotic forms.

Craniosynostosis Syndromes

There is well-defined eye involvement in craniosynostosis syndromes that requires careful follow-up and management. Proptosis is secondary to maldeveloped, small orbits and can further be complicated by lagophthalmos, exposure keratopathy, or globe subluxation. Globe subluxation, when the globe protrudes anteriorly to the eyelids, is an ocular emergency that needs to be treated by the caregiver or medical personnel immediately in order to avoid optic nerve ischemic damage with permanent vision loss. One approach for globe subluxation is to place a finger on the visible conjunctiva in the interpalpebral area and apply firm pressure until the globe is behind the eyelids. This approach avoids damage of the cornea. Lagophthalmos with exposure keratopathy and possible corneal scar is another cause of vision loss requiring an aggressive approach consisting of frequent lubrication, moist chamber, taping the eyelids

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closed at night, and tarsorrhaphy. The definitive treatment of lagophthalmos is orbital expansion. The optic nerve can develop edema or atrophy. Edema is secondary to increased intracranial pressure, secondary to difficult expansion of the cranium, and less often due to compressive optic neuropathy in a tight optic canal. Optic atrophy is the end result of longstanding optic nerve edema. Strabismus is a common occurrence in craniosynostosis with V pattern exotropia and inferior oblique overaction seen as characteristic types.

Because of comparable cranial and orbital anomalies, eye findings can be similar in the other craniosynostosis syndromes such as Crouzon syndrome, Apert syndrome,[58] Saethre-Chotzen syndrome, and Pfeiffer syndrome.

Hemifacial Microsomia

Ocular manifestations can range from clinical anophthalmia to minor fissure asymmetry. Goldenhar syndrome is probably a variant of this group, with characteristic limbal dermoids and orbital lipodermoids. Limbal dermoids are reported more frequently than lipodermoids and are occasionally bilateral. Another common finding is an upper eyelid coloboma, almost always on the more affected side. Less frequent findings are Duane syndrome and microphthalmia.[114]

Terminal Transverse Defects With Orofacial Malformations and Oromandibular-Limb Hypogenesis

These are a heterogeneous collection of syndromes with a wide variety of facial and limb anomalies; they include Möbius syndrome. The minimal findings of this syndrome are abduction weakness (cranial nerve 6 palsy) and facial nerve palsy, with frequent limb and tongue anomalies.

Pierre Robin Sequence

The Pierre Robin sequence is characterized by micrognathia, glossoptosis, and cleft palate. Pierre Robin sequence can occur in isolation or be part of a syndrome. About 10% of patients with Pierre Robin sequence have Stickler syndrome as well, with the additional features of high myopia, propensity for retinal detachment, cataracts, deafness, and arthritis.[30]

Waardenburg Syndrome

Waardenburg syndrome is transmitted as an autosomal dominant trait and has been divided into four types based on clinical attributes. The most common is Waardenburg syndrome type 1. It is associated with lateral displacement of the medial canthi (i.e., telecanthus), abnormal position of the lacrimal puncta, coalescing of eyebrows (i.e., synophrys), white forelock, heterochromia irides, retinal pigmentary changes, and sensorineural deafness.

Cornelia de Lange Syndrome

The typical facial appearance in infants with Cornelia de Lange syndrome is a low hairline, synophrys, long eyelashes, and a small upturned nose. Eye disorders, which are less frequently encountered, include hypertelorism and downslanting palpebral fissures, dacryostenosis, strabismus, nystagmus, ptosis, severe myopia, and pupillary abnormalities.[83]

CHARGE Association

This heterogeneous group of anomalies (colobomas, heart defects, choanal atresia, restricted growth, genital hypoplasia, and ear malformations) presents with typical coloboma of the optic nerve, choroid, or iris in the inferior nasal direction. Other eye involvements have been described: microphthalmia, refractive errors, and vertical strabismus.[76]

Deformation Syndromes

Congenital deformations resulting from intrauterine restraints are common and may involve craniofacial structures. Congenital torticollis is one of the deformation syndromes that can have ophthalmic implications, as it may be confused with superior oblique palsy with compensatory head posture.[15]

Eye Findings in Neurocutaneous Disorders (Phakomatoses)

Eye findings are important manifestations in phakomatoses, which are a group of disorders featuring discrete hamartomas in multiple organ systems including the skin and the brain. Four disorders have been designated as classic phakomatoses with other conditions sometime included as well. From the four classic phakomatoses—neurofibromatosis, tuberous sclerosis, encephalotrigeminal angiomatosis, and retinal angiomatosis—only the first three are active in infancy or early childhood.

Neurofibromatosis

Neurofibromatosis (NF) is described in two types. Both NF type 1 and 2 are autosomal dominant genetic conditions with high penetrance and high spontaneous mutation rates. NF1 (von Recklinghausen disease) is characterized by melanocytic and glial cell lesions distributed in the brain, skin, and eye. The occurrence of these lesions is highly age dependent with some features present early in life with stabilization or regression while other features start late with subsequent progression throughout life. Overall NF1 is rarely diagnosed in neonates. Early ophthalmic manifestations of NF1 are plexiform neurofibroma of the upper eyelid, glaucoma, optic nerve glioma, and sphenoid

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dysplasia. Neuroimaging should be obtained in patients with ocular pulsations, neurofibromas of the eyelid, afferent pupillary defect, or optic nerve swelling. Plexiform neurofibroma in the area suggests a 50% risk for glaucoma. Progressive enlargement of the globe or buphthalmos is seen if glaucoma with high intraocular pressure is present before 2 years of life. Optic nerve glioma, although rare with a rate of up to 5%, is an important cause of morbidity and mortality in NF1. Iris Lisch nodules that are often sought to help in early diagnosis are rarely seen in infant and in only a 25% minority by 2 years with presence in 90% by puberty.[86] Despite this, Lisch nodules are valuable features as they have a tendency to be present before the hallmark lesion of NF1, nodular neurofibromas of the skin. NF2 is less common than NF1 and has the hallmark lesion of bilateral eighth nerve tumors, hence the name of central NF. Early-onset posterior subcapsular or wedge-shape cataracts have been described in NF2.

Encephalofacial Angiomatosis (Sturge-Weber Syndrome)

As the name implies, this condition encompasses angiomas of the facial skin with ipsilateral leptomeningeal vascular malformation. There is no apparent hereditary pattern. Ocular complications of Sturge-Weber syndrome include glaucoma and chorioretinal angioma. Glaucoma can present in two types, one of them resembling congenital glaucoma with enlargement of the globe, high myopia, and amblyopia. The associated choroidal angioma is usually indistinct and difficult to visualize without indirect ophthalmoscopy. If present, it may lead to macular edema and decreased visual acuity.

Tuberous Sclerosis (Bourneville Disease)

Hamartomas of the brain that cause seizures and mental retardation associated with hamartomas in the eyes, kidney, heart, lungs, and skin are the hallmarks of this autosomal condition. The spontaneous rate of mutation is very high, similar to that with NF. Retinal lesions, called astrocytic hamartomas (or phakomas) have one of two distinct appearances. Phakoma type 1 is seen at very young age and has the appearance of gray-white nodules with smooth, flat surface and indistinct borders. Consequently, these lesions are difficult to visualize and special techniques are employed on indirect ophthalmoscopy in order to avoid missing the early lesions.

Ocular Trauma

Two types of eye trauma are seen only in this age group: birth trauma and shaken baby syndrome. Regular contusions and lacerations happen at this age also but with decreased frequency compared with late ages owing to decreased mobility in infants.

Birth Trauma

Birth trauma to the eyes is associated with the duration of labor and difficulty of delivery.[92] Lid petechiae and hemorrhages, observed more often with face presentations than with vertex presentations, usually resolve rapidly without treatment. Subconjunctival hemorrhages are also common and require no treatment. Such findings, however, should increase the suspicion of associated intraocular injuries.

Retinal hemorrhages are common after delivery, occurring in 78% of newborns after vacuum delivery, 30% after normal vaginal delivery or with forceps assists, and only 8% after cesarean delivery.[53] These retinal hemorrhages are usually small, multiple, and scattered throughout the retina; they may persist for months and must be considered in the differential diagnosis of suspected nonaccidental trauma (shaken baby syndrome).[53] Bleeding into the orbital contents (retrobulbar hemorrhage) can result from birth trauma. This bleeding produces a unilateral proptosis that tends to increase gradually in size during the first 3 or 4 hours after birth. Ecchymosis of the lids can be associated findings immediately or 1-2 days later. The differential diagnosis includes dermoid cysts, teratomas, and other congenital tumors of the orbit. The hematoma usually absorbs spontaneously over 1-2 weeks. It is important during this time to ensure that the cornea is not dry from exposure or abraded and that the retinal circulation is not compromised. A detailed fundoscopic exam is indicated, and if it shows impairment of arterial or venous circulation, immediate surgical decompression of the orbit is required. Forceps deliveries, particularly when associated with improper application, can produce bruises and lacerations of the lid or globe.[48] A forceps mark or lid laceration requires a careful and complete examination of the orbit and globe for associated injuries.[75] Forceps application can produce a rupture in the cornea's endothelial basement membrane (Descemet membrane). Seen with magnification, these ruptures appear as vertical lines in the posterior portion of the cornea. They can lead to rapid corneal edema (hydrops) due to compromised water pump mechanism of the endothelium, with a cloudy appearance that must be differentiated from other congenital corneal opacities. Children with Descemet membrane ruptures can develop astigmatism and dense amblyopia. Traumatic forceps delivery has been known to cause a variety of other ocular injuries, including Purtscher retinopathy, choroid ruptures, and traumatic optic neuropathy.[57] Ocular injury in the newborn has also been reported as a result of fetal monitors,[66,79] surgical instruments,[110] phototherapy lights,[88] prenatal maternal injury, and amniocentesis.[85]

Shaken Baby Syndrome

Forceful, repeated back and forth movement of the head can result in devastating and blinding ocular injuries. Characteristic hemorrhages involve preretinal, intraretinal, and

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subretinal spaces; are numerous; and extend in the far periphery of the fundus.

Dome-shaped hemorrhagic lesions with white borders represent hemorrhagic retinoschisis and when associated with characteristic hemorrhages are said to be diagnostic of shaken baby syndrome. The retina can even be folded in a circumferential manner along the vascular arcades surrounding the macula, another finding highly suggestive of shaken baby syndrome. Retinal hemorrhages may resolve without sequelae, but involvement of the optic nerve, macula, or occipital cortex can produce profound lifelong visual loss.[60] The extent and type of retinal hemorrhages that occur in shaken baby syndrome can be pathognomonic of the syndrome and may support the legal prosecution of the offender[116] (see Fig. 95.23). Accidental head trauma and cardiopulmonary resuscitation in infants do not result in the type and extent of retinal hemorrhage seen in shaken baby syndrome.[87,115]

Neonatal Ocular Infections

Neonatal Conjunctivitis (Ophthalmia Neonatorum)

Neonatal conjunctivitis represents inflammation or infection of the conjunctiva in the neonatal period. What makes an otherwise benign condition a public health concern requiring prophylaxis at birth in all neonates is the possibility of long-term vision loss and systemic associated conditions. Neonatal conjunctivitis is the most common infection in the first month of life with incidence from 1%-24%.[33] The four categories of neonatal conjunctivitis are chemical, bacterial, chlamydial, and viral. Conjunctival injection, chemosis, discharge, and eyelid edema can occur with all subtypes of neonatal conjunctivitis. Clinical history, most importantly prenatal history, and clinical elements such as character of the discharge, presence of chemosis and membranes, or skin vesicles can suggest the specific etiology and direct laboratory testing.

Chemical conjunctivitis occurs 1-2 days after instillation of silver nitrate 1% or other antibiotics for prophylaxis at birth. Typical chemical conjunctivitis is bilateral and has a low amount of purulence; the Gram stain shows no organisms, and it resolves spontaneously within 2 days. Alternative treatments for neonatal prophylaxis other than silver nitrate 1% include erythromycin ointment 0.5%, povidone iodine 2.5%, and tetracycline ointment 1%.

Chlamydial conjunctivitis is now a common infection in the neonatal period with higher rates in absent prenatal care. The infection is typically acquired from the mother as the child passes through the birth canal, although it can occur after cesarean section. This type of conjunctivitis develops typically in the 2nd week of life with unilateral or bilateral mucopurulent discharge with possible pseudomembranes. Evolution is chronic with disappearance of discharge after weeks or months, but with the possibility of scarring of the conjunctiva or cornea and possibility of systemic spread and complications. The usual cultures and Gram staining are unhelpful in the diagnosis of chlamydia. Cell culture is the gold standard because of high specificity but is expensive. Diagnosis can be made more conveniently by Giemsa staining of a conjunctival scraping or by a variety of commercially available antibody or PCR tests. Chlamydial conjunctivitis is treated with erythromycin ointment three times a day for 2-3 weeks. Systemic antibiotics are necessary because chlamydia can cause pneumonia, otitis, or nasal congestion.[98]

Neisseria gonorrhoeae is an acute, severe, purulent conjunctivitis with an incubation period of 2-5 days. If *N. gonorrhoeae* is the cause of the conjunctivitis, immediate treatment with systemic and topical antibiotics is necessary. In cases of infection with organisms resistant to penicillin, a third-generation cephalosporin is indicated.

Ophthalmia neonatorum also can result from other common pathogens such as staphylococci, pneumococci, streptococci, or Gram-negative bacteria. These bacterial infections usually appear several days after birth. Most respond well to topical antibiotics or ointment.

Older infants with chronic or recurrent mucous or purulent discharge usually have a blocked nasolacrimal duct as the underlying cause. The duct frequently opens spontaneously during the first year of life. Treatment with topical antibiotics and massage of the lacrimal sac can help resolve the problem.

Ocular Manifestations of Intrauterine Infections

A number of intrauterine infections have important ophthalmic manifestations. These congenital infections are known by the acronym TORCH. These infections include *t*oxoplasmosis, "*o*ther infections", *r*ubella, *c*ytomegalovirus, and *h*erpes simplex. The "other" designation is used for syphilis and varicella, as well as lymphocytic choriomeningitis virus. Some infections result from maternal infections that either cross the placental barrier or are transmitted during passage through the birth canal. Congenital toxoplasmosis manifests with necrotizing retinochoroiditis with associated vitritis and retinal vasculitis. These lesions result in chorioretinal scars characterized by white areas of exposed sclera circumscribed by well-defined darkly pigmented borders. Retinochoroiditis in toxoplasmosis is a recurrent condition; new lesions develop topically at the border of a scar, although it can develop in areas devoid of scar or in the other eye. Serologic confirmation of congenital infection is done by elevated IgM and IgA titers.[77] Syphilis can affect most structures of the eye ranging from eyelid skin rash, orbital inflammation, interstitial keratitis, and various types of intraocular inflammation to cranial nerve involvement and central visual pathway involvement, including optic nerve atrophy and pupillomotor disturbances. The interstitial keratitis associated with congenital syphilis is

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a late finding, not apparent until after the age of 5 years. Treatment with penicillin in the neonatal period does not prevent later development of interstitial keratitis.[69] The most common eye finding in lymphocytic choriomeningitis virus infection is generalized chorioretinal scars.[77] Neonatal herpes infection is most often acquired during passage through the birth canal and can cause typical herpetic eye disease such as blepharoconjunctivitis, keratitis, iritis, or chorioretinitis. Ocular involvement with either congenital cytomegalovirus disease or varicella is unusual but can result in chorioretinitis, keratitis, or cataract. Ocular involvement in congenital rubella is common, including microphthalmia, corneal haze, cataract, glaucoma, uveitis, and retinopathy. The characteristic "salt and pepper" retinopathy is the most common occurrence but cataract is responsible for the greatest visual loss.[120] The incidence of children with congenital human immunodeficiency virus (HIV) is decreasing dramatically with the advent of new drugs. Chorioretinitis secondary to various other infectious agents including herpes, CMV, and toxoplasma were described in this population.[9,26]

Preseptal and Orbital Cellulitis

The diagnosis of infective orbital cellulitis requires urgent evaluation and treatment in order to prevent rapid worsening with cavernous sinus thrombosis, cerebral abscess, osteomyelitis, and septicemia. Orbital cellulitis is the most common cause of proptosis in older children but is fortunately rare in neonates. Bacterial spread from paranasal sinuses is the main etiology with hematogenous or direct inoculation very infrequent at this age. The disease is characterized by the rapid onset of progressive proptosis, often with erythema of the lids, chemosis of the conjunctiva, limited motility, and systemic signs of toxicity and hyperpyrexia. Rapid loss of vision caused by compression of the orbital structures can occur and persists as a sequela if compression is not reversed in a timely manner. Afferent pupillary defect is a sign of compression in this setting. Diagnosis is made by clinical appearance and radiologic evaluation of the orbits and sinuses. Treatment includes admission to a hospital, CT scan of the orbits, intravenous administration of antibiotics, application of warm compresses, and surgical drainage of persistent orbital abscesses if necessary.[129] At this early age, the subperiosteal fluid collection in the orbit has high likelihood of being devoid of bacteria and resolves with intravenous antibiotics only.[129]

In preseptal cellulitis, the infection is limited to the lids and does not extend past the orbital septum to involve the orbital contents. It is usually caused by streptococcal and staphylococcal bacteria. In older children, it can be treated on an outpatient basis with oral antibiotics, but in infants, admission to the hospital for intravenous antibiotics is indicated. Widespread vaccination has dramatically decreased Haemophilus-associated orbital and preseptal cellulitis.[107]

Ocular Tumors in Infants

Hemangioma

Discussed in Eyelid Lesions.

Lymphatic Malformation (Lymphangioma)

Lymphatic malformations are slowly progressive, diffuse, soft tumors composed of thin-walled vascular channels that can involve the orbit, conjunctiva, and lids. They may be present at birth or develop during the first several years of life and cease growing by early adulthood. An upper respiratory tract infection and spontaneous hemorrhage may increase the size of the lesion and cause rapid proptosis. The tumors can also cause ptosis, strabismus, or anisometropia. Amblyopia is common and must be aggressively treated. MRI can be exceedingly helpful in diagnosing a lymphatic malformation. The lesion itself is difficult to treat, because it does not regress spontaneously or respond to radiation or corticosteroid therapy. Surgery is rarely used, as results are not always satisfactory. Reports on using percutaneous sclerotherapy using interventional radiology techniques show promise in this difficult-to-treat tumor.[18]

Dermoid Cysts

Dermoid cysts are thought to arise from a congenital rest of primitive ectoderm at the site of closure of a fetal cleft. They usually contain connective tissue, sebaceous glands, and hair follicles. Cysts are often located near the orbital rim, where they are attached to bone at suture sites. The most frequent location is in the lateral third of the brow or upper lid. The skin overlying the soft cyst is freely movable, although the cyst remains attached to the periosteum at the site of the embryonic cleft. Cysts located within the orbit produce proptosis and vertical or horizontal displacement of the globe. Radiographic examination might document bone erosion where the cyst is attached. Local trauma can produce a hemorrhage into a dermoid cyst or cyst rupture, leading to a clinical picture resembling cellulitis. Surgical excision is recommended and is usually curative, especially for the dermoids external to the orbit (see Figs. 95.13 and 95.14).

Teratoma

Teratoma is a primary orbital tumor composed of the three embryonic cell layers. It can differentiate into a variety of tissues containing cartilage, connective tissue, skin, hair, and sebaceous glands, or into endodermal epithelium. Bone is a common component and can be identified by CT. Orbital teratomas that are present at birth produce a striking massive proptosis. Treatment is early excision of the teratoma. Malignant transformation can occur but is rare in the orbit.

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Rhabdomyosarcoma

Rhabdomyosarcoma is the most common malignant tumor of the orbit in children although is rare in infants. Rhabdomyosarcoma develops in the orbit more often than elsewhere in the body. Orbital involvement produces proptosis that develops over a few weeks. Diagnosis is made by biopsy. Treatment involves chemotherapy and radiation therapy.

Retinoblastoma

See Intraocular Tumors.

Ocular Manifestations of Maternal Substance Abuse

An increasing number of infants are born bearing the physical, mental, and social consequences of maternal drug and alcohol abuse. Miller and colleagues described many of the ocular findings of fetal alcohol syndrome, including refractive errors, strabismus, anterior segment abnormalities, cataract, ptosis, long eyelashes, telecanthus, and optic nerve hypoplasia.[78]

Maternal ingestion of cocaine can result in optic nerve abnormalities, delayed visual maturation, and prolonged eyelid edema.[39]

Maternal cigarette smoking has been identified as a risk factor for strabismus.[42] As more information is gathered, additional evidence of the teratogenicity of various illicit drugs may be obtained.

Key Points

- Ocular problems are very common in the neonatal period, so a thorough examination with at least a simple pen light should be performed in every child.
- Ocular findings can be the precursor of systemic findings, and some specific ocular findings can lead to definitive diagnosis for many vague systemic findings. Ophthalmology consultation should be initiated for such guidance and possible ocular involvement.
- Nystagmus, copious discharge that is refractory to broad spectrum topical antibiotics, poor red reflex, cloudy corneas, droopy eyelids, constant large misalignment of the eyes, and frank anatomic abnormalities of the eyes and the orbit require prompt pediatric ophthalmology consultation.

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Retinopathy of Prematurity

YE SUN, ANN HELLSTRÖM, AND LOIS E. H. SMITH

Introduction

Retinopathy of prematurity (ROP) was first described ~70 years ago as *retrolental fibroplasia*. The introduction of closed incubators with the use of high levels of supplemental oxygen caused inhibition of the growth of retinal vessels in premature infants, followed by vasoproliferation and traction eventually resulting in a complete retinal detachment behind the lens. Supplemental oxygen increased the risk of blindness but also improved survival.[62] When oxygen use was curtailed in the 1950s, ROP incidence decreased but mortality and morbidity increased.[62] Optimal oxygenation saturation levels balancing ROP risk against improved survival at each gestational age are still undefined. Large multicenter studies suggest that oxygen saturation target ranges of 85%-89% versus 91%-95% decrease the incidence of severe ROP but increase mortality.[59,67] The results from several separate randomized controlled trials that found that the frequency of death before 18-24 months was reduced when SpO_2 targets were raised to 91%-95%, compared to when targets were 85%-89%.[65] However, Manja et al. performed a systematic review and meta-analysis of those results and found that the quality of evidence was moderate or low for the outcomes of mortality rates.[48]

Although oxygen is now much better controlled, ROP still persists because of increased survival of infants with extremely low gestational age and birth weight[35] and very immature retinas at high risk for ROP. The lack of factors normally provided in utero such as insulin-like growth factor 1 (IGF-1) also significantly impact the risk of ROP.[10,43] Without the necessary growth factors normally provided in utero, it is more likely that the immature state will persist, predisposing the eye to hypoxia, which then precipitates retinal neovascularization.

Incidence

Worldwide, approximately 10% of births occur preterm (before 37 completed weeks' gestational age).[5] In countries with advanced neonatal intensive care units (NICUs), most cases of ROP now occur among extremely low gestational age newborns (born <28 weeks' gestational age). Determining the current incidence of ROP in population-based studies, even among more developed countries, is challenging because there is considerable variability in study design and in gestational age of included premature infants, as well as in survival rates.[73] Taken as a whole, reports suggest that there has not been a significant change in ROP incidence over time,[20,68] perhaps explained by an increase in survival rates among very immature infants at high risk for ROP balanced against improved NICU care, which lowers ROP risk. Worldwide, the incidence of ROP is also influenced by the fact that even more mature infants at no risk for ROP with more advanced NICU care are at risk in regions with uncontrolled oxygen delivery and less intensive neonatal care.[13] The overall incidence of ROP of any severity was reported by gestational age as shown in Fig. 96.1.

Pathogenesis

Retinopathy of prematurity is initiated as an arrest of normal retinal neuronal and vascular development in the preterm infant. The lower the gestational age at birth, the less complete the retinal development. Vascular growth may resume normally, but when it does not, there can be a pathologic aberrant vascularization of the retina. ROP is usually classified in two postnatal phases[10]—phase 1: cessation of normal vascular growth (as well as obliteration of immature vessels with high oxygen use), and phase 2: pathologic vessel growth (Fig. 96.2).

Phase 1 ROP

Relative hyperoxia is an important driver for the arrest of vascular growth in phase 1 in both animal models and human studies.[18,66] In 1952, Patz first demonstrated the clinical association between oxygen and ROP.[52] In 1954, Ashton established the concepts of oxygen toxicity (phase 1) followed by hypoxia-mediated vasoproliferation (phase 2) in ROP in a kitten model.[3]

As the intrauterine environment has a mean partial pressure of oxygen (PO_2) below 50 mm Hg, unregulated supplemental oxygen given to premature infants with respiratory distress can drive oxygen saturations to abnormally high levels. Hyperoxia suppresses oxygen-regulated angiogenic growth factors such as erythropoietin[9,7] and vascular

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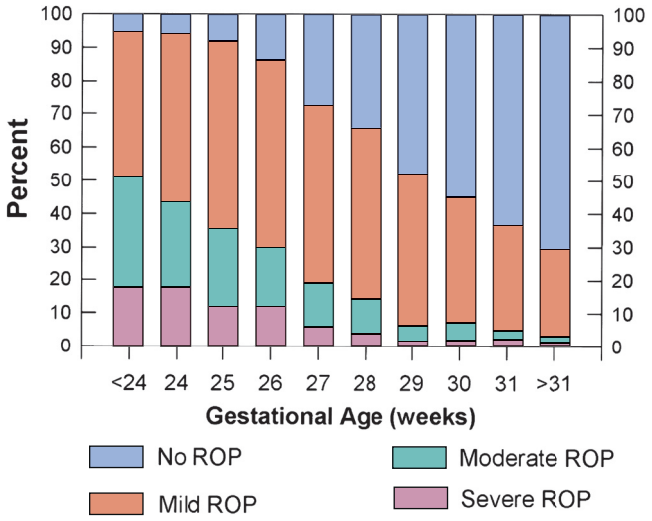
Abstract

Retinopathy of prematurity (ROP) was first described around 70 years ago as retrolental fibroplasia. The introduction of closed incubators with the use of high levels of supplemental oxygen caused inhibition of the growth of retinal vessels in premature infants, eventually resulting in a complete retinal detachment behind the lens. Supplemental oxygen increased the risk of blindness but also improved survival. When oxygen use was curtailed in the 1950s, ROP incidence decreased but mortality and morbidity increased. Optimal oxygenation saturation levels balancing ROP risk against improved survival are still unknown. Although oxygen is now much better controlled, ROP still persists because of increased survival of infants with extremely low gestational age and birth weight and very immature retinas at high risk for ROP. The lack of factors normally provided in utero such as insulin-like growth factor 1 (IGF-1) also significantly impacts the risk of ROP. Without the necessary growth factors normally provided in utero, it is more likely that the immature state will persist, predisposing the eye to hypoxia in phase 1 of ROP, which then precipitates retinal neovascularization.

Keywords

retinopathy of prematurity
incidence
pathogenesis
risk factors
classification
therapy
examination schedule

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• **Fig. 96.1** Incidence of mild (less than prethreshold), moderately severe (prethreshold), and severe (threshold) retinopathy of prematurity (ROP). (Data from Phelps DL. Retinopathy of prematurity: history, classification, and pathophysiology. *Neoreviews*. 2001;2:e153; and the ROP definitions from Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: 32-year outcome-structure and function. *Arch Ophthalmol*. 1993;111:339.)

endothelial growth factor (VEGF).[54] Phase 1 is partially reversed in a mouse model with replacement of VEGF and erythropoietin, proving that dysregulation of these particular oxygen-regulated factors contributes to phase I of ROP.[7,9,54]

Besides oxygen, another important driver of vascular growth arrest is loss of growth factors normally present at optimal levels in utero, such as insulin-like growth factor 1 (IGF-1).[32] IGF-1 is critical for normal growth and development of many tissues including brain and blood vessels. Other factors provided by the maternal–fetal interaction often lost after preterm birth are omega long-chain polyunsaturated fatty acids (omega LCPUFA), which are also crucial to retinal development. Loss of omega 3 and 6 LCPUFAs in particular appears to play a role in ROP pathogenesis,[12] and replacement might prove clinically helpful.[53]

Phase 2 ROP

Phase 2 of ROP is characterized by proliferation of blood vessels in response to markedly elevated increases in VEGF and erythropoietin and other factors (as opposed to suppression in phase 1).[2,70] In severe ROP, phase 2 characteristically begins when the increasingly metabolically active yet poorly vascularized retina (owing to the initial suppression of vessel growth in phase 1) becomes hypoxic. The neovessels (induced by growth factor overshoot) poorly perfuse the retina and are leaky, leading to fibrous scar formation and retinal detachment. In most preterm babies, the retina revascularizes relatively normally and ROP regresses spontaneously, although neural deficits (loss of photoreceptor function) may remain even in cases of mild ROP.[21] The transition between phase 1 and phase 2 usually occurs independent of chronologic age at postmenstrual age 32-37 weeks (peaking at postmenstrual age 34-36 weeks).

Risk Factors

Oxygen and ROP

It is clear that unmonitored high oxygen supplementation contributes to ROP, but the optimum level balancing the risk of ROP with high oxygen saturation versus morbidity that occurs with insufficient oxygenation is not known. After the first epidemic of ROP when the use of 100% oxygen made mildly premature babies blind, oxygen was restricted to 50% of inspired oxygen, which resulted in about 16 deaths per case of blindness prevented.[6]

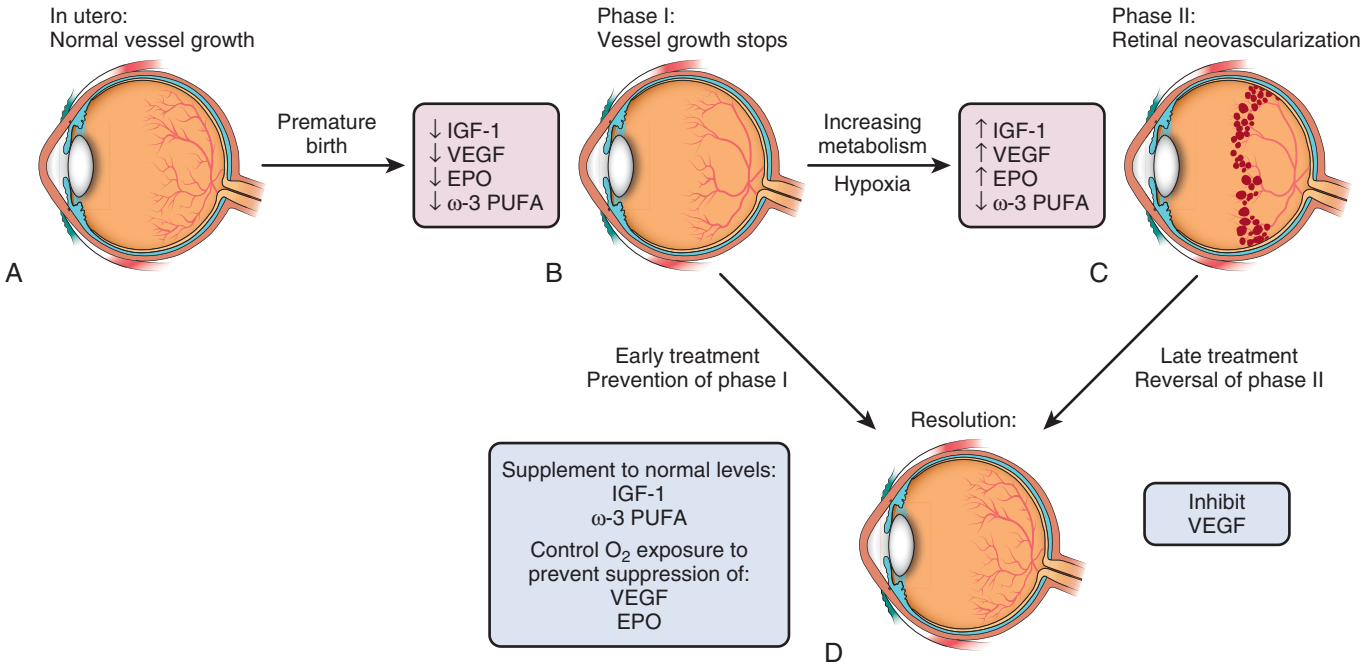
Theoretically, oxygen in phase 2 of ROP could suppress high levels of oxygen-sensitive growth factors such as VEGF that cause proliferative disease. This premise has been examined in several studies. The Benefits of Oxygen Saturation Targeting trial was a multicenter, double-blind, randomized controlled trial in Australia on 358 babies with gestational age less than 30 weeks who were dependent on oxygen supplementation at 32 weeks, thus investigating the effect of oxygen targets during a time corresponding to the second phase of ROP. No benefit was seen with higher targets in phase 2. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity study found no change in progression of prethreshold ROP to proliferative disease by increasing oxygen saturation to 96%-99% from conventional 89%-94% for at least 2 weeks. However, increased target oxygen was associated with more pulmonary complications.[69]

Individually, these studies did not show a benefit from higher oxygen in phase 2. Chen et al. performed a meta-analysis of 10 publications to assess at different phases of ROP the association between severe ROP and high or low target oxygen saturation. They found that low oxygen saturation (70%-96%) in the first several postnatal weeks was associated with reduced risk and that high oxygen saturation (94%-99%) at or after 32 weeks' postmenstrual age was associated with decreased risk for progression to severe ROP,[11] and that the control of oxygen in the first phase was more important than the higher oxygen saturation in the second phase. Oxygen level fluctuations during the first few weeks of life are also associated with increased ROP risk,[29] as is frequent intermittent hypoxia during the first 8 weeks of life.[14]

Gestational Age and Birth Weight

Low gestational age and low birth weight, which reflect the degree of immaturity of retinal neural and vascular development at birth and, therefore, the degree of retinal vulnerability to insult are major risk factors for ROP.[47] Loss of growth factors normally found in utero is also a major risk factor for the disease. The lower the gestational age and birth weight, the more profound is the loss of factors provided by the intrauterine environment.

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• **Fig. 96.2** Progression of retinopathy of prematurity. **A,** Oxygen tension is low in utero. **B,** Phase 1: After birth until ≈30 weeks' postmenstrual age, retinal vascularization is inhibited because of hyperoxia and loss of the nutrients and growth factors provided at the maternal–fetal interface. Blood-vessel growth stops and as the retina matures and metabolic demand increases, hypoxia results. **C,** Phase 2: The hypoxic retina stimulates expression of the oxygen-regulated factors such as erythropoietin (EPO) and vascular endothelial growth factor (VEGF), which stimulates retinal neovascularization. Insulin-like growth factor 1 (IGF-1) concentrations increase slowly from low concentrations after preterm birth to concentrations high enough to allow effects on the concentration of VEGF pathways. **D,** Resolution of retinopathy might be achieved through prevention of phase 1 by increasing IGF-1 to in utero concentrations and by limiting oxygen to prevent suppression of VEGF; alternatively, VEGF can be suppressed in phase 2 after neovascularization with laser therapy or an antibody. EPO, Erythropoietin; ω-3 PUFA, ω-3 polyunsaturated fatty acids. (Adapted from Smith LE. Through the eyes of a child: understanding retinopathy through ROP: the Friedenwald lecture. *Invest Ophthalmol Vis Sci.* 2008;49:5177-5182, by permission of the Association for Research in Vision and Ophthalmology.)

Low IGF-1

In babies born preterm, there is a strong association between early postnatal low serum IGF-1 concentrations and later ROP as well as other prematurity-related morbidities.[32] In utero, plasma levels of IGF-1 increase with gestational age, particularly during the third trimester of pregnancy, and decrease after preterm birth.[42,45] Most infants born before 33 weeks' gestational age have a very slow increase in IGF-1 production after birth until 40 weeks' postmenstrual age. Full-term infants by comparison have a rapid increase in serum IGF-1 levels postnatally.[45] Postnatal IGF-1 levels are nutrition-dependent in older preterm infants and are reduced with starvation, infection, and stress.[41]

IGF-1-deficient mice have retinal vessel growth suppression, suggesting that low IGF-1 levels contribute to vascular growth suppression in ROP.[31] In preterm infants, low IGF-1 serum levels, as well as directly correlating with the severity of ROP, also correlate with poor brain growth as measured by head circumference and MRI at term.[24] IGF-1 acts as a permissive factor for VEGF-dependent vascular endothelial cell growth and survival.[31,63,64] Increased levels of the major IGF-1 binding protein found in serum, insulin-like growth factor binding protein 3 (IGFBP3), also improve vessel survival in a mouse model of oxygen-induced retinopathy. Importantly, IGFBP3 levels are significantly diminished in infants with ROP.[46]

Hyperglycemia and Insulin Use

Elevated neonatal glucose levels are a risk factor for ROP.[1,51] In a study of 372 infants born after 30 weeks' gestational age,[39] increased nutrition alone (without IGF-1 supplementation) caused increased hyperglycemia, precipitating increased insulin use. Both hyperglycemia and insulin use were associated with an increase in ROP. These studies underline the importance of an integrated approach to ROP prevention.

Increasing nutrition alone also does not influence weight gain (normalized for gestational age)[22] or IGF-1 levels in extremely low birth weight infants, who appear to be unable to either increase IGF-1 levels with increased calories or to use calories for growth with low IGF-1 levels.[22] Exogenous IGF-1 can improve growth in experimental states of undernutrition. In rats fed half of needed calories, exogenous IGF-1 improved weight gain.[17] As postnatal weight gain

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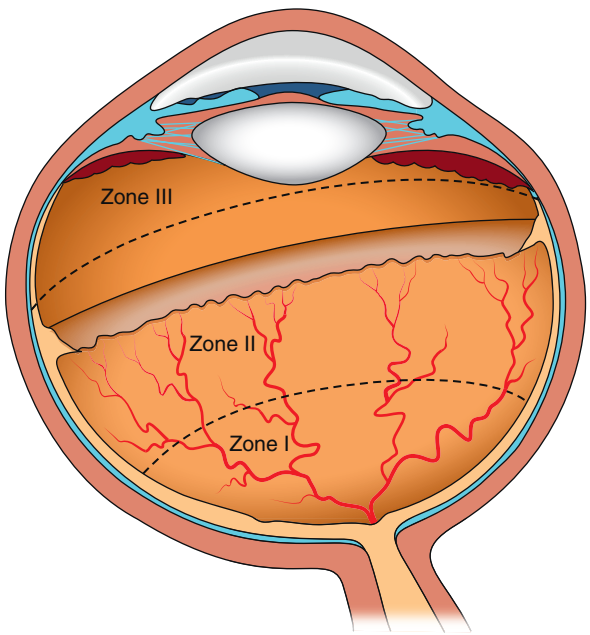
predicts ROP risk,[4] this suggests that both increased nutrition and adequate IGF-1 levels are required for postnatal growth and for a reduction in ROP risk.

Additional attention must also be paid to nutritional components such as adequate protein and appropriate fats, as well as appropriate use of glucose and other carbohydrates. In particular, it has been shown in animal studies that lack of omega 3 polyunsaturated fatty acids increases susceptibility for retinopathy.[12] Given that total parenteral nutrition (TPN) rarely contains any omega 3 or 6 LCPUFAs, it is likely that adding these essential lipids to nutrients would be beneficial.[53] It is noteworthy that in a study of ≈2000 infants with ROP in North America, those with extended total parenteral nutrition use were at high risk for ROP, independent of weight gain.[72]

Classification

The International Classification of Retinopathy of Prematurity was developed in 1984 and 1987 to clearly define stages of ROP for physicians and investigators. It was published in two parts throughout the world[36,37] and was revisited in 2005.[38]

The retina is divided into three zones (Fig. 96.3). ROP located in the most immature zone I has a much worse prognosis. Second, the extent of the disease is described by the number of clock hours involved within the zone. Therefore, one can describe how many clock hours of retina are affected by which severity in detail by using this description method (e.g., stage 3 seen between 7 and 10 o'clock as well as 2-5 o'clock and the remaining clock hours were stage 2 in zone II). Third, the change in posterior pole venous dilation and arterial tortuosity that occurs in aggressive disease is identified as "plus disease" (or "preplus disease" if it is not normal but does not meet criteria for plus disease). As in previous classifications, the degree of vasculopathy at the vascular-avascular transition is divided into stages 1 through 5. Stages 1 through 3 are increasing degrees of abnormal blood vessel growth (neovascularization) with vessels growing into the vitreous in stage 3. Stage 4 is partial retinal detachment, and stage 5 is complete retinal detachment, both of which carry a poor prognosis for normal vision. Stages 1 and 2 are mild and likely to regress spontaneously. In stage 3, extraretinal neovascularization may become severe enough to cause total retinal detachment (stage 5), which most often leads to blindness. The Early Treatment for Retinopathy of Prematurity (ETROP) Study[15] reclassified ROP into type 1 (requiring treatment) and type 2 (to be followed) to include a more virulent form of retinopathy in extremely low birth weight babies (aggressive, posterior ROP), which involves very central neovascularization with plus disease.[37]

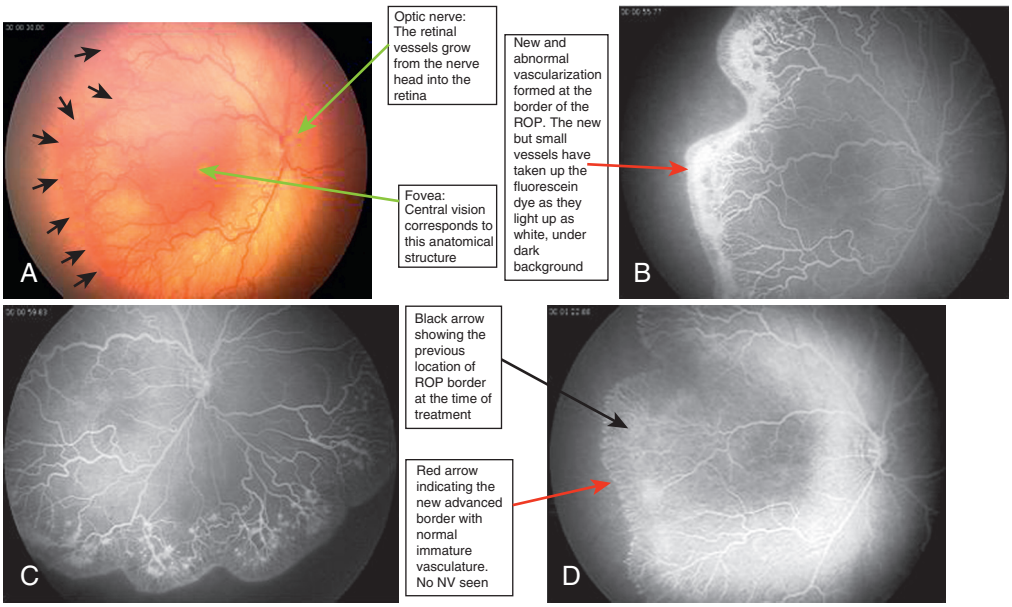


• **Fig. 96.3** Artist's rendering of half of the eye with zone II, stage 3 retinopathy of prematurity with plus disease. The view is from the top of the head, with the temporal side of the retina to the reader's left, and the nasal side to the right. Zones I, II, and III are drawn onto the retina to assist in visualizing their positions within the eye.

Clinical Course

Infants at risk for severe ROP are examined according to national guidelines, usually starting at about 31 weeks' postmenstrual age to detect those needing treatment. The sequential development of the stages of ROP is monitored until "threshold," or "type 1" disease, a point when the ROP is equally likely to regress or to progress to advanced disease, at the time-point ROP is treated. If no ROP is seen by 36-42 weeks' postmenstrual age, the risk of developing disease is very low.[70] However, if ROP is treated with anti-VEGF therapy, incomplete retinal vascularization with the risk of further ROP is extended. Rates of progression are variable, and the worst prognosis is associated with onset of severe disease in zone I (most immature) that can rapidly progress to type 1 disease with high risk of retinal detachment. Onset in zone II, or a slower evolution of the disorder, leads more often to complete resolution. ROP with an onset in zone III has a good prognosis for full recovery.[58] Infants who develop only mild ROP (i.e., stage 1 or 2 without plus disease) usually heal without a residual cicatrix and have only a slightly increased incidence of myopia/hyperopia, strabismus, and amblyopia compared with term infants.[6] However, for those infants who develop type 1 ROP and receive laser ablation, severe myopia, glaucoma, and associated sequelae are common.[34] The infants who have a residual cicatrix without retinal detachment are also more likely to have any of these problems and are at risk for retinal detachment and acuity loss in later decades.[56,29] Therefore, physicians must refer these high-risk infants to early intervention programs and support their families. Retinal fluorescein angiography can be used to visualize the pathology better, because sometimes it could be difficult to see the extent and the severity of the pathology with simple direct visualization (Fig. 96.4).

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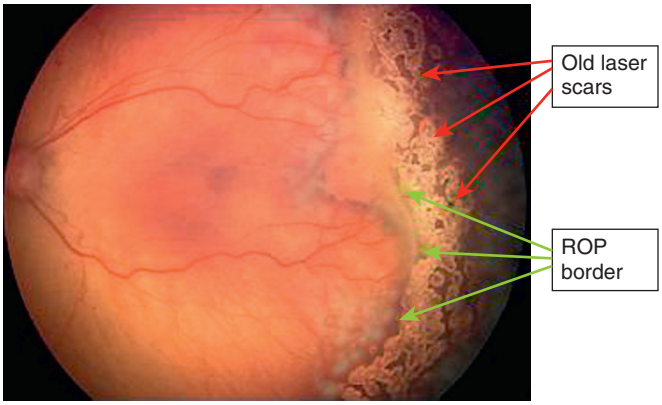
• **Fig. 96.4** A single patient with zone I, stage 3 ROP with plus disease. **A,** Small arrows indicate the border where the vascular zone ends and the avascular (part of retina that does not have any vessels to bring oxygen and nutrition) zone starts. Along that border, the red thick line indicates significant neovascularization (NV) at that border. Also note dilation of veins and tortuosity of the arteries. It is still somewhat difficult to see the detail because of the underlying pinkish hue that masks the contrast. **B,** Fluorescein angiography documents retinal vascular anatomy in much better detail, as the fluorescein dye lights up only the retinal vasculature and every other structure is dark. Bright white structures at the border are all significant neovascularization. **C,** Fluorescein angiography shows the inferior retina. The border is visible again with less but present neovascularization seen as light bulbs on a tree. **D,** Fluorescein angiography performed 1 month after treatment with anti-VEGF therapy. Note that the normal retinal vasculature has grown, and neovascularization has completely disappeared. Plus disease has also regressed with no tortuosity seen in the arteries.

Therapy

The only completely effective prophylaxis for ROP is the prevention of premature deliveries or the development of treatment that normalizes factors missing after preterm birth and avoids factors not found in utero (e.g., hyperoxia). Meticulous oxygen monitoring is necessary to reduce the incidence of ROP, but it does not eliminate the disease.[29] Other factors must also be matched with the prenatal environment, adjusted for the adaptation to the postnatal environment.

The question also remains of the balance between lower oxygen supplementation in the early postnatal period to prevent blood vessel loss versus higher oxygen in the later postnatal period to support oxygenation of the retina in phase 2 of ROP.

After ROP has developed to a point in phase 2 that is as likely to regress as progress to retinal detachment (defined as type 1 by the ETROP study), the standard treatment is laser therapy to ablate the entire peripheral avascular retina, which is overproducing angiogenic factors and driving the blood vessels to grow abnormally (Fig. 96.5). Although this treatment does not always succeed in preventing retinal detachment, it reduced the incidence of poor retinal outcomes for type 1 ROP at 2 years in treated versus controls from 15.4% to 9.1%.[19] At 15 years' follow-up, the benefit of ablative therapy persists, with respect to preventing poor structural outcome (which is greater than the benefit for visual function).[56] The criteria for laser treatment established by the ETROP multicenter trial first published in 2003 are shown in Box 96.1. Ablative treatment of nonvascularized retina helps to prevent blindness but does not address the underlying cause of retinopathy of prematurity or other co-morbidities, which is the failure of normal neural and vascular growth. Furthermore, peripheral retina is destroyed to save central vision.



• **Fig. 96.5** Fundus photography taken 4 weeks after laser treatment. The laser spots/scars are seen as white/black areas beyond the border of ROP.

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• BOX 96.1 Criteria for Peripheral Ablative Therapy for Retinopathy of Prematurity

Zone II: Plus disease with stage 2 or 3 ROP
Zone I: Plus disease with stage 1 or 2 ROP
Zone I: Stage 3 ROP

ROP, Retinopathy of prematurity.
Adapted from Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity Randomized Trial. *Arch Ophthalmol*. 2003;121:1684.

Treatment of proliferative retinopathy with humanized antibody fragments that block VEGF (by intravitreal injection) (see Fig. 96.4) has been reported in many small case series, for example, by Harder and colleagues.[28] In a trial of 150 infants randomly assigned to receive laser or intravitreal bevacizumab treatment, recurrence was slightly less likely in the bevacizumab group than in the laser-treated group at 54 weeks' postmenstrual age.[50] A significant treatment effect with bevacizumab was seen for retinopathy of prematurity in zone I but not zone II.[50] However, visual outcomes and adverse systemic effects were not reported. Bevacizumab injected into the eye leaks into systemic circulation and reduces systemic VEGF concentrations for at least several weeks to months[57] and might suppress systemic vascular growth or have other as-yet-unknown negative effects.[25] Additional studies to assess the best choice of an anti-VEGF drug, the optimum dose, the pharmacokinetics, and short-term and long-term safety are underway.[26] When total or subtotal retinal detachment occurs, the usual prognosis is that there will be little useful vision, even when attempts are made to reattach the retina.[55]

Candidate Interventions for Prevention and Treatment

Addressing the postnatal risk factors for retinopathy of prematurity might help to normalize postnatal growth and reduce risk. Increasing nutrition alone seems to be insufficient to increase IGF-1 and promote postnatal weight gain in the early postnatal period in the most immature babies,[23] and insufficient to decrease risk of retinopathy of prematurity.[71] Instead, hyperglycemia and insulin requirement are raised, both of which are associated with an increased risk.[40] Because persistently low serum IGF-1 concentrations in preterm infants are associated with ROP and other morbidities,[30] and because supplemental IGF-1 seems to improve food utilization in undernutrition,[17] supplementation with exogenous IGF-1 might improve early postnatal growth and outcome. A pharmacokinetic and dosing study[44] of intravenous IGF-1-IGFBP3 complex in preterm infants showed no adverse effects and an increase in serum IGF-1 to in utero concentrations. An IGF-1–IGFBP3 phase II replacement trial (NCT01096784) has been performed in 120 preterm infants and reported no effects on ROP outcome. However, significant reduction in bronchopulmonary dysplasia was seen as well as a significant tendency for a reduction in severe brain injury. A phase III study is now under way, with reduction in the severity of pulmonary disease as the primary endpoint and brain injury and ROP as secondary endpoints.

During the third trimester of pregnancy, a massive transfer of essential fatty acids (ω-3 and ω-6 long-chain polyunsaturated fatty acids) from the mother to the fetus takes place; these essential fatty acids [especially the ω-3 fatty acids: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and omega-6 fatty acid arachidonic acid (AA)] are not provided in parenteral solutions after preterm birth.[49] In a study in mice, adequate ω-3 long-chain polyunsaturated fatty acids reduced retinopathy by 50%,[12] which suggests that replacement of these fatty acids in infants would reduce the risk of retinopathy of prematurity.

The β blocker propranolol has been proposed as a potential treatment to reduce retinal neovascularization,[16] and clinical studies are underway in Israel and Italy. However, investigators of a 2012 study[8] report that propranolol does not reduce retinopathy in a mouse model of retinopathy of prematurity. Results of a meta-analysis suggest that the carbohydrate inositol can reduce the number of infants with stage 3 or higher cases of retinopathy of prematurity.[33] However, a randomized trial of inositol was stopped early for increased deaths without an impact on retinopathy of prematurity or BPD.[53a]

Recommendations for Examination Schedule

A trained clinician must examine at-risk premature infants with indirect ophthalmoscopy to detect ROP before it has reached well-established clinical criteria for the application of laser therapy (or cryotherapy) to prevent progression of the disease.[60-61] The ophthalmic and pediatric societies periodically publish recommendations for the screening guidelines, which may vary between countries (Box 96.2). Largely, infants at risk are suggested to be those weighing less than 1500 g or born at 30 weeks' gestation or less, and those more mature preterm infants with birth weight of 1500-2000 g who had an unstable medical course. These children should be examined initially by 31 weeks' postmenstrual age or 4 weeks' chronologic age until the retina is vascularized to the ora serrata. If there is normal vascularization into zone III, ROP is unlikely to develop or is likely to be mild, and repeated examinations are done at 2- to 4-week intervals until complete vascularization is noted. Infants with normal retinal vascularization into zone II should be followed at least every 2 weeks to observe for the development of ROP, which may require therapy. Infants with normal vascularization only into zone I are at greatest risk for severe ROP and should be followed closely on the

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• BOX 96.2 Schedule for First Indirect Ophthalmoscopy in Premature Infants

Who

- All infants 30 weeks' gestation or less, or weighing less than 1500 g at birth
- Infants born at 1500 to 2000 g who have a medically unstable course

When

- By the later of 31 weeks' postmenstrual age* or 4 weeks after birth
- Recommend first examination before discharge from the hospital

*Postmenstrual age in weeks is equal to the gestational age at birth plus the chronologic age in weeks after birth.
Adapted from American Academy of Pediatrics, American Association for Pediatric Ophthalmology and Strabismus, and American Academy of Ophthalmology. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2006;117:152 and 2006;118:1324.

basis of the presence, severity, and rate of progression of any ROP, particularly if vascular dilation (plus disease) is found.

Because fewer than 10% of children examined are found to need treatment, the use of an algorithm that predicts later development of ROP (WINROP) can be very helpful in adjusting the number of eye examinations based on predicted risk.[27] WINROP (winrop.com) is free for use. The algorithm is based on deviations of an infant's weight gain velocity from an established norm for infants who do not develop ROP and predicts on average the future development of ROP 2 months before treatment is needed. The algorithm must be used in conjunction with regular screening, but in Sweden it has reduced the number of eye examinations by up to 35%.

Neonatologists and ophthalmologists must work closely together to ensure an efficient tracking system for timely examination of these infants and to be certain that follow-up examinations occur at the best times both in the hospital and after discharge or transfer. Because ROP develops in the majority of infants born at less than 26 weeks' gestation, the index of suspicion must be high, and follow-up examinations must be frequent in these babies. At 26-28 weeks' gestational age at birth, the incidence drops, and at 29-30 weeks' gestational age at birth, few infants develop severe ROP requiring treatment. The goal is to ensure that infants who reach criteria for retinal ablation are treated to minimize vision loss.

After the acute process has resolved, continued follow-up is dictated by the worst degree of ROP that occurred in the acute course. For infants who have had laser or cryotherapy for ROP, close observation of the retina as well as assessment for refractive errors, strabismus, amblyopia, or late retinal detachments through childhood is also important.[34] Research must continue in order to learn about the basic mechanisms involved in the control of retinal vascular development and neovascularization. Such knowledge may permit prevention of ROP.

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Key Points

- ROP incidence is reduced by improved neonatal care.
- Oxygen-regulated as well as non-oxygen-regulated growth factors are key in the pathogenesis of ROP.
- Oxygen, gestational age, birth weight, IGF1 level, hyperglycemia, and insulin use are risk factors for ROP.
- Candidate interventions for prevention and treatment.
- Recommended examination schedules should be followed to optimize available therapeutic interventions.

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Musculoskeletal Disorders in Neonates

RAYMOND W. LIU AND GEORGE H. THOMPSON

Musculoskeletal abnormalities of the extremities, spine, and pelvis are common in the neonate. Some are pathologic and others physiologic in origin from normal in utero positioning. The congenital absence of all or part of a limb, deformities of the feet or hands, and abnormalities of the spine are rarely diagnostic problems, whereas others, such as developmental dysplasia of the hip (DDH), may escape diagnosis even after repeated screenings by experienced examiners. Bone and joint infections in the neonatal period produce few of the diagnostic signs and symptoms present in the older child and require a high index of suspicion and careful diagnostic evaluation. When an infection is diagnosed early and prompt treatment rendered, the growth potential of the neonate yields an excellent prognosis for normal development and function.

Normal Embryology

Because many neonatal musculoskeletal disorders are congenital in origin, it is important to understand the basic aspects of musculoskeletal embryology. Prenatal development is divided into two major stages: the embryonic period, consisting of the first trimester, and the fetal period, consisting of the middle and last trimesters of pregnancy. The components of the musculoskeletal system differentiate during the first trimester; the second and third trimesters are periods of further growth and development.[10,21] Abnormalities during the embryonic period produce congenital malformations, whereas the fetal period produces deformations and alterations in the configuration of essentially normal parts.

Embryonic Development

The early embryonic development of the musculoskeletal system is oriented around the notochord, a tubular column of cells running cranially and caudally along the long axis of the embryo. During the 3rd week of gestation, the neural crests develop dorsally and on either side of the notochord. These crests fold over and are joined dorsally to produce the neural tube, from which the spinal cord and associated spinal nerves develop. At the same time, paraxial collections of mesodermal tissue develop on either side of the notochord and segment in the cranial to caudal axis into 44 distinct condensations called *somites*. From the primitive mesodermal tissue comprising the somites, the skeletal tissues, muscle, and dermal elements of the body develop.

Extremities

The upper and lower extremities develop from the limb buds. They become recognizable during the 4th week of gestation. These buds grow and differentiate rapidly in a proximal to distal sequence during the next 4 weeks. The cells differentiate into three segments: the dermatomes, which become skin; the myotomes, which become muscle; and the sclerotomes, which become cartilage and bone. By the 5th week, the hand plate forms, and mesenchymal condensations occur in the limbs. By the 6th week, the digits become evident, and chondrification of the mesenchymal condensations occurs. Notches appear between the digit rays during the 7th week. The failure of the rays to separate at this time results in syndactyly. Also during the 7th week, the upper and lower limbs rotate in opposite directions. The lower limbs rotate internally to bring the toes to the midline, whereas the upper limbs rotate 90 degrees externally to the position of the thumb on the lateral side of the limb.

Spine

The differentiation of the spinal column begins during the 4th week of the embryonic period. The somites first appear in the occipital region of the embryo; further development occurs simultaneously in a cranial-to-caudal direction. Dorsal and anterolateral migrations of the mesodermal tissue derived from the somites give rise to the connective tissue elements of the trunk and limbs. Anteromedial extensions of the somatic mesoderm migrate to surround the notochord, separating it from the neural tube and forming the primitive anlage of the vertebral bodies. The differentiation of the neural and vascular elements of the spinal column occurs simultaneously to somite development.

Definitive formation of the spinal column occurs from the 4th through the 6th week of gestation. The somatic mesodermal tissue surrounding the notochord differentiates into a less cellular and dense upper portion and a more cellular and dense lower portion. The somites cleave together,

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Abstract

Neonatal musculoskeletal abnormalities of the extremities, spine, and pelvis are common disorders. Some are pathologic while others are physiologic or acquired. The embryonic period constitutes the first trimester while the second and third trimesters are the fetal period. Abnormalities during the embryonic period produce congenital malformations while those occurring during the fetal period cause deformations and alterations in normal parts. Congenital malformations may include the spine (congenital scoliosis and kyphosis), extremity failure of formation and differentiation of parts, and other congenital abnormalities and teratogenic malformations. Fetal period disorders include those secondary to in utero positioning (tibial torsion, metatarsus adductus, developmental hip dysplasia), spinal injury, brachial plexus injuries, muscular torticollis, and fractures (clavicle, proximal humeral epiphyseal separation). It is important to be able to recognize these abnormalities and assess for related but less obvious abnormalities.

Keywords

musculoskeletal embryology
embryonic period
fetal period
trimesters
congenital malformations
deformations
alterations of normal parts
teratogenic abnormalities
genetic disorders
congenital limb malformations
spinal defects
in utero positioning
trauma
brachial plexus injury
muscular torticollis
fractures

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the lower portion of the superior somite joining with the upper portion of the inferior somite. The intervertebral disc develops at the site of the cleavage. The notochord, which is contained within the newly joined primitive vertebral bodies, degenerates, and those portions at the site of cleavage become the nucleus pulposus of the intervertebral disc. The neural arches and ribs develop from the dense portions of the somite, and the vertebral body develops from the less dense portions.

Chondrification begins in the primitive mesodermal vertebrae during the 6th week of pregnancy. It progresses rapidly to form cartilaginous models of the vertebral body by the end of the first trimester. Ossification of the cartilaginous models begins during the second trimester. The ossification of each side of the neural arch and of the body at each level proceeds separately. In the neonate, the ossified vertebral body and neural arches at each level are clearly visible radiographically, separated as they are by the nonossified synchondritic junctions. The ossification centers of the neural arches and body coalesce during the first 3 years of postnatal development.

The first and second cervical segments are embryologically and anatomically distinct from the remainder of the spinal column. The first cervical vertebra—the atlas—lacks the physical form characteristic of other vertebrae, having instead only a narrow anterior arch. This arch is not ossified at birth or during the neonatal period but is most often visible by 1 year of age.

The most striking feature of the second cervical vertebra—the axis—is the prominent odontoid process, derived from the caudal portion of the first cervical somite. The odontoid process joins with the remainder of the C2 body through synchondritic links with each neural arch and the vertebral body. The synchondrosis with the centrum lies below the level of the neural arches and may be radiographically confused with a fracture line; it closes by 3 years of age. The vertical synchondroses separating the centrum from the neural arches of C2 close by 7 years of age.

The radiographic evaluation of the neonatal spine requires experience. In the lateral view, the vertebral bodies are often notched at their waists and are trapezoidal rather than rectangular. In the anteroposterior view, the synchondritic links between the neural arches and vertebral bodies are not ossified and may give the false impression of a fracture. In the cervical region, the odontoid process may be confusing to those not familiar with the normal developmental anatomy of the region. Fortunately, fractures of the cervical spine are uncommon in the neonatal period and, when present, are usually associated with a suggestive history and other signs on physical examination.

Fetal Development

The appendicular and axial skeletons are preformed in cartilage. By the end of the first trimester, primary ossification centers are present in the long bones of the extremities. Further increases in length occur through endochondral growth at the ends of the long bones. This growth continues in the postnatal period until the end of adolescence, when growth plates close and the epiphyseal regions fuse with the remainder of the long bone.

Congenital Abnormalities

Teratogenic influences and genetic abnormalities occurring during the embryonic period can adversely affect the normal differentiation of the musculoskeletal system, resulting in malformations of the extremities or spine. Other organ systems differentiating at the same time are often concomitantly affected, such as the association of cardiac and genitourinary abnormalities with congenital spinal deformities (see Chapter 30).

Teratogenic Abnormalities

It has been estimated that 5% of all malformations are the result of the action of known teratogens on the developing embryo. Irradiation, industrial chemicals, therapeutic drugs, and certain maternal infections produce primary musculoskeletal malformations or secondarily affect the growth and development of the musculoskeletal system. Thalidomide is the best-known cause of musculoskeletal malformation, causing limb reduction deficits in addition to a variety of other congenital abnormalities. Rubella, cytomegalic inclusion disease, and congenital herpes produce lesions of the central nervous system that may secondarily affect the musculoskeletal system.

Genetic Disorders

Genetic disorders that affect the musculoskeletal system may be divided into three categories: Mendelian, chromosomal, and multifactorial.

Mendelian Disorders

Mendelian disorders are characterized by an abnormality in a single gene obeying the rules of Mendelian inheritance. Skeletal dysplasias such as achondroplasia and diastrophic dwarfism, Marfan syndrome, hemophilia, and rickets resistant to vitamin D are examples of Mendelian disorders. Skeletal dysplasias are often diagnosed in the neonate, whereas other entities do not become clinically recognizable until later in childhood.

Chromosomal Abnormalities

There are many varieties of chromosomal abnormalities. Aneuploidy is the presence of more or fewer chromosomes than normal and includes Down syndrome as well as Turner syndrome. Translocations are also changes that are detectable on ultrastructural analysis. Trisomies are common examples. Deletion and inversion can be more subtle and are discovered on specialized genetic testing. Although they are striking, the musculoskeletal manifestations of these conditions are frequently the least serious of the infant's problems in other organ systems.

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Multifactorial Conditions

These conditions are determined by a combination of genetic predisposition and intrauterine environmental influences. Such conditions typically occur in families with a frequency that is greater than expected but do not follow the obvious rules of Mendelian inheritance. Talipes equinovarus (clubfoot) is such a disorder. The overall incidence of clubfoot is 1 case per 1000 live births, but the incidence of deformity among first-degree relatives is 20-30 times higher than that in the general population. Three percent of dizygous twins and 40% of monozygous twins share the deformity. An increased incidence of clubfoot occurs among breech and twin births.

Congenital Limb Malformations

Congenital limb malformations are relatively common among neonates. Some are grossly obvious, such as a congenital amputation, whereas others are subtle and perhaps unrecognizable for years, such as a congenital proximal radioulnar synostosis (fusion). Congenital limb malformations are classified according to the parts that have been primarily affected by embryologic failure. Swanson and colleagues developed a seven-group classification system.[24]

1. Failure of formation of parts (e.g., arrested development)
2. Failure of differentiation (e.g., separation) of parts
3. Duplication
4. Overgrowth (e.g., hyperplasia, gigantism)
5. Undergrowth (e.g., hypoplasia)
6. Congenital constriction band syndrome
7. Generalized skeletal abnormalities

These various malformations are caused by alterations in the organization of the limb mesenchyme; the time of the insult, the sequential development of the part, and the location of the destructive process determine the type of ensuing deformity. The presentation, diagnosis, and treatment of the more common congenital limb malformations are discussed in later sections.

Failure of Formation of Parts

This group is subdivided into transverse and longitudinal deficiencies. A transverse deficiency is manifested as an amputation type of stump that is classified by naming the level at which the remaining limb terminates. All elements distal to the level are absent. Longitudinal deficiencies represent all other skeletal limb deformities. These deficiencies are separated into preaxial and postaxial divisions of the limb and include longitudinal failure of the formation of an entire limb segment, such as phocomelia, or of the preaxial (i.e., radius, tibia), central, or postaxial (i.e., ulna, fibula) components of the limb. The more common deformities include phocomelia, a partially or completely absent radius (i.e., radial clubhand), and a partially or completely absent fibula (i.e., fibular hemimelia).[3,9,11]

Failure of Differentiation of Parts

In failure of the differentiation of parts, the basic units of the extremity developed, but the final form was not completed. The common disorders of this group include an undescended scapula (i.e., Sprengel deformity), proximal radioulnar synostosis, and syndactyly of the fingers and toes.

Duplication

Duplication occurs as the result of a particular insult to the limb bud at an early stage such that the splitting of the original embryonic part occurs. Polydactyly of the thumb, fingers, great toe, and lesser toes is the most common of the neonatal musculoskeletal disorders. Although a simple duplication is often an isolated finding, a complex toe duplication raises concern for associated tibial hemimelia (Fig. 97.1).

Overgrowth

Overgrowth disorders, such as congenital hemihypertrophy, can result from an excess of skeletal growth or soft tissues. The overgrowth frequently increases in size with development because of the asymmetric growth of the involved part.



• **Fig. 97.1** Complex polydactyly can be associated with tibial hemimelia. This child has an equinovarus position of the ankle that was resistive to casting. Eventual workup of this child demonstrated additional subtle signs of tibial hemimelia.

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Undergrowth

Undergrowth, such as brachydactyly, usually represents the defective or incomplete development of parts. It can involve an entire extremity or only a portion of it. Overgrowth disorders are more common than undergrowth disorders.

Congenital Constriction Band Syndrome

Congenital constriction band syndrome may represent focal necrosis of the limb after the embryonic period or an acquired deformity owing to amniotic bands.

Generalized Skeletal Abnormalities

Generalized skeletal abnormalities manifest generalized disorders, some of which may be inherited. Examples include skeletal dysplasia and syndromes such as Marfan syndrome and neurofibromatosis.

Spinal Defects

Errors in the embryologic derivation of the spine cause a number of congenital defects of the spine and spinal cord. These errors range in severity from isolated hemivertebrae to the complex errors of vertebral formation and segmentation associated with massive defects of the neural tube or spinal cord. When such errors result in asymmetric vertebral formation or produce asymmetric vertebral growth potential, structural spinal curves such as congenital scoliosis or kyphosis develop. Partial or complete failure of the formation of a vertebra (i.e., hemivertebra) or errors in the normal pattern of vertebral segmentation and recombination (i.e., unsegmented bars and trapezoidal, butterfly, and block vertebrae) may occur as single anomalies or be associated with other malformations of the osseous, neural, and organ systems. When vertebral defects are unbalanced and have growth potential, striking spinal deformities may occur, such as with a unilateral unsegmented bar with a contralateral hemivertebrae. The nature of the deformity depends on the growth potential of the abnormal segments and their positions in the spinal column. For example, lateral abnormalities produce congenital scoliosis, and anterior or posterior midline defects result in congenital kyphotic or lordotic deformities.

Malformations of the head and neck, especially the internal and external auditory apparatuses, maxillae, and mandibles, occur frequently in patients with high thoracic and cervical curves. The association of a short neck, low posterior hairline, and restriction in neck motion caused by the congenital fusion of cervical vertebrae represents Klippel-Feil syndrome. Renal anomalies, the congenital elevation of the scapulae (i.e., Sprengel deformity), impaired hearing, and congenital heart disease are common associated anomalies in affected patients. The VACTERL syndrome (vertebral defects, imperforate anus, cardiac anomalies, tracheoesophageal fistula, renal dysplasia, and limb deficiencies often in the radius) underscores the complex nature of the relationships between the rapidly evolving organ systems and the musculoskeletal system during the first trimester of pregnancy. Any child with congenital scoliosis should be specifically screened for cardiac and renal defects, while other VACTERL components are generally more diagnostically obvious.

McMaster reported a high incidence of occult intraspinal abnormality in patients with congenital scoliosis.[19] Possible anomalies included intradural and extradural lipoma cysts, teratoma, spinal cord tethers, diplomyelia, and meningocele. In some instances, the spinal cord may be split by a bony, fibrous, or cartilaginous bar extending from the posterior aspect of the vertebral body to the vertebral arches. This condition, known as diastematomyelia, commonly occurs in association with defects at the thoracolumbar junction. Given this, children with spinal defects are typically evaluated with an MRI of the entire spine.

The association of vertebral anomalies with neural tube or spinal cord defects is to be expected, given the intimate relationships of their embryonic development. Spina bifida occulta is the most common and least serious and myelomeningocele the most severe of such anomalies. Not all anomalies are easily identified on physical or radiographic examination. Unless the spurs are ossified, they are not easily visualized by conventional radiographic techniques. The physical signs of underlying spinal dysraphism include hairy patches, midline dimpling, nevi, inequality in the length of the lower extremities or circumferential asymmetry, and asymmetry in foot size. Screening MRI of the spine is considered when there is a significant or draining defect, or if there are progressive changes in the neurologic exam (see Chapter 58).

In Utero Positioning

The imprint of in utero positioning is frequently seen in the neonate. It can produce joint and muscle contractures and torsional and angular variations in the long bones, especially those of the lower extremities. It can also produce craniofacial distortion and positional contracture of the neck. The upper extremities are usually less affected.

The expression of in utero positioning depends on fetal position and the amount of compressive force applied. Intrinsic and extrinsic factors contribute to these variables. The intrinsic factors include oligohydramnios, multiple fetuses, a large fetus, abnormal fetal positioning (e.g., breech and transverse), and abnormal fetal muscle tone. The extrinsic factors include a small maternal pelvis and uterine deformities (e.g., bicornuate). These factors can lead to increased uterine compression and secondary changes in the neonate. Some of the more common problems related to in utero positioning include developmental dysplasia of the hip, metatarsus adductus, calcaneovalgus foot, tibial bowing, internal and external tibial torsion, and hyperextended knees. Craniofacial abnormalities, which are much less common, may include plagiocephaly, mandibular

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asymmetry, flattened facies, and crumpled ears. Therefore, most of these abnormalities are physiologic rather than pathologic in origin and resolve with normal growth and development. Others, such as developmental dysplasia of the hip, may not resolve and may cause significant disability unless they are recognized and appropriately managed. The speed of resolution depends on the severity of the deformity and the rate of growth of the involved area.

It is a common misconception that the bowed appearance of the neonate's lower extremities is an abnormality. All term neonates have 20- to 30-degree hip and knee flexion contractures that decrease to the neutral position by 4-6 months of age. The newborn hip is externally rotated in extension to 80-90 degrees and has a limitation of internal rotation of 0-10 degrees. Metatarsus adductus results from the tucked-under position, in which each foot is wrapped around the posterolateral aspect of the opposite thigh. The same position also produces lateral tibial bowing and inward (internal) rotation of the tibia. Tibial bowing and internal tibial torsion contribute to the bowed appearance of the lower extremity during the first year of life as well as a mild pigeon-toed or in-toed gait during the second year. However, this condition must be recognized as a normal variation resulting from the in utero position; it typically resolves with normal growth and development.

Trauma

See Chapter 29. Neonatal musculoskeletal injuries are frequently the result of a difficult or traumatic delivery. An abnormal intrauterine presentation and forcible extraction are associated with clavicular fractures, brachial plexus injuries, and occasionally long-bone fractures or epiphyseal separations (e.g., proximal humeral epiphysis) in otherwise healthy term infants. Prematurity, low birth weight, and underlying systemic disease may also predispose an infant to birth trauma and neonatal injury. These fractures are not usually associated with neurologic injury, and the prognosis for healing and subsequently normal function is excellent. Generally, these can be treated with minimal immobilization, such as pinning the arm sleeve to the body of the shirt. In contrast, fractures associated with neurologic injuries are more complex and have a more guarded prognosis.

Neonatal fractures resulting from abuse are uncommon but do unfortunately occur. Long-bone fractures in association with vague histories or suspicious causes must be investigated.

Spine

Neonatal spinal trauma may be classified as an injury directly to the spine (i.e., vertebrae, intervertebral discs, and supporting ligamentous structures) or indirectly to the surrounding structures. The latter includes injuries to the brachial plexus and the sternocleidomastoid muscle (e.g., muscular torticollis) of the neck.

Spinal Injury

Difficult delivery is the most frequent cause of neonatal spinal injury. Breech presentation, especially when associated with intrauterine neck hyperextension, traction during delivery, and forceps traction, puts the spine and enclosed neural elements at risk for injury. Injuries of the cervical spine are more common than those of the thoracic or lumbar spine; upper cervical injuries are more common than lower ones.

Spinal cord injury may occur with or without vertebral fracture. Excessive ligamentous laxity and the relative weakness of supporting musculature predispose the neonate to stretch injuries of the spinal cord without obvious skeletal damage. This stretch can produce spinal cord ischemia caused by vertebral artery or segmental vessel injuries and result in neurologic abnormality in some neonates. Extensive areas of vascular damage in the spinal cord have been reported in neonates who died as a result of obstetric trauma.

Fractures, dislocations, and subluxations of the occipitoatlantal, atlantoaxial, and second and third cervical articulations have been reported. The neonatal spine is incompletely ossified, and skeletal injury may be difficult to detect on routine radiography. Radioisotope scanning or magnetic resonance imaging may be useful for documenting injury in questionable cases.

Injuries of the brainstem and spinal cord may be fatal if the respiratory centers are compromised. For infants who survive, the goal of treatment is to improve function. When fracture or dislocation is documented, reduction and immobilization may be necessary to achieve segmental stability. Unfortunately, reduction rarely improves neurologic function.

Brachial Plexus Injury

See Chapter 29. Injuries of the brachial plexus have long been recognized as a consequence of difficult labor and delivery.[22] In 1877, Wilhelm Heinrich Erb described isolated upper plexus palsy and localized the site of damage to the junction of the C5 and C6 nerve roots, known thereafter as the *Erb point*. Erb's description remains an accurate assessment of the most common variety of plexus injury, with traction damage to spinal nerves C5, C6, and C7. The arm is held in a characteristic waiter's tip position, with the shoulder adducted and internal rotated, the elbow extended, the forearm pronated, and the wrist flexed.

Other patterns of brachial plexus injury are less common but well documented. Isolated injuries to the lower portion of the brachial plexus described by Klumpke are uncommon in infants. Wickstrom reported 11 such cases in his series of 87 patients.[29] Hoffer and associates observed four cases of posterior plexus damage in their series of 39 patients.[13] Total or mixed plexus involvement is reported to be the second most common pattern of injury after isolated upper plexus palsy.

The incidence of brachial plexus injury at birth is 0.1%-0.3% of live births. Risk factors include elevated birth

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weight, prolonged labor, shoulder dystocia, and breech presentation, as well as high maternal body mass index and fetal asphyxia. Additionally, a humerus fracture is a risk factor for brachial plexus injury, whereas a clavicle fracture is not. Cesarean delivery does not fully protect children from birth palsy[1]; 10% of the affected patients have a history of cesarean delivery.

Traction damage of the plexus may occur at any level from the origins of the cervical nerve roots at the spinal cord to the terminal branches of the plexus and may range in severity from stretch with intact neural tissues to avulsion of nerve roots. The physical findings at birth reflect the degree of involvement. With lesions of the upper plexus, active wrist flexion and finger flexion may be present. In complete injuries, these motions are absent. An avulsion of the nerve root, or preganglionic lesion, is generally associated with the presence of Horner syndrome (sympathetic chain), elevated hemidiaphragm (phrenis nerve), or winged scapula (long thoracic nerve). The injury must be differentiated from other causes of decreased active motion in the neonatal period, such as fracture of the clavicle or upper humerus and septic arthritis or osteomyelitis. The diagnosis can usually be established from a history of difficult delivery, physical examination, and radiographic evaluation of the upper limb and trunk.

The prognosis varies with the extent of damage to neural tissues. Up to 90% of patients with incomplete lesions involving the upper plexus can expect full recovery with no treatment. In general, these children recover biceps function within 1 month of life and quickly become normal. Patients with complete injuries or injuries of the lower plexus do not fare as well. Most recovery occurs within the first 3 months of life, but continued slow improvement for up to 5 years after birth has been reported by Tada and colleagues for patients with complete injury.[25] Partial recovery occurs in most cases. Surgical repair of the brachial plexus has been recommended by Waters for children who have no return of biceps function by 6 months of age.[28] Compared with the natural history of the lesion, improved but not normal function is possible. Shoulder contracture and osseous deformity (nonspherical humeral heads and abnormal glenoids) are common in patients with birth palsies. They commonly occur in children who have incomplete recovery and are also seen in those who eventually have complete neurologic recovery if that recovery does not start within the first 3 weeks of life.[12]

Infants with nerve root avulsion have the worst prognosis; no motor recovery can be expected in such cases, although some sensory recovery may occur. Fortunately, avulsion injuries are uncommon. Surgical repair of infants without elbow flexion using ulnar and/or medial nerve fascicle transfers has demonstrated partial efficacy in infants with nerve root avulsion, late presentation, dissociative recovery, and failed nerve grafting.[8]

In most cases of neonatal brachial plexus palsy, no treatment is necessary. Abduction splinting of the limb in the first few months of life is unnecessary and may further complicate lower plexus injury. Gentle range-of-motion exercises may be used to prevent adduction and internal rotation contracture. Infants with incomplete recovery may require later reconstructive surgery to minimize deformity and functional disability. In young children without fixed contractures and secondary bony deformities, tendon transfers may be used to balance asymmetric forces.[13,27] In older children, humeral osteotomy is occasionally necessary to correct internal rotational deformity.[17]

Muscular Torticollis

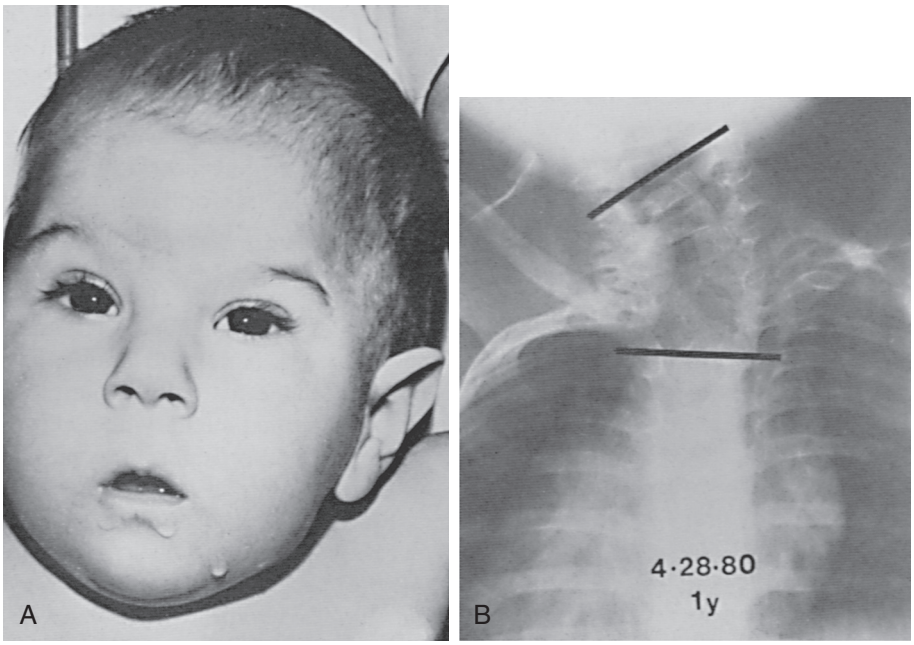
Torticollis in the neonatal period is most commonly associated with abnormalities of the sternocleidomastoid muscle. Shortening of the sternocleidomastoid muscle results in tilting of the head toward the affected muscle and rotation of the chin toward the opposite side. Birth trauma, intrauterine malposition, muscle fibrosis, and venous abnormality within the muscle have all been implicated, but no single cause has been identified. Davids and associates demonstrated that the sternocleidomastoid muscle is contained within a separate fascial compartment.[6] They thought that a stretch or tear of the sternocleidomastoid muscle that caused bleeding could result in a compartment syndrome, leading to significant muscle damage and contracture. A palpable mass is sometimes present within the affected muscle during the first few weeks of life. Flattening of the head and slight facial asymmetry or plagiocephaly are usually present. If the deformity is not corrected, contractures of the soft tissues on the side of the affected muscle occur, and pronounced plagiocephaly may develop.

Torticollis is occasionally associated with developmental dysplasia of the hip (DDH) severe enough to require treatment; this varies between 3.7% and 10% of patients, depending on the study.[20,26] It is also seen in association with metatarsus adductus.[15] All of these conditions are often the consequence of tight in utero positioning.

Torticollis may also be the result of congenital cervicovertebral anomalies (Fig. 97.2). Ballock and colleagues reported that Klippel-Feil syndrome and congenital scoliosis were diagnosed in 5% of all torticollis patients referred to a large tertiary children's hospital.[2] The severity of the curvature and associated head deformity depend on the nature of the vertebral defect. Cervical hemivertebrae are sometimes less deforming than unsegmented, unilateral cervical bars. As in all cases of congenital spinal curvature, a careful search for other systemic anomalies, such as those involving the cardiac and genitourinary systems, must be made.

The cause of torticollis should be established before treatment is initiated. Careful radiographic examination of the cervical spine is recommended. Anteroposterior and lateral views of the neck should be obtained initially; computed tomography may be necessary in some cases. Particular attention should be given to the upper cervical spine, especially the occipitoatlantal (occiput-C1) and the atlantoaxial (C1-C2) regions. If no underlying skeletal abnormalities are identified, a program of stretching exercises is indicated to lengthen the contracted sternocleidomastoid muscle. The

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• **Fig. 97.2** Congenital scoliosis may be manifested as torticollis. **A,** Clinical photograph of a 1-year-old child with congenital cervical scoliosis. The chin is tilted toward the right and the occiput toward the left. **B,** Radiographic views of the cervical spine in this patient show multiple hemivertebrae formation and an unsegmented congenital bar on the left side of the lower cervical spine. By convention, scoliosis films are viewed as if the examiner is facing the patient's back.

head is first tilted toward the opposite shoulder, and the chin is then rotated toward the affected side. Exercises should be performed gently, and the corrected position should be maintained for 5-10 seconds on each repetition. A program of 10-15 repetitions performed four times daily is sufficient in most cases. Stretching should begin early. This procedure seldom fails if begun during the first 3 months of life, but seldom succeeds if begun after 18 months of age.[7] Positioning the infant's crib with the normal side of the neck toward the wall sometimes stimulates an infant who lies prone to turn his head and stretch the sternocleidomastoid muscle. However, this is not always reliable and should not replace manual exercises.

The surgical release of sternocleidomastoid contracture is indicated if there is significant deformity after 6 months of vigorous therapy or for older children with untreated torticollis.[4] Early surgery provides the best outcome, although children can benefit from surgery up to 10 years of age.[5] Delayed treatment results in significant plagiocephaly, and surgery before 5 years of age was associated with more improvement in craniofacial curvature than surgery after 5 years, although both groups had improvement.[16] Recurring contracture is a problem in older children.

The treatment of torticollis resulting from congenital cervical scoliosis is difficult because the primary cause of torticollis in these patients is skeletal, and soft tissue stretching cannot provide lasting correction. Surgical fusion of the affected area may be necessary to halt progression. It may be impossible to reverse the facial asymmetry that has developed because of head tilting.

Fractures

See Chapter 29. Neonatal fractures usually involve the upper extremity, particularly the shoulder region, and are the result of a difficult delivery. Fractures of the lower extremity are less common and may be indicative of an underlying neuromuscular disorder, especially those that limit joint mobility, such as arthrogryposis multiplex congenita. Fractures may also result from a bone disorder, such as osteogenesis imperfecta.

Clavicle

Fractures of the clavicle are the most common type of fracture in neonates. The incidence of clavicular fractures ranges from 2-7 cases per 1000 live births. McBride and coworkers reported 9106 newborns prospectively screened for clavicular fracture.[18] In this study, the risk factors included high birth weight, shoulder dystocia, and mechanically assisted delivery. Breech positioning was a factor in previous decades but not in this study. The liberal use of cesarean delivery appears protective. Of the 9106 babies reviewed, 1789 were delivered by cesarean section for various indications, including breech positioning. There were no clavicular fractures in these patients, although other authors have reported clavicular fractures after cesarean delivery.[14]

Fractures may be complete or incomplete (e.g., greenstick fracture). Complete fractures are more likely to be accompanied by classic symptoms and signs. Irritability and pseudoparalysis (e.g., decreased motion because of pain) of

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the involved limb are common. Discoloration, tenderness, and crepitation at the fracture site are common physical findings. Brachial plexus palsy, neonatal sepsis, traumatic separation of the proximal humeral epiphysis, humeral shaft fracture, and shoulder dislocation must be considered in the differential diagnosis.

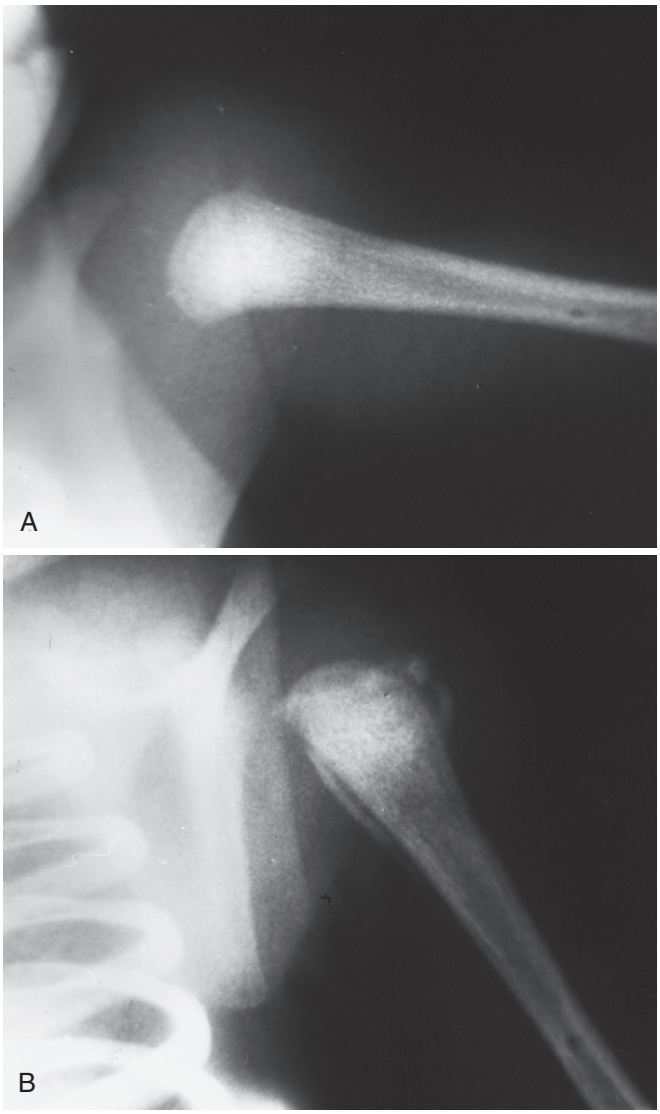
The treatment of clavicular fracture is simple; asymptomatic patients with incomplete fractures need no immobilization. Symptomatic infants, usually those with complete fractures, should be treated. The treatment can include applying a figure-eight harness of gauze and tape or securing the affected arm to the chest with a bandage for 7-10 days. Pinning the sleeve of the infant's shirt to the front is often sufficient. An elastic bandage loosely applied around the chest and involved extremity after a cotton pad has been placed in the axilla can be considered for larger infants.

Congenital pseudarthrosis of the clavicle is a rare condition that is distinguished from a neonatal clavicle fracture by the lack of birth trauma and the lack of healing callus on follow-up images. Isolated right-sided involvement is most common, with bilateral involvement less common and isolated left-sided involvement generally seen only in the context of dextrocardia. It is postulated that compression from the subclavian artery may explain the predilection for right-sided disease, and cervical ribs may account for bilateral disease. Congenital pseudarthrosis of the clavicle is generally asymptomatic in infants, with operative repair delayed until early childhood.

Long-Bone Fractures

Fractures of other long bones are occasionally seen after a difficult delivery. Fractures or separations of the proximal humeral epiphysis may occur with the same force that produces clavicular fracture and brachial plexus injury. Symptoms and signs may be similar; pseudoparalysis, swelling, pain on passive motion, and crepitation with shoulder joint motion are usually present. In contrast to the clavicle, the proximal humeral epiphysis is not ossified at birth, and routine radiography cannot demonstrate fracture or epiphyseal separation (Fig. 97.3). Ultrasonography can be used to establish the diagnosis in some cases, but most often the diagnosis is not confirmed until healing callus formation is seen radiographically 7-14 days later. Arthrography and magnetic resonance imaging can also be used to establish the diagnosis. When the diagnosis is confirmed soon after injury, the affected limb can be immobilized in a Velpeau bandage, although simply pinning the shirt to restrict motion is often adequate. Treatment is unnecessary if the diagnosis is delayed until callus formation has occurred. Scaglietti pointed out that late contractures of the shoulder in patients with fractures or separations resulting from a severely displaced proximal humerus may be difficult to distinguish from contractures caused by brachial plexus injury.[22]

Fractures of the humeral and femoral shafts occasionally occur during delivery or with the routine management of a premature infant or an infant with a severe metabolic or neurologic disorder. Such injuries are the result of an underlying weakness of the bone rather than traumatic handling, and accompanying soft tissue injury is rarely severe. Such fractures can usually be treated successfully with the application of a simple plaster splint until radiographic callus formation occurs. Spica casts are often used for fractures of the femur shaft, although in the infant, a Pavlik harness may simplify care without any delay in healing or additional deformity.[23] The remodeling potential of the neonatal skeletal system is extraordinary, and long-term sequelae from long-bone fractures are not common.



• **Fig. 97.3** **A,** Normal-appearing radiograph of the humerus in a female newborn who had pseudoparalysis and appeared to have pain with passive motion of the left shoulder. **B,** Repeated radiograph 1 week later demonstrates subperiosteal new bone formation, indicating that there had been a traumatic separation of the proximal humeral epiphysis at delivery. The arm is now asymptomatic, and voluntary shoulder motion has returned.

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Key Points

- Many neonatal musculoskeletal disorders are congenital in origin. The first trimester is the embryonic period producing congenital malformations, while the second and third trimester are the fetal period. This period produces deformations and alterations of essentially normal parts.
- Common embryonic period abnormalities include congenital spinal deformities, teratogenic limb and spinal malformations, and genetic disorders.
- Common fetal period abnormalities include in utero positioning problems (tibial torsion, metatarsus adductus, developmental dysplasia of the hip), trauma at birth producing spinal injuries, brachial plexus injuries, muscular torticollis, and fractures, especially of the clavicle and proximal humeral metaphysis.

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Bone and Joint Infections in Neonates

ALLISON GILMORE AND GEORGE H. THOMPSON

Bacterial infections of the neonatal skeletal system are potentially disabling because of damage to the articular cartilage and epiphysis. Prompt diagnosis and treatment are imperative to prevent sequelae.[2,18] Unfortunately, neonates with skeletal infections do not usually have the classic symptoms or laboratory findings of sepsis early on because of their immature immune systems. Feeding intolerance, reduced movement, and/or irritability may be the only early signs of infection. Diagnosis requires a high index of suspicion and appropriate evaluation. When infections involve the bone, the disease process is called *osteomyelitis.* When the synovium (the membrane lining of the joint) is the primary site of infection, the process is called *septic arthritis* (see Part 9: The Immune System).[10]

Osteomyelitis

Pathology and Etiology

Bone infection, or osteomyelitis, occurs by three mechanisms: bacteremia or hematogenous spread; direct inoculation from a puncture wound, such as a heel or femoral vein stick; and a contiguous spread from an adjacent focus of infection. In neonates, as in infants and children, most bone infections are hematogenous in origin. The most common site of osteomyelitis is the metaphysis, the region of the bone immediately adjacent to the physis or growth plate. The anatomic arrangement of metaphyseal vessels and the dynamics of blood flow in this region permit bacteria to lodge and proliferate. The nutrient artery ascends to the metaphysis from a central location within the bone. When the arterioles reach the physis, they make 180-degree turns and empty into the venous sinusoids. This process creates an area of sluggish blood flow and an opportunity for bacteria to become trapped and proliferate. A separate set of vessels nourishes the epiphysis.

In childhood, there is no connection between the epiphyseal and metaphyseal blood supply. The physis creates a barrier that is seldom penetrated by the spread of infection from the metaphysis to the epiphysis or from the epiphysis to the metaphysis. However, during the first 12-18 months of life, this barrier to the spread of infection does not exist, because there are vessels passing through the physis that connect the epiphyseal and metaphyseal circulations.[2,3,17] These vessels allow infections to cross the physis, which may account for the increased incidence of physeal damage seen in neonatal osteomyelitis when compared with childhood osteomyelitis.[2,10,18] Peters and associates observed the late onset of growth disturbance after neonatal osteomyelitis and recommended that the affected neonates be followed to skeletal maturity to monitor for growth disturbances.[18]

When bacteria lodge in the metaphyseal vessels and begin to proliferate, inflammation followed by abscess formation occurs. The pressure from the purulent material causes extrusion of the pus through the haversian canals to the cortex and subsequently into the subperiosteal space. The continued subperiosteal accumulation of purulent material strips the periosteum from the bone. Because the periosteum supplies blood to the cortex, this stripping process interrupts cortical blood flow. As a result, large areas of cortical bone may become devascularized. This dead bone, or sequestrum, can serve as a site for chronic infection, which is isolated from limited neonatal defense mechanisms and antibiotics.[17] The elevated periosteum produces new bone in an attempt to repair the injured bone. This process in turn produces the involucrum, which surrounds the sequestrum.

Draining cutaneous sinuses may arise when pus ruptures through the periosteum, adjacent soft tissues, and skin. Infection may occasionally spread into an adjacent joint space, causing secondary septic arthritis. The destruction of the epiphysis may occur through the direct spread of infection into it. This process can result in subsequent shortening, angular deformity, or both, of the involved extremity.[18] In neonates, complete physeal closure can occur, resulting in shortening.[2] Damage to the articular surface of the joint may result in the loss of motion and ultimately degenerative osteoarthritis.

The etiologic organisms responsible for neonatal osteomyelitis are variable. *Staphylococcus aureus* has traditionally been the most common causative organism.[2] Methicillin-resistant *S. aureus* (MRSA) has been reported in neonates, which is especially destructive.[13] Group B streptococcus (*Streptococcus agalactiae*) and Gram-negative organisms (*E. coli* and *Klebsiella pneumonia*) are all seen in the neonatal

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Abstract

Bacterial infections of the neonatal skeletal system are uncommon. Most will be hematogenous (blood borne) in origin. When bone is the primary focus it is termed osteomyelitis; if the synovial lining of a joint is the primary site it is septic arthritis. Limitation of motion, pain, joint effusion, and increased warmth are common findings. Involved neonates typically appear less ill because of the persistence of maternal antibodies. They have less fever, leukocytosis, and elevation of erythrocyte sedimentation rate and C-reactive protein. Plain radiographs can be helpful. Technetium bone scan and magnetic resonance imaging are frequently necessary in establishing the diagnosis and location. Early and accurate treatment is important. Antibiotics alone can be successful during the early inflammatory stage while surgery to drain an established septic arthritis, subperiosteal, or bone abscess in osteomyelitis is frequently necessary. Delaying adequate treatment can result in chronic osteomyelitis, bone and joint destruction, avascular necrosis, and other complications.

Keywords

osteomyelitis
septic arthritis
hematogenous
bone/joint aspiration
antibiotics
surgical drainage

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period.[5] *Candida albicans* can also cause osteomyelitis in those neonates at high risk for infection.

Diagnosis

The clinical manifestations of osteomyelitis in children vary with age. In previously healthy neonates, it usually occurs during the first 2 weeks of life. Limitation of spontaneous movement with pseudoparalysis of the involved extremity is the most common sign. Localized tenderness, erythema, increased warmth, and swelling may occur. Associated septic arthritis with accompanying joint effusion and increased warmth occurs in many cases. Term neonates usually appear less ill than would be expected because of the persistence of maternal antibodies. They have less fever, leukocytosis, and elevation of the C-reactive protein and erythrocyte sedimentation rate[2] than older children with similar infections. Less commonly, neonatal osteomyelitis presents as septicemia. The presentation and course of osteomyelitis are strongly correlated with the health of the infant before presentation. Infants with multiple sites of infection are usually ill before its onset and have an increased incidence of placement of umbilical catheters or other lines. They are also more ill than those neonates presenting with only one site of infection.[2]

Some neonates are at increased risk for osteomyelitis; they also have a more severe course of the disease. Bergdahl and colleagues identified the following risk factors in a study of 40 neonates with osteomyelitis: a birth weight of less than 2500 g or gestational age of less than 37 weeks, emergency cesarean delivery, a congenital malformation requiring neonatal surgery, respiratory distress syndrome, hyperbilirubinemia, large vessel (usually umbilical) catheterization, perinatal asphyxia, scalp laceration after vacuum extraction, and renal vein thrombosis.[2] Twenty-one neonates were found to have risk factors but 19 did not. Of the 21, most had multiple sites of infection; 13 of the 21 (62%) neonates with risk factors had serious skeletal sequelae. In the remaining 19 neonates, multiple sites of infection were uncommon, and serious skeletal sequelae occurred in less than 20%.

The early diagnosis of osteomyelitis is based on obtaining purulent material, blood, or both for cultures and antibiotic sensitivities. Early in the course of the disease, radiographs and bone scans may be normal.[1,3,6] Bone aspiration is usually positive. The cultures of subperiosteal metaphyseal pus yield a pathogen in about 70% of cases. The point of maximal swelling, bone tenderness, and fluctuation on physical examination is the most appropriate location for needle aspiration. The skin overlying the affected region should be prepared with an antiseptic solution and draped with sterile towels. After infiltration of the area with local anesthetic, an 18-gauge spinal needle, with the stylet in place, is passed through the skin to the bone. The subperiosteal space is aspirated first. If the tap is dry, the needle with the stylet should be gently twisted through the bone cortex into the metaphysis, which is then aspirated. The aspirated fluid or blood should be immediately Gram-stained and cultured. The organism may also be recovered from other sources. Blood cultures are positive in 60% of children with osteomyelitis. When osteomyelitis complicates meningitis, the organism may be recovered from cultures of the cerebrospinal fluid.

Imaging

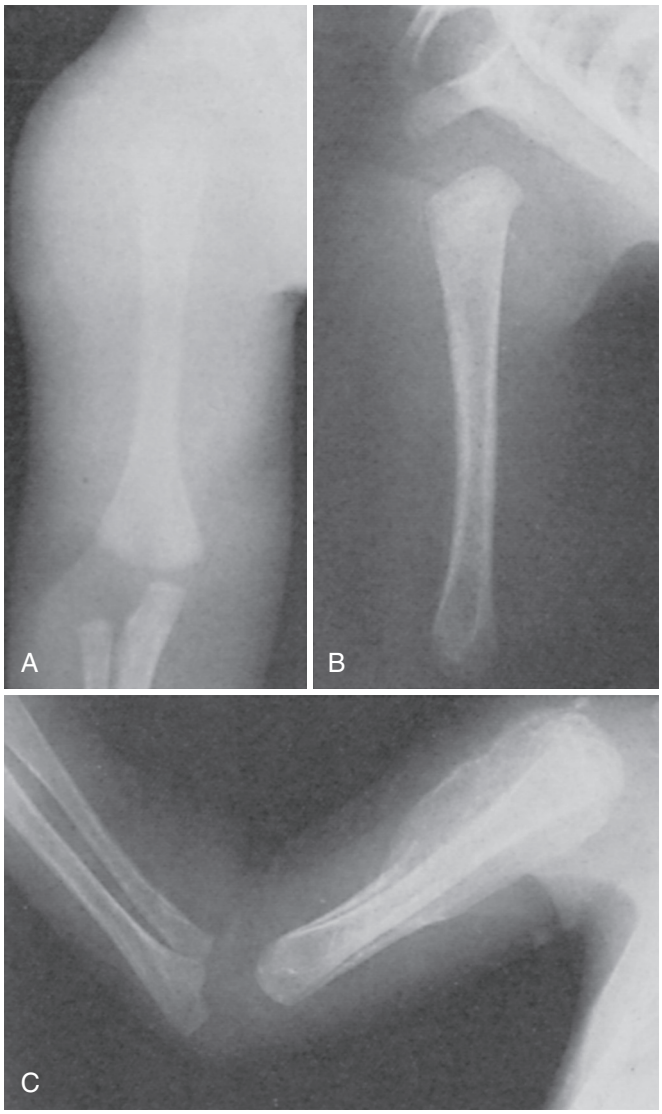
See Chapter 38. A diagnosis cannot be easily made by bone aspiration during the inflammatory phase before abscess formation. At this point, imaging can be helpful. Plain radiographs of the suspected bone are often a valuable procedure. Within a few days of the onset of infection, deep edema, joint effusion, and sometimes bone destruction can be detected.[2] The edema is visible sooner in neonates than in children, because the neonate has very porous bones and a loosely attached periosteum (Fig. 98.1), which permits the earlier collection of subperiosteal abscesses in neonates than in children. This fact also accounts for the relatively favorable results of diagnostic aspiration in neonates.

If radiographs are unproductive, ultrasound can be useful in localizing the areas of deep edema (subperiosteal fluid collection or abscess) and joint effusion, as well as periosteal thickening or elevation.[15] Magnetic resonance imaging is very sensitive for early detection of osteomyelitis and will show details of bone involvement, abscess formation, and septic arthritis. Limitations include possible need for sedation and patient stability to transfer to the MRI unit.[9] Technetium bone scanning is currently used less often; however, it may be helpful in neonates with suspected multifocal infection.[11] There is some controversy over the merits of bone scanning in neonates because of their decreased inflammatory response and the large amount of isotope uptake from the very active adjacent epiphysis. In 1980, Ash and Gilday[1] concluded that it was very unreliable. However, Bressler and co-workers[3] and others[6] have suggested that technetium bone scans can be helpful. Bressler's group scanned 33 infants suspected of having osteomyelitis. Each of the 25 sites of proven osteomyelitis in 15 infants was demonstrated on bone scanning. Another 10 sites that were radiographically negative were also demonstrated to be positive on bone scanning. The bone scan, if negative, does not exclude osteomyelitis.

The results of indium and gallium scans for acute osteomyelitis in neonates have not been reported. A concern about gallium scans is related to the pathology of osteomyelitis. If there is extensive septic embolization of metaphyseal vessels, labeled blood cannot penetrate the metaphysis. If the periosteum is stripped off the cortex, devascularizing the cortical bone, there can be no blood flow in the cortex. Under these circumstances, the uptake by bone may be difficult to predict. However, Demopulos and associates recommended an indium scan if the technetium bone scan in the neonate is not highly suggestive of osteomyelitis.[6]

Another concern in the assessment of osteomyelitis is the determination of whether metaphyseal aspiration can

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• **Fig. 98.1** Radiologic changes in neonatal osteomyelitis. **A,** Early proximal humeral osteomyelitis. Soft tissue has become swollen around the affected bone. **B,** Periosteal elevation is manifested by subperiosteal bone formation. **C,** Massive subperiosteal new bone formation. The humeral shaft has become surrounded by new bone.

produce a positive bone scan. Canale and colleagues[4] assessed the effects of bone, and joint aspiration on the bone scan results in healthy dogs. They used multiple aspiration techniques on the bones and joints of 15 dogs and scanned them between 5 hours and 10 days of aspiration. In no case did joint aspiration lead to a positive bone scan. Metaphyseal drilling and periosteal scraping with needles occasionally led to positive bone scans after a 2-day delay. Thus, bone aspiration does not initially affect a technetium bone scan.

Treatment

Treatment must not be delayed for neonates with suspected osteomyelitis. Antimicrobial therapy should be initiated, usually with a combination of agents, as soon as a presumptive diagnosis is made and appropriate material for cultures has been obtained. Treatment can later be appropriately altered according to culture results and antibiotic sensitivities. For neonates, optimal coverage is provided by penicillinase-resistant penicillin coupled with an aminoglycoside. The new third-generation cephalosporins have been successfully used in the treatment of a form of osteomyelitis caused by enteric bacilli. However, these agents should not be used alone as the initial treatment, because their activity against group B streptococci is inadequate. When these drugs are used as part of the initial therapeutic regimen, penicillinase-resistant penicillin should be used concomitant with them. After an organism is isolated, focused antibiotic treatment is possible. The duration of treatment should be at least 3 weeks and probably not more than 6 weeks for acute hematogenous osteomyelitis. Nelson suggests a clinical approach to antibiotic management.[16] After local inflammation subsides and measures of inflammation such as CRP and erythrocyte sedimentation rate return to normal, he recommends 14 more days of antibiotics for group A streptococci and encapsulated bacteria such as pneumococci and 21 more days for staphylococcal infection. Historically, neonates were treated solely with intravenous antibiotics. New literature may suggest treating neonates with osteomyelitis with sequential intravenous–oral antibiotic therapy. A Dutch neonatal ward successfully treated proven methicillin-susceptible *Staphylococcus aureus* osteomyelitis with 2-3 weeks of intravenous antibiotics followed by oral clindamycin for 3 weeks without relapse or sequelae. This theoretically could decrease morbidity from intravenous access as well as associated costs.[7]

Primary surgical treatment depends on the results of bone aspiration. If grossly purulent material is recovered from the subperiosteal space or the metaphysis, an abscess has formed. In these cases, surgical drainage is necessary to decompress the abscess. This procedure facilitates blood flow and the subsequent delivery of antibiotics. Surgical drainage also allows the removal of the bone sequestrum. When pus is not recovered at the time of initial aspiration, the patient's infection is in the cellulitic or inflammatory phase. The aspirated blood is used to obtain blood cultures, and antibiotic therapy is initiated. It is assumed that the bone blood flow is still adequate in the cellulitic phase to deliver antibiotics to the site of infection, because there is no pus under pressure. The affected limb should be immobilized with splints. Neonates must be carefully followed during the early phases of treatment. Surgical intervention may become necessary if an adequate clinical response is not obtained within 48 hours of initial antimicrobial therapy.[14] An inadequate response implies that an abscess is forming. Reassessment, including repeated aspiration, is indicated. If an abscess is identified, surgical drainage will be necessary.

La Mont and co-workers[14] reviewed 69 children (15 neonates) retrospectively and 44 children (4 neonates) prospectively, all with acute hematogenous osteomyelitis. They

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concluded that surgery was seldom necessary because most of the prospective group improved clinically after 48 hours of appropriate intravenous antibiotics, and few of them had abscesses aspirated. In their study, surgery was infrequently used, and the results were excellent. It was their impression that the aspiration of pus from the bone was an indication for surgery but was seldom encountered. Drainage was also recommended for an extraosseous abscess.

It is believed that the surgical decompression of long bones such as the femur, tibia, humerus, radius, and ulna is necessary if pus is aspirated from bone or the subperiosteal space.[2] Decompression consists of drilling a hole in the metaphysis or removing a small cortical window. The wound is then closed loosely to allow it to drain. If a drain is placed, it is removed 24-48 hours later. Surgical decompression is also necessary if there is not a good clinical response to antibiotics within 48-72 hours, even if no pus is aspirated from the bone.

If osteomyelitis is localized to flat bones, such as the pelvis or vertebrae, the administration of antibiotics without surgical decompression is usually sufficient treatment. However, caution is necessary because Bergdahl and associates reported one death and one case of tetraparesis resulting from neonatal vertebral osteomyelitis.[2]

Septic Arthritis

Pathology and Etiology

The mechanisms responsible for joint or synovial infections in neonates and children parallel those for osteomyelitis: septicemia, contiguous spread from an adjacent focus of infection, and traumatic penetration of the joint space. Osteomyelitis in the proximal femur (hip), proximal radius (elbow), proximal humerus (shoulder), and distal tibia (ankle) in neonates may progress to a septic joint, because the metaphyses of these bones are intra-articular. The risk factors include prematurity, umbilical catheterization, perinatal asphyxia, and a difficult birth.[12] Regardless of the source, the ensuing inflammatory response results in synovial hypertrophy and altered capillary permeability. Purulent material accumulates within the joint, and fibrinous clots may coat the joint surfaces. The diffusion of nutrients across the articular cartilage of the joint is interrupted, and the normal lubrication processes are altered. Lysosomal enzymes, which are released in neutrophil degeneration, attack the mucopolysaccharide components of articular cartilage. Hypertrophic granulation tissue forms a pannus that can erode articular cartilage and may allow the extension of infection to subchondral bone. Fibrous ankylosis of the joint may develop, with a permanent loss of motion.[19] Increased intra-articular pressure may occlude the vessels that supply the epiphyses and the physis, resulting in epiphyseal death or avascular necrosis. This process is especially applicable to the hip. The rupture of pus through the synovial membrane and into the surrounding tissues produces soft tissue abscesses that may later develop into draining sinuses.

Neonatal septic arthritis often results from osseous infection, and the bacterial agents responsible for the joint infections are similar to those previously described for neonatal osteomyelitis: *S. aureus*, streptococci, and enteric bacilli. Septic arthritis occurs less frequently as a primary entity; the Enterobacteriaceae family, the species of *Pseudomonas*, and *Neisseria gonorrhoeae* may be isolated in these cases. Fink and Nelson reported septic arthritis from *Haemophilus influenzae* in neonates as young as 3 days of age.[8] About 25% of the neonates with *H. influenzae* septic arthritis also have meningitis.

Diagnosis

The clinical presentation of neonatal septic arthritis is similar to that described for neonatal osteomyelitis. Joint effusion, increased warmth, and limited motion are often observed on physical examination. Often, early diagnosis is delayed because physical findings may be subtle.

The definitive diagnosis of septic arthritis requires aspiration of the affected joint. The causative agent can be recovered in about 60% of cases. The procedure should be performed under sterile conditions by an experienced physician, because repeated attempts to penetrate the joint may further damage the joint surface and the underlying bone. After culture and Gram staining of the fluid, determinations of the cellular count as well as glucose and protein concentrations should be obtained. Infected synovial fluid typically contains more than 50,000 white blood cells per cubic millimeter (primarily polymorphonuclear leukocytes); a glucose concentration of less than 40 mg/dL, or less than 30% of the serum concentration; and an elevated protein concentration. Blood cultures should also be obtained.

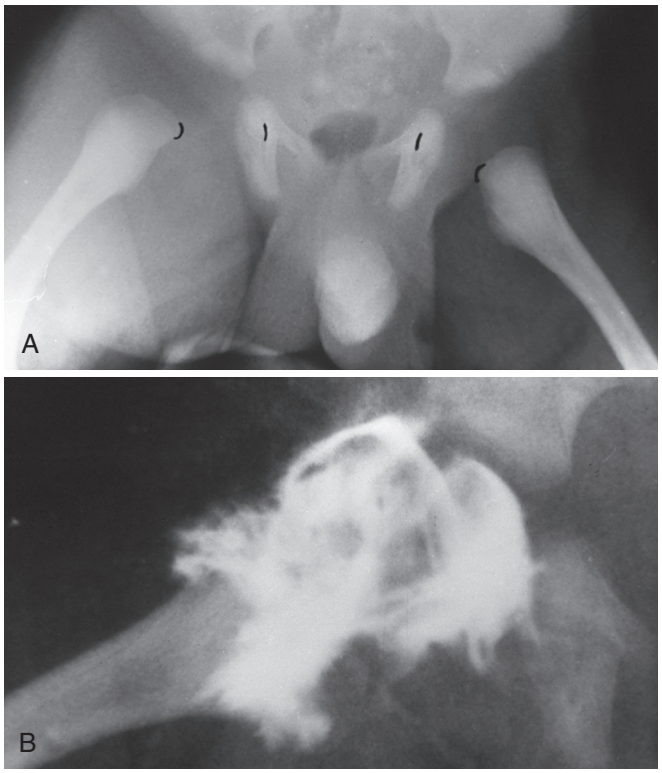
Imaging

Neonatal septic arthritis has the same recommendations as those for osteomyelitis (Fig. 98.2). Ultrasound is especially useful in neonatal hip infection. An ultrasound of both hips should be performed. Ultrasound, however, cannot differentiate between a septic and a sterile effusion. Magnetic resonance imaging may be difficult to obtain expeditiously, but can identify a joint effusion and subperiosteal abscess. Bone scans are used less often in neonates. Of special interest are the findings of Canale and colleagues that joint aspiration in dogs is never associated with a positive technetium bone scan.[4] Consequently, the aspiration of joints should never be discouraged on the basis of a belief that it may affect a later bone scan.

Treatment

Neonatal septic arthritis, like osteomyelitis, requires prompt treatment. Irreversible joint damage may occur unless

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• **Fig. 98.2 A,** Anteroposterior pelvic radiograph of a 2-week-old boy who had been irritable during diaper changes for 1 week. There were no systemic symptoms, such as fever, although the child had been quite irritable and not feeding normally. The femoral heads are not visible, because they do not begin to ossify until 4-6 months of age. Observe the widening between the acetabulum and the ossified medial corner of the proximal femoral metaphysis, which indicates lateral displacement or subluxation of the femoral head. **B,** Arthrocentesis revealed only a small amount of purulent material. An attempted arthrogram revealed gross distortion of the hip joint caused by inspissated purulent material. At the time of hip arthrotomy, clotted, purulent material was removed. This child subsequently developed avascular necrosis as a consequence of septic arthritis with subluxation. Fortunately, he made a satisfactory recovery and regained essentially normal hip function.

intra-articular pus is evacuated and effective antimicrobial therapy initiated.[16,21] Neonates should be managed jointly by pediatricians and orthopedic surgeons.

Combinations of antibiotics are selected to cover the most likely pathogens. A penicillinase-resistant penicillin and an aminoglycoside or cephalosporin usually provide adequate coverage pending the results of the cultures and antibiotic sensitivities (see Part 9: The Immune System).

Joint decompression is an essential component of successful therapy for pyogenic arthritis. However, opinions vary on the most effective method, specifically surgical drainage compared with repeated aspiration. Primary decompression is usually accomplished at the time of initial joint aspiration and may be sufficient in peripheral joints such as the knee, ankle, and elbow, which are easily aspirated and in which blood flow to intra-articular epiphyses is not at risk. Needle aspiration is not sufficient for decompression of the hip because increased intra-articular pressure may occlude blood flow to the femoral head, resulting in avascular necrosis. Immediate surgical drainage is mandatory for septic arthritis of the hip.[20]

The repeated aspiration of joints other than that of the hip may be appropriate. The morbidity for careful aspirations is less than that for arthrotomy, but persistent infection after repeated aspiration is probably more harmful than the risk for primary arthrotomy. Poorly executed needle aspiration may damage the articular surfaces and inoculate underlying bone with purulent fluid.

Like the therapy for osteomyelitis, effective antimicrobial therapy for pyogenic arthritis is a function of the agent, route, and duration of drug administration. After the pathogen has been isolated and antibiotic sensitivities are known, a single agent may be used. Intra-articular antibiotic instillation is unnecessary, because adequate drug concentrations are achieved in synovial fluid by the intravenous and parenteral routes.

Joint infections caused by *H. influenzae* require 2-3 weeks of therapy, whereas infections caused by other agents or those complicated by osteomyelitis may require up to 6 weeks of therapy. The treatment of neonatal gonococcal arthritis differs significantly from that of arthritis caused by other pathogens. Penicillin G, ampicillin, amoxicillin, tetracycline, and erythromycin have all been used successfully in therapy for gonococcal arthritis in 7- to 10-day courses. Other than diagnostic arthrocentesis, no surgical intervention is necessary for this disease.

Acknowledgment

The author and editors acknowledge the important contributions of Daniel R. Cooperman to the previous editions of this chapter, portions of which remain unchanged.

Key Points

- Neonatal skeletal infections are uncommon, but early diagnosis and treatment is critically important to prevent complications.
- Most skeletal infections are hematogenous (blood borne) in origin. If bone is the primary focus, it is termed osteomyelitis; if the synovium of the joint is involved, it is septic arthritis.
- Evaluation and diagnosis are primarily clinical, although plain radiographs and specialized imaging studies can be useful. Hematologic studies other than bone/joint aspirates and blood cultures and sensitivities are less helpful.
- Treatment is either by antibiotics, surgical drainage of abscess, or both, depending on the location, radiographic findings, and initial response to antibiotic therapy alone.

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99

Congenital Abnormalities of the Upper and Lower Extremities and Spine

JOCHEN P. SON-HING AND GEORGE H. THOMPSON

Upper Extremities

Congenital abnormalities of the upper extremities are those that occur during the embryonic period. Developmental deformities are those that occur primarily in the fetal or neonatal period. Because a developmental deformity may have a prenatal association, such as in utero positioning, it could be misinterpreted as a congenital abnormality. Congenital and developmental disorders of the upper extremities are less common than those affecting the lower extremities.

Shoulder

The failure of the scapula and the upper extremities to descend to their normal locations is called Sprengel deformity, which can vary from mild to severe. In this condition, the scapula is typically located abnormally elevated with respect to the child's neck and thorax, producing webbing of the skin at the base of the neck and a low posterior hairline. In the severe form, an accessory bone (the omovertebral bone) may connect the scapula to the spinous processes of the cervical spine and allow virtually no scapulothoracic motion. The severe forms are more likely than the mild forms to be diagnosed in the neonate. Associated muscle contractures that further limit the strength and stability of the shoulder girdle may also be present. In the mild form, the scapula is slightly elevated, with less than normal motion. There may be an association with congenital cervicovertebral abnormalities, particularly Klippel-Feil syndrome, and this association suggests the possibility of other congenital abnormalities, such as those in the cardiovascular and genitourinary systems. When Sprengel deformity is diagnosed, abnormalities in these other systems must be assessed.

Treatment is usually delayed until middle childhood and depends on the function of the child's shoulder and extremity. In severe forms, surgical repositioning and occasionally partial resection of the scapula may be necessary.

Elbow

Congenital radioulnar synostosis is an uncommon disorder that represents a failure of separation, or congenital fusion, between the proximal radius and ulna. It occurs from the 5th to the 8th week of gestation, when there is separation of the humerus, radius, and ulna from a common block of cartilage in the limb bud. This disorder is bilateral in approximately 50% of all patients and limits forearm pronation and supination. It is rarely recognized during the neonatal period, because there is no obvious deformity, only a loss of forearm rotation. In most cases, the forearm is in a physiologic position of 45-60 degrees of pronation. Only if there is extreme supination may the disorder be recognized in the neonatal period. The diagnosis of this disorder, which is confirmed radiographically, should be suspected in any neonate with restricted forearm pronation or supination.

Treatment is rarely indicated unless there is an abnormal position of the forearm that interferes with the function of the hand. The method of treatment, a rotational osteotomy through the synostosis, is usually delayed until middle childhood so that an adequate assessment of function can be determined. Attempts at restoring forearm pronation and supination by excising the synostosis have been unsuccessful.

Forearm and Wrist

Radial Hypoplasia and Clubhand

Hypoplasia of the radius is a commonly discussed and infrequently encountered entity, occurring in 1 in 100,000 live births. It is bilateral in 50% of cases. The deformity can vary from mild shortening of the radius to its complete absence (e.g., radial clubhand). As the radius shortens, the deformity becomes more apparent. In complete absence of the radius, the hand is radially angulated 90 degrees to the long axis of the forearm, the ulna is markedly bowed, and the ulna and humerus can be one-half the length of the opposite normal

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Abstract

Congenital abnormalities of the upper and lower extremities and spine are common neonatal problems. These develop during the embryonic period. Those involving the upper extremities are much less common than those involving the lower extremities and spine. Upper extremity malformations include Sprengel deformity of the scapula; proximal radius and ulna synostosis; radial dysplasia and clubhand; constriction bands; congenital amputations and reduction anomalies; and syndactyly, polydactyly, and macrodactyly of the fingers. Congenital spinal deformities are predominantly scoliosis, kyphosis, or sacral agenesis. The common abnormalities of the lower extremities include congenital angular deformities of the tibia and fibula (posteromedial and anterolateral angulation); proximal femoral focal deficiency; subluxation/dislocation of the knee; congenital talipes equinovarus deformities (clubfeet); congenital vertical tali; amputations and reduction anomalies of the lower leg; and syndactyly, polydactyly and macrodactyly of toes. Deformities associated with syndromes include skeletal dysplasias, osteogenesis imperfecta, neurofibromatosis, arthrogryposis multiplex congenita, VACTERL, and others. Most will be recognizable on clinical examination and require radiographic confirmation. Appropriate referrals to specialists are important in their management.

Keywords

embryonic period
first trimester
upper extremities
lower extremities
spine
syndromes

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• **Fig. 99.1** Clinical photograph of a 1-year-old boy with a right radial clubhand and hypoplastic index finger.

side by maturity. As the deformity becomes profound, so does thumb involvement (e.g., an absent first ray, thumb hypoplasia) (Fig. 99.1).

The entire extremity may be involved, including the scapula and clavicle. The radially based muscles of the forearm are also hypoplastic or absent. There is hypoplasia or absence of the radial artery, leaving the ulnar artery as the main blood supply to the hand. There is no radial nerve innervation to the skin distal to the elbow, leaving the median and ulnar nerve to anastomose to provide dorsal sensation. Radial clubhand is not simply a bony defect.

The most frequently associated abnormalities are blood dyscrasias and heart defects. Fanconi syndrome is a pancytopenia seen in some children with radial clubhand (see Chapter 79). Thrombocytopenia with an absent radius (TAR) syndrome is also seen. Holt-Oram syndrome, in which the primary manifestation is an absent thumb with atrioseptal defects, has a well-recognized association with radial clubhand.

Radial hypoplasia alone is inherited sporadically. There is no definitively identifiable inheritance pattern; the careful scrutiny of relatives seldom yields another affected individual. However, radial hypoplasia as part of a syndrome frequently has a defined inheritance pattern. Holt-Oram syndrome is inherited in a dominant pattern and Fanconi syndrome is inherited in a recessive pattern.

Treatment comprises both operative and nonoperative options and is recommended for cosmetic and functional reasons. The treatment begins with stretching. During the first 6 months of life, casts and splints are used to stretch the radially deviated hand to conform to a more neutral alignment. If the deformity is corrected, the patient wears a splint full-time for the first 6 years of life and then only at night after that. If the deformity is not corrected, the hand is centralized onto the ulna. At surgery, the carpus is fused to the ulna after an osteotomy to straighten the ulna. If the patient has a nonfunctional thumb, the index finger occasionally undergoes pollicization—in essence, it is turned into a thumb. The surgery is frequently performed when the patient is between 6 months and 1 year of age. After surgery, bracing is maintained full-time for the first 6 years of life. In bilateral cases, the surgery is staged, with one hand operated on at 6 months and the other hand at about 3 years of age.

The contraindications to surgery are a serious blood dyscrasia, heart problems, and profound muscle imbalance. If the elbow flexors are overpowered by the elbow extensors such that a child cannot touch the hand to the face even after physical therapy, surgery is not likely to provide a functionally useful hand.

Constriction Bands

Congenital constriction bands or amniotic band syndrome, also known as Streeter dysplasia or annular bands, features defects of the skin that result in ringlike strictures about the limbs and occasionally the trunk (Fig. 99.2).[23] It is seen in 1 in 15,000 live births, and multiple extremities are usually involved. The upper extremities, especially the hands, are involved more frequently than the lower extremities. The cause appears to be early amniotic rupture followed by temporary oligohydramnios; this may result in intrauterine compression and the subsequent constriction of fetal appendages by cords or bands of torn amnion[71] (see Chapter 24).

Patterson developed diagnostic criteria for congenital constriction band syndrome.[50] These criteria include simple band constrictions; band constrictions accompanied by deformity of the distal part with or without lymphedema; band constrictions accompanied by fusions of distal parts ranging from fenestrated or terminal syndactyly (e.g., acrosyndactyly) to exogenous syndactyly; and intrauterine amputations. Other congenital abnormalities frequently occur, such as clubfoot (30%), pseudarthrosis, peripheral hand palsy, and lower extremity length discrepancies.[24]

Rigid clubfoot distal to deep constriction bands may be difficult to correct.[1] Treatment involves the surgical release of the bands if the distal aspect is swollen and has lymphedema. The surgery is usually performed in two stages, although Greene has demonstrated that a complete one-stage release can be performed safely.[26]

Thumb and Fingers of the Hand

Congenital Amputations

Congenital amputation is the best example of a failure of formation. In general, the greater the loss of length, the rarer is the lesion. For instance, a child with congenital amputation at the forearm level is encountered in 1 in 20,000 live births, and one with a missing arm is encountered in 1 in 270,000 live births.

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• **Fig. 99.2** Clinical photographs of a newborn female with multiple annular bands. **A,** The right lower extremity demonstrates a band with complete transection of the skin and subcutaneous tissue. The associated talipes equinovarus (clubfoot) deformity has a duplication of the great toe. **B,** A similar lesion is present in the right upper extremity, with a significant amount of distal edema from lymphatic and venous obstruction. **C,** The left hand shows multiple bands with segmented edema and partial amputations.

When treating patients with congenital amputations of the upper extremities, it is necessary to define a goal for the patient. The arm serves as a positioning device for the hand. Consequently, treatment revolves around providing the patient with some sort of terminal device at the end of the usable arm. In the earlier stages, as the child achieves sitting balance, a soft terminal device is fitted. This device allows "two-handed" activities and is used to help pin objects against the normal hand. As the child reaches 2-3 years of age, prehension by means of a terminal device becomes possible. Early training allows children to become quite comfortable with these devices.

Syndactyly

Syndactyly is the most common form of congenital abnormality in the upper extremities and represents a failure of separation of two fingers (Fig. 99.3). This failure of separation occurs sometime between 5 and 8 weeks of gestational life and is seen in 1 in 2250 live births. The abnormality appears to be sporadic in 80% of cases; the other 20% are the result of genetic transmission. Because all forms of genetic transmission have been linked to syndactyly, genetic counseling is quite difficult. The classification of syndactyly



• **Fig. 99.3** Clinical photograph of a 3-month-old boy with complete syndactyly between the third and fourth fingers. There is hypoplasia of the distal phalanges of the index and small fingers.

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is defined by the degree of interconnection between the fingers. In complete syndactyly, the webbing extends to the tips of the fingers; in incomplete syndactyly, it does not. Simple syndactyly involves only the skin, whereas complex syndactyly involves bony fusion. Abnormalities of the blood vessels, nerves, and tendons are also seen.

Treatment is aimed at separating the digits to improve function. The affected digits are usually separated early, particularly when they are of unequal length. If the thumb and index finger are syndactylized, the longer digit becomes tethered and deformed by the shorter digit.[78] Surgery within the first year of life is suggested. When the digits are of nearly equal length, such as the long finger and the index finger, the surgery can wait until 2 or 3 years of age without difficulty.

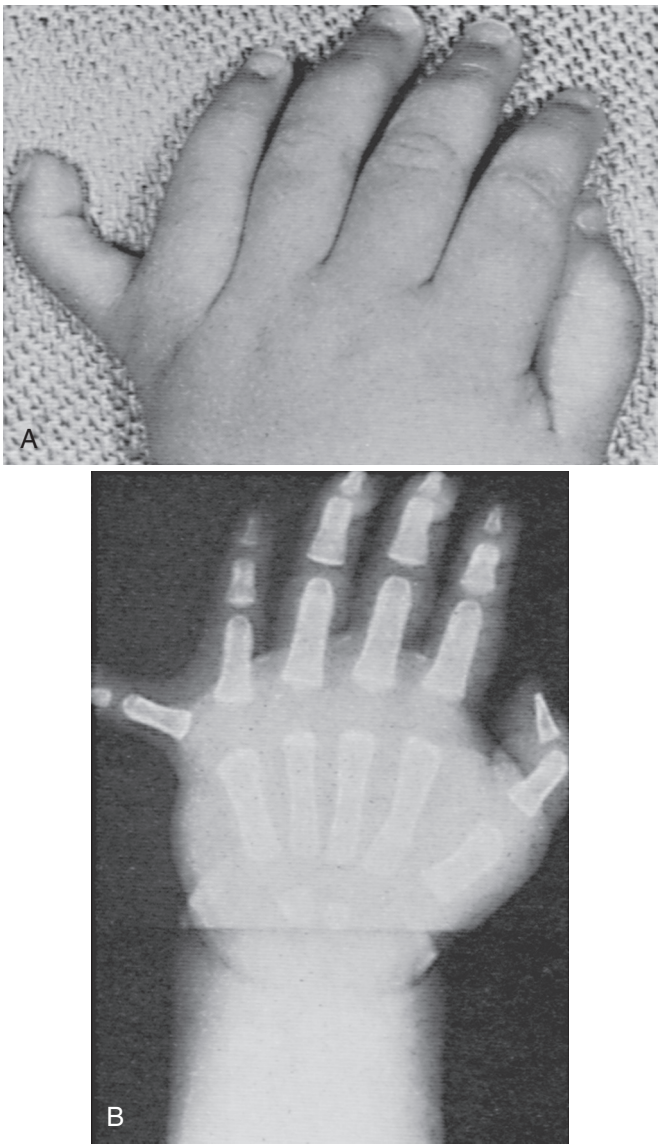
Polydactyly

See Chapter 30. Polydactyly is a common duplication abnormality of the hand (Fig. 99.4). It is seen in 1 in 300 African-American and 1 in 3000 Caucasian live births in the United States. The incidence of thumb polydactyly is identical in African Americans and Caucasians (0.8 in 1000 live births). Little-finger polydactyly is common in African Americans, with 1 in 300 affected, and is usually seen without associated abnormalities. In Caucasian infants, little-finger polydactyly is infrequent and often associated with other skeletal abnormalities, including syndactyly, coalescence of carpal bones, radioulnar synostosis, hypoplasia and aplasia of the tibia and fibula, hemivertebrae, and dwarfism. Other disorders also seen are hydrocephalus, cleft lip, hypogonadism, kidney abnormalities, and imperforate anus.

The surgical approach to polydactyly is based on the vascular and bony anatomy of the digits, and it is individualized. The surgery is usually performed sometime after 6 months but before 18 months of age to minimize the anesthetic consequences.

Macrodactyly

Macrodactyly of the hand, also known as idiopathic local gigantism,[72] may involve one or more fingers and is bilateral in 5% of cases. All structures in the affected finger are enlarged, including the bone, blood vessels, nerves, and other soft tissues. True macrodactyly must be differentiated from other processes that create gigantism, because the treatment is different. Local enlargement of the hand occurs in neurofibromatosis, lymphedema, hemangioma, lymphangioma, arteriovenous fistulas, fibrous dysplasia, aneurysmal bone cysts, and lipomas. The treatment for these disorders is individualized to the process. In typical macrodactyly, the child is followed carefully until the affected digit(s) is about adult size, which usually happens between 7 and 8 years of age. At this point, growth arrests of all the bones in the affected digit(s) are performed and soft tissues are debulked. Occasionally, the growth is uncontrollable, and cosmesis is so poor that the parents and child prefer amputation. In contrast, ray resection with soft tissue reduction is the method of choice for managing macrodactyly of the foot, especially when it affects only the lesser toes.[8]



• **Fig. 99.4** Clinical photograph **(A)** and radiograph **(B)** show congenital polydactyly, the most common digit duplication, with complete bones, tendons, and nerves. The recommended treatment is early ablation by amputation.

Spine

Spinal disorders diagnosed during the neonatal period are uncommon.[49] Most of them are congenital in origin. Some of them, such as myelodysplasia and sacral agenesis, are obvious at birth, but others, such as congenital scoliosis and kyphosis, may not be recognized for months or years. Idiopathic spinal deformities can also occur but are rare.

Infantile Idiopathic Scoliosis

Scoliosis without a clearly identifiable cause is called idiopathic scoliosis. Idiopathic spinal deformities are classified

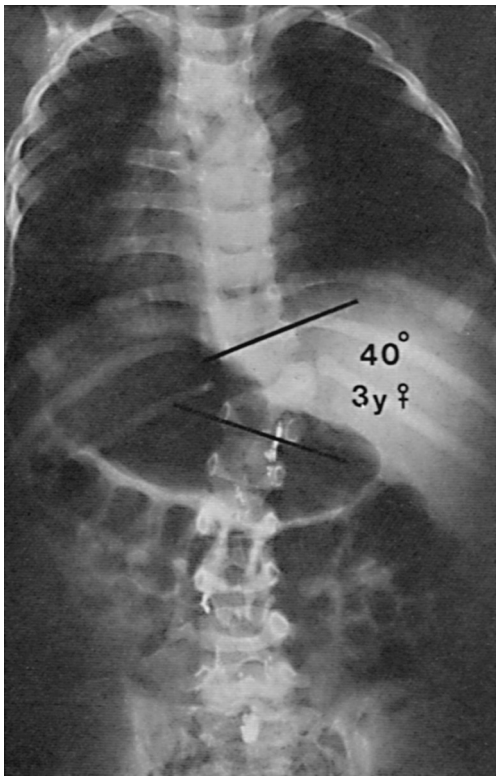
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as infantile, with the onset between birth and 3 years of age; juvenile, with the onset between 4 and 10 years of age; and adolescent, with the onset at 11 years of age or older. The adolescent type is the most common form of scoliosis and the infantile type is the least common. The infantile type is more common in the United Kingdom than in North America, although the reason for this is unknown.

When a neonate or infant is found to have a spinal deformity, a very careful physical examination and radiographic assessment are necessary to determine if an underlying cause is present. A diagnosis of idiopathic scoliosis is really a diagnosis of exclusion. Physical examination includes evaluation of the spine for mobility and areas of tenderness. The skin should be inspected for cutaneous lesions that may indicate underlying spinal dysraphism. The lower extremities need to be evaluated carefully for symmetry and neurologic function.

Plain radiographs usually determine whether there is a spinal deformity. However, additional studies, such as magnetic resonance imaging (MRI), may be necessary to evaluate the spinal canal and spinal cord for possible lesions.

The treatment of infantile scoliosis is variable. Some curves may be observed and even improve spontaneously with growth. However, others are progressive and require cast or orthotic management and possibly surgical intervention. It is important that all neonatal spinal abnormalities be referred to an orthopedic surgeon experienced in the management of pediatric spinal deformities.



• **Fig. 99.5** Radiograph of congenital scoliosis in a 3-year-old girl. A hemivertebra at T12 produces a 40-degree curve over a short segment of the spine. The mixed formation and segmentation defects in the upper thoracic spine are balanced and have not produced a significant curve.

Congenital Spinal Deformities

Abnormalities of vertebral formation can result in structural deformities of the spine that may be evident in the neonate or become more obvious during the first year of life. Deformities in the coronal plane produce congenital scoliosis, whereas those in the sagittal plane produce congenital kyphosis. The total or partial failure of formation of the sacrum is called *sacral agenesis,* typically associated with infants of diabetic mothers. If the lower lumbar spine is also absent, it is called *lumbosacral agenesis*.

Congenital Scoliosis

Congenital scoliosis is classified as failure of formation (e.g., hemivertebrae), failure of segmentation (e.g., unsegmented bars), or mixed (Fig. 99.5). A failure of formation or segmentation can be partial or complete and may occur as a single abnormality or in combination with other bone, soft tissue, or neurologic abnormalities of the axial or appendicular skeleton.[19] Congenital genitourinary malformations occur in 20% of children with congenital scoliosis. Unilateral renal agenesis is the most common abnormality. Most genitourinary abnormalities do not require treatment, but approximately 6% of the affected patients have a silent obstructive uropathy.[25] Renal ultrasound should be performed on all neonates with congenital scoliosis to search for possible genitourinary abnormalities. Congenital heart disease (10%-15%) and spinal dysraphism (20%) also occur in neonates with congenital scoliosis. Intraspinal abnormalities include tethered spinal cord, intradural lipoma, syringomyelia, and diastematomyelia (Fig. 99.6).[5,7,44,48,76] They are frequently associated with cutaneous lesions of the back, such as hairy patches, skin dimples, and hemangiomas, and with abnormalities of the feet and lower extremities, such as cavus feet, calf atrophy, asymmetric foot size, and neurologic changes. An ultrasound examination and MRI can be useful in the evaluation of spinal dysraphism in a neonate with congenital scoliosis. Congenital scoliosis may also occur in association with syndromes such as Klippel-Feil and VATERL and with spinal dysraphism, such as myelodysplasia.[77]

The risk for progression of congenital scoliosis depends on the growth potential of the malformed vertebrae.[75] Defects such as block vertebrae have little growth potential, whereas unilateral unsegmented bars invariably produce progressive deformities.[47] Approximately 75% of children with congenital scoliosis demonstrate some progression that typically continues until skeletal growth stops. Approximately 50% require treatment.[46] Rapid progression can be expected during periods of rapid growth, such as those between birth and 2 years of age and those after 10 years of age. Orthotic management is usually contraindicated, because it poorly mitigates such a growth disorder. When progression is aggressive, surgery is necessary. This may consist of

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• **Fig. 99.6** Metrizamide myelogram demonstrates cartilaginous diastematomyelia at L2 in a 3-year-old boy. Observe the midline filling defect and the increased widening or interpedicular distance in the middle lumbar region.

combined anterior and posterior hemi-epiphysiodesis on the convex side or possibly posteriorly approached osteotomies to halt progression and allow for some correction from growth on the concavity of the curvature.

Congenital Kyphosis

Congenital kyphosis includes (1) failure of formation of all or part of the vertebral body with preservation of the posterior elements, and (2) failure of anterior segmentation of the spine (e.g., anterior unsegmented bar). The more severe deformities are usually recognized in the neonate, and they rapidly progress thereafter. The less obvious deformities may not appear until several years later. After progression begins, it does not cease until the end of growth. The most important factor regarding congenital kyphosis is the possibility that a progressive deformity in the thoracic spine can result in paraplegia.[45] This potential outcome is usually associated with failure of formation of the vertebral body. When necessary, the treatment of congenital kyphosis is operative.[37]

Sacral Agenesis

Sacral agenesis comprises a group of disorders with partial or complete absence of the sacrum. If the lower lumbar spine is also involved, it is called lumbosacral agenesis.[2,3,51] Motor function is typically lacking below the level of the remaining spine; however, sensation tends to be present at a much more caudal level. The disorder can be classified by the amount of sacrum remaining and the articulation between the spine and pelvis. It is a rare disorder, occurring in approximately 1 in 25,000 live births, and the exact cause is unknown. The incidence is increased among the children of diabetic mothers[27,57] (see Chapters 18 and 86).

The presentations of neonates with sacral agenesis can vary considerably. In severe forms, there is a small pelvis with pterygia anteriorly at the hips and posteriorly at the knees, as well as bilateral foot deformities, typically clubfoot. There may be spinopelvic instability. The neurologic examination tends to show no motor function below the last existing vertebra or sacral segment. However, sensation can be more variable. Children with sacral agenesis also have other visceral abnormalities similar to those seen in congenital scoliosis.

The treatment of sacral agenesis is variable. Those patients with only partial agenesis and a stable spinopelvic articulation can be observed. Those who are unstable may require a spinopelvic fusion in childhood for stabilization. This operation can enhance sitting balance and improve the function of the upper extremities. The problems associated with the lower extremities also require orthopedic intervention. If a child has the potential for ambulation, these problems need to be corrected to allow the child to assume an upright posture. Orthotics are usually necessary to support the extremities after they have been corrected.

Lower Extremities

The most common neonatal congenital and developmental abnormalities of the lower extremities include torsional and angular deformities; developmental dysplasia of the hip; proximal femoral focal deficiency (PFFD); congenital hyperextension, subluxation, and dislocation of the knee; clubfoot; metatarsus adductus; vertical talus; calcaneovalgus foot; and toe deformities, such as syndactyly and polydactyly.

Torsional and Angular Deformities

Physiologic Bowleg

The lower extremities of neonates commonly have mild to moderate bowing (i.e., genu varum) and internal rotation of the lower leg because of in utero positioning. The bowed appearance is actually a torsional combination of the external rotation of the hip (i.e., tight posterior hip capsule) and internal tibial torsion from in utero positioning. With the onset of standing and independent walking, the bowing and torsion are spontaneously corrected over a 6- to 12-month period. Significant improvement does not occur during the neonatal period or the first year of life. The typical neonate has 15 degrees of genu varum, which decreases to approximately 10 degrees by 1 year of age. By 2 years of age, most children have straight or neutrally aligned lower extremities.

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Treatment is indicated for children older than 2-3 years of age who have had no documented improvement with growth.

Tibial Torsion

Torsional changes of the tibia may be internal or external, depending on in utero positioning. The degree of tibial torsion may be measured by the thigh-foot angle. With the child in the prone position, the knee is flexed to 90 degrees to neutralize the normal tibiofemoral rotation. The foot is placed in a neutral or simulated weight-bearing position. The long axis of the foot is compared with the long axis of the thigh. An inwardly rotated foot is assigned a negative value and represents internal tibial torsion. An outwardly rotated foot represents external tibial torsion and is given a positive value. It is important that the measurements be recorded on each visit to document the improvement. Radiographic evaluation is of no value in the assessment of tibial torsion.

Internal Tibial Torsion

Internal tibial torsion is the most common cause of pigeon-toed children from birth to 2 years of age. It is the major component of physiologic bowleg, or genu varum. Because this condition is physiologic, spontaneous resolution can be anticipated with normal growth and development. The persistence of internal tibial torsion in the older child or adolescent is uncommon.

External Tibial Torsion

External tibial torsion is a common deformity and is always associated with a calcaneovalgus foot. It is caused by a variation in the normal in utero position. The sole of the foot lies pressed against the wall of the uterus, forcing the limb into a hyperdorsiflexed, everted position. This physiologic configuration produces the calcaneovalgus foot and, secondarily, the external tibial torsion. When these two conditions are combined with a normally externally rotated hip from a tight posterior hip capsule, they produce a very externally rotated or out-toed position. Because they are also physiologic in origin, both undergo spontaneous resolution and follow a clinical course similar to that of internal tibial torsion.

Congenital Angular Deformities of the Tibia and Fibula

Congenital angular deformities of the tibia and fibula are uncommon neonatal problems. They are classified according to the direction of angulation—posteromedial or anterolateral. Posteromedial angulation is less common but is characterized by spontaneous resolution with growth and development. Anterolateral angulation is more common and is typically associated with other underlying congenital abnormalities, such as congenital absence of the fibula (e.g., fibular hemimelia), congenital absence of the tibia (e.g., tibial hemimelia), and congenital pseudarthrosis of the tibia (e.g., neurofibromatosis).



• **Fig. 99.7** **A,** A 1-month-old boy with posteromedial angulation of the left tibia. This condition resembles a calcaneovalgus foot, because the dorsum of the foot comes in contact with the lower leg. However, there is posterior angulation of the tibia in this case. **B,** The medial angulation is visible when viewed from the front.

Posteromedial Angulation

Posteromedial angulation has three associated clinical problems: angular deformity, the calcaneovalgus foot, and length discrepancy of the lower extremities. The angular deformity occurs at the junction of the middle and distal thirds of the shafts. The deformity is usually unilateral (Fig. 99.7). The neonates are normal and healthy, and there is no increased incidence of other congenital abnormalities. The degree of angulation varies between 25 and 65 degrees and is equal in both posterior and medial directions. The foot is hyperdorsiflexed and has a marked calcaneovalgus position. Radiographs are necessary to confirm the diagnosis. The cause of congenital posteromedial angulation in the tibia and fibula is unknown.

Posteromedial angulation resolves with growth, especially during the first 3 years of life. The posterior bowing tends to resolve more quickly than the medial bowing, which may not resolve until 5 years of age. However, the associated shortening of the tibia and fibula persists and progresses during growth. The fibula tends to be slightly shorter

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than the tibia. The appearance of the foot also improves, although a pes planovalgus appearance may persist.

Nonoperative treatment is indicated in the neonatal period.[69] If the bowing does not resolve by 3 or 4 years of age, a tibial or fibular osteotomy may be necessary. The most common sequela of posteromedial angulation is a discrepancy in leg length. Most of these children have enough discrepancy to require equalization. An appropriately planned epiphysiodesis (physeal closure) of the longer limb is the most common procedure. Lengthening of the shorter limb may sometimes need to be considered.

Anterolateral Angulation

When anterolateral bowing is encountered, it is usually associated with a significant underlying pathologic disorder, such as congenital pseudarthrosis of the tibia or congenital longitudinal deficiencies of the tibia or fibula. Careful clinical and radiographic evaluation is necessary to establish the correct diagnosis. Congenital pseudarthrosis of the tibia is typically associated with neurofibromatosis.

Hip

The most common neonatal hip disorders include developmental dysplasia of the hip and septic arthritis and osteomyelitis. Septic arthritis and osteomyelitis are discussed in Chapter 98. Another congenital abnormality, although uncommon, is proximal femoral focal deficiency (PFFD).

Developmental Dysplasia of the Hip

Developmental dysplasia of the hip (DDH) is the most common neonatal hip disorder.[66,73] It was initially thought to be congenital in origin but is now recognized as developmental, hence the change in terminology from congenital dysplasia of the hip to DDH. At birth, an involved hip is rarely dislocated; instead, it is dislocatable. Whether the hip stabilizes, subluxates, or ultimately dislocates depends on postnatal factors. Most developmental dislocations are postnatal in origin; however, the exact time of their occurrence is controversial.

Neonatal hip dislocations are classified into two major groups: the typical, which is found in a neurologically normal infant, and the teratologic, which is found in an infant with an underlying neuromuscular disorder, such as myelodysplasia, arthrogryposis multiplex congenita, or a complex of syndromes. Teratologic dislocations occur in utero and are, therefore, truly congenital in origin. This section concentrates on typical DDH, because it is the more common form.

Pathology and Etiology

The pathogenesis and causes of typical DDH are multifactorial: genetic, physiologic, and mechanical factors are involved. The genetic factors include a positive family history (20%) and generalized ligamentous laxity, an inherited trait. The physiologic factors include female predominance (9 : 1) and maternal estrogen and other hormones associated with pelvic relaxation during labor and delivery. The mechanical factors include primigravida, breech presentation, and postnatal positioning. Positioning has a significant effect in determining which hip stabilizes and which may progress to dislocation.

The genetic and physiologic aspects are related etiologic factors. Most neonates with DDH have generalized ligamentous laxity, which can predispose to hip instability. The maternal estrogen and other hormones associated with pelvic relaxation at delivery cross the placenta and result in further, albeit temporary, relaxation of the newborn hip joint.

Approximately 60% of those children with typical DDH are first-born, and 30%-50% develop it as a result of the breech position. In this position, there is extreme hip flexion and a limitation of hip motion that results in the stretching of an already lax hip capsule and ligamentum teres and in the posterior uncovering of the femoral head. Decreased hip motion results in the lack of normal stimulation for the growth and development of the cartilaginous acetabulum.[54]

Congenital muscular torticollis and metatarsus adductus are associated with DDH. The presence of either of these conditions necessitates a careful examination of the hips.

Postnatal factors are important determinants in ultimate hip stability. Positioning an unstable hip in adduction and extension may lead to dislocation. These positions put the unstable hip under abnormal pressure as a result of the normal hip flexion and abduction contractures. Consequently, an unstable femoral head can be displaced from the acetabulum over several days or weeks.

Because the hips are not dislocated at birth, the components of the hip joints, excluding the hip capsule and ligamentum teres, are usually relatively normal. There may be some variation in the shape of the cartilaginous acetabulum. If a subluxation or dislocation is not recognized, it will lead to progressive acetabular dysplasia and maldirection, excessive femoral anteversion (e.g., torsion), and hip muscle contracture.[12] It is critical that an early diagnosis be made and appropriate treatment instituted. The longer a dislocation continues, the more complex the treatment becomes.

Diagnosis

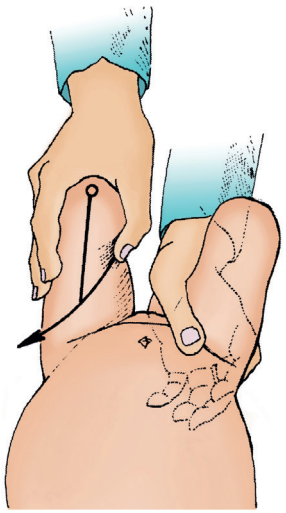
The physical findings in neonates with DDH include a positive Barlow test (i.e., dislocatable hip) or positive Ortolani test (i.e., dislocated hip), asymmetric thigh skinfolds, uneven knee levels (i.e., Allis or Galeazzi sign), and the absence of normal knee flexion contractures.

The Barlow and Ortolani tests are the most sensitive for neonatal hip instability (Fig. 99.8). The Barlow[4] test is a provocative means of diagnosing an unstable hip and is the most important maneuver in examining the neonatal hip. With the infant supine, this test is performed by stabilizing the pelvis with one hand, flexing and adducting each hip separately, and applying a posterior force with the other hand (Fig. 99.9). If a hip is dislocatable, it is usually felt as a "clunk." After release of the posterior pressure, the hip usually spontaneously relocates. It has been estimated that

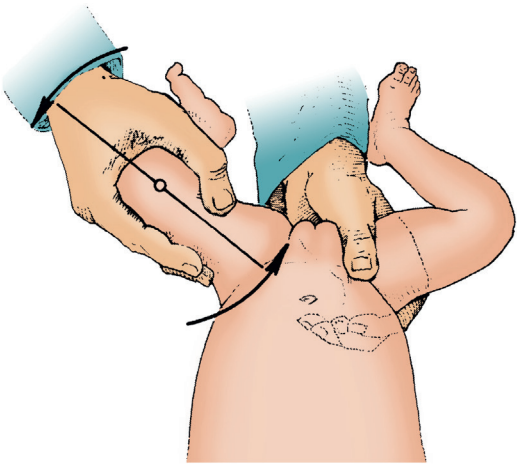
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• **Fig. 99.8** Positioning of the hip in the newborn to perform two diagnostic tests. The Ortolani sign, or click of reduction, is elicited when abducting the hip in this manner. The reverse Ortolani, or Barlow, maneuver is performed by bringing the femur into adduction with flexion, causing a click of exit or dislocation.



• **Fig. 99.9** The Barlow test permits the early diagnosis of hip instability. It is a provocation test for dislocatability. The pelvis is steadied with one hand while the leg to be tested is grasped with the other. The thumb of the examiner's hand should lie over the lesser trochanter and the tip of the middle finger over the greater trochanter. With the hip and knee in flexion, gentle pressure is exerted with the thumb over the lesser trochanter. Dislocatability is manifested by a sudden shift of the proximal femur. Dislocation may be reduced with the Ortolani test.



• **Fig. 99.10** In the Ortolani test, the pelvis is held steady with one hand while the limb to be examined is grasped with the other. The hip and knee are flexed. While gently pulling the femur forward, the examiner abducts the limb under examination, using the greater trochanter as a fulcrum. Reduction of dislocation is manifested by a sudden shift in the position of the proximal femur, often accompanied by a palpable or audible clunk. There must be sufficient ligamentous laxity to permit relocation of the proximal femur into the acetabulum; therefore, the test is useful primarily in the neonatal period.



• **Fig. 99.11** Clinical photograph showing the limitation of abduction of the thighs when the hips are flexed at 90 degrees.

approximately 1 in 100 newborns has a clinically unstable hip (i.e., subluxatable or dislocatable) and that 1 in 800-1000 infants eventually develops a true dislocation.

The Ortolani test is a procedure to reduce a recently dislocated hip (Fig. 99.10). It is most likely to be positive in infants who are 1-2 months of age because adequate time must have passed for true dislocation to occur. This test is performed concomitant with the Barlow test. With the hip flexed, the thigh is abducted and the femoral head lifted anteriorly into the acetabulum. If a reduction occurs, it is felt as a "clunk." Clunks should not be confused with hip "clicks," which are common in neonates. A variety of normal factors produce a clicking sensation during examination of the hip, including the breaking of surface tension across the hip joint, the snapping of gluteal tendons, patellofemoral motion, and femorotibial (knee) rotation. These normal characteristics are commonly misinterpreted as a sign of instability. After 2 months of age, the Ortolani test usually becomes negative. It is no longer possible to relocate a dislocated hip because of the development of soft tissue contractures.

When the hip is dislocated, its abduction is limited by soft tissue contractures (Fig. 99.11). There are also an increased number of thigh skinfolds on the involved side owing to redundant soft tissues, the appearance of a shortened extremity, and a positive Allis or Galeazzi sign. The latter sign is demonstrated by placing the feet of the supine neonate together on the examining table and assessing the relative heights of the knees. An apparent shortening is observed on the involved side. With a proximal displacement of the femoral head, the quadriceps and hamstrings become relaxed. This effect can be demonstrated best by the

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so-called "hamstring" test. Both hips are flexed and abducted with the knees flexed. Attempts to extend the knee are resisted on the normal side because of increased tightness in the hamstrings. If a dislocated hip is present, the knee can come into full extension because of the lack of proximal stability, which otherwise produces a fixed fulcrum for the hamstring muscles.

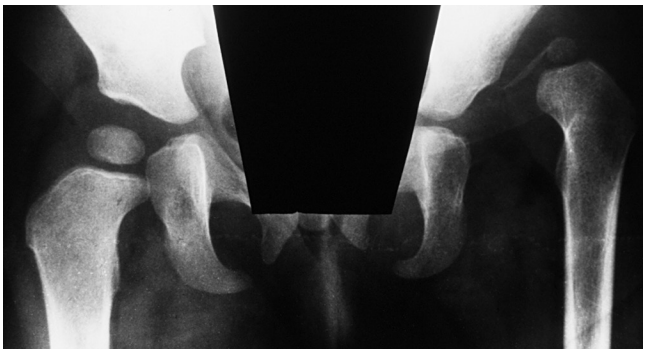
The presence of bilateral limitation of hip abduction in the young infant may be a normal variant and is an inaccurate clinical sign in the diagnosis of pathologic DDH. Limitation of hip abduction should be actively sought after 8 weeks of age and, if present, should be followed by a formal ultrasound or radiographic examination to confirm whether or not the hip is developing in a satisfactory manner.[9]

Imaging

The imaging of neonatal DDH is best accomplished with ultrasonography and plain radiographs. Ultrasonography[29] is becoming an increasingly popular method for the evaluation and assessment of the neonatal hip, because the femoral head does not ossify until 4-7 months of age. Hip stability and acetabular and femoral head development can be accurately assessed by an experienced ultrasonographer. Ultrasonography allows avoidance of the effects of ionizing radiation but is very user dependent and expensive. It is so sensitive that false-positive results are common. In large screening programs in which all births are screened, it is common to identify 7.5% of neonates with abnormal results.[10] This percentage decreases to a more appropriate level of 0.4% by 6 weeks, but the expense, anxiety, and administrative stress of retesting can be considerable. At present, there is no agreement about the efficacy of routine screening for all infants.[36,62] Some large centers suggest it,[43] although others claim that selective ultrasonography is as effective as universal screening when it is accompanied by a good clinical screening program.[20] Additionally, a stable, normal ultrasound does not assure normal hips after 6 months of age. Gwynne Jones has reported on seven developmental dislocations in five babies (age 6-22 months) in whom ultrasound demonstrated stable and reduced hips.[28] The Pediatric Orthopedic Society of North America warns that late-onset dislocation can be expected in 1 in 5000 infants who are clinically stable in the newborn period.[59] Anteroposterior and frog lateral radiographs of the pelvis may also be obtained. The limitation of plain radiographs is owing to the lack of ossification of the femoral head, which may be further delayed in DDH (Fig. 99.12). Line measurements are drawn to determine the development of the acetabulum and the relationship between the femoral head and acetabulum (see Chapters 28 and 38).

Treatment

The treatment of neonatal DDH is simple and effective. The most important factor in the treatment of this disorder is an accurate and early diagnosis. When an unstable or dislocatable hip (Barlow positive) is recognized at birth,



• **Fig. 99.12** Anteroposterior pelvic radiograph of a 9-month-old girl with a complete dislocation of the left hip. Observe the hypoplasia of the proximal femur and ossific nucleus of the femoral head. The right hip is normal.



• **Fig. 99.13** The Pavlik harness is a safe, reliable means of treating hip instability and dislocation in the neonate.

maintenance of the hip in the position of flexion and abduction, or the "human position," is usually sufficient. This position maintains reduction of the femoral head in the acetabulum and allows the progressive tightening of the ligamentous structures as the child grows. It also stimulates the normal growth and development of the acetabulum. The methods that can be used to maintain the hip in this position include double or triple diapers, the Pavlik harness, the Frejka pillow splint, and a variety of abduction orthoses. Double or triple diapers, although controversial, are commonly used in early infancy because the harness, pillow splint, and abduction orthoses usually do not fit satisfactorily. Treatment is continued until there is clinical stability of the hip and the ultrasonographic or radiographic results are normal, both of which usually take place within 3-4 months.

There may also be a true dislocation (Ortolani positive) during the neonatal period. As a consequence, treatment is directed toward the reduction of the femoral head in the true acetabulum.

The Pavlik harness is the major mode of treatment in this age group (Fig. 99.13). The harness places the hips in the human position by flexing them more than 90 degrees

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(preferably 100-110 degrees) and maintaining relatively full but gentle abduction (50-70 degrees). This position redirects the femoral head toward the acetabulum. A spontaneous reduction usually occurs within 3-4 weeks. The Pavlik harness is approximately 95% successful for Barlow-positive hips and 80% successful for Ortolani-positive hips. If true dislocations are initially irreducible, treatment with the Pavlik harness may not be effective. Lerman and coworkers reported on 93 DDH patients treated with a Pavlik harness.[42] There were 82% who were successfully treated. Six patients had initially irreducible hips and less than 20% ultrasound coverage; all six failed treatment with the Pavlik harness. If the reduction of a dislocated hip is achieved, treatment is continued until ultrasonography or the radiographic parameters have returned to normal. If a spontaneous reduction does not occur, closed reduction by surgery will be necessary. This approach sometimes consists of preliminary skin traction for 1-3 weeks to stretch the existing soft tissue contractures, followed by an examination under anesthesia, percutaneous hip adductor muscle tenotomy, closed reduction, an arthrogram to assess the concentricity of the reduction, and the application of a hip spica cast in the human position. A post-reduction CT or MRI scan is obtained to confirm reduction. Treatment is continued until the radiographic parameters are within normal limits. The indications for an open reduction in the neonate up to the first 6 months of life are limited. Follow-up for at least 1 year is necessary, because dysplastic hips that improve with treatment can still subsequently deteriorate. If this deterioration occurs, further treatment is indicated.

The complications associated with treatment of neonatal DDH include failure of reduction and re-dislocation. Avascular necrosis of the capital femoral epiphysis, which is the most devastating complication of this disorder, develops in approximately 5% of infants, regardless of how careful initial management may have been.

Proximal Femoral Focal Deficiency

Proximal femoral focal deficiency (PFFD) is a congenital abnormality affecting the development of the proximal end of the femur and possibly the acetabulum. There is considerable variation, ranging from a mildly shortened femur to severe shortening with an absence of the femoral head and acetabulum. It may be bilateral or unilateral; bilateral cases tend to have more severe involvement. The cause of PFFD is unknown, but it results from embryologically abnormal formation of the hip that occurs during limb bud formation.

The clinical examination is usually diagnostic. The thigh is shortened, and the hip held in flexion, abduction, and external rotation (Fig. 99.14). There are usually hip- and knee-flexion contractures. Because of the proximity of the lower leg to the trunk, the entire extremity appears similar to a funnel. There may also be abnormalities of the lower leg. Approximately 50%-70% of affected neonates also have fibular hemimelia with or without the absence of the lateral portion of the foot.



• **Fig. 99.14** Clinical photograph of a newborn boy with significant shortening of the right thigh caused by proximal femoral focal deficiency.

Radiographs are necessary in the assessment of children with PFFD. However, the components may not be fully visualized because of the lack of ossification. If an acetabulum is present, there will usually be a femoral head. Magnetic resonance imaging scans can be helpful in difficult cases to determine the shape of the proximal femur and acetabulum.

The most important therapeutic component of the treatment of neonatal PFFD is observation. It is important that a careful evaluation be performed to search for other associated congenital abnormalities. The ultimate treatment depends on the length of the extremity, the stability of the hip, the presence or absence of a functional foot, and a determination of whether the disorder is unilateral or bilateral. Possible treatment options include prosthetic fitting; knee fusion, Syme amputation, and prosthesis; surgical reconstruction; and lengthening of the femur. The lengthening of the femur is considered only if the hip and knee are relatively normal and the degree of predicted shortening is less than 15 to 20 cm at skeletal maturity.

Knee

Hyperextension, Subluxation, and Dislocation of the Knee

The congenital abnormality comprising hyperextension, subluxation, and dislocation of the knee is uncommon. The tibia is displaced anterior to the femur, and the knee is hyperextended. The cause is multifactorial, with mechanical and genetic elements. Most cases are sporadic, with no particular predisposition; however, patients with inherited Larsen disease frequently demonstrate congenital subluxation and dislocation of the knee. Breech presentation is

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more frequently seen in children with congenital subluxation and dislocation of the knee, suggesting that mechanical factors are also important.

The pathologic picture is complex, and associated disorders are common. Curtis and Fisher reported on 11 patients, and in every case they noted congenital hip abnormalities.[15] Seven patients had clubfoot and seven were thought to have arthrogryposis multiplex congenita. Fibrosis of the quadriceps muscle was found in all surgical cases. The quadriceps muscle effectively runs from the anteroinferior iliac spine to the tibial tubercle, and progressive fibrosis would thereby provide pressure for anterior subluxation of the tibia and hip deformity, as well as a tendency to hyperextend the knee.

The diagnosis is made on physical examination. Hyperextension at the knee sometimes approaches 90 degrees (Fig. 99.15). A lateral radiograph can demonstrate that the tibia is anterior to the femur. A line is drawn down the long axis of the tibia and the long axis of the femur; it does not meet at the normal axis of the knee joint.

In benign hyperextension of the knee, hyperextension of 15-30 degrees is common. Flexion is frequently limited to a few degrees. In this "packing deformity," the radiographs demonstrate that the tibia is not anterior to the femur and that the center of rotation of the knee joint is normal, unlike congenital dislocation and subluxation of the knee. It is important to obtain the radiographs of knees that hyperextend considerably to determine whether an epiphyseal fracture is responsible for hyperextension of the knee. The results of treatment are very different when benign hyperextension of the knee is compared with congenital dislocation of the knee. In benign hyperextension of the knee and, to a certain extent, congenital subluxation of the knee, manipulation and serial casting provide an adequate result. Early manipulation and casting are often successful in uncomplicated congenital dislocation of the knee if treatment is begun during the first few weeks of life. The prognosis is much worse when the knee dislocation is associated with Larsen disease or arthrogryposis multiplex congenita.[39] Children with congenital dislocation of the knee who fail casting may benefit from traction delivered through skeletal pins in the tibia and femur. The goal of treatment is to achieve at least 100-110 degrees of knee flexion and full, stable knee extension before the child reaches walking age. If these objectives cannot be attained with casting, splinting, or traction, then surgery before the child reaches walking age is recommended.

Foot and Toes

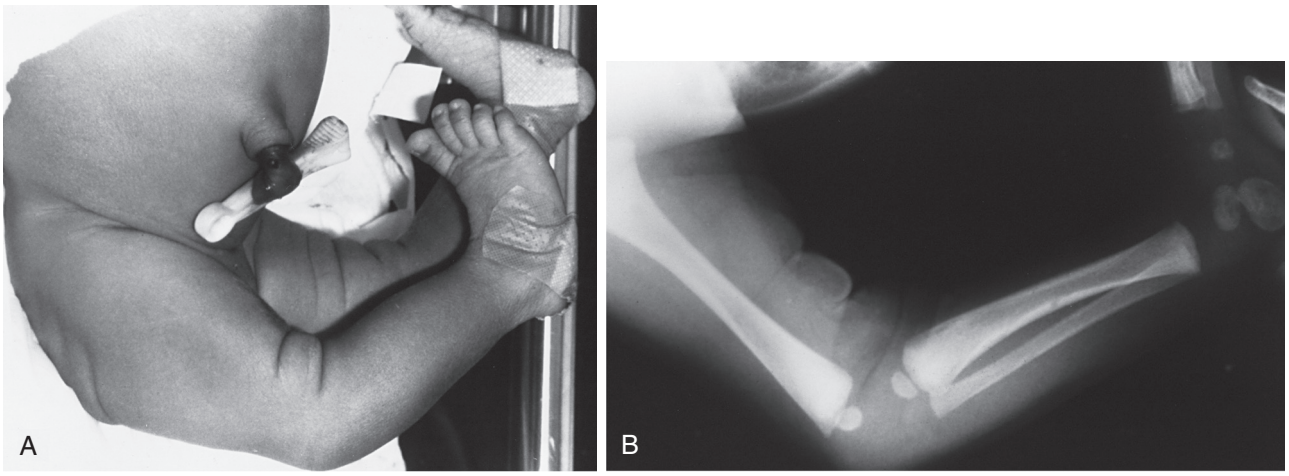
The most common foot and toe disorders include metatarsus adductus, the calcaneovalgus foot (pes calcaneovalgus), talipes equinovarus (clubfoot), congenital vertical talus, and syndactyly and polydactyly of the toes.

Metatarsus Adductus

Metatarsus adductus, or forefoot adduction, is probably the most common neonatal foot problem. It results from in utero positioning, occurring equally in boys and girls, and is bilateral in approximately 50% of neonates. The disorder has hereditary tendencies and is more common in the first-born than subsequent children because of an increased molding effect from the primigravid uterus and abdominal wall. It is also associated with hip dysplasia. Approximately 10% of children with metatarsus adductus have DDH; careful examination of the hips is necessary in any neonate with metatarsus adductus.[41]

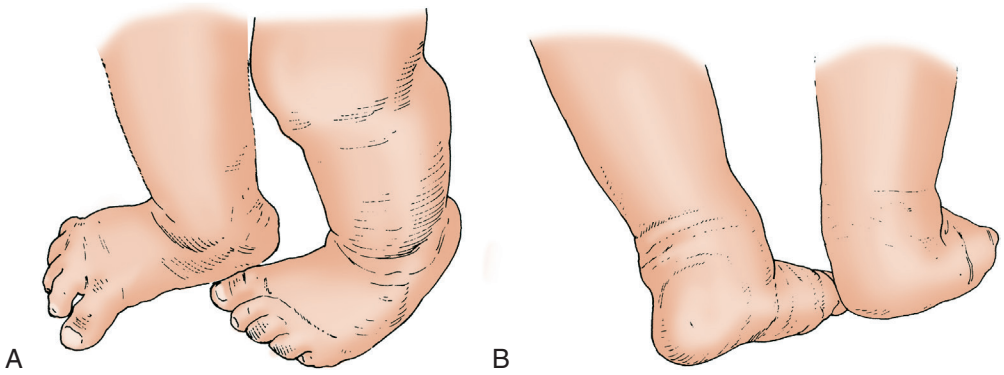
Diagnosis

Clinically, the forefoot is adducted and occasionally supinated. The hindfoot and midfoot are normal. The lateral border of the foot is convex, and the base of the fifth metatarsal appears to be prominent (Fig. 99.16). The medial border of the foot is concave. There is usually an increased interval between the first and second toes, with the great toe being held in a greater varus position. Ankle dorsiflexion



• **Fig. 99.15** **A,** Clinical photograph of a newborn boy with bilateral congenital or developmental subluxation of the knees. The knees are hyperextended and have limited flexion. **B,** Lateral radiograph demonstrating the hyperextension or subluxation of the right knee.

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• **Fig. 99.16** Bilateral metatarsus adductus. **A,** Dorsomedial and dorsolateral views. The medial border of the foot is concave; the lateral border is convex. The medial arch may be accentuated. **B,** Posterior view. A slightly valgus hindfoot may be present in the standing position.

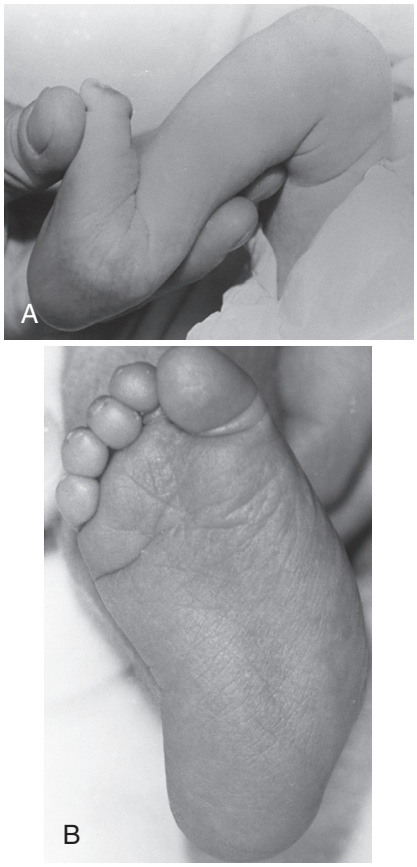
and plantar flexion are normal. These characteristics distinguish metatarsus adductus from a congenital clubfoot. Forefoot flexibility is variable. Passive flexibility is assessed by stabilizing the hindfoot in a neutral position with one hand and applying pressure over the first metatarsal head with the other. Active flexibility is assessed by gently stroking the lateral border of the involved foot. This approach induces reflex activity in the peroneal muscles along the lateral aspect of the calf. The forefoot is typically classified as flexible, moderately flexible, or rigid.[14] In flexible metatarsus adductus, the forefoot achieves an overcorrected position actively and passively. In moderately flexible metatarsus adductus, the forefoot can be corrected to the neutral position. In rigid metatarsus adductus, the forefoot cannot be corrected to the neutral position.

Imaging

Routine radiographs are unnecessary in the evaluation of metatarsus adductus. Radiographs do not demonstrate forefoot mobility; however, anteroposterior and lateral simulated weight-bearing radiographs of the foot are necessary to assist in the diagnosis of rigid deformities and those in which a diagnosis by other means is uncertain.

Treatment

Approximately 85% of neonatal metatarsus adductus deformities resolve spontaneously by 3 years of age,[53,56] and 95% resolve by 16 years of age.[74] Treatment is seldom recommended for metatarsus adductus, because most patients develop normal foot position and mobility without treatment, and even those with some residual deformity generally have normal function.



• **Fig. 99.17** **A,** A 3-month-old boy with a calcaneovalgus foot. The foot can be dorsiflexed to allow the dorsum to come in contact with the anterior aspect of the lower leg. **B,** There is abduction of the forefoot and increased valgus alignment of the hindfoot. This condition is always associated with external tibial torsion.

Calcaneovalgus Foot

The calcaneovalgus foot is a common physiologic variant.[68] It results from in utero positioning. This condition is manifested by a hyper-dorsiflexed foot, with an abducted forefoot and valgus hindfoot. It is usually associated with external tibial torsion. It typically occurs unilaterally but also occasionally occurs bilaterally. In utero, the plantar surface of the foot lies against the uterine wall, forcing it into a hyper-dorsiflexed, abducted, and externally rotated position (Fig. 99.17). This position produces the calcaneovalgus foot and external tibial torsion. When these two conditions are combined with the normal, increased external rotation of the hip (e.g., tight posterior hip capsule) in the neonate, the result is a lower extremity that appears excessively externally rotated.

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Diagnosis

The neonate typically presents with external rotation of the involved extremity and a calcaneovalgus foot. The forefoot is abducted, and the heel is in an everted (valgus) position. The foot can be hyper-dorsiflexed to bring its dorsal surface in contact with the anterior aspect of the lower leg. This condition should not be confused with the neonatal maturity classification of Dubowitz. External tibial torsion of 20-50 degrees is common. Ankle motion usually shows normal to nearly normal plantar flexion.

Three conditions must be distinguished from the benign calcaneovalgus foot: congenital vertical talus, posteromedial bowing of the tibia, and neuromuscular disorders that are associated with paralysis of the gastrocnemius muscles.[68] This differentiation can usually be established by clinical examination.

Imaging

Routine imaging of a benign calcaneovalgus foot is unnecessary; it is predominantly a clinical diagnosis. However, in severe deformities or in those with limited mobility, anteroposterior and lateral simulated weight-bearing radiographs of the foot and possibly the lower leg are necessary. These radiographs allow the recognition of a congenital vertical talus or posteromedial bowing of the tibia.

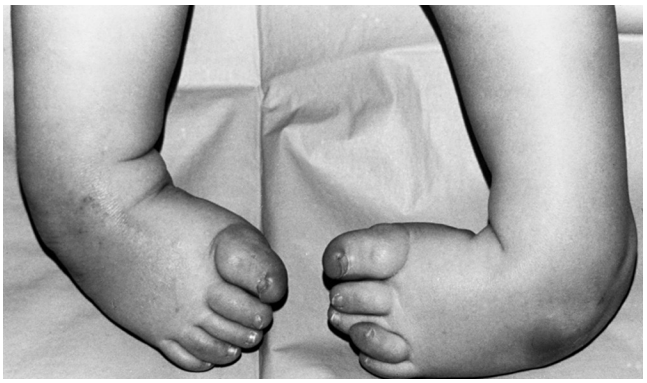
Treatment

The benign calcaneovalgus foot does not require treatment. This deformity usually resolves during the first 6 months of life. However, external tibial torsion follows the same natural history as that of internal tibial torsion. Spontaneous improvement does not take place until the child begins to pull to stand and walk independently. It takes 6-12 months thereafter to achieve complete correction. Most neonates presenting with a benign calcaneovalgus foot and external tibial torsion have a normally aligned foot and lower extremity by 2 years of age.

Talipes Equinovarus (Clubfoot)

A congenital clubfoot is one of the most common pathologic entities affecting the neonatal foot. It is a deformity of the foot and the entire lower leg. It is classified as congenital, teratologic, or positional. The congenital clubfoot is usually an isolated abnormality, whereas the teratologic form is associated with an underlying neuromuscular disorder, such as myelodysplasia or arthrogryposis multiplex congenita. Positional clubfoot refers to a normal foot that has been held in an equinovarus position in utero.

The cause of congenital clubfoot is unknown. There are hereditary factors and they are considered multifactorial, with a major influence from a single autosomal dominant gene. It develops more commonly in boys (2:1) and is bilateral in 50% of cases. The probability of the deformity occurring randomly is 1 in 1000 live births, but within affected families the probability is approximately 3% for subsequent siblings and 20%-30% for the offspring of affected parents. Muscle biopsies of the extrinsic muscles, electromyographic studies of these muscles, and histologic analysis of the associated connective tissue have indicated a probable neuromuscular etiology.[21,30] There are disproportionate fiber types and increased neuromuscular junctions within these muscles. These findings contrast with previous etiologic theories in which the deformity of the talus was thought to be the primary abnormality. These findings also suggest a reason as to why clubfoot is ubiquitous in syndromes and neuromuscular disorders; any child with a clubfoot deformity requires a careful musculoskeletal and neurologic evaluation to search for other abnormalities.



• **Fig. 99.18** Clinical photograph of a 9-month-old boy with bilateral talipes equinovarus (clubfoot) deformity.

Diagnosis

A congenital clubfoot is characterized by equinovarus deformity of the foot and ankle; variable rigidity of the deformity; mild calf atrophy; and mild hypoplasia of the tibia, fibula, and bones of the foot (Fig. 99.18).[67]

Imaging

Anteroposterior and lateral standing or simulated weight-bearing radiographs are used in the assessment of clubfoot. Multiple different radiographic measurements can be made. The navicular bone, which is the primary site of the deformity, does not ossify until 3 years of age in girls and 4 years of age in boys. Line measurements are required to determine the position of the unossified navicular bone and the overall alignment of the foot.

Treatment

Both nonoperative and operative methods are used in the treatment of clubfoot deformities. Nonoperative methods include taping, malleable splints, and serial plaster casts. Taping and malleable splints are particularly useful in premature infants until they attain an appropriate size for casting. Serial plaster casting is the major nonoperative method of treatment. For each cast change, the foot is gently manipulated toward the corrected position. Casts are changed at 1- to 2-week intervals to allow for progressive correction.

Complete clinical and radiographic correction should be achieved by 3 months of age. The failure to achieve

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clinical and radiographic correction by 3 months of age is an indication for surgical treatment, because further attempts at casting may result in articular damage or a midfoot break (e.g., rocker-bottom deformity). Previously, primary operative treatment of congenital clubfoot often required a complete soft tissue release, usually performed between 6 and 12 months of age, and satisfactory long-term results were anticipated in 80%-90% of cases. However, over the last decade, the aforementioned Ponseti method of serial casting[53] (augmented with percutaneous tendo Achilles tenotomy when necessary) has become widely accepted. The Ponseti casting technique and tendo Achilles tenotomy are followed by a prolonged period of bracing, which lasts from 2-4 years. Strict adherence to the bracing protocol is mandatory for a positive outcome.[16]

Congenital Vertical Talus

Congenital vertical talus is an uncommon neonatal foot deformity, but its etiology is similar to that of clubfoot.[11,18] It must be distinguished from the benign calcaneovalgus foot, which is a much more common deformity. Congenital vertical talus typically presents as a rigid rocker-bottom deformity. Most of these deformities are associated with an underlying disorder such as teratologic malformation, myelodysplasia, arthrogryposis multiplex congenita, or a syndrome such as trisomy 18.

Diagnosis

The clinical characteristic of congenital vertical talus is a rocker-bottom foot (Fig. 99.19). There is an equinus hindfoot, a valgus hindfoot, a convex plantar surface, forefoot abduction and dorsiflexion, and rigidity. A careful musculoskeletal and neurologic examination must be performed on all neonates to search for associated disorders or syndromes.

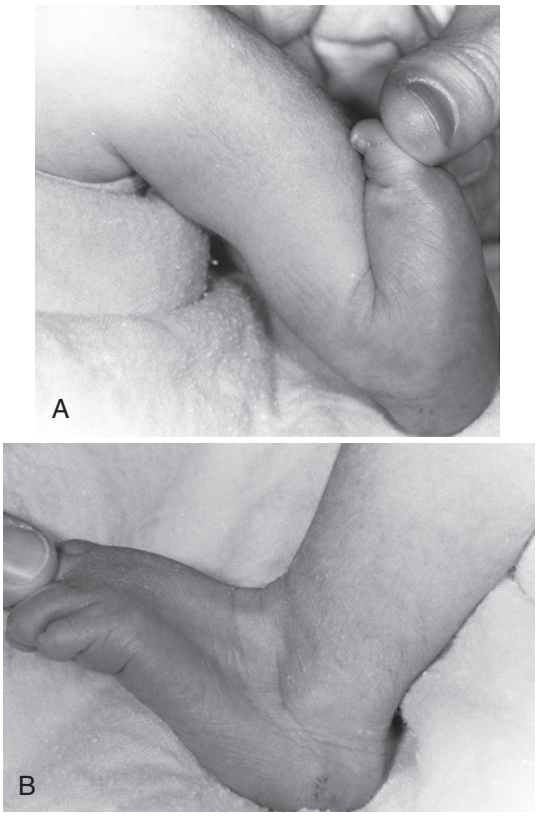
Imaging

The radiographic evaluation of congenital vertical talus is similar to that of clubfoot. Anteroposterior and lateral simulated weight-bearing radiographs of the feet are obtained (Fig. 99.20) and typically reveal a vertically oriented talus, dorsal displacement of the midfoot on the hindfoot, and a valgus hindfoot.

Treatment

As in clubfoot, nonoperative treatment is the initial method of management. Dobbs has advocated a program of serial casting beginning at birth.[17] The forefoot is manipulated into an equinus position in an attempt to reduce the dorsally dislocated navicular bone onto the head of the talus. Once this is achieved, the talonavicular joint is pinned and a percutaneous tendo Achilles tenotomy then allows the ankle to be dorsiflexed without losing reduction at the joint. This technique has shown promise in decreasing the need for extensive initial soft tissue releases.

The goals for the treatment of congenital vertical talus are modest and include obtaining a plantigrade, painless foot on which a shoe can be worn. Orthotic management is frequently necessary postoperatively to maintain alignment and minimize the risk for recurrent deformity.[11]



• **Fig. 99.19 A,** A newborn girl with congenital vertical talus. The dorsum of the foot also comes in contact with the anterior aspect of the lower leg. The foot has a rocker-bottom appearance. **B,** An attempted plantar flexion shows the tightness of the anterior musculature and a persistent rocker-bottom appearance of the midfoot and hindfoot.



• **Fig. 99.20** Radiograph of a 9-month-old infant showing the vertical alignment of the talus, equinus hindfoot, and dorsal angulation of the midfoot and forefoot.

Syndactyly and Polydactyly of the Toes

Syndactyly and polydactyly are common disorders of the toes.[22,70] Syndactyly of the toes is almost always asymptomatic and rarely requires treatment but may be associated with a positive family history. Syndactyly may be classified

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as zygodactyly (a complete or incomplete webbing usually involving the second and third toe) or polysyndactyly (polydactyly of the fifth toe and syndactyly between the duplicated toes).[70] Zygodactyly does not interfere with wearing shoes or normal function and does not require treatment; polysyndactyly usually requires treatment.

Polydactyly of the toes can be preaxial (i.e., great toe), central, or postaxial (i.e., fifth toe).[70] It occurs in approximately 2 of 1000 live births and is more common among African Americans than Caucasians. Postaxial deformities are the most common (80%) and can be subdivided into type A (articulated) and type B (rudimentary). Approximately 30% of neonates with polydactyly have a positive family history. It is usually an isolated disorder with autosomal dominant inheritance. Concomitant polydactyly of the hands and associated metatarsal deformities are common.

The goal of treatment is to restore a relatively normal contour to the forefoot to allow the appropriate fitting of shoes. Rudimentary digits can be ligated at birth, whereas articulated digits are removed at 9-12 months of age.[70] The more central of the involved digits are usually preserved and the more peripheral ones amputated.

Syndromes

Skeletal Dysplasias

See Chapter 30. Skeletal dysplasias constitute a group of disorders that produce short stature. Antenatal ultrasound diagnosis usually occurs or is suspected. Many of these disorders are recognizable at birth, whereas others are manifested during growth and development. The defects can occur in the epiphysis or physis (growth plate) or as abnormalities of bone remodeling that may affect the metaphysis or diaphysis. The most common skeletal dysplasia is achondroplasia, which produces short-limb dwarfism that is caused by a defect in a gene that encodes one of the fibroblast growth factor receptors. Diagnostic and prenatal testing is available. It is inherited as an autosomal dominant trait, but approximately 80% of cases are new mutations. It is caused by abnormal endochondral ossification of the physis. Achondroplasia produces a rhizomelic pattern of shortening, with the proximal segments (i.e., humerus and femur) more involved than the distal segments (i.e., radius and ulna or tibia and fibula). Periosteal and intramembranous ossification is normal.

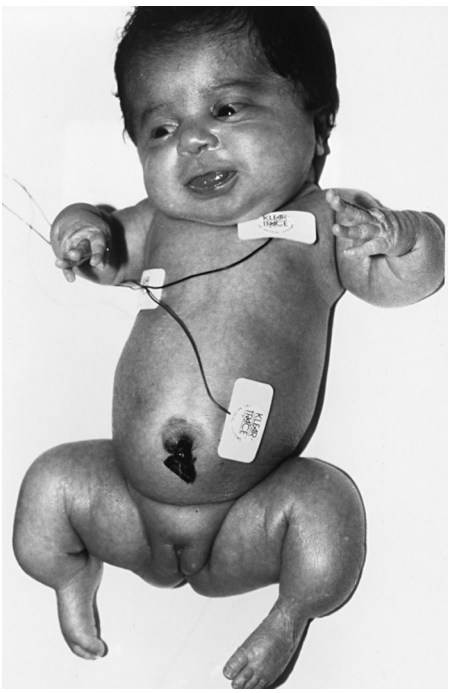
The diagnosis is usually made at birth because of the characteristic features of the head, face, and short extremities. The head is typically enlarged; there are disproportionately short limbs and a normal trunk. Facial features include frontal bossing, flattening of the nasal bridge, midfacial hypoplasia, and prominence of the mandible. The trunk appears relatively normal but the abdomen is usually protuberant. The hands characteristically have a space between the long and ring fingers, producing a "trident" hand. The thoracolumbar spine may show an acute kyphotic deformity (gibbus) before the onset of walking. The lower extremities are usually bowed and the musculature appears enlarged. It is important to make an early diagnosis so that genetic counseling can be performed.

Treatment is usually not indicated in the neonatal period or during the first year. The one possible exception is the presence of a gibbus deformity of the thoracolumbar spine, which may benefit from orthotic management.

Osteogenesis Imperfecta

Osteogenesis imperfecta is an inherited disorder of connective tissues. It is caused by mutations in the *COL1A1* and *COL1A2* genes, which code for type I procollagen.[40] More than 150 separate mutations have been identified. Because type I collagen is the primary matrix protein for bone, dentin, sclerae, and ligaments, there is a heterogeneous mix of phenotypes. All children with osteogenesis imperfecta have increased bone fragility and susceptibility to fracture. Some children also present with blue sclerae, defective dentinogenesis, growth restriction, presenile hearing loss, scoliosis and kyphosis, and multiple angular deformities of bone (Fig. 99.21). Osteogenesis imperfecta is uncommon, occurring in fewer than 1 in 20,000 children. In its mildest form, children have a few fractures, normal teeth, sclerae with a slightly blue tinge, minimal hearing loss, and somewhat short stature. In its most severe form, perinatal death occurs. These children have blue sclerae and their bones collapse in utero.

Sillence and Danks and Sillence suggested a comprehensive classification scheme of osteogenesis imperfecta based



• **Fig. 99.21** Clinical photograph of a newborn girl with severe congenital osteogenesis imperfecta. The child had multiple fractures at birth. Observe the severe shortening of the extremities and darkened (blue) sclera.

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on genetic inheritance and clinical manifestations.[63,64] In type I, patients have increased bone fragility, distinct blue sclerae, and presenile hearing loss. Some of these patients have defective dentinogenesis, although others do not. The inheritance pattern is autosomal dominant. In type II, the children are severely affected. Most of them die perinatally, because their bones collapse in utero. The inheritance pattern is autosomal recessive. At present, efforts to establish a relationship between genotype and phenotype are ongoing but complex. Bodian and co-workers analyzed 63 subjects with type II and found 61 distinct heterozygous mutations in type I collagen, of which 43 had not been previously seen. To say that osteogenesis imperfecta is heterogeneous would be an understatement.[6] In type III, the bone fragility is quite marked but compatible with survival. These children are born with multiple fractures and have progressive bowing of bones throughout life. Early on, their sclerae are quite blue but become less so as they mature; by adolescence, the sclerae are essentially normal in appearance. The inheritance pattern is autosomal recessive. In type IV, the bone fragility is modest. These patients usually have white sclerae; some have defective dentinogenesis, although others do not. They have modest bowing of bones. Some of these children may be difficult to differentiate from the normal population early in life.

The goal of orthopedic treatment in osteogenesis imperfecta is to maximize comfort and function. In modestly affected children, this approach frequently focuses on the closed treatment of fractures. The management of fractures in such children is not dissimilar to that in the average population. Children with increased bone fragility frequently benefit from orthotics, which are used to protect their bones as they are mobilized. Recently, intravenous pamidronate has shown promise for increasing bone density in children with moderate to severe osteogenesis imperfecta. Investigators also report reduced bone pain, a decreased incidence of fracture, and improved ambulation.[52,55,79] Children occasionally develop severe angular deformities from the poorly developed union of fractures or the insidious collapse of bones. As the deformities increase in magnitude, stress is concentrated at these angular deformities and children become increasingly susceptible to fracture. Osteotomies to straighten bones and intramedullary rods to maintain alignment may be helpful in assisting these children with their mobility. The rod provides internal support for the bone, and the elimination of angular deformities decreases stress within the bones.

Children with osteogenesis imperfecta do not necessarily have cognitive impairment. Every effort should be made to maximize their ability to attend school and interact with their peers.

Neurofibromatosis

Neurofibromatosis is a relatively common disorder that may or may not be diagnosable in the neonatal period. The presence of multiple café au lait spots or anterolateral bowing of the tibia suggests neurofibromatosis (Fig. 99.22). The café au lait spots frequently do not appear until the child is at least 2 years of age. The criteria for diagnosis have been outlined by Crawford[13] and include at least two of the following: multiple café au lait spots; a positive family history; a definitive biopsy; and characteristic bony lesions such as pseudarthrosis of the tibia, hemihypertrophy, or short and angulated spinal curvature. The café au lait spots are typically smooth; the presence of at least five spots larger than 0.5 cm in diameter is considered diagnostic.



• **Fig. 99.22** Clinical photograph of a 6-month-old boy with multiple café au lait spots resulting from neurofibromatosis.

Arthrogryposis Multiplex Congenita

Arthrogryposis multiplex congenita refers to a symptom complex (syndrome) characterized by multiple joint contractures that are present at birth. The involved muscles are replaced partially or completely by fat and fibrous tissue. However, it is not a single disease, because approximately 150 different syndromes are associated with multiple congenital contractures. The major form of arthrogryposis multiplex congenita is known as amyoplasia,[58,60] which refers to the classic syndrome in which the upper and lower extremities are involved. It accounts for approximately 40% of all children with multiple congenital contractures. Its cause is unknown. Children with this disorder have a decreased number of anterior horn cells in their spinal cords, suggesting a neuropathic origin. The clinical features include adduction, internal rotation, and contractures of the shoulders; fixed flexion or extension contractures of the elbows; rigid

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• **Fig. 99.23** **A,** A 1-month-old girl with arthrogryposis multiplex congenita involving the upper and lower extremities. The elbows are stiff in extension, whereas the wrist, fingers, and thumb are flexed. The hips are flexed and externally rotated. There are knee flexion contractures and bilateral talipes equinovarus clubfoot deformities. **B,** Serial casting is initiated at birth to improve the alignment of the lower extremities. Occupational therapy and splinting are used at a later time on the upper extremities.

volar flexion/ulnar deviation or dorsiflexion/radial deviation contractures of the wrists; thumb and palm deformities; rigid interphalangeal joints of the thumb and fingers; flexion, abduction, and external rotation contractures of the hips, with dislocation of one or both; fixed flexion or extension contractures of the knees; and severe, rigid, bilateral clubfeet (Fig. 99.23). Radiographs of all involved joints are obtained to assess their development; specialized studies are ordered as necessary.

Treatment modalities during the neonatal period consist of physical therapy and serial casting. Occasionally, orthotics and surgical intervention may be necessary; however, surgery is usually delayed until early childhood.[65]

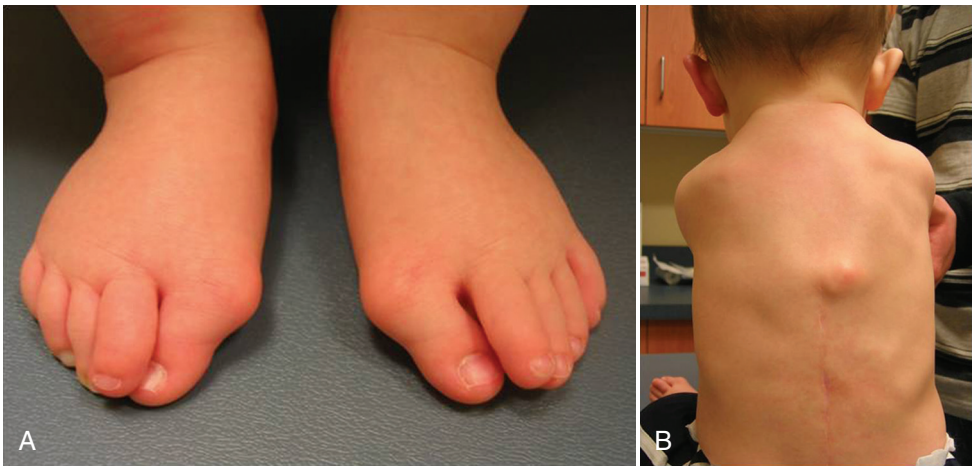
Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease (incidence about 1 in 1.6 million) characterized by skeletal malformations and episodic heterotopic bone formation leading to progressive loss of mobility. Although FOP was first described in the seventeenth century, most individuals with FOP are initially misdiagnosed, and many suffer permanent disability from inappropriate diagnostic or therapeutic interventions. Two likely causes for these harmful diagnostic errors are the lack of teaching exposure to FOP in most medical schools and the lack of coverage of FOP in most medical textbooks.

The mode of inheritance of FOP is autosomal dominant with complete penetrance, but almost all cases result from a spontaneous activating mutation in the gene encoding activin receptor IA/activin like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein type I receptor. Only seven small multigenerational families are known worldwide.[31-35,38,61]

The two classic findings in FOP are distinctive malformations of the great toes and episodic "flare-ups" characterized by soft tissue tumor-like swellings that often result in heterotopic ossification at the lesional site. The invariant malformations of the great toes are caused by hypoplasia or agenesis of the proximal phalanges that result in short great toes with a valgus deformity (Fig. 99.24*A*). The toe malformations are present at birth and may be the only congenital sign of FOP. Flare-ups, especially in the occipital region, may commence in the neonatal period and are often mistaken for cephalohematomas. However, flare-ups are usually recognized later in the first decade and typically appear on the head, neck, back, or shoulders (see Fig. 99.24*B*). The onset of a tender soft tissue swelling often appears overnight, triggered by soft tissue trauma or viral illnesses or may occur spontaneously. The soft tissue swellings

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• **Fig. 99.24 A,** A photograph of the feet of an infant with fibrodysplasia ossificans progressiva (FOP) showing the characteristic findings of short great toes and hallux valgus. **B,** A photograph of the back of a very young child with a tumor-like swelling on his back that represents an early FOP flare-up. Note the surgical scar from an unnecessary biopsy that exacerbated the disease process.

may resolve completely but most often result in heterotopic bone formation.

Microscopically, perivascular lymphocytic, mast cell, and macrophage infiltration occurs in striated muscle, followed by widespread death of muscle cells. Subsequently, an angiogenic fibroproliferative lesion forms, evolving through a cartilage stage and finally into mature heterotopic bone through a characteristic endochondral mechanism. This process involves striated muscles, ligaments, tendons, and aponeuroses, but spares the diaphragm, tongue, extraocular muscles, and cardiac and smooth muscle.

Additional common findings may include short thumbs; short, broad femoral necks; proximal medial tibial osteochondromas; tall, narrow cervical vertebrae; and ankylosis of facet joints of the cervical spine. Findings later in life include hearing loss and atypical facies, which usually develops in the second decade of life and is caused by mandibular hypoplasia.[34]

Fibrodysplasia ossificans progressiva can be diagnosed clinically and with great accuracy when the clinician recognizes the pathognomonic combination of great toe malformations with the presence of rapidly appearing soft tissue tumors in characteristic anatomic locations. In most cases, the swellings are misdiagnosed, most commonly as cancer or aggressive fibromatosis, often because the physician is unfamiliar with FOP. In newborns, FOP should be suspected when the typical malformations of the great toes are present. For suspected cases, diagnostic genetic testing is readily available from a simple blood test.[31]

There is no effective treatment for FOP. The process of heterotopic ossification is often accelerated by trauma, including traumatic medical interventions. These include biopsies, intramuscular injections (including neonatal vitamin K), immunizations, and surgical procedures, all of which should be avoided. For flare-ups involving major joints or the airway, a brief (3- to 4-day) course of high-dose corticosteroids will reduce soft tissue swelling and may prevent ossification.

Episodic heterotopic bone formation in FOP leads to progressive immobilization of the joints and restrictive disease of the chest wall.[32] Malnutrition is common if there is ossification of the jaw muscles leading to restricted mouth opening and swallowing. Average life expectancy is 40 years (range, 3-77 years). Identification of the responsible gene provides hope for future effective treatment of FOP.

Key Points

- Upper extremity malformations are much less common than those involving the lower extremities or spine.
- Common upper extremity congenital malformations include Sprengel deformity of the scapula; proximal radius and ulna synostosis; radial dysplasia and club-hand; constriction bands; congenital amputations; and syndactyly, polydactyly, and macrodactyly of the fingers.
- Congenital spinal abnormalities are predominantly scoliosis, kyphosis, and sacral agenesis.
- Common lower extremity congenital malformations include congenital angular deformities of the tibia and fibula; proximal femoral focal deficiency; subluxation/dislocations of the knee; congenital talipes equinovarus deformities (clubfeet); congenital vertical tali; reduction anomalies and amputations of the lower leg; and syndactyly, polydactyly, and macrodactyly of the toes.
- Syndromes can also be associated with congenital musculoskeletal malformations, especially spinal deformities.

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Appendix A

Therapeutic Agents

Jacquelyn D. McClary

Agent	Dosage	Comments
Anti-infective Agents		
Antibacterials		
Amikacin*	15-18 mg/kg/dose every 24-48 hr	Monitor serum concentrations if treating >48 hr
Ampicillin*	Meningitis: 100 mg/kg/dose IV every 6-12 hr Non-CNS infections: 25-50 mg/kg/dose IV, IM every 6-12 hr	
Azithromycin	Pertussis/ureaplasma infections: 10 mg/kg/dose PO, IV every 24 hr Chlamydial conjunctivitis: 20 mg/kg PO, IV every 24 hr x 3 days	IV dosing is not well-defined in neonates
Aztreonam*	30 mg/kg/dose IV, IM every 6-12 hr	
Cefazolin*	25 mg/kg/dose IV, IM every 6-12 hr	First-generation cephalosporin; commonly used for perioperative prophylaxis and treatment of urinary tract and soft tissue infections
Cefepime*	30-50 mg/kg/dose IV, IM every 12 hr	Fourth-generation cephalosporin; reserved for treatment of infections caused by multidrug-resistant organisms
Cefotaxime*	Sepsis or meningitis: 50 mg/kg/dose IV, IM every 6-12 hr Disseminated gonococcal infection: 25 mg/kg/dose IV, IM every 12 hr for 7 days if meningitis not present	Broad-spectrum, third-generation cephalosporin; may use to treat Gram-negative meningitis
Cefoxitin	30 mg/kg/dose IV, IM every 8 hr	Use limited to skin, intra-abdominal, and urinary tract infections
Ceftazidime*	30 mg/kg/dose IV, IM every 8-12 hr	Third-generation cephalosporin effective against *Pseudomonas* species
Ceftriaxone	Sepsis: 50 mg/kg/dose IV, IM every 24 hr Meningitis: 100 mg/kg/dose IV, IM every 24 hr Disseminated gonococcal infection: 25-50 mg/kg/dose IV, IM every 24 hr Gonococcal infection prophylaxis/ophthalmia: 25-50 mg/kg (max 125 mg) IV, IM single dose	Not recommended for infants with hyperbilirubinemia; do not administer in the same IV line with calcium-containing solutions
Clindamycin*	5-7.5 mg/kg/dose IV, PO every 6-12 hr	Do not use to treat meningitis; may cause pseudomembranous colitis
Erythromycin	10-12.5 mg/kg/dose PO every 6 hr Severe infection: 5-10 mg/kg IV every 6 hr	Higher dose used to treat chlamydial pneumonitis and conjunctivitis, and pertussis
Gentamicin*	4-5 mg/kg/dose IV, IM every 24-48 hr	Monitor serum concentrations if treating >48 hr

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Agent	Dosage	Comments
Imipenem/cilastatin	20-25 mg/kg/dose (imipenem component) IV every 8-12 hr	Restrict use to treatment of non-CNS infections; seizures occur frequently in patients with meningitis
Linezolid	10 mg/kg/dose IV, PO every 8 hr (premature infants <7 days of age: dose every 12 hr)	Use for Gram-positive infections refractory to conventional therapy
Meropenem*	20-40 mg/kg/dose IV every 8-12 hr	Reserve for infections caused by multidrug-resistant organisms; restrict use of 40 mg/kg doses to full-term infants with meningitis
Metronidazole*	Loading dose: 15 mg/kg/dose IV, PO Maintenance dose: 7.5 mg/kg/dose IV, PO every 8-48 hr	
Nafcillin*	Sepsis: 25 mg/kg/dose IV every 6-12 hr Meningitis: 50 mg/kg/dose IV every 6-12 hr	Greatest CSF penetration of antistaphylococcal penicillins; predominantly biliary excretion; irritating to veins
Oxacillin*	25-50 mg/kg/dose IV every 6-12 hr	Poor CSF penetration; irritating to veins
Penicillin G*	25,000-150,000 units/kg/dose IV, IM every 6-12 hr	Higher doses suggested for severe group B streptococcal infections
Piperacillin/tazobactam*	100 mg/kg/dose (as piperacillin component) IV every 8-12 hr	For non-CNS infections caused by susceptible β-lactamase-producing bacteria
Rifampin	PO: 10-20 mg/kg/dose every 24 hr IV: 5-10 mg/kg/dose every 12 hr Prophylaxis against meningococcal disease: 5 mg/kg/dose PO every 12 hr for 2 days Prophylaxis against *Haemophilus influenzae* type B disease: 10 mg/kg/dose PO every 24 hr for 4 days	Used in combination with vancomycin or aminoglycosides for treatment of persistent staphylococcal infections
Tobramycin*	4-5 mg/kg/dose every 24-48 hr	Monitor serum concentrations if treating >48 hr
Vancomycin*	10-15 mg/kg/dose every 6-18 hr	Target trough concentrations 10-15 μg/mL for most infections; 15-20 μg/mL may be necessary for meningitis, pneumonia, and other severe infections
Antifungals		
Amphotericin B	1-1.5 mg/kg/dose IV every 24 hr	Infuse over 2-6 hours; monitor serum creatinine and prolong dosing interval if creatinine increases >0.4 mg/dL from baseline
Amphotericin B liposome (Ambisome)	2.5-7 mg/kg/dose IV every 24 hr	Infuse over 2 hours; less nephrotoxic than amphotericin B
Amphotericin B lipid complex (Abelecet)	2.5-5 mg/kg/dose IV every 24 hr	Infuse over 2 hours; less nephrotoxic than amphotericin B
Caspofungin	25 mg/m^2/dose IV every 24 hr	Limited data in neonates—reserve for treatment of refractory candidemia or patients intolerant to amphotericin
Fluconazole*	Systemic infection: loading dose 12-25 mg/kg/dose IV, PO then 6-12 mg/kg/dose every 24-48 hr Prophylaxis: 3-6 mg/kg/dose IV, PO two times/week Thrush: 6 mg/kg/dose PO on day 1, then 3 mg/kg/dose PO every 24 hr	Higher doses used for severe infections; consider extended dosing interval if serum creatinine >1.3 mg/dL; may cause reversible elevations of transaminases; may interfere with metabolism of phenytoin, barbiturates, caffeine, and midazolam

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Agent	Dosage	Comments
Flucytosine	12.5-37.5 mg/kg/dose PO every 6 hr	Use in conjunction with amphotericin B or fluconazole; increase dosing interval in presence of renal dysfunction
Micafungin	10 mg/kg/dose IV every 24 hr	Limited data in neonates—reserve for treatment of refractory candidemia or for patients intolerant to amphotericin
Nystatin	Topical: apply to affected area every 6 hr Thrush: 1 mL (premature) to 2 mL (full term) of 100,000 unit/mL suspension; swab inside mouth every 6 hr	Continue for 3 days after symptoms subside
Antivirals		
Acyclovir*	HSV treatment: 20 mg/kg/dose IV every 6-12 hr HSV chronic suppression: 300 mg/m^2/dose PO every 8 hr Varicella-zoster virus: 10-15 mg/kg/dose IV every 8 hr	Administer every 12-24 hours in patients with severe renal/hepatic impairment; neutropenia, phlebitis may occur
Ganciclovir	Treatment: 6 mg/kg/dose IV every 12 hr Chronic suppression: 30-40 mg/kg/dose PO every 8 hr	Significant neutropenia occurs in most patients; reduce dose by half for ANC <500 cells/mm^3
Lamivudine	2 mg/kg/dose PO every 12 hr	Refer to the Perinatal Guidelines at http://www.aidsinfo.nih.gov/ for the latest treatment information (accessed October 4, 2017)
Nevirapine	Birth weight 1.5-2 kg: 8 mg/dose PO for 3 doses Birth weight >2 kg: 12 mg/dose PO for 3 doses Dose 1: within 48 hr of birth Dose 2: 48 hr after dose 1 Dose 3: 96 hr after dose 2	Refer to the Perinatal Guidelines at http://www.aidsinfo.nih.gov/ for the latest treatment information
Oseltamivir*	1-3 mg/kg/dose PO every 12 hr for 5 days	Limited data available for preterm infants; may cause transient rise in transaminases
Valganciclovir	16 mg/kg/dose PO every 12 hr	Neutropenia occurs frequently; dose adjustment may be required
Zidovudine*	IV: 1.5-3 mg/kg/dose every 12 hr PO: 2-4 mg/kg/dose every 12 hr	Initiate therapy within 6-12 hours of birth; anemia and neutropenia may occur; refer to the Perinatal Guidelines at http://www.aidsinfo.nih.gov/ for the latest treatment information
Cardiovascular Drugs		
Antiarrhythmics		
Adenosine	Give 50 mcg/kg as a rapid IV bolus followed by a flush; increase dose in 50 mcg/kg increments every 2 minutes until response obtained (usual maximum dose of 250 mcg/kg)	May cause transient asystole or bradycardia prior to return of normal sinus rhythm
Amiodarone	Loading dose: 5 mg/kg IV over 20-60 minutes Continuous IV infusion: start at 7 mcg/kg/min, may increase to 15 mcg/kg/min PO: 5-10 mg/kg/dose every 12 hr	For treatment of refractory supraventricular arrhythmia; long elimination half-life; may cause hypothyroidism or hyperthyroidism, hepatitis, pulmonary fibrosis
Atropine	Bradycardia: 0.01-0.03 mg/kg/dose IV, IM, ET every 10-15 minutes up to total dose of 0.04 mg/kg Premedication for intubation: 0.02 mg/kg/dose IV	For reversal or prevention of sinus bradycardia

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Agent	Dosage	Comments
Digoxin*	<37 weeks, loading dose: IV: 15-20 mcg/kg divided into 3 doses over 24 hr PO: 20-25 mcg/kg divided into 3 doses over 24 hr Maintenance dose: IV: 4-5 mcg/kg every 24 hr PO: 5-6 mcg/kg every 24 hr ≥37 weeks, loading dose: IV: 30-40 mcg/kg divided into 3 doses over 24 hr PO: 40-50 mcg/kg divided into 3 doses over 24 hr Maintenance dose: IV: 4-5 mcg/kg every 12 hr PO: 5-6 mcg/kg every 12 hr	Be aware of drug interactions; obtain periodic ECGs to assess for desired effects and signs of toxicity; hypokalemia, hypomagnesemia, hypermagnesemia, hypercalcemia, and renal impairment predispose patients to digoxin toxicity; target trough concentration of 0.8-2 ng/mL
Digoxin immune Fab	Chronic digoxin toxicity: Dose (in mg) = 40 mg × (serum digoxin concentration in ng/mL × weight in kg)/100 Acute ingestion: Dose (in vials) = (digoxin ingested in mg × bioavailability)/0.5 mg	Each vial contains 40 mg and will bind 0.5 mg digoxin; after administration, digoxin serum concentrations can no longer be determined accurately; bioavailability of digoxin solution = 0.85, tablets = 0.8
Flecainide	Begin at 2 mg/kg/dose PO every 12 hr; adjust based on response and serum concentrations to a maximum of 4 mg/kg/dose PO every 12 hr	Used for treatment of SVT not responsive to conventional therapies; can cause new or worsened arrhythmias
Lidocaine	Initial bolus: 0.5-1 mg/kg dose by slow IV push; may be repeated every 10 min up to total of 5 mg/kg Maintenance IV infusion: 10-50 mcg/kg/minute	Adverse effects include hypotension, seizures, respiratory depression, asystole
Procainamide	Initial bolus: 7-10 mg/kg/dose IV push Maintenance IV infusion: 20-80 mcg/kg/minute	Treatment of SVT refractory to vagal maneuvers and adenosine
Propranolol	PO: starting dose 0.25-1 mg/kg/dose every 6 hr; increase up to 3.5 mg/kg/dose every 6 hr IV: 0.01 mg/kg/dose IV every 6 hr; increase up to 0.15 mg/kg/dose every 6 hr	Adverse effects related to β receptor blockade include bradycardia, bronchospasm, and hypoglycemia
Sotalol	1 mg/kg/dose PO every 12 hr; increase to a maximum of 4 mg/kg/dose PO every 12 hr	For treatment of refractory ventricular and supraventricular tachyarrhythmias; has β blocking properties and prolongs cardiac action potential duration
Antihypertensive Agents		
Captopril	0.01-0.05 mg/kg/dose PO every 8-12 hr	Treatment of hypertension and CHF; monitor renal function and serum potassium; contraindicated in patients with bilateral renovascular disease
Enalapril (PO) Enalaprilat (IV)	PO: 40 mcg/kg PO every 24 hr; increase up to 150 mcg/kg PO every 6 hr IV: 10 mcg/kg IV every 24 hr; increase dose and interval based on response	Treatment of hypertension and CHF; monitor renal function and serum potassium; contraindicated in patients with bilateral renovascular disease
Hydralazine	IV: 0.1-0.5 mg/kg/dose every 6-8 hr; gradually increase to a maximum of 2 mg/kg/dose every 6 hr PO: 0.25-1 mg/kg/dose every 6-8 hr	Treatment of hypertension via vasodilation
Sodium nitroprusside	0.25-0.5 mcg/kg/min continuous IV infusion; increase dose every 20 min as needed Maintenance dose is usually <2 mcg/kg/min For hypertensive crisis, can use doses as high as 10 mcg/kg/min for ≤10 min	Must have continuous intra-arterial blood pressure monitoring; may produce profound hypotension, metabolic acidosis, thrombocytopenia, and/or CNS symptoms; cyanide toxicity can occur

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Agent	Dosage	Comments
Hemodynamic Support Agents		
Dobutamine	2-25 mcg/kg/min continuous IV infusion	Typical starting dose is 5-10 mcg/kg/min, then titrate to effect; increases myocardial contractility and cardiac output; tachycardia may occur
Dopamine	2-20 mcg/kg/min continuous IV infusion	Typical starting dose is 5-10 mcg/kg/min, then titrate to effect; increases myocardial contractility and cardiac output and causes vasoconstriction; predominant effects vary with dose; tachycardia may occur
Epinephrine	Resuscitation: 0.01-0.03 mg/kg/dose IV push; 0.05-0.1 mg/kg/dose ET Continuous IV infusion: 0.05-1 mcg/kg/min	Increases blood pressure via direct myocardial stimulation, increased heart rate, and vasoconstriction; monitor for hyperglycemia and tachycardia
Isoproterenol	0.05-0.5 mcg/kg/min continuous IV infusion; titrate to maximum of 2 mcg/kg/min	Primarily acts by increasing heart rate; monitor for tachycardia
Milrinone	Loading dose: 75 mcg/kg IV over 60 min Maintenance infusion: 0.2-0.75 mcg/kg/min	Has both inotropic and vasodilatory properties; hypotension occurs frequently with bolus dose
Patent Ductus Arteriosus Agents		
Alprostadil	Initial dose: 0.05-0.1 mcg/kg/min continuous IV infusion Maintenance doses may be as low as 0.01 mcg/kg/min	Apnea occurs in 10%-12% of neonates
Ibuprofen lysine	First dose: 10 mg/kg IV Second and third doses: 5 mg/kg IV; administer at 24 hr intervals	Monitor urine output; can inhibit platelet aggregation
Indomethacin	Initial dose: 0.2 mg/kg IV Subsequent doses: If <2 days, 0.1 mg/kg/dose IV every 12-24 hr for 2 doses If 2-7 days, 0.2 mg/kg/dose IV every 12-24 hr for 2 doses If >7 days, 0.25 mg/kg dose IV every 12-24 hr for 2 doses	Monitor urine output; can cause platelet dysfunction; avoid concomitant steroid therapy to decrease risk of GI perforation
Central Nervous System Drugs		
Analgesics and Narcotics		
Acetaminophen*	PO: 10-15 mg/kg/dose every 6-12 hr Rectal: 15-20 mg/kg/dose every 6-12 hr IV: GA ≥32 weeks, 12.5 mg/kg every 6 hr	Dosing interval dependent on postmenstrual age
Fentanyl	Slow IV push: 1-4 mcg/kg/dose every 2-4 hr Continuous IV infusion: 0.5-5 mcg/kg/hr	Synthetic opioid; may cause chest wall rigidity with higher doses or with rapid infusion
Methadone	0.05-0.1 mg/kg/dose every 6-24 hr	Treatment of neonatal abstinence syndrome; adjust dose in 10%-20% increments based on signs and symptoms of withdrawal
Morphine	IV, IM, subcutaneous: 0.05-0.2 mg/kg/dose every 4 hr Continuous IV infusion: 10-20 mcg/kg/hr; increase based on response Neonatal abstinence syndrome: 0.02-0.2 mg/kg/dose PO every 3-4 hr; adjust dose based on abstinence scoring	May exacerbate hypotension and cause respiratory depression

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Agent	Dosage	Comments
Anticonvulsants		
Fosphenytoin	Loading dose: 15-20 mg PE/kg IV, IM Maintenance dose: 4-8 mg PE/kg IV, IM every 24 hr	Fosphenytoin 1 mg PE = phenytoin 1 mg; monitor trough serum phenytoin concentrations; term infants >1 week of age may require more frequent dosing; use with caution in neonates with hyperbilirubinemia
Levetiracetam	10 mg/kg/dose IV, PO every 24 hr; increase dose as needed up to maximum of 30 mg/kg/dose every 12 hr	Treatment of seizures refractory to phenobarbital and other anticonvulsants
Lidocaine	Loading dose: 2 mg/kg IV over 10 minutes Maintenance infusion: 6 mg/kg/hr for 6 hr, then 4 mg/kg/hr for 12 hr, then 2 mg/kg/hr for 12 hr	Preterm newborns and newborns undergoing hypothermia treatment are at risk for drug accumulation; precise dosing in these infants is uncertain
Phenobarbital	Loading dose: 20 mg/kg slow IV push; additional 5-10 mg/kg doses may be given up to a total of 40 mg/kg Maintenance dose: 3-5 mg/kg/dose IV, IM, PO every 24 hr	Monitor serum concentrations and adjust dose to maintain concentrations at 15-40 mcg/mL
Phenytoin	Loading dose: 15-20 mg/kg IV over 30 minutes Maintenance dose: 4-8 mg/kg/dose IV, PO every 8-24 hr	Infants >1 week of age may require more frequent dosing
Neuromuscular Blockers[†]		
Pancuronium	0.1 mg/kg IV push every 1-2 hr as needed	Tachycardia, hypotension, and hypertension occur frequently
Rocuronium	0.3-1.2 mg/kg IV push, repeat as needed (every 30-60 min)	Short duration of action; use limited to premedication for procedures such as intubation
Vecuronium	0.1 mg/kg IV push, every 1-2 hr as needed Continuous IV infusion: 0.06-0.2 mg/kg/hr	Minimal cardiovascular side effects
Sedatives/Tranquilizers		
Clonidine	0.5-1 mcg/kg/dose PO every 4-6 hr	Adjunct treatment of neonatal abstinence syndrome; limited data available
Lorazepam	0.05-0.1 mg/kg/dose IV push	May cause respiratory depression; may be used acutely to stop seizures; some products contain benzyl alcohol
Midazolam	IV, IM: 0.05-0.15 mg/kg/dose every 2-4 hr Continuous IV infusion: 10-60 mcg/kg/hr; increase as needed Intranasal: 0.2-0.3 mg/kg/dose prior to procedure Oral: 0.25 mg/kg/dose every 4-6 hr	Dosage requirements are decreased by concurrent use of narcotics; monitor for respiratory depression and hypotension; may cause myoclonic seizure-like activity
Pentobarbital	2-6 mg/kg/dose IV push	Short-acting barbiturate for short-term use
Diuretics		
Bumetanide[*]	0.005-0.1 mg/kg/dose IV, IM, PO every 12-24 hr	May cause hyponatremia, hypokalemia, and hypochloremic alkalosis; may displace bilirubin from albumin-binding sites when given in high doses or for prolonged periods
Chlorothiazide	PO: 10-20 mg/kg/dose every 12 hr IV: 5-10 mg/kg/dose every 12 hr	May cause hypokalemia and alkalosis; effective in treatment of nephrocalcinosis secondary to loop diuretics

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Agent	Dosage	Comments
Furosemide*	IV: 1-2 mg/kg/dose every 6-24 hr PO: 2-6 mg/kg/dose every 6-24 hr	Potentially ototoxic; may cause hypokalemia, hyponatremia, alkalosis, nephrocalcinosis; consider alternate-day therapy for long-term use
Hydrochlorothiazide	1-2 mg/kg/dose PO every 12 hr	May cause hypokalemia
Spironolactone	1-3 mg/kg/dose PO every 24 hr	Use in combination with other diuretics; may cause hyperkalemia
Endocrine Agents		
Dexamethasone	DART (Dexamethasone: A Randomized Trial) protocol: 0.075 mg/kg/dose IV, PO every 12 hr for 3 days then wean over 7 days (10-day course) Airway extubation: 0.25-0.5 mg/kg/dose IV, PO every 8 hours for 1-3 doses	Treat only those infants at highest risk of chronic lung disease; adverse effects include growth failure, hypertension, hyperglycemia, increased risk for cerebral palsy; do not use concurrently with indomethacin or ibuprofen because of risk for GI perforation
Diazoxide	2-5 mg/kg/dose PO every 8 hr	Reserved for treatment of severe, persistent hypoglycemia caused by hyperinsulinism; often causes sodium and fluid retention; may cause GI distention
Hydrocortisone	Physiologic dose: 7-9 mg/m^2/day IV, PO divided q 8-12 hr Stress dose: 20-50 mg/m^2/day IV divided every 8-12 hr	Adverse effects include hyperglycemia, hypertension, water and salt retention; there is an increased risk of GI perforation when treating concurrently with indomethacin/ibuprofen
Glucagon	0.2 mg/kg/dose IV, IM, or subcutaneous (maximum dose 1 mg)	Reserved for treatment of refractory hypoglycemia; watch for rebound hypoglycemia approximately 2 hours after dose
Insulin	Continuous IV infusion: 0.01-0.1 unit/kg/hr	Binds to plastic tubing—to saturate tubing binding sites fill tubing with insulin solution and wait at least 20 minutes prior to administration
Levothyroxine	PO: 10-14 mcg/kg/dose every 24 hr IV: 5-8 mcg/kg/dose every 24 hr	Adjust oral doses in 12.5 mcg increments, always round up; assess thyroid function 2 weeks after dosing change
Octreotide	Hyperinsulinemic hypoglycemia: 1 mcg/kg/dose IV, subcutaneous every 6 hr; titrate to desired effect; maximum dose is 10 mcg/kg/dose every 6 hr Chylothorax: 1 mcg/kg/hr, titrate up by 1 mcg/kg/hr every 24 hr; maximum dose is 10 mcg/kg/hr	May cause vomiting, diarrhea, abdominal distention; NEC has been reported in term neonates
Gastrointestinal Agents		
Cimetidine	2.5-5 mg/kg/dose PO, IV every 6-12 hr	Monitor for drug interactions; may increase risk for late-onset bacterial sepsis and fungal sepsis
Erythromycin	10 mg/kg/dose PO every 6 hr for 2 days, then 4 mg/kg/dose every 6 hr for 5 days	Treatment of feeding intolerance caused by GI dysmotility
Famotidine	IV: 0.25-0.5 mg/kg/dose every 24 hr PO: 0.5-1 mg/kg/dose every 24 hr	May increase risk for late-onset bacterial sepsis and fungal sepsis
Lansoprazole	0.73-1.66 mg/kg/dose PO every 24 hr	Limited data available in neonates
Metoclopramide	0.03-0.1 mg/kg/dose IV, PO every 8 hr	Facilitates gastric emptying and gastrointestinal motility; observe for dystonic reactions

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Agent	Dosage	Comments
Nizatidine	2-5 mg/kg/dose PO every 12 hr	May increase risk for late-onset bacterial sepsis and fungal sepsis; limited data available in neonates
Omeprazole	0.5-1.5 mg/kg/dose PO every 24 hr	Limited data available in neonates
Ranitidine	PO: 2 mg/kg/dose every 8 hr IV preterm: 0.5 mg/kg/dose every 12 hr IV term: 1.5 mg/kg/dose every 8 hr Continuous IV infusion: 0.04-0.1 mg/kg/hr	May increase risk for late-onset bacterial sepsis and fungal sepsis
Ursodiol	10-15 mg/kg/dose PO every 12 hr	May cause vomiting, abdominal pain, constipation
Hematologic Agents		
Alteplase (t-PA)	Dissolution of intravascular thrombi: 200 mcg/kg/hr for 6-48 hr Restoration of patency for central venous catheter: instill a 1-mg/mL solution into the catheter and dwell up to 120 minutes; may repeat once if needed	Thrombi dose is a range of that used in case reports (20-500 mcg/kg/hr)
Enoxaparin	Term: 1.7 mg/kg/dose subcutaneous every 12 hr Preterm: 2 mg/kg/dose subcutaneous every 12 hr	Adjust dosage to maintain antifactor Xa level between 0.5 and 1 unit/mL
Epoetin alfa	200-400 units/kg/dose subcutaneous 3-5 times/week	Patient should be on supplemental iron therapy; higher doses under investigation for neuroprotective benefits
Heparin	Thrombosis: 75 units/kg IV, then 28 units/kg/hr Maintenance of central line patency: 0.5-1 unit/mL of IV fluid	For thrombosis, adjust dose based on aPTT or anti-factor Xa level
IVIG	400-1000 mg/kg/dose IV over 2-6 hr	If more than one dose needed, may repeat in 12-24 hr
Minerals/Vitamins		
Calcium carbonate	20-80 mg/kg/day elemental calcium PO every 6-12 hr	
Calcium gluconate 10%	Acute treatment: 100-200 mg/kg/dose IV (equivalent to 10-20 mg/kg elemental calcium) Maintenance treatment: 200-800 mg/kg/day by continuous IV infusion (20-80 mg/kg elemental calcium)	Monitor serum calcium and ionized calcium if possible
Ferrous sulfate	2-6 mg/kg/day elemental iron divided q12-24 hr	Higher dose for infants on epoetin therapy
Iron dextran	0.4-1 mg/kg/day continuous IV infusion in parenteral nutrition solution	For infants unable to tolerate oral iron therapy
Potassium chloride	Acute treatment of symptomatic hypokalemia: begin with 0.5-1 mEq/kg IV over 1 hr, then reassess Initial oral replacement: 0.5-1 mEq/kg/day PO divided and administered with feedings	Maximum concentrations: 40 mEq/L for peripheral, 80 mEq/L for central venous infusions
Pyridoxine (vitamin B_6)	Initial diagnostic dose: 50-100 mg IV, IM Maintenance dose: 50-100 mg PO every 24 hr	May cause bradycardia, apnea, hypotension
Sodium bicarbonate	1-2 mEq/kg/dose IV over at least 30 minutes	Maximum concentration 0.5 mEq/mL; treatment of normal anion gap metabolic acidosis caused by renal or GI losses; not a recommended therapy in neonatal resuscitation

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Agent	Dosage	Comments
Vitamin D	Supplementation: 400 units PO every 24 hr Treatment of deficiency: 1000 units/day divided every 12-24 hr	Vitamin D_3 (cholecalciferol) has been shown to be more effective in raising 25(OH)-D levels when compared with vitamin D_2 (ergocalciferol)
Vitamin K_1	Prophylaxis: >32 weeks' gestational age: 0.5-1 mg IM at birth <32 weeks' gestational age: >1000 g birth weight: 0.5 mg IM <1000 g birth weight: 0.3 mg/kg IM Treatment of HDN: 1-10 mg IV	
Ophthalmic Agents		
Cyclopentolate	1-2 drops in the eye 10-30 minutes before funduscopy	Use solutions with concentrations of 0.5% or less in neonates; anticholinergic effects if absorbed systemically; apply pressure to lacrimal sac during and for 2 minutes after instillation
Phenylephrine	1 drop in eye 10-30 minutes before funduscopy	Use only the 2.5% solution in neonates; apply pressure to lacrimal sac during and for 2 minutes after instillation
Tropicamide	1 drop in eye 10-30 minutes before funduscopy	Use only the 0.5% solution in neonates; anticholinergic effects if absorbed systemically; apply pressure to lacrimal sac during and for 2 minutes after instillation
Pulmonary Agents		
Beractant (Survanta®)	4 mL/kg/dose intratracheally; may repeat every 6 hr up to a total of 4 doses	
Calfactant (Infasurf®)	3 mL/kg/dose intratracheally; may repeat every 12 hr up to a total of 3 doses	
Lucinactant (Surfaxin®)	5.8 mL/kg/dose intratracheally; may repeat every 6 hr up to a total of 4 doses	Only synthetic peptide-containing surfactant
Poractant alfa (Curosurf®)	2.5 mL/kg/dose intratracheally; may repeat dose of 1.25 mL/kg every 12 hr up to a total of 3 doses	
Albuterol	Nebulizer: 0.1-0.5 mg/kg/dose every 2-6 hr MDI: 1 puff every 2-6 hr	Selective β_2-agonist
Aminophylline	Loading dose: 8 mg/kg IV Maintenance dose: 1.5-3 mg/kg/dose IV every 8-12 hr	Follow serum trough concentrations—target 7-12 mcg/L
Theophylline	1.5-3 mg/kg/dose every 8-12 hr	IV aminophylline dose is equivalent to PO theophylline dose; follow serum trough concentrations—target 7-12 mcg/L
Caffeine citrate	Loading dose: 20-25 mg/kg IV, PO (equivalent to 10-12.5 mg/kg caffeine base) Maintenance dose: 5-10 mg/kg/dose IV, PO every 24 hr (equivalent to 2.5-5 mg/kg caffeine base)	Monitoring serum levels is not necessary if using recommended doses
Dornase alpha	1.25-2.5 mL via nebulizer or 0.2 mL/kg instilled directly into endotracheal tube every 12-24 hr	Desaturation and/or airway obstruction may occur, owing to rapid mobilization of secretions
Ipratropium bromide	MDI: 2-4 puffs every 6-8 hr Nebulizer: 75-175 mcg/dose every 6-8 hr	Precise dosing is uncertain, although therapeutic margin is wide

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Agent	Dosage	Comments
Reversal Agents/Antidotes		
Flumazenil	IV: 5-10 mcg/kg/dose; repeat every 45 seconds up to maximum cumulative dose of 50 mcg/kg or 1 mg (whichever is smaller) Intranasal: 40 mcg/kg/dose divided between each nostril Rectal: 15-30 mcg/kg/dose; repeat after 15-20 minutes if needed	Reversal of sedative effect from benzodiazepines
Hyaluronidase	150 units subcutaneous as 5 separate injections around the site of extravasation	Initiate treatment as soon as possible after extravasation
Naloxone	0.1 mg/kg/dose IV every 2-3 minutes; may need to repeat doses in 20-60 minutes	Reversal of narcotic-induced respiratory/CNS depression; not recommended as part of delivery room resuscitation
Phentolamine	Inject 1-5 mL of a 0.5 mg/mL solution subcutaneous into the periphery of the affected area	Prevention of dermal necrosis caused by extravasation of vasoconstrictive agents
Protamine	0.25-1 mg per 100 units heparin received IV; maximum dose 50 mg	Heparin antagonist; exact dose depends on time in minutes since last heparin dose; may cause hypotension, pulmonary edema, and pulmonary hypertension

ANC, Absolute neutrophil count; CHF, congestive heart failure; CNS, central nervous system; CSF, cerebrospinal fluid; ECG, electrocardiogram; GA, gestational age; GI, gastrointestinal; HDN, hemolytic disease of the newborn; HSV, herpes simplex virus; IV, intravenous; IVIG, intravenous immunoglobulin; IM, intramuscular; MDI, metered-dose inhaler; NEC, necrotizing enterocolitis; PE, phenytoin equivalent; PO, per oral route; SVT, supraventricular tachycardia.
*Exact dose and dosing interval are dependent on postmenstrual and postnatal age.
†These agents must be used in conjunction with an effective sedative/analgesic agent. They do not provide any analgesia or amnesia.
Adapted from data from Truven Health Analytics Clinical Editorial Staff. *Neofax.* Ann Arbor, MI: Truven Health Analytics LLC; 2017.

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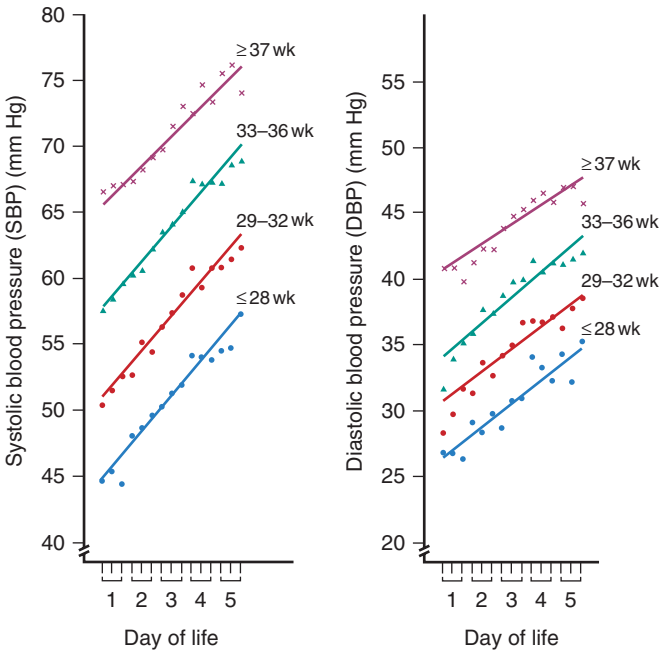
Appendix B

Tables of Normal Values

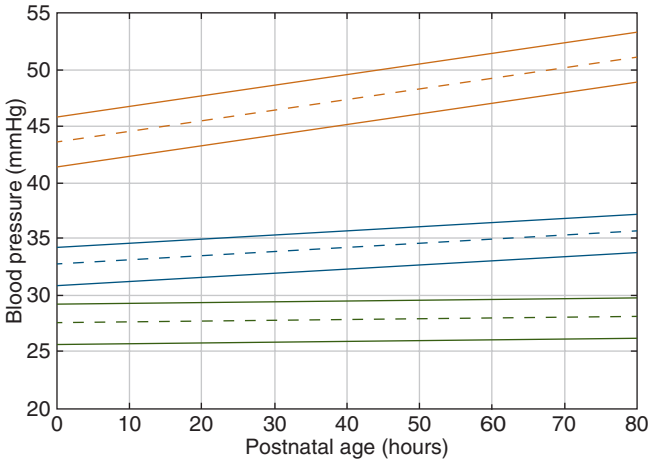
Mary L. Nock and Arielle L. Olicker

Physiologic Parameters

Blood Pressure

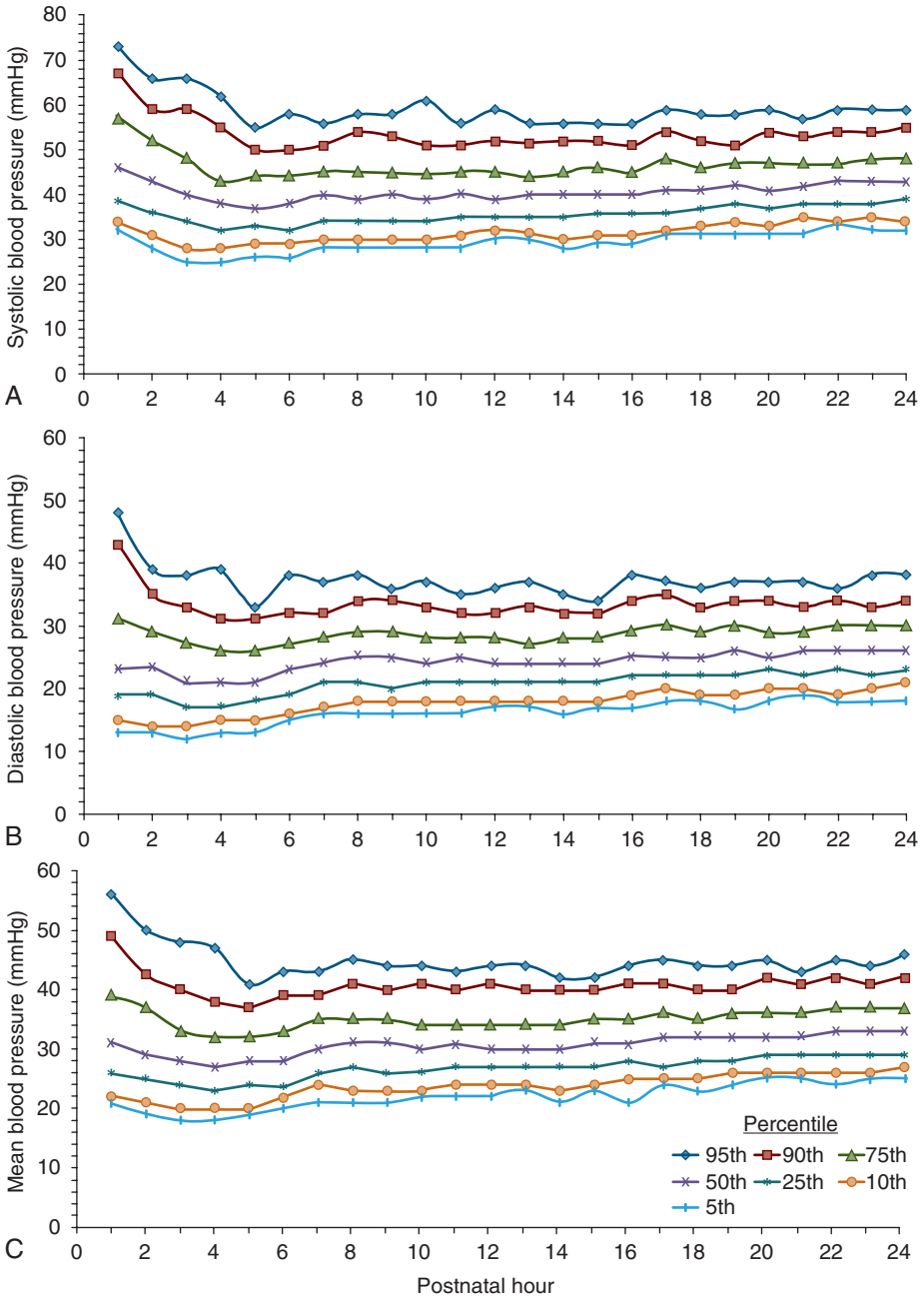


• **Fig. B.1** Systolic and diastolic blood pressures plotted for the first 5 days of life, with each day subdivided into 8-hour periods. Infants are categorized by gestational age into 4 groups: ≤28 weeks (n = 33), 29-32 weeks (n = 73), 33-36 weeks (n = 100), and ≥37 weeks (n = 110). (From Zubrow AB, et al. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. *J Perinatol*. 1995;15:470.)



• **Fig. B.2** Population estimate of blood pressure values by postnatal age in hours. Dashed line represents the blood pressure estimate, whereas the solid line represents the boundaries of the 95% confidence interval. Orange, SBP; blue, MABP; green, DBP. DBP, diastolic blood pressure; MABP, mean arterial blood pressure; SBP, systolic blood pressure. (From Vesoulis ZA, et al. Empirical estimation of the normative blood pressure in infants <28 weeks' gestation using a massive data approach. *J Perinatol*. 2016;36:291-295.)

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• **Fig. B.3** Systolic **(A)**, diastolic **(B)**, and mean **(C)** arterial blood pressure curves over the first 25 hours for extremely preterm infants (n = 367). (From Batton B, et al. Evolving blood pressure dynamics for extremely preterm infants. *J Perinatol.* 2014;34(4):301-305.)

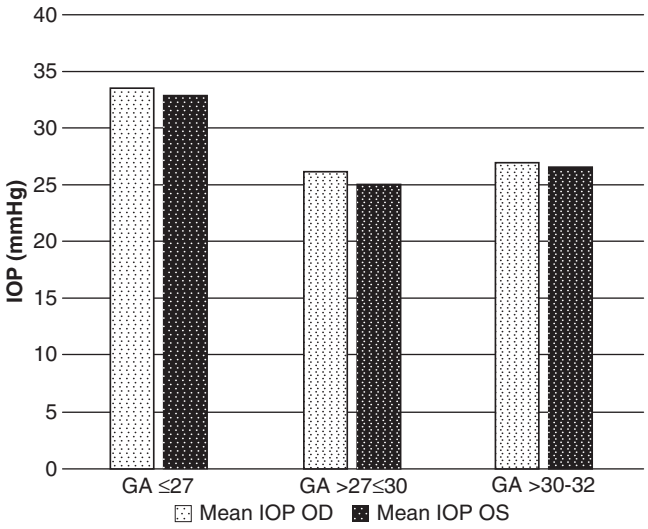
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TABLE B.1 Blood Pressure Values in Neonatal Period after Two Weeks of Age, by Gestational Age

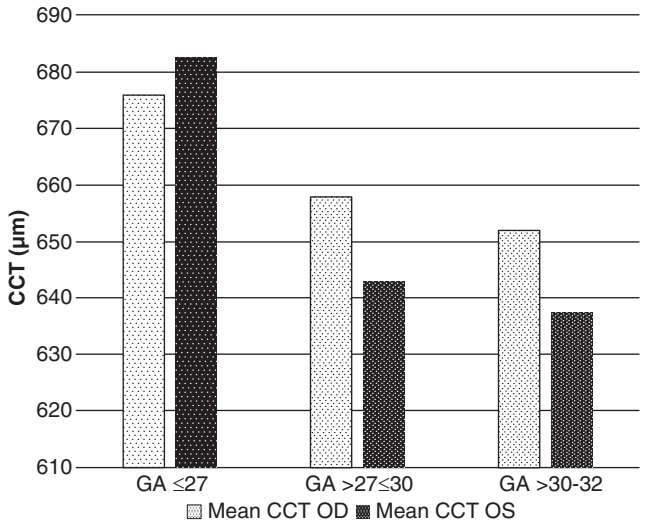
Gestational Age (weeks)	Percentile	Blood Pressure (mm Hg)		
		Systolic	Diastolic	Mean
26-28	50th	55-60	30-38	38-45
	95th	72-75	50-50	57-58
	99th	77-80	54-56	63-63
30-32	50th	65-68	40-40	48-48
	95th	80-83	55-55	63-64
	99th	85-88	60-60	68-69
34-36	50th	70-72	40-50	50-57
	95th	85-87	55-65	65-72
	99th	90-92	60-70	70-71
38-40	50th	77-80	50-50	59-60
	95th	92-95	65-65	74-75
	99th	97-100	70-70	79-80
42-44	50th	85-88	50-50	62-63
	95th	98-105	65-68	76-80
	99th	102-110	70-73	81-85

Modified from Nickavar A and Assadi F. Managing hypertension in newborn infants. *Int J Prev Med*. 2014;5(Suppl 1):S39-S43.

Intraocular Pressure

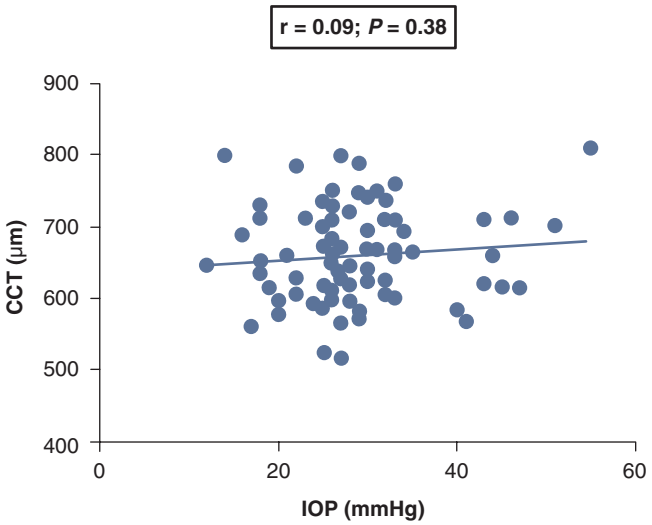


• **Fig. B.4** Intraocular pressure (IOP) measured at different gestational ages (GA) in weeks. OD, right eye; OS, left eye. (From Grover S, et al. Intraocular pressure in premature low birth weight infants. *J Pediatr Ophthamol Strabismus*. 2016;53(5):300-304.)

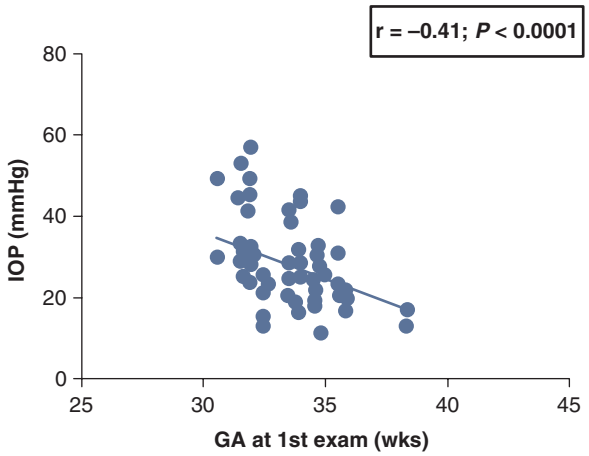


• **Fig. B.5** Changes in mean central corneal thickness (CCT) at different gestational ages (GA) in weeks. OD, right eye; OS, left eye. (From Grover S, et al. Intraocular pressure in premature low birth weight infants. *J Pediatr Ophthamol Strabismus*. 2016;53(5):300-304.)

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• **Fig. B.6** Correlation between the intraocular pressure (IOP) and central corneal thickness (CCT) in premature low birth weight infants. (From Grover S, et al. Intraocular pressure in premature low birth weight infants. *J Pediatr Ophthamol Strabismus*. 2016;53(5):300-304.)



• **Fig. B.7** Correlation between the gestational ages (GA) at first examination and the intraocular pressure (IOP) in premature low birth weight infants. (From Grover S, et al. Intraocular pressure in premature low birth weight infants. *J Pediatr Ophthamol Strabismus*. 2016;53(5):300-304.)

Time of First Void and Stool

TABLE B.2 **Time of First Void in 500 Infants**

	395 Term Infants		80 Preterm Infants		25 Post-term Infants	
Hours	No. of Infants	Cumulative %	No. of Infants	Cumulative %	No. of Infants	Cumulative %
In delivery room	51	12.9	17	21.2	3	12
1-8	151	51.1	50	83.7	4	38
9-16	158	91.1	12	98.7	14	84
17-24	35	100	1	100	4	100
>24	0	–	0	–	0	–

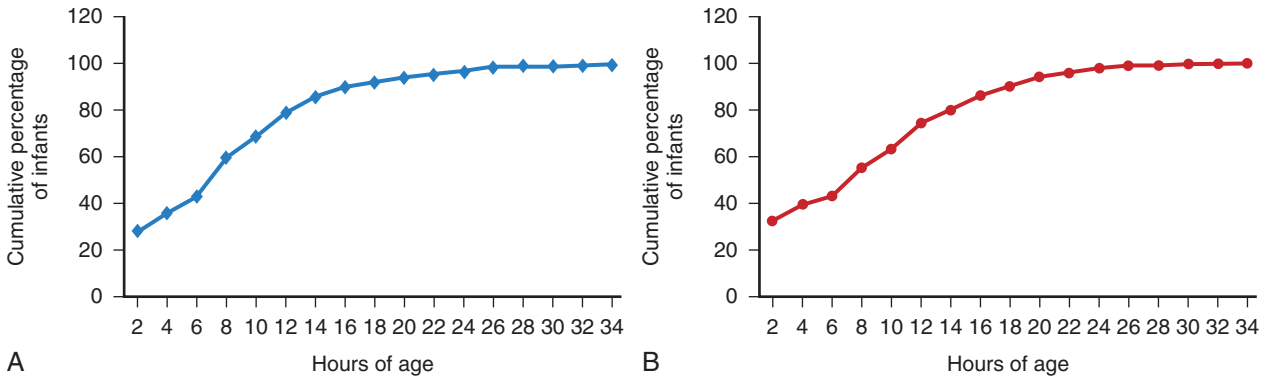
From Clark DA. Times of first void and first stool in 500 newborns. *Pediatrics.* 1977;60:457.

TABLE B.3 **Time of First Stool in 500 Infants**

	395 Term Infants		80 Preterm Infants		25 Post-term Infants	
Hours	No. of Infants	Cumulative %	No. of Infants	Cumulative %	No. of Infants	Cumulative %
In delivery room	66	16.7	4	5	8	32
1-8	169	59.5	22	32.5	9	68
9-16	125	91.1	25	63.8	5	88
17-24	29	98.5	10	76.3	3	100
24-48	6*	100	18†	98.8	0	–
>48	0	–	1‡	100	0	–

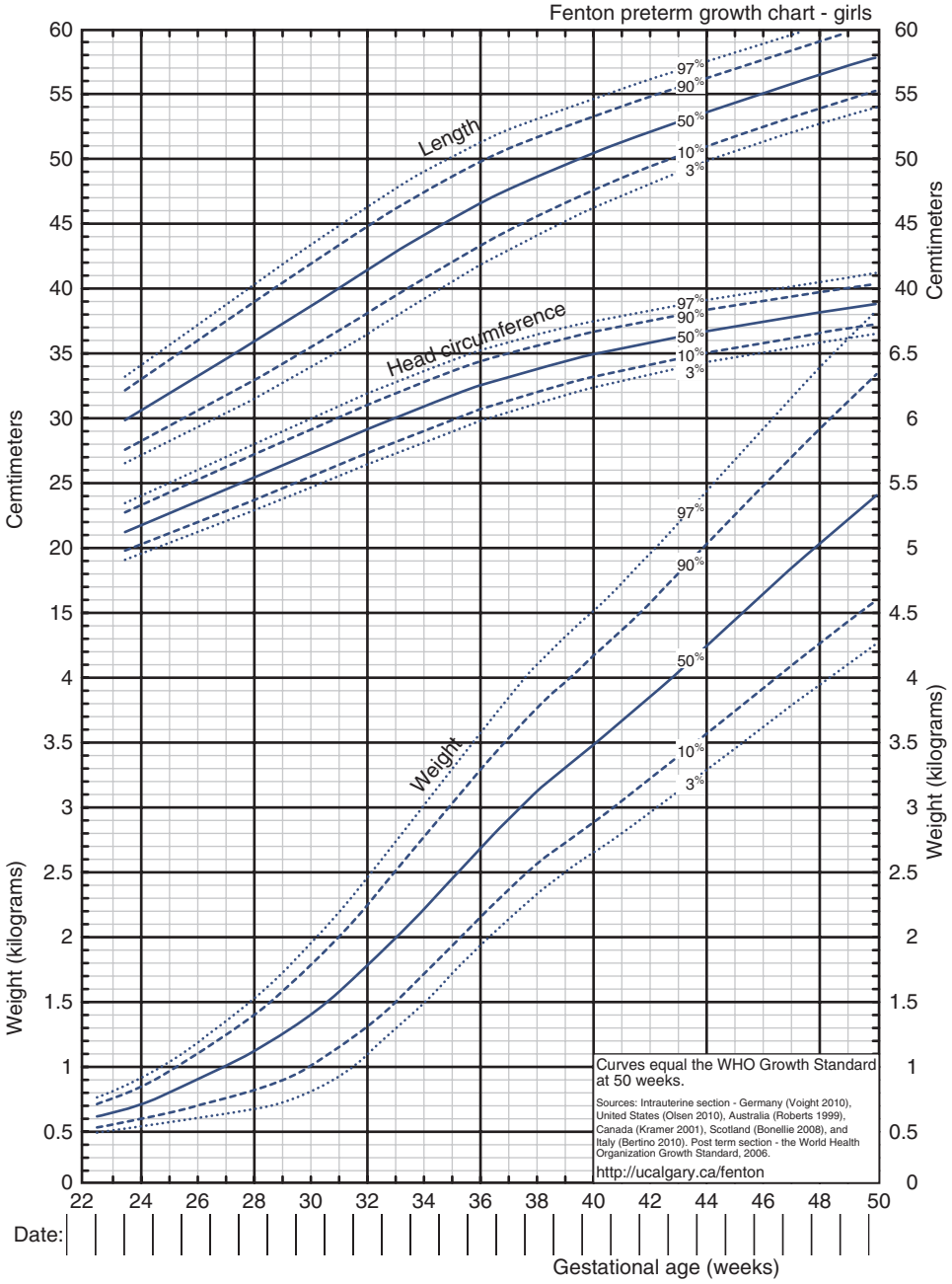
*At 25, 26, 27, 28, 33, and 37 hours.
†Five infants produced a stool more than 36 hours after birth: at 38, 39, 40, 42, and 47 hours.
‡At 59 hours.
From Clark DA. Times of first void and first stool in 500 newborns. *Pediatrics.* 1977;60:457.

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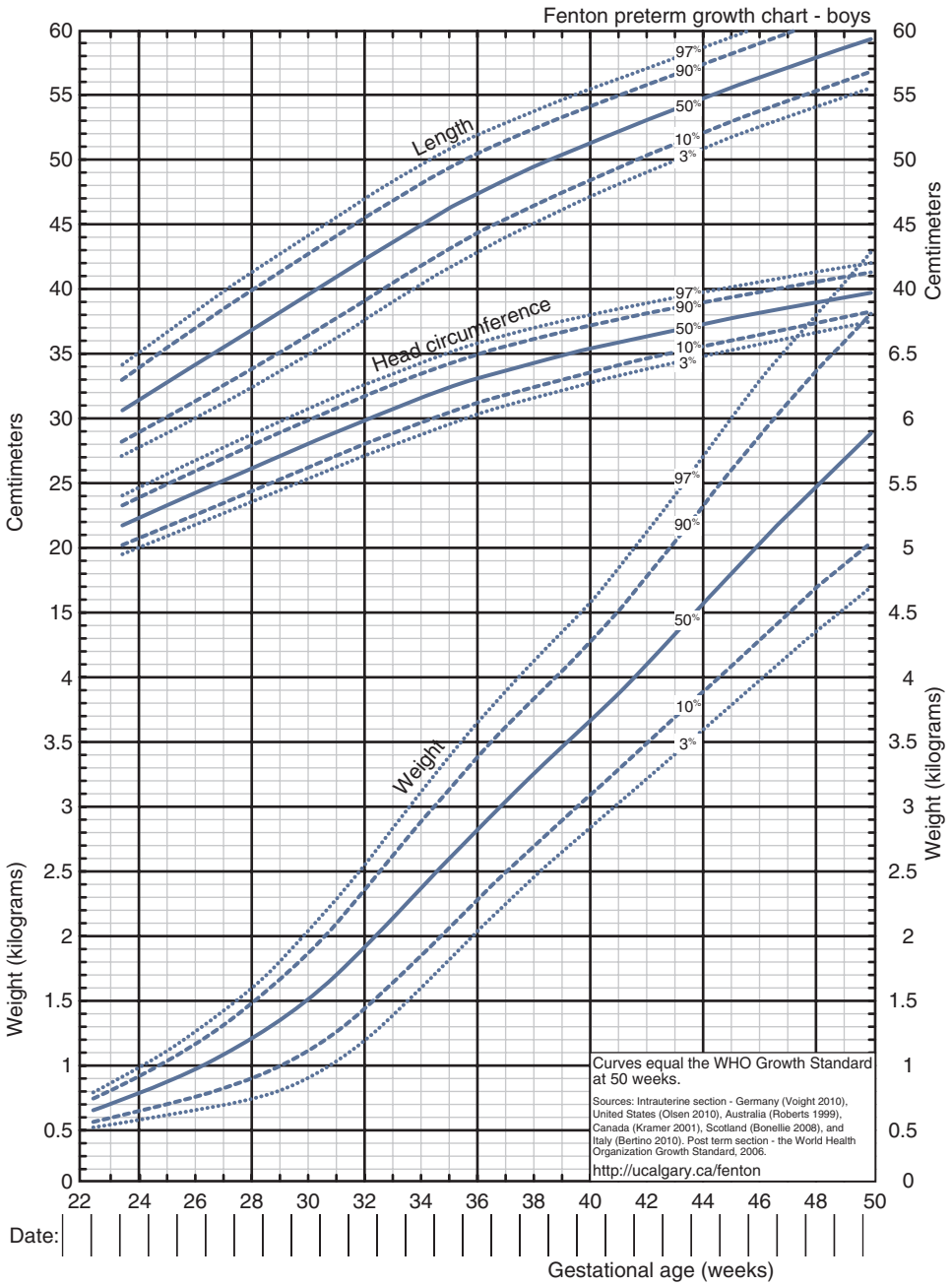
• **Fig. B.8** Graphs depicting the cumulative percentage of infants ≥34 weeks' gestational age who had their first stool **(A)** or first urine **(B)** by a certain hour of age (n = 979). (From Metaj M, et al. Comparison of breast- and formula-fed normal newborns in time to first stool and urine. *J Perinatol*. 2003;23:627.)

Growth Charts



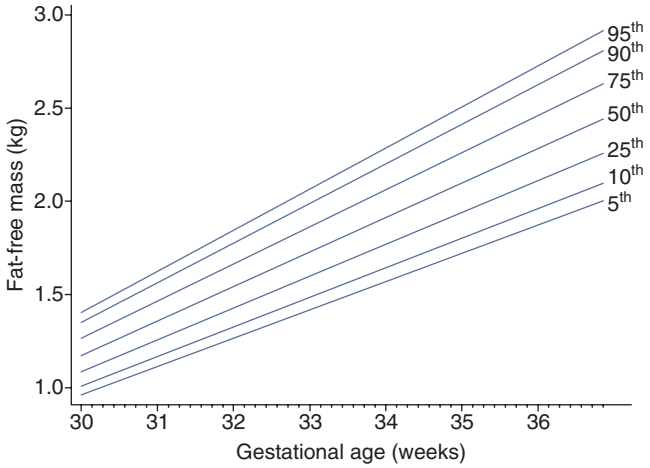
• **Fig. B.9** Revised growth chart for girls. (From Fenton TR, et al. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59.)

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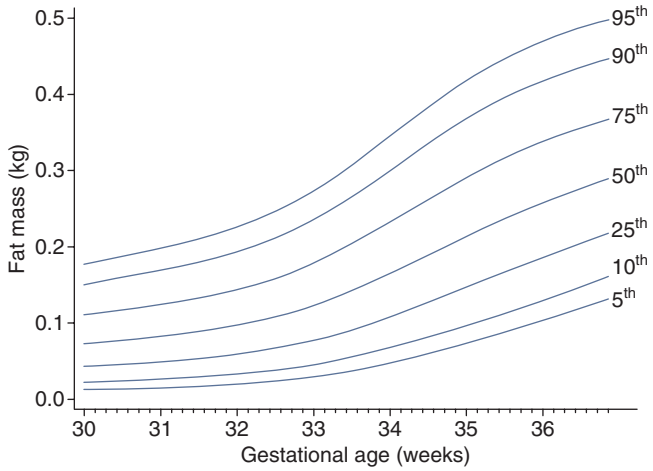


• **Fig. B.10** Revised growth chart for boys. (From Fenton TR, et al. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59.)

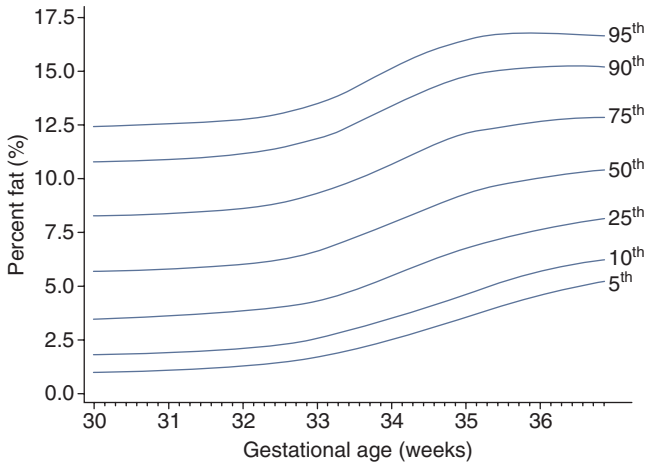
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• **Fig. B.11** Fat-free mass percentile curves for 223 appropriate for gestational age, medically stable preterm infants born at 30-36 weeks' gestation measured within 72 hours of birth. (From Demerath E, et al. New body composition reference charts for preterm infants. *Am J Clin Nutr.* 2017;105:70-77.)



• **Fig. B.12** Fat mass percentile curves for 223 appropriate for gestational age, medically stable preterm infants born at 30-36 weeks' gestation measured within 72 hours of birth. (From Demerath E, et al. New body composition reference charts for preterm infants. *Am J Clin Nutr*. 2017;105:70-77.)



• **Fig. B.13** Percentage body fat percentile curves for 223 appropriate for gestational age, medically stable preterm infants born at 30-36 weeks' gestation measured within 72 hours of birth. (From Demerath E, et al. New body composition reference charts for preterm infants. *Am J Clin Nutr*. 2017;105:70-77.)

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Chemistry Values

TABLE B.4 Reference Intervals by Gestational Age for Cord Blood Phosphate, Calcium, Albumin-Adjusted Calcium, Magnesium, and Alkaline Phosphatase

Gestational Age (Weeks)	N	Phosphate (mg/dL) Mean ± SD	LL	UL	Phosphate (mmol/L) Mean ± SD	LL	UL
23-27	51	6.5 ± 0.9	4.9	8.2	2.1 ± 0.3	1.6	2.6
28-31	119	6.3 ± 1	4.3	8.2	2 ± 0.3	1.4	2.7
32-34	191	6.1 ± 0.8	4.6	7.8	2 ± 0.2	1.5	2.5
35-36	119	6.1 ± 1	4.2	8	2 ± 0.3	1.4	2.6
>36	52	5.7 ± 0.7	4.3	7.1	1.8 ± 0.2	1.4	2.3
		Calcium (mg/dL)			Calcium (mmol/L)		
23-27	51	10 ± 1	8.1	11.9	2.5 ± 0.2	2	3
28-31	115	10.2 ± 1.2	8	12.5	2.6 ± 0.3	2	3.1
32-34	176	10.5 ± 1	8.6	12.4	2.6 ± 0.2	2.2	3.1
35-36	110	10.4 ± 1.1	8.3	12.5	2.6 ± 0.3	2.1	3.1
>36	52	10.9 ± 0.5	9.8	11.9	2.7 ± 0.1	2.5	3
		Albumin-Adjusted Calcium (mg/dL)			Albumin-Adjusted Calcium (mmol /L)		
23-27	49	10.8 ± 0.9	8.9	12.6	2.7 ± 0.2	2.2	3.2
28-31	109	10.9 ± 1.1	8.8	12.9	2.7 ± 0.3	2.2	3.3
32-34	175	11.1 ± 0.9	9.3	12.7	2.8 ± 0.2	2.3	3.2
35-36	116	10.9 ± 0.9	9	12.8	2.7 ± 0.2	2.3	3.2
>36	51	11.2 ± 0.5	10.2	12.2	2.8 ± 0.1	2.6	3
		Magnesium (mg/dL)			Magnesium (mmol/L)		
23-27	48	1.9 ± 0.2	1.6	2.3	0.79 ± 0.07	0.65	0.94
28-31	127	1.9 ± 0.3	1.4	2.4	0.79 ± 0.1	0.58	0.99
32-34	193	1.8 ± 0.2	1.5	2.2	0.76 ± 0.08	0.6	0.92
35-36	120	1.8 ± 0.2	1.4	2.3	0.76 ± 0.09	0.58	0.93
>36	53	1.9 ± 0.2	1.5	2.2	0.77 ± 0.08	0.63	0.92
		Alkaline Phosphatase (Units/L)					
23-27	50	201 ± 61	80	321			
28-31	130	196 ± 68	61	330			
32-34	197	174 ± 55	66	283			
35-36	123	166 ± 56	57	275			
>36	52	159 ± 49	62	256			

LL, lower limit; UL, upper limit; SD, standard deviation.
Modified from Fenton TR, et al. Cord blood calcium, phosphate, magnesium, and alkaline phosphatase gestational age-specific reference intervals for preterm infants. *BMC Pediatrics.* 2011;11:76.

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TABLE B.5 Serum Magnesium, Calcium, Phosphate, and Alkaline Phosphatase in Extremely Low Birth Weight Infants in the First Weeks of Life

Day of Life	Magnesium (mmol/L)	Calcium (mmol/L)	Phosphate (mmol/L)	Alkaline Phosphatase (IU/L)
1	0.85 ± 0.14	2.18 ± 0.27	1.99 ± 0.48	—
2	0.96 ± 0.18	2.24 ± 0.33	1.94 ± 0.56	—
3	1.05 ± 0.13	2.55 ± 0.19	1.49 ± 0.47	—
4	1.09 ± 0.1	2.65 ± 0.17	1.39 ± 0.44	—
5	1.06 ± 0.1	2.72 ± 0.27	1.29 ± 0.37	—
6	1.02 ± 0.12	2.71 ± 0.2	1.3 ± 0.37	—
7	0.98 ± 0.10	2.66 ± 0.16	1.37 ± 0.3	—
14	0.91 ± 0.1	2.57 ± 0.12	1.64 ± 0.38	1323 ± 639
21	0.89 ± 0.08	2.61 ± 0.16	1.71 ± 0.34	1359 ± 430
28	0.91 ± 0.1	2.61 ± 0.16	1.74 ± 0.35	1238 ± 439
Reference Range	0.7-1.17	1.8-2.7	1.62-2.52	146-1000

All values are mean ± SD, n = 51
From Noone D, et al. Serum magnesium in the first weeks of life in extremely low birth weight infants. *Neonatology*. 2012;101:276.

TABLE B.6 Whole Blood Ionized Calcium

Term Neonates			Premature Neonates		
AGE (h)	Ca^{2+}, mEq/L*	Ca^{2+}, mmol/L*	Age (h)	Ca^{2+}, mEq/L*	Ca^{2+}, mmol/L*
1-12	2.48 ± 0.22	1.24 ± 0.11	5-12	2.42 ± 0.32	1.21 ± 0.16
13-24	2.38 ± 0.24	1.19 ± 0.12	13-19	2.34 ± 0.24	1.17 ± 0.12
25-48	2.42 ± 0.26	1.21 ± 0.13	25-48	2.41 ± 0.32	1.21 ± 0.16
49-72	2.44 ± 0.28	1.22 ± 0.14	51-72	2.56 ± 0.36	1.28 ± 0.18
73-99	2.58 ± 0.34	1.29 ± 0.17	77-99	2.68 ± 0.28	1.34 ± 0.14
99-120	2.70 ± 0.24	1.35 ± 0.12	108-140	2.76 ± 0.26	1.38 ± 0.13
121-144	2.74 ± 0.24	1.37 ± 0.12	150-185	2.80 ± 0.32	1.40 ± 0.16
146-168	2.76 ± 0.32	1.38 ± 0.16			
178-264	2.80 ± 0.20	1.40 ± 0.10			

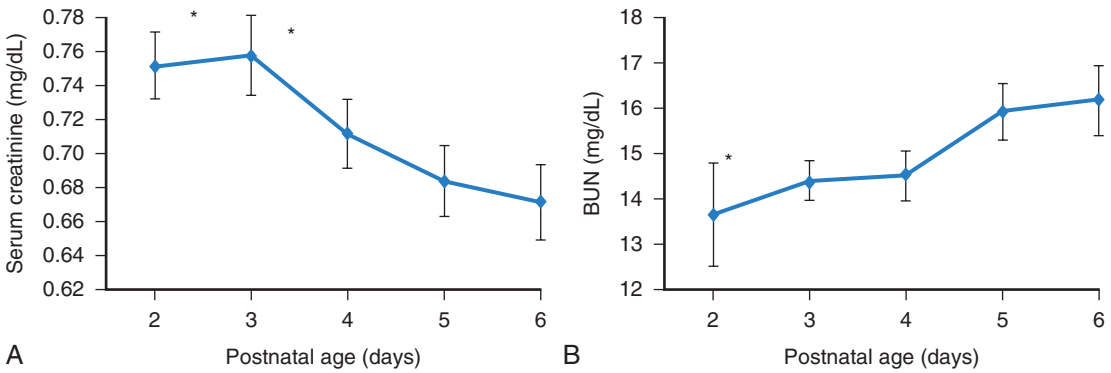
*Values given as mean ± SD.
Data from Wandrup J, et al. Age-related reference values for ionized calcium in the first week of life in premature and full-term neonates. *Scand J Clin Lab Invest*. 1988;48:255; Wandrup J. Critical analytical and clinical aspects of ionized calcium in neonates. *Clin Chem*. 1989;35:2027.

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TABLE B.7 Bone Mineral Reference Intervals in Healthy Infants

Plasma Analytes, Median (Range)	Age (Months)					
	1	2	3	6	9	12
Ionized calcium, mmol/L*	1.4 (1.29-1.52)	1.39 (1.22-1.48)	1.38 (1.3-1.49)	1.35 (1.16-1.42)	1.33 (1.26-1.43)	1.33 (1.24-1.39)
Total calcium, mmol/L	2.53 (2.32-2.69)	2.54 (2.37-2.72)	2.55 (2.32-2.76)	2.51 (2.32-2.71)	2.48 (2.18-2.65)	2.47 (2.25-2.65)
Phosphate, mmol/L	2.06 (1.75-2.39)	1.95 (1.61-2.25)	1.87 (1.56-2.31)	1.77 (1.29-2.18)	1.73 (1.44-2.14)	1.77 (1.32-2.2)
Creatinine, µmol/L	13 (8-28)	13 (7-24)	14 (7-26)	15 (7-31)	15 (8-31)	14 (7-37)
Alkaline phosphatase, U/L	302 (141-608)	272 (140-540)	248 (2-541)	190 (77-362)	203 (94-488)	210 (86-745)

*Whole blood ionized calcium.
Modified from Gallo S, et al. Redefining normal bone mineral clinical biochemistry reference intervals for healthy infants in Canada. *Clin Biochem*. 2014;47:27-32.



• **Fig. B.14** Serum creatinine **(A)** and serum blood urea nitrogen **(B)** in very low birth weight (≤1500 g) infants during their first days of life. Data presented as mean ± SEM, n = 138. *Indicates a statistically significant difference with day 6 of life. (From Auron A, et al. Serum creatinine in very low birth weight infants during the first days of life. *J Perinatol*. 2006;26:756.)

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TABLE B.8 Predicted Mean Serum Creatinine (95th Percentile) Values by Chronological Age and Gestational Age Group

	25-27 Weeks		28-29 Weeks		30-33 Weeks	
Age (Days)	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL
0	69.8(100.8)	0.79(1.14)	86.6(115.8)	0.98(1.31)	83.1(107.8)	0.94(1.22)
0-1	84(114.9)	0.95(1.3)	86.6(115.8)	0.98(1.31)	84(107.8)	0.95(1.22)
2-3	84(114.9)	0.95(1.3)	80.4(111)	0.91(1.26)	71.6(99.1)	0.81(1.12)
4-5	81.3(112.8)	0.92(1.28)	78.7(108)	0.89(1.22)	64.5(90.8)	0.73(1.03)
6-7	76.9(108.7)	0.87(1.23)	74.3(103.9)	0.84(1.18)	58.3(83.9)	0.66(0.95)
8-9	71.6(103.2)	0.81(1.17)	66.3(97)	0.75(1.1)	53(78.2)	0.6(0.88)
10-14	66.3(97.3)	0.75(1.1)	61(90.3)	0.69(1.02)	50.4(74.1)	0.57(0.84)
15-19	61(89.1)	0.69(1.01)	54.8(81.4)	0.62(0.92)	43.3(65.9)	0.49(0.75)
20-24	53.9(79.9)	0.61(0.9)	46.9(71.8)	0.53(0.81)	38.9(59.2)	0.44(0.67)
25-29	46(70.2)	0.52(0.79)	42.4(64.3)	0.48(0.73)	38.9(56.3)	0.44(0.64)
30-34	42.4(63.6)	0.48(0.72)	36.2(57)	0.41(0.69)	30.9(50.2)	0.35(0.57)
35-39	36.2(56.2)	0.41(0.65)	35.4(53.6)	0.4(0.61)	29.2(*)	0.33(*)
40-44	37.1(54.8)	0.42(0.62)	33.6(51.6)	0.38(0.58)	28.2(*)	0.32(*)
45-49	32.7(50.6)	0.37(0.57)	28.8(*)	0.33(*)	24.1(*)	0.27(*)
50-54	30.1(47.3)	0.34(0.54)	29.2(*)	0.33(*)	25(*)	0.28(*)
55-59	27.4(44.9)	0.31(0.51)	28.8(*)	0.33(*)	22.2(*)	0.25(*)

*Because of hospital discharges and lack of clinical need for testing, there were too few serum creatinine values to compute accurate variance estimates.
Modified from Bateman BA, et al. Serum creatinine concentration in very-low-birth-weight infants from birth to 34-36 weeks' postmenstrual age. *Pediatr Res.* 2015;77(5):696-702.

TABLE B.9 Umbilical Cord Arterial Blood Gas Values (Mean ± SD) in a Reference Group of 46,199 Deliveries, Stratified by Gestational Age

Gestational Age (weeks)	n	pH	Base Deficit (mEq/L)	Po_2 (mm Hg)	Pco_2 (mm Hg)
28-31	62	7.29 ± 0.10	4.2 ± 3.2	21.8 ± 7.5	48.9 ± 12.8
32-36	1,429	7.27 ± 0.07	3.8 ± 2.9	24.8 ± 14.3	51.9 ± 9.8
37-41	41,756	7.25 ± 0.07	4.6 ± 3.2	23.3 ± 15.0	54.9 ± 10.5
42	2,952	7.23 ± 0.07	5.4 ± 3.3	22.6 ± 15.0	57.2 ± 10.5

Modified from Skiold B, et al. Population-based reference curve for umbilical cord arterial pH in infants born at 28-42 weeks. *J Perinatol.* 2017;37:254-259.

TABLE B.10 Capillary Blood Gas Reference Values in Healthy Term Neonates

Variable	*n*	Mean ± SD	2.5 Percentile	97.5 Percentile
pH	119	7.395 ± 0.037	7.312	7.473
Pco_2 (mm Hg)	119	38.7 ± 5.1	28.5	48.7
Po_2 (mm Hg)	119	45.3 ± 7.5	32.8	61.2
Lactate (mmol/L)	114	2.6 ± 0.7	1.4	4.1
Hemoglobin (g/dL)	122	20.4 ± 11.6	14.5	23.9
Glucose (mg/dL)	122	69 ± 14	38	96
iCa (mmol/L)	118	1.21 ± 0.07	1.06	1.34

Samples collected at 48 ± 12 hours of life.
Modified from Cousineau J, et al. Neonate capillary blood gas reference values. *Clin Biochem.* 2005;38:906.

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TABLE B.11 Distribution of Neonatal Whole Blood Amino Acid Concentrations

Amino Acid (μmol/L)	Mean	Median	2.5%-97.5% (All)	2.5%-97.5% (Male)	2.5%-97.5% (Female)
Phenylalanine	54	51	30-97	29-108	32-47
Tyrosine	79	72	34-151	36-147	34-165
Isoleucine	30	28	12-66	12-92	13-50
Leucine	64	60	31-130	34-174	31-109
Valine	100	95	46-224	41-246	50-184
Threonine	187	169	66-415	55-448	69-370
Serine	249	234	130-472	127-462	138-550
Glycine	350	329	182-637	163-493	229-691
Methionine	22	21	10-39	10-40	12-37
Glutamine	495	489	238-808	203-773	257-850
Glutamate	337	324	193-566	175-500	217-629
Citrulline	13	12	5-23	6-21	5-25
Arginine	11	9	<1-36	<1-36	<1-39
Ornathine	48	45	19-105	21-111	18-103
Homocitrulline	1	1	<1-4	<1-4	<1-4
Alanine	201	188	104-394	98-400	115-394
Hydroxyproline	34	33	18-53	15-51	19-55
Proline	159	155	94-245	92-251	94-244
Lysine	61	56	29-119	28-112	34-131
β-Aminoisobutyrate	4	3	<1-16	<1-15	<1-20
β-Alanine	8	8	4-15	5-15	3-15
Sarcosine	1	1	<1-4	<1-4	<1-5
γ-Aminobutyrate	2	2	<1-4	<1-4	<1-4
Histidine	48	46	24-98	25-101	22-98
α-Amino-n-butyrate	18	17	3-39	4-39	3-40

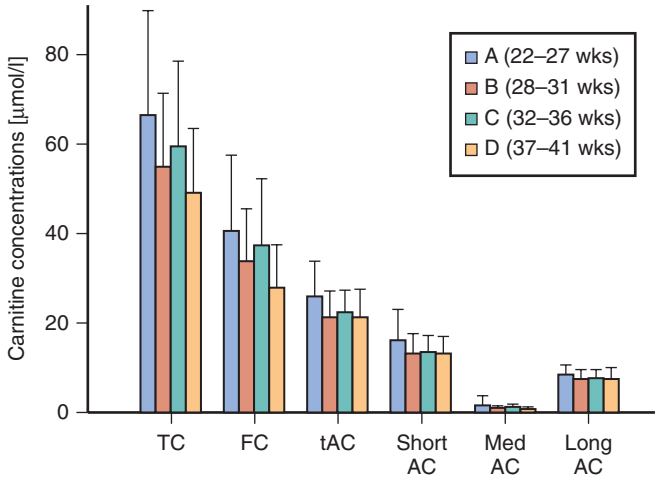
Modified from Dietzen DJ, et al. Dried blood spot reference intervals for steroids and amino acids in a neonatal cohort of the National Children's Study. *Clin Chem.* 2016;62(12):1658-1667.

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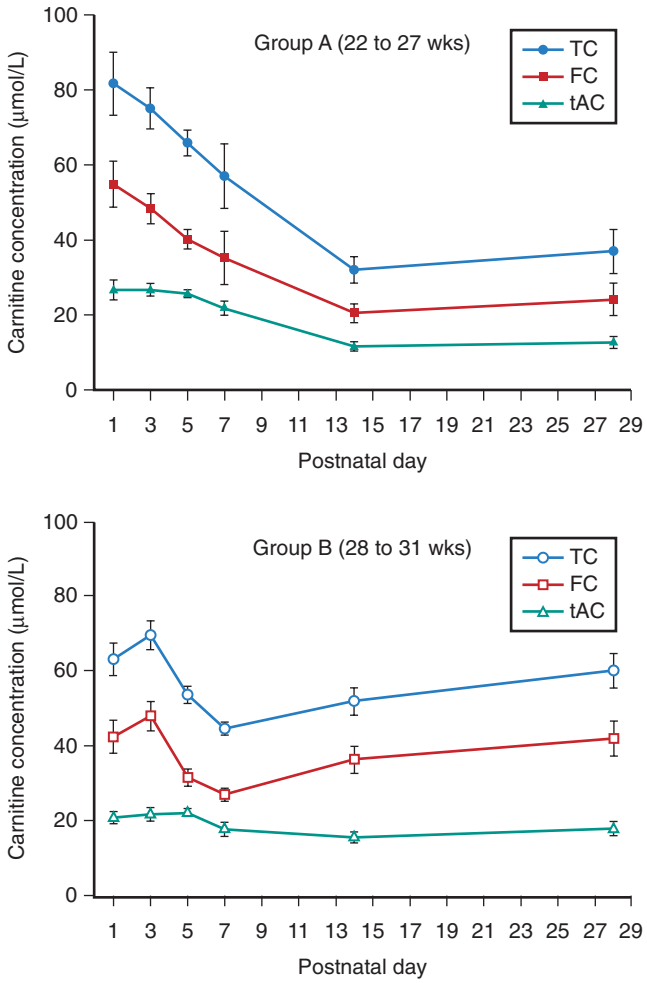
TABLE B.12 Plasma Ammonia Levels in Preterm Infants 32 Weeks' Gestational Age or Less

Age (d)	Ammonia Level* mmol/L	mg/dL
Birth	71 ± 26	121 ± 45†
1	69 ± 22	117 ± 37
3	60 ± 19	103 ± 33
7	42 ± 14	72 ± 24
14	42 ± 18	72 ± 30
21	43 ± 16	73 ± 28
28	42 ± 15	72 ± 25
Term infants at birth	45 ± 9	77 ± 16

*Values represent mean ± SD.
†Significant decline in plasma ammonia level from birth to 7 days of age ($P < 01$).
Modified from Usmani SS, et al. Plasma ammonia levels in very low birth weight preterm infants. *J Pediatr*. 1993;123:798.



• **Fig. B.15** Concentrations of total carnitine (TC), free carnitine (FC), total acylcarnitine (tAC), short-chain acylcarnitines (short AC), medium-chain acylcarnitines (med AC), and long-chain acylcarnitines (long AC) on the fifth postnatal day by gestational age. Bars and error bars represent mean and SD. (From Meyburg et al. Acylcarnitine profiles of preterm infants over the first four weeks of life. *Pediatr Res*. 2002;52:722.)



• **Fig. B.16** Concentrations of total carnitine (TC), free carnitine (FC), and total acylcarnitine (tAC) during the first 4 weeks of life in 22-27 weeks' gestational-age infants (*group A, upper panel*) and in 28-31 weeks' gestational-age infants (*group B, lower panel*). (From Meyburg et al. Acylcarnitine profiles of preterm infants over the first four weeks of life. *Pediatr Res*. 2002;52:722.)

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TABLE B.13 Observed Values of AST and ALT for Preterm Infants by Corrected Gestational Age (CGA)

CGA (Weeks)	Postnatal Age (Days)	AST (IU/mL)				ALT (IU/mL)			
		n	10th Percentile	50th Percentile	90th Percentile	*n*	10th Percentile	50th Percentile	90th Percentile
23	3 (1-7)	12	28	80	1367	21	0	7	224
24	4 (0-7)	51	24	55	396	72	1	15	81
25	6 (1-19)	108	22	59	260	154	5	13	82
26	10 (1-25)	175	21	42	211	228	5	12	84
27	13 (1-31)	204	21	37	177	280	5	12	70
28	17 (1-45)	235	20	32	156	343	6	11	67
29	16 (0-52)	277	19	33	98	376	6	11	50
30	17 (1-52)	257	19	31	111	398	5	11	42
31	18 (0-66)	254	20	31	87	407	6	11	37
32	16 (0-73)	237	19	29	75	416	6	11	30
33	15 (1-73)	235	19	31	83	440	6	11	32
34	16 (0-78)	235	20	31	82	424	7	12	29
35	15 (0-94)	180	22	34	91	377	8	13	38
36	13 (0-101)	145	22	40	98	315	8	13	42

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CGA, corrected gestational age.
Modified from Victor S, et al. Plasma aminotransferase concentrations in preterm infants. *Arch Dis Child Fetal Neonatal.* 2011;90:F144-F145.

TABLE B.14 Tests of Liver Function

Test	Chronologic Age	Value		Unit of Measurement
Albumin	0-5 days (<2.5 kg)	20-36		g/L
	0-5 days (>2.5 kg)	26-36		
	1-30 days	26-43		
	31-182 days	28-46		
	183-365 days	28-48		
Prothrombin Time		***30-36 Weeks' GA***	***Full Term***	Seconds
	1 day	10.6-16.2	11.6-14.4	
	5 days	10-15.3	10.9-13.6	
	30 days	10-13.6	10.6-13.1	
	90 days	10-14.6	10.8-13.1	
	180 days	10-15	11.5-13.1	
Partial Thromboplastin Time		***30-36 Weeks' GA***	***Full Term***	Seconds
	1 day	27.5-79.4	31.7-48.7	
	5 days	26.9-74.1	34-51.2	
	30 days	26.9-62.5	33-47.8	
	90 days	28.3-50.7	30.6-43.6	
	180 days	21.7-53.3	31.8-39.2	
Ammonia	1-90 days	42-144		μmol/L
	3-11 months	34-133		
Alkaline Phosphatase	0-5 days	110-300		units/L
	1-30 days	48-406		
	31-365 days	82-383		

All values for full-term infants unless otherwise noted.
Adapted from Rosenthal P. Assessing liver function and hyperbilirubinemia in the newborn, National Academy of Clinical Biochemistry. *Clin Chem*. 1997;43:228.

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TABLE B.15 Coagulation Status by Gestational Age Group in Extremely Preterm Infants on Day 1

Gestational Age	PT (s)			APTT (s)			Fibrinogen (g/L)		
	n	Mean ± SD	Median (Range)	*n*	Mean ± SD	Median (Range)	n	Mean ± SD	Median (Range)
23 0/7–24 6/7	49	22.63 ± 7.0	22.25 (13.9-39)	45	82.62 ± 37.2	79.45 (34.9-191.6)	25	1.99 ± 1.37	1.3 (0.5-4.8)
25 0/7–26 6/7	95	20.96 ± 0.42	22.3 (13.3-31.4)	91	71.59 ± 21.0	79.7 (40.2-131.3)	55	1.79 ± 1.02	1.37 (0.7-4.8)

Modified from Neary E, et al. Laboratory coagulation parameters in extremely premature infants born earlier than 27 gestational weeks upon admission to a neonatal intensive care unit. *Neonatology.* 2013;104:222-227. Copyright © 2013 Karger Publishers, Basel, Switzerland.

TABLE B.16 Estimated Reference Ranges of Gamma Glutamyl Transferase during the First Week of Life for Each Gestational Age (All Values in IU/L)

GA (Weeks)	n	Mean ± SD (Range)	5%	10%	25%	50%	75%	90%	95%
22-23	9	83.1 ± 58.1 (18-199)	25.35	31.57	44.46	64.27	94.52	139.83	183.18
24-25	36	76.6 ± 53.0 (25-315)	29.06	36.86	52.76	76.82	113.59	170.31	227.06
26	20	142 ± 79.1 (50-345)	32.62	42.4	61.95	90.95	135.4	206.63	282.13
27	26	147.4 ± 123.4 (7-604)	36.07	47.75	70.83	104.62	156.44	241.22	334.06
28	30	152 ± 92.7 (47-423)	40.33	53.07	78.48	115.9	172.89	263.66	359.38
29	36	130.6 ± 77.8 (47-400)	44.82	57.98	84.7	124.71	184.99	276.43	366.43
30	38	156.8 ± 128.5 (31-742)	49.25	62.59	90.28	132.45	195.34	286.03	369.21
31	70	168.7 ± 132.0 (20-807)	53.75	67.23	95.83	140.14	205.57	295.52	372.71
32	89	172.2 ± 93.6 (39-445)	57.44	71.13	100.69	147.07	215.02	305.19	378.92
33	148	175.5 ± 95.0 (37-600)	59.21	73.09	103.37	151.19	220.91	311.55	383.66
34	336	175.1 ± 99.6 (26-762)	58.58	72.41	102.72	150.78	220.62	310.42	380.85
35	311	168.5 ± 97.5 (31-720)	55.84	69.26	98.81	145.75	213.87	300.9	368.6
36	167	164.1 ± 105.4 (28-748)	51.83	64.6	92.82	137.76	202.9	285.8	349.96
37	242	144.8 ± 90.4 (24-594)	47.8	59.93	86.83	129.75	191.94	270.87	331.74
38	250	149.1 ± 100.1 (23-643)	44.45	56.1	82	123.44	183.49	259.51	317.95
39	148	143.2 ± 88.6 (28-446)	41.27	52.45	77.41	117.41	175.37	248.59	304.72
40	120	126.2 ± 70.9 (19-383)	37.87	48.49	72.28	110.49	165.84	235.61	288.94
41-42	15	116.8 ± 73.3 (21-258)	34.5	44.52	67.05	103.33	155.86	221.91	272.26

Modified from Kim DB, et al. Determination of reference range of gamma glutamyl transferase in the neonatal intensive care unit. *J Matern Fetal Neonatal Med*. 2017;30(6):670-672.

TABLE B.17 Serum Bile Acid Levels in Full Term (FT) and Preterm Neonates

	n		Total Serum Bile Acids (µmol/L)	
	All	Female/Male	Median	Interquartile Range
FT controls (all)	84	47/37	8	4.6-12.9
FT controls (feeding status known)	47	27/20	7.8	5-13
Fed	30	13/17	10.1	6.2-15.5
Fasting >24 hours	17	13/4	5.8	4.3-7.9
Preterm controls	101	47/54	10.1	5.7-15.7

Modified from Zöhrer E, et al. Serum bile acids in term and preterm neonates, a case-control study determining reference values and the influence of early onset sepsis. *Medicine*. 2016;95(44):e5219.

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TABLE B.18 **Plasma Albumin and Total Protein in Preterm Infants from Birth to 8 Weeks**

Gestation (wk)	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Albumin (g/dL)																	
Reference range (95% confidence limits)	—	1.18-3.06	1.09-2.87	1.20-2.74	1.21-2.75	1.63-2.75	1.08–3.20	1.38-3.14	1.44-3.34	0.53-3.87	1.15-3.87	1.96-3.44	1.50-4.10	1.89-4.15	2.07-4.05	2.04-3.90	2.08-3.90
Corrected Age																	
26-28 wk		2.13	2.10	2.58	2.29	2.39				2.73							
29-31 wk					2.02	2.14	2.44	2.44	2.54				2.82				
32-34 wk								2.35	2.42	2.46	2.38	2.44				3.35	
Total Protein (g/dL)																	
Reference range (95% confidence limits)	—	1.28-7.94	3.03-5.03	2.18-5.84	2.64-5.80	3.26-5.66	3.63-5.81	3.57-5.87	3.57-6.59	1.52-8.62	3.85-6.91	4.69-6.95	3.32-9.16	4.17-8.25	4.26-8.08	3.73-8.47	3.24-8.76
Corrected Age																	
26-28 wk		4.07	4.45	4.84	4.49	4.45				4.41							
29-31 wk					3.93	4.42	4.70	4.82	4.51				4.55				
32-34 wk								4.54	4.93	4.78	4.86	4.81				4.96	

Modified from Reading RF, et al. Plasma albumin and total protein in preterm babies from birth to eight weeks. *Early Human Dev*. 1990;22:81.

TABLE B.19 Cardiac Troponin T (cTnT) and Cardiac Troponin I (cTnI) Levels in 869 Healthy Term Newborns by Gender

	cTnT		cTnI	
	Male	Female	Male	Female
Mean	0.017	0.012	0.011	0.007
Median	0.01	0	0	0
Minimum	0	0	0	0
Maximum	1.26	0.58	0.71	0.98
99th percentile	0.093	0.101	0.206	0.094

Modified from Baum H, et al. Reference values for cardiac troponins T and I in healthy neonates. *Clin Biochem*. 2004;37:1080.
All values are µg/L.
Cardiac troponin T measured with Roche Elecsys® 2010 3rd generation assay; cardiac troponin I measured on a DadeBehering Dimension RxL assay.
Diagnostic cut-off value for adults with possible myocardial damage is at 99th percentile of apparently healthy reference population; same cut-off has been proposed for neonates.

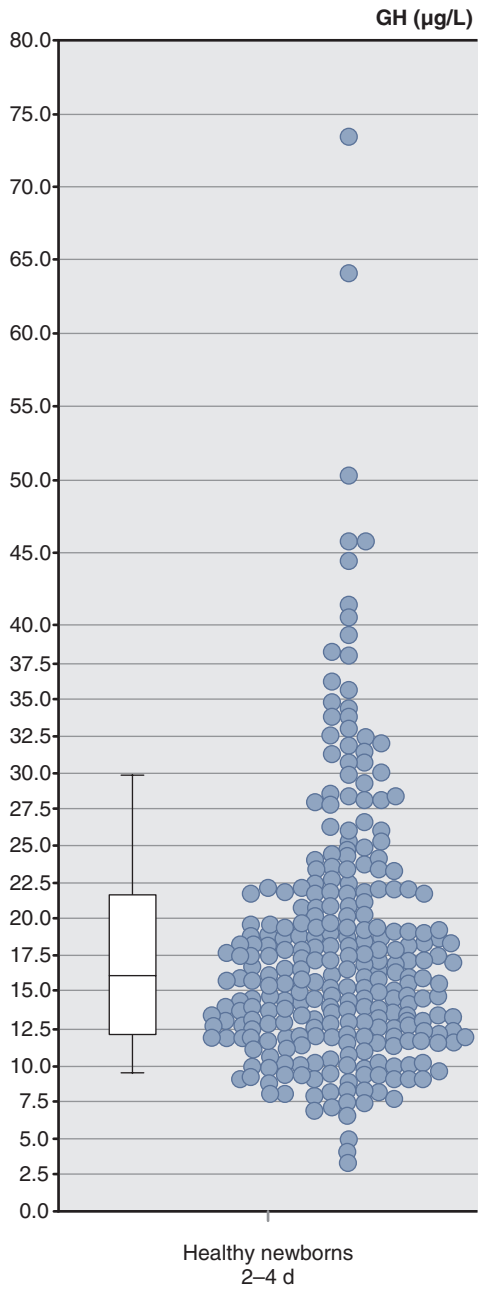
TABLE B.20 Longitudinal Serum Levels of Cystatin-C in Preterm Infants

	Weeks' Gestational Age								
	27-30		31-33		34-36		27-36		
Chronological Age	n	Cys-C (mg/L)	n	Cys-C (mg/L)	n	Cys-C (mg/L)	n	Median Cys-C (mg/L)	95% Reference interval
6-30 days	15	1.67 (1.325-2.275)	93	1.747 (0.912-2.275)	153	1.795 (1.325-2.237)	261	1.776	1.355-2.189
3-5 months	10	1.339 (0.979-1.632)	60	1.258 (0.538-1.747)	37	1.229 (0.95-1.594)	107	1.248	0.881-1.64
7-9 months	9	1.066 (0.902-1.296)	43	1.018 (0.528-1.469)	19	1.046 (0.797-1.344)	71	1.037	0.722-1.339
12-14 months	6	0.984 (0.739-1.546)	26	0.965 (0.749-1.2)	7	0.941 (0.893-1.104)	39	0.96	0.688-1.24

Modified from Nakashima T, et al. Longitudinal analysis of serum cystatin C for estimating the glomerular filtration rate in preterm infants. *Pediatr Nephrol*. 2016;31:983-989.

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Hormone Levels



• **Fig. B.17** Growth hormone levels (µg/L) from 314 healthy newborns (blue circles). The box of the box plot indicates the mean and 50% confidence interval; the whiskers indicate the 80% confidence interval. (From Binder G, et al. Rational approach to the diagnosis of severe growth hormone deficiency in the newborn. *J Clin Endocrinol Metab*. 2010;95(5):2222.)

TABLE B.21 Serum Procalcitonin Levels According to Gestational Age (GA) and Postnatal Age (PNA)

			Serum Procalcitonin (ng/mL)		
GA (weeks)	PNA (days)	n	median	Range	95% Reference Interval
≤32	7-14	64	0.37	0.10-11	0-3.53
	14-30	90	0.25	0.08-4.17	0-1.66
	30-60	120	0.15	0.06-2.51	0.06-1.7
33-36	7-14	102	0.16	0.07-1.51	0-0.53
	14-30	119	0.12	0.07-6.6	0-0.56
	30-60	44	0.11	0.08-0.26	0.01-0.21
≥37	7-14	127	0.11	0.05-1.31	0.05-0.54
	14-30	153	0.11	0.03-2.67	0.06-0.9
	30-60	95	0.10	0.04-1.37	0-0.53

There were 914 samples from 425 infants enrolled in the study.
From Hahn W, et al. Reference intervals of serum procalcitonin are affected by postnatal age in very low birth weight infants during the first 60 days after birth. *Neonatology.* 2015;108:63. Copyright © 2015 Karger Publishers, Basel, Switzerland.

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TABLE B.22 Age- and Sex-Specific Reference Intervals for Fertility Hormones in Healthy Children

		Female Reference Intervals				Male Reference Intervals			
Hormone	Age	Lower Limit	Upper Limit	Lower Limit CI	Upper Limit CI	Lower Limit	Upper Limit	Lower Limit CI	Upper Limit CI
Total Te* (nmol/L)	0 to <1 y	≤0.08	0.45	≤0.08	0.45-0.5	≤0.08	13.86	≤0.08	11.38-16.81
SHBG* (nmol/L)	0 to <1 y	29.48	236.97	13.49-45.68	223.83-250.39	29.48	236.97	13.49-45.68	223.83-250.39
Estradiol# (pg/mL)	15 d to <1 y	NA	25	NA	22-38	NA	25	NA	22-38
Progesterone# (ng/dL)	4 d to <1 y	NA	132	NA	88-230	NA	66	NA	63-94
FSH# (mIU/mL)	30 d to <1 y	0.38	10.35	0.05-0.58	9.34-10.97	0.09	2.41	0.05-0.13	2.19-2.65
LH# (mIU/mL)	4 d to <3 m 3 m to <1 y	NA NA	2.41 1.19	NA NA	1.74-2.91 0.56-1.6	0.19 NA	3.81 2.89	0.07-0.4 NA	3.47-4 2.33-4.32
Prolactin# (ng/mL)	4 d to <30 d 30 d to <1 y	12.57 6.26	212.77 113.73	0.6-25.71 4.41-7.25	202.5-233.18 97.28-141.08	12.57 6.26	212.77 113.73	0.06-25.71 4.41-7.25	202.5-233.18 97.28-141.08

FSH, Follicle stimulating hormone; LH, luteinizing hormone; NA, not applicable; SHBG, sex hormone binding globulin; Te, testosterone.
Total Te lower limits calculated below the sensitivity of the assay are presented as ≤0.08 nmol/L.
When the lower limit of the reference interval was at the limit of detection, no value is given and the reference interval should be < upper limit.
*These data are from a cohort of healthy community children not studied in other CALIPER (Canadian Laboratory Initiative for Pediatric Reference Intervals) studies.
*Modified from Raizman JE, et al. Pediatric reference intervals for calculated free testosterone, bioavailable testosterone, and free androgen index in the CALIPER cohort. *Clin Chem Lab Med.* 2015;53(10):e240.
#These data from 1234 healthy children from a multiethnic population as part of the CALIPER study.
#Modified from Konforte D, et al. Complex biological pattern of fertility hormones in children and adolescents: a study of healthy children from the CALIPER cohort and establishment of pediatric reference intervals. *Clin Chem.* 2013;59(8):1219-20.

TABLE B.23 Hormone Reference Intervals in Healthy Children

	Age	Geometric Mean	Lower Limit	Lower Limit CI	Upper Limit	Upper Limit CI
Cortisol (µg/dL)	2 d to <15 d 15 d to <1 y	3.24 4.82	0.47 0.52	0.12-0.71 0.37-0.77	12.3 16.6	10.98-18.1 15.6-17.75
iPTH (pg/mL)	6 d to <1 y	26.79	6.42	3.96-8.58	88.58	74.81-146.04
25 (OH)D (ng/mL)	5 d to <15 d 15 d to <3 m 3 m to <1 yr	10.27 19.19 23.73	1.7 6.16 6.94	0.99-3.41 4.25-8.21 5.5-9.04	33.99 40.48 47.28	28.56-39.3 35.63-43.72 44.15-49.91

iPTH, intact parathyroid hormone; 25 (OH)D, 25(OH)vitamin D.
The CALIPER (Canadian Laboratory Initiative for Pediatric Reference Intervals) program used a total of 1482 samples from ethnically diverse healthy children ages 2 days to 18 years to establish pediatric reference intervals.
Modified from Bailey D, et al. Marked biological variance in endocrine and biochemical markers in childhood: establishment of pediatric reference intervals using healthy community children from the CALIPER cohort. *Clin Chem.* 2013;59(9):1395-1397.

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TABLE B.24 Pituitary and Steroid Hormone Reference Intervals (RI) in Preterm Neonates

		Median	Mean	Standard Deviation	Minimum	Maximum	95% RI 2.5%	95% RI 97.5%
FSH (IU/L)	Male	1.1	1.3	0.9	0.1	5.6	0.2	3.6
	Female	57	58.4	43	0.9	200	2.6	181.1
LH (IU/L)	Male	1.9	2.6	2.4	0.1	13.5	0.1	9.2
	Female	13.3	24.8	30.8	0.1	143.1	0.2	133.9
Prolactin (IU/L)		2046	2304	1318	365	7596	516	5734
Cortisol (ng/mL)		33.35	45.31	38.79	1.45	210.61	3.73	164.14
Cortisone (ng/mL)	≤30 wk	46.67	47.72	15.58	9.63	82.65	18.24	80.09
	≥31 wk	38.8	39.43	12.58	13.83	74.93	17.23	67.33
Androstenedione (ng/mL)		0.72	0.95	0.7	0.06	3.71	0.15	2.76
Testosterone (ng/mL)	Male	0.32	0.46	0.56	0.02	3.69	0.05	1.96
	Female	0.05	0.08	0.12	0.01	0.96	0.01	0.46
17 OHP (ng/mL)	≤30 wk	3.77	5.13	4.37	1.01	27.71	0.96	18.82
	≥31 wk	2.6	3.25	2.24	0.47	10.74	0.61	9.75

FSH, Follicle stimulating hormone; LH, luteinizing hormone; 17 OHP, 17-hydroxyprogesterone.
Samples were from 248 preterm neonates born between 24 and 32 weeks' gestation without ambiguous genitalia or other endocrine abnormalities.
From Greaves RF, et al. Hormone modeling in preterm neonates: establishment of pituitary and steroid hormone reference intervals. *J Clin Endocrinol Metab*. 2015;100(3):1102.

TABLE B.25 Hormone Reference Intervals (RI) by Day of Age for Preterm Infants 23-26 Weeks' Gestational Age

		Day of Age 1	4	7	14	21	28	42
Cortisol*	Median	11.4	10.5	7.9	5.8	6.3	4.8	3
	Geometric Mean	11.5	9.5	8.2	6.2	6.6	4.5	3.2
	95% RI	1.2-113.5	2.6-34.7	2.3-29	2.1-18.4	1.5-28.9	2.2-14	0.7-16
DHEAS*	Median	0.23	0.31	0.3	0.2	0.18	0.17	0.15
	Geometric Mean	0.22	0.3	0.29	0.18	0.17	0.16	0.15
	95% RI	0.1-0.52	0.13-0.69	0.12-0.71	0.08-0.38	0.08-0.38	0.07-0.39	0.08-0.29
Estradiol*	Median	70	52	50	48	42	37	34
	Geometric Mean	72	54	48	46	41	37	35
	95% RI	36-142	26-111	24-98	24-89	<20-89	<20-88	<20-80
GH*	Median	56	12	14	27	25	25	21
	Geometric Mean	53	12	11	23	21	21	20
	95% RI	23-122	2-84	3-47	5-117	3-122	6-73	6-65
Progesterone*	Median	4.7	4.7	4.2	4.3	5.2	4.2	3.3
	Geometric Mean	4.7	4.3	4.4	4.3	5	4.4	3.2
	95% RI	1.9-11.5	1.6-11.5	1.6-12	1.5-12.4	1.7-14.4	1.8-11.2	1.2-8.7

*μg/dL
DHEAS, Dehydroepiandrosterone sulfate; GH, growth hormone.
Modified from Greaves RF et al. Establishment of hormone reference intervals for infants born <30 weeks' gestation. *Clin Biochem*. 2014;47:105.

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TABLE B.26 Hormone Reference Intervals (RI) by Day of Age for Preterm Infants 27-29 Weeks' Gestational Age

		Day of Age						
		1	4	7	14	21	28	42
Cortisol*	Median	5.7	7.4	7.4	4.9	3.9	4.1	2.5
	Geometric Mean	6.7	7.5	7.4	5.1	4.1	4.1	3
	95% RI	0.8-60.1	1.8-31.4	2.5-21.5	1.2-21.1	0.9-18	0.9-17.2	0.7-13.8
DHEAS*	Median	0.2	0.18	0.2	0.17	0.16	0.17	0.16
	Geometric Mean	0.19	0.18	0.2	0.17	0.16	0.16	0.15
	95% RI	0.08-0.45	0.08-0.38	0.09-0.42	0.08-0.32	0.09-0.27	0.08-0.33	0.07-0.32
Estradiol*	Median	69	44	42	37	32	34	35
	Geometric Mean	71	47	42	34	34	34	39
	95% RI	28-176	20-108	<20-95	<20-77	<20-79	<20-65	<20-139
GH*	Median	40	20	13	20	22	21	18
	Geometric Mean	38	18	15	19	20	21	18
	95% RI	12-126	4-81	3-72	6-60	7-56	10-44	7-45
Progesterone*	Median	6	3.9	3.2	2.6	2.6	3.4	1.9
	Geometric Mean	5.8	3.9	3.2	2.7	2.8	2.9	2
	95% RI	2.1-16.3	1.5-10.1	1.3-7.9	1.2-6	1-8	1-8.6	0.6-6.2

*µg/dL
DHEAS, Dehydroepiandrosterone sulfate; GH, growth hormone.
Modified from Greaves RF et al. Establishment of hormone reference intervals for infants born <30 weeks' gestation. *Clin Biochem*. 2014;47:105.

TABLE B.27 Reference Intervals for Thyroid Hormones in Healthy Children

	Age	Geometric Mean	Lower Limit	Lower Limit CI	Upper Limit	Upper Limit CI
FT3 (pg/mL)	4 d to <1 y	3.68	2.32	2.23-2.55	4.87	4.79-5.19
TT3 (ng/dL)	4 d to <1 y	152.34	84.64	73.57-97.01	234.38	225.91-242.84
FT4 (ng/dL)	5 d to <15 d	2.07	1.05	0.87-1.31	3.21	3.04-3.35
	15 d to <30 d	1.52	0.68	0.55-0.89	2.53	2.31-2.65
	30 d to <1 y	1.23	0.89	0.83-0.92	1.7	1.65-1.84
TT4 (µg/dL)	7 d to <1 y	9.12	5.87	4.62-6.27	13.67	13.44-14.55
TSH (mIU/L)	4 d to <6 m	2.31	0.73	0.367-0.98	4.77	4.27-5.54

FT3, Free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine.
The CALIPER (Canadian Laboratory Initiative for Pediatric Reference Intervals) program used a total of 1482 samples from ethnically diverse healthy children ages 2 days to 18 years to establish pediatric reference intervals.
Modified from Bailey D, et al. Marked biological variance in endocrine and biochemical markers in childhood: establishment of pediatric reference intervals using healthy community children from the CALIPER cohort. *Clin Chem.* 2013;59(9):1396-1397.

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TABLE B.28 Thyroid Hormones in Premature Neonates 26-32 Weeks' Gestational Age According to Postnatal Age

	1st Week of Life n = 196	2nd Week of Life n = 186	3rd-4th Weeks of Life n = 178
TT4 (nmol/L)	136.3 ± 85	143.9 ± 92	189.5 ± 98.1
FT4 (pmol/L)	16.9 ± 4.8	16.2 ± 4.4	16.2 ± 3.8
TT3 (nmol/L)	1.2 ± 0.7	1.5 ± 0.9	1.6 ± 0.9
FT3 (pmol/L)	3.7 ± 0.9	3.5 ± 0.9	3.6 ± 1
TSH (IU/L)	5.2 ± 5.1	5 ± 3	4.8 ± 3.8

Values are mean ± SD.
FT3, Free triiodothyronine; FT4, free thyroxine; TSH thyroid stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine.
From Dilli D, et al. Serum thyroid hormone levels in preterm infants born before 33 weeks of gestation and association of transient hypothyroxinemia with postnatal characteristics. *J Pediatr Endocrinol Metab*. 2010;23(9):899-912.

Cerebrospinal Fluid

TABLE B.29 Cerebrospinal Fluid Findings in Preterm and Term Infants Hospitalized in the Neonatal Intensive Care Unit

	Preterm Infants (<37 weeks)			Term Infants		
	All n = 148	≤7 Days n = 66	>7 Days n = 82	All n = 170	≤7 Days n = 130	>7 Days n = 40
CSF WBC, cells/μL						
All infants						
Median (IQR)	3 (1-6)	3 (1-7)	3 (1-4)	3 (1-6)	3 (1-6)	2 (1-4)
95th percentile	16	18	12	26	23	32
Antibiotic-unexposed						
95th percentile	11	17	10	32	31	53
CSF Protein, mg/dL						
All infants						
Median (IQR)	104 (79-131)	116 (93-138)	93 (69-122)	74 (54-96)	78 (60-100)	57 (42-77)
95th percentile	203	213	203	137	137	158
Antibiotic-unexposed						
95th percentile	195	195	136	136	136	284
CSF Glucose, mg/dL						
All infants						
Median (IQR)	49 (42-62)	53 (43-65)	47 (40-58)	51 (44-57)	50 (44-56)	52 (45-64)
5th percentile	33	33	33	36	35	38
Antibiotic-unexposed						
5th percentile	33	33	35	33	33	33

Studied infants were aged <6 months and underwent LP for evaluation for sepsis. Infants were excluded if there was culture-proven bacterial meningitis, unknown CSF culture results, positive CSF viral PCR, a ventriculoperitoneal shunt present, seizures, bacteremia, or CSF RBC >500 cells/μL.
Modified from Srinivasan L, et al. Cerebrospinal fluid reference ranges in term and preterm infants in the neonatal intensive care unit. *J Pediatr*. 2012;161:731.

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Urine

TABLE B.30 Urine Biomarkers by Gestational Age

	<28 Weeks *n* = 4	29-33 Weeks *n* = 10	34-36 Weeks *n* = 25	>37 Weeks *n* = 13
ALB (mcg/mL)	6 (3.2, 11)	4.9 (3, 7.9)	4 (3.3, 4.8)	4.4 (3, 6.4)
ALB (mcg/mg)	43.8 (24, 31)	37.4 (25, 56)	24.6 (18, 34)	21.8 (14, 34)
B2M (mcg/mL)	0.36 (0.1, 2.3)	0.79 (0.6, 1.1)	0.52 (0.3, 0.9)	0.29 (0.1, 0.7)
B2M (mcg/mg)	2.6 (0.3, 26.2)	6 (3.9, 9.3)	3.2 (1.8, 5.7)	1.5 (0.7, 3.3)
CysC (ng/mL)	207 (30, 1424)	94 (31, 285)	29 (19, 43)	42 (15, 122)
CysC (ng/mg)	1521 (212, 10905)	718 (226, 2288)	176 (112, 278)	210 (86, 513)
EGF (ng/mL)	0.46 (0.2, 1.1)	2.1 (1.2, 3.9)	1.8 (1.2, 2.6)	3.8 (2.4, 5.9)
EGF (ng/mg)	3.4 (2, 7)	16.4 (9, 29)	10.9 (8, 16)	18.7 (12, 30)
NGAL (ng/mL)	424 (217, 827)	78 (30, 201)	69 (40, 119)	68 (33, 137)
NGAL (ng/mg)	3113 (1936, 5005)	597 (221, 1612)	424 (225, 797)	335 (135, 834)
OPN (ng/mL)	132 (13, 1303)	237 (164, 342)	69 (32, 151)	78 (22, 282)
OPN (ng/mg)	972 (78, 12051)	1814 (1171, 2809)	424 (199, 903)	377 (138, 1030)
UMOD (mcg/mL)	1.1 (0.2, 7.8)	2.5 (1.4, 4.5)	2.9 (2.3, 3.7)	4.7 (3.6, 6.1)
UMOD (mcg/mL)	7.8 (2, 32)	19.3 (10, 37)	17.8 (14, 23)	23.3 (13, 41)
Urine Cr (mg/ml) ± SD	0.14 ± 0.05	0.15 ± 0.07	0.22 ± 0.25	0.32 ± 0.35

Reported as geometric mean (95% CI) as units/urine volume and units/mg urine creatinine.
ALB, Albumin; B2M, beta-2-microglobulin; Cr, creatinine; CysC, cystatin C; EGF, epidermal growth factor; NGAL, neutrophil gelatinase-associated lipocalin; OPN, osteopontin; UMOD, uromodulin.
From DeFreitas MJ, et al. Longitudinal patterns of urine biomarkers in infants across gestational ages. *Pediatr Nephrol*. 2016;31:1184.

Immunoglobulin Values

TABLE B.31 Serum IgG Levels (mg/dL) in Newborn Infants

Gestational Age (weeks)	*n*	Geometric Mean ± SD	Minimum-Maximum	95% CI
≤28	67	371.3 ± 150	152-963	339.9, 406.9
29-31	64	543.1 ± 143	312-873	508.5, 579.9
32-37	85	671.8 ± 165.4	330-1100	638.1, 705.7
≥38	84	791.5 ± 234.9	406-2080	748.1, 838.5

Studied infants were hospitalized within 72 hours of life and without congenital anomalies, congenital or acquired infections, metabolic disease, immune deficiency, transfusion before blood draw, small for gestational age status.
IgG quantified by nephelometric assay.
From Ozdemir SA, et al. Reference values of serum IgG and IgM levels in preterm and term newborns. *J Matern Fetal Neonatal Med.* 2016;29(6):973.

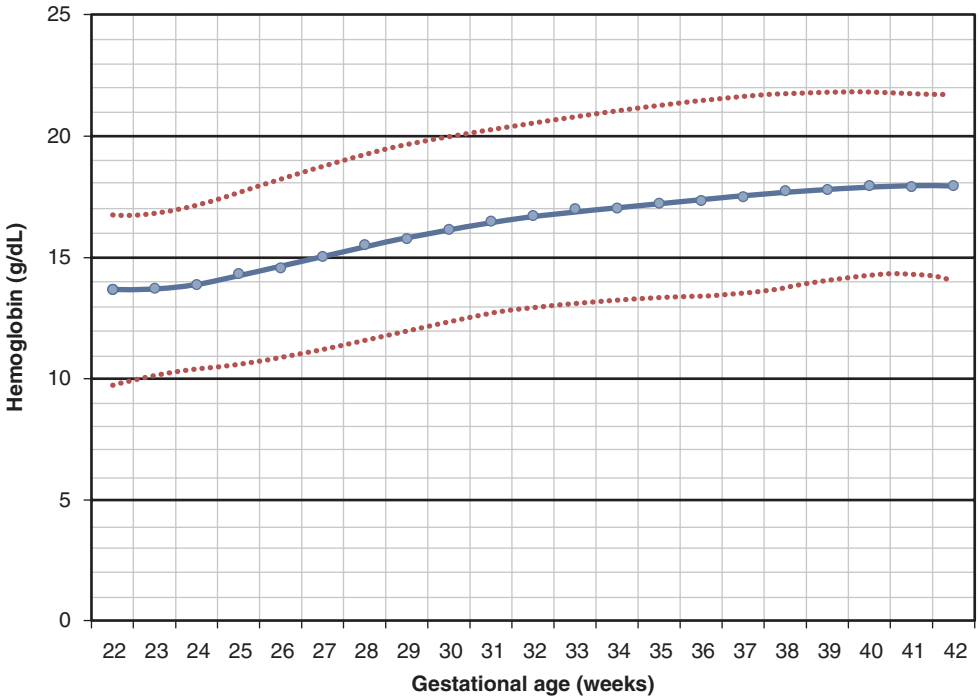
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TABLE B.32 Serum IgM Levels (mg/dL) in Newborn Infants

Gestational Age (weeks)	n	Geometric Mean ± SD	Minimum-Maximum	95% CI
≤28	67	5.8 ± 3.4	4-17.3	5.3, 6.4
29-31	64	7.3 ± 3	4-24.6	6.6, 8
32-37	85	9.2 ± 5.5	4-34.5	8.3, 10.2
≥38	84	10.6 ± 6.7	4-39.3	9.6, 11.8

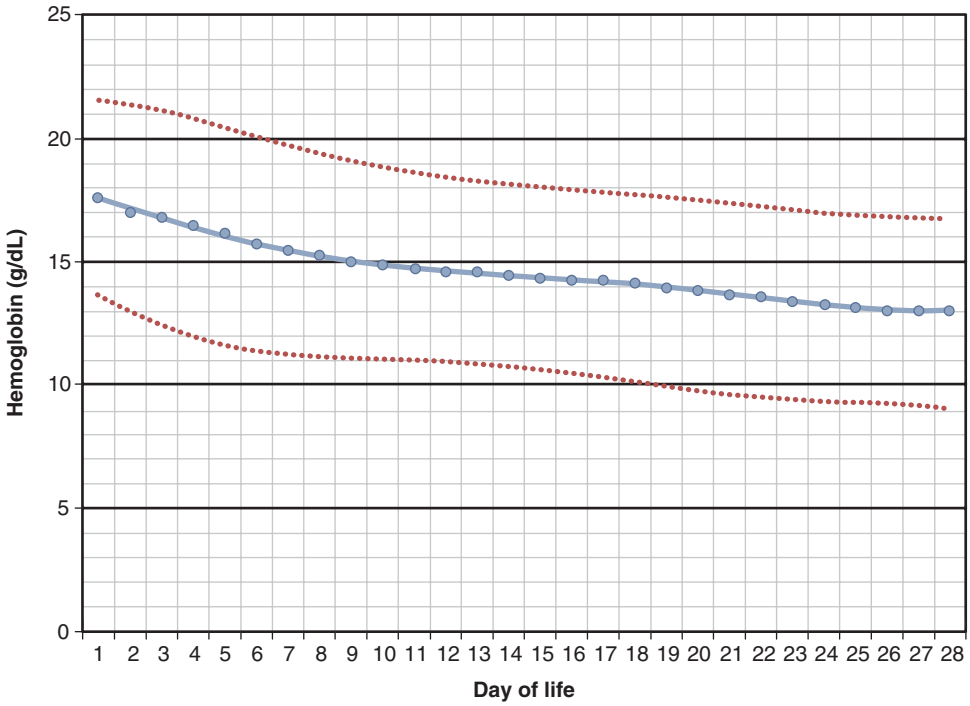
Studied infants were hospitalized within 72 hours of life and without congenital anomalies, congenital or acquired infections, metabolic disease, immune deficiency, transfusion before blood draw, small for gestational age status.
IgM quantified by nephelometric assay.
From Ozdemir SA, et al. Reference values of serum IgG and IgM levels in preterm and term newborns. *J Matern Fetal Neonatal Med*. 2016;29(6):973.

Hematologic Values

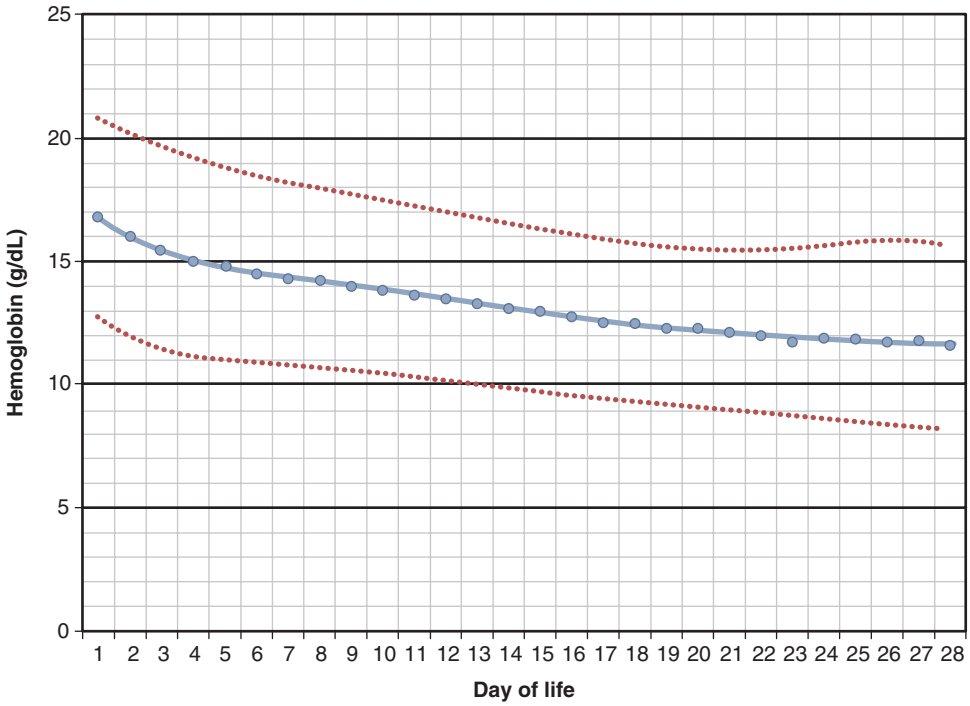


• **Fig. B.18** Blood hemoglobin concentration on the day of birth according to gestational age. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:485.)

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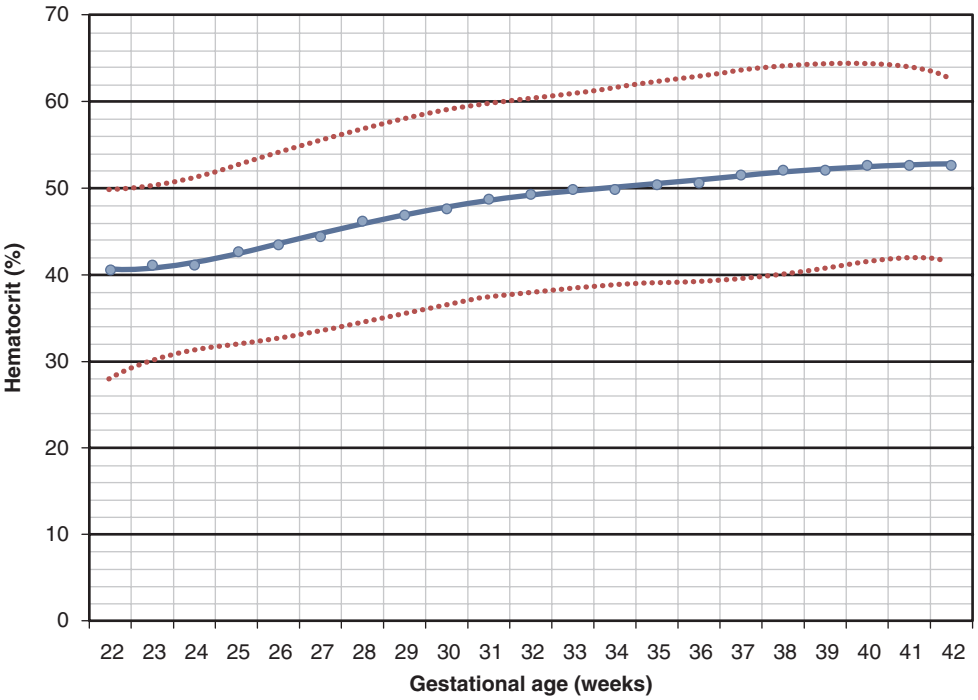


• **Fig. B.19** Blood hemoglobin concentration over the first 28 days of life for neonates born at 35-42 weeks' gestation. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:485.)

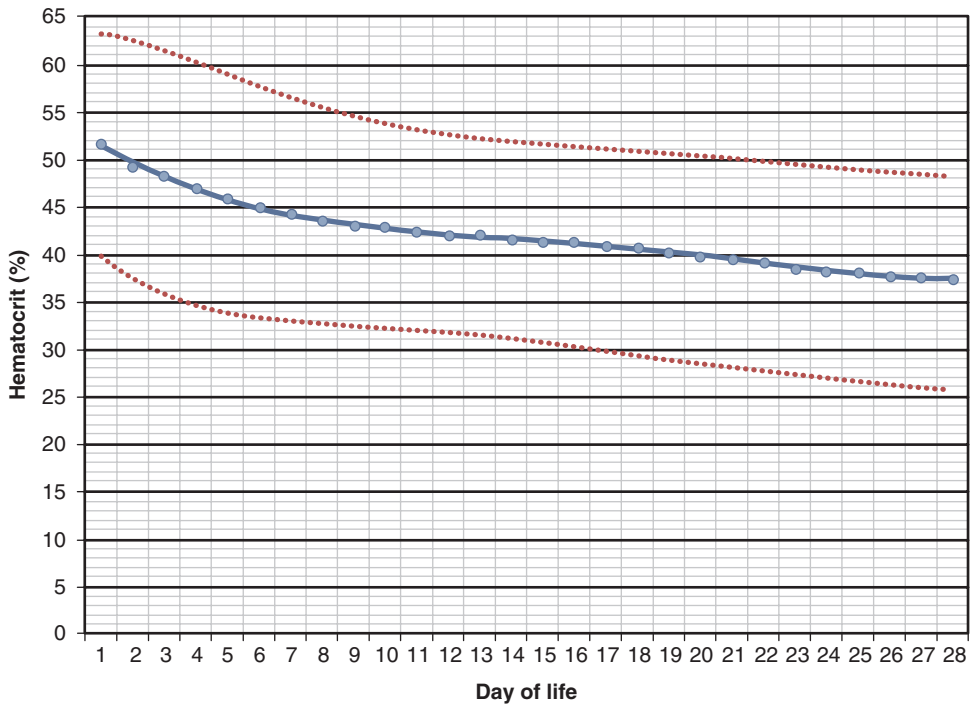


• **Fig. B.20** Blood hemoglobin concentration over the first 28 days of life for neonates born at 29-34 weeks' gestation. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:486.)

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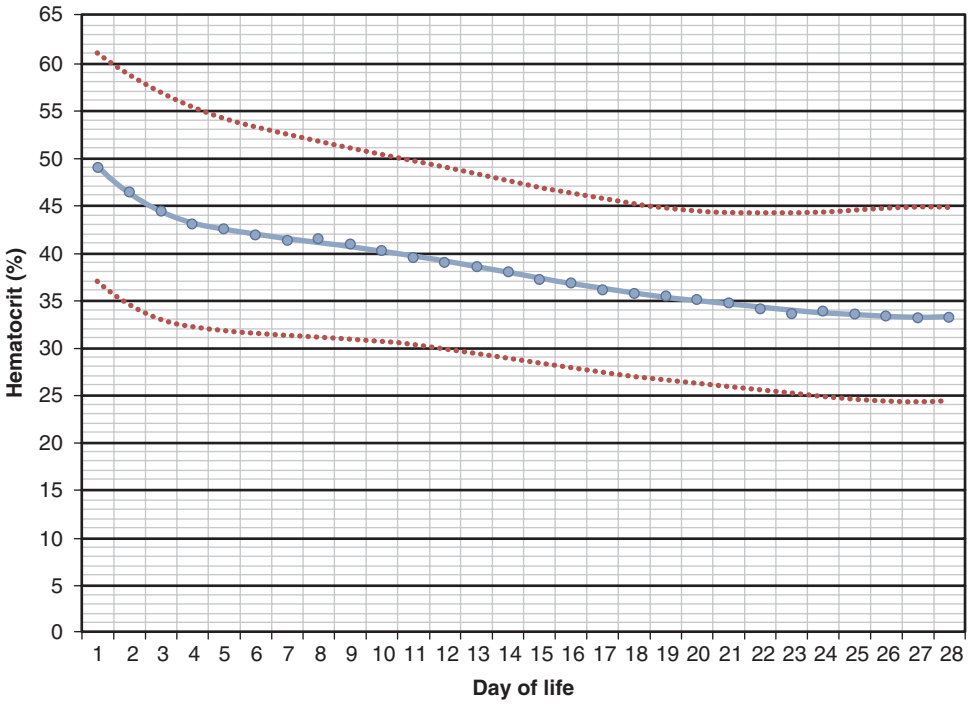


• **Fig. B.21** Hematocrit on the day of birth according to gestational age. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:486.)

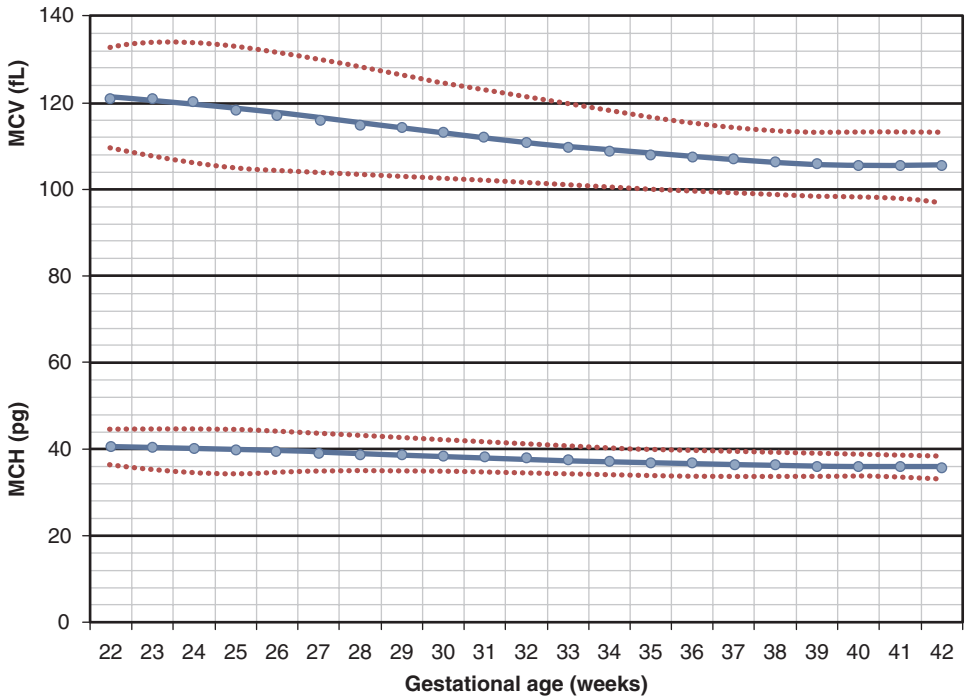


• **Fig. B.22** Hematocrit over the first 28 days of life for neonates born at 35-42 weeks' gestation. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:487.)

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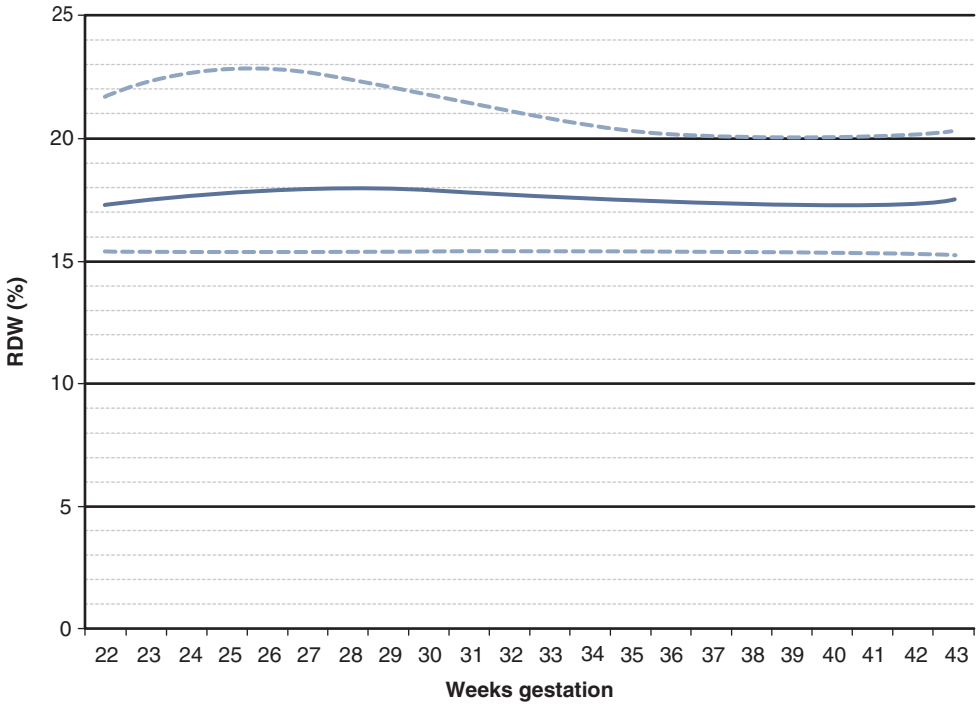


• **Fig. B.23** Hematocrit over the first 28 days of life for neonates born at 29-34 weeks' gestation. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:487.)

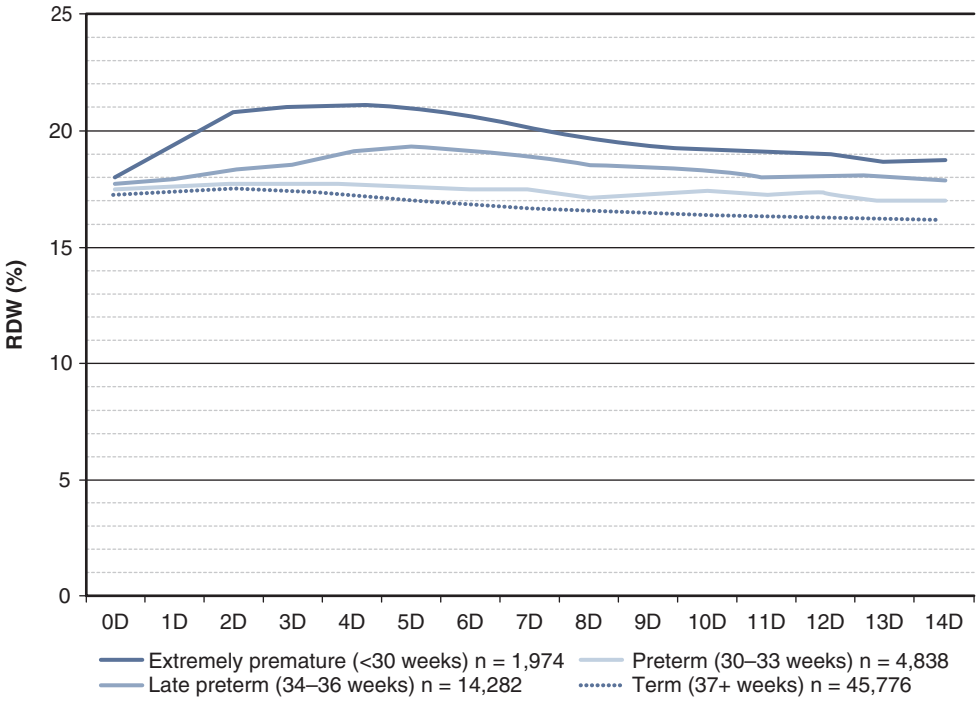


• **Fig. B.24** MCV and MCH on the day of birth according to gestational age. For each, the lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:488.)

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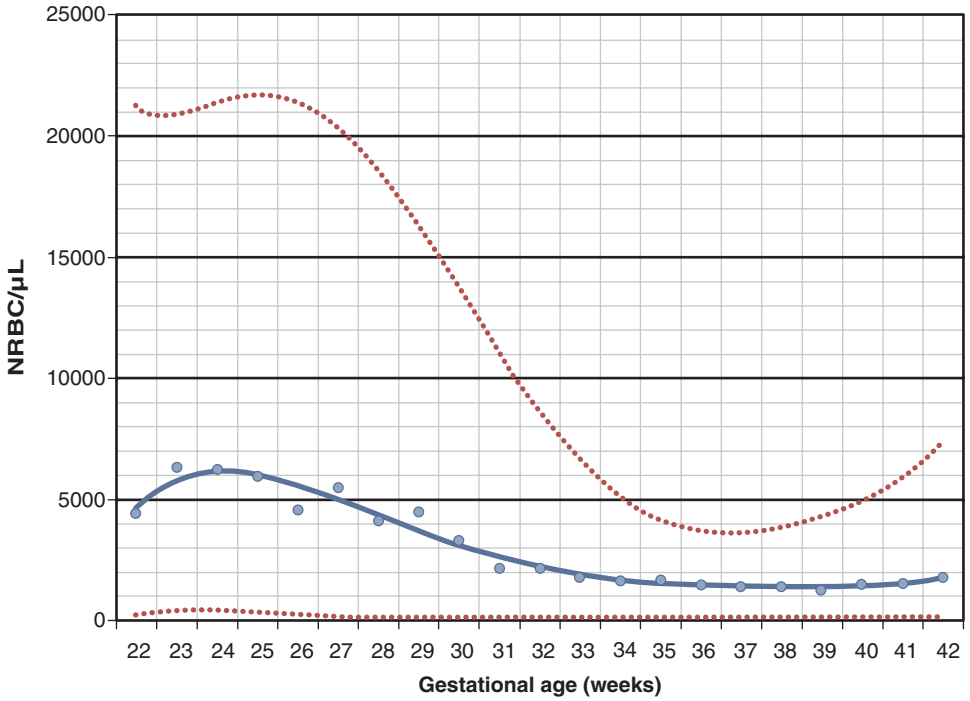


• **Fig. B.25** Reference intervals for red blood cell distribution width (RDW) on the day of birth by gestational age (*n* = 57658). The lower dashed line is the 5th percentile, the solid middle line is the mean, and the upper dashed line is the 95th percentile. (From Christensen RD, et al. Red blood cell distribution width: reference intervals for neonates. *J Matern Fetal Neonatal Med*. 2015;28(8):884.)



• **Fig. B.26** Mean red blood cell distribution width (RDW) over the first 14 days (D) of life according to gestational age at birth (*n* = 57,658 at 0 days plus 68,108 through 14 days). (From Christensen RD, et al. Red blood cell distribution width: reference intervals for neonates. *J Matern Fetal Neonatal Med*. 2015;28(8):885.)

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• **Fig. B.27** Nucleated red blood cell (NRBC) levels on the day of birth according to gestational age. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:489.)

TABLE B.33 Iron Parameters of Very Low Birth Weight Infants during the First 6 Weeks of Life

			Percentiles								
	Day of Life	*n*	3	5	10	25	Median	75	90	95	97
Ferritin (ng/mL)	3*	431	27	35	48	80	140	204	279	360	504
	12-14	130	43	65	89	128	168	243	329	410	421
	24-26	128	27	44	57	93	153	234	300	355	383
	40-42	93	17	20	35	62	110	191	290	420	457
Serum iron (µmol/L)	3	181	0.8	1.0	1.6	3.5	7.5	13.8	18.6	22.4	26.7
Transferrin saturation (%)	3	179	2.6	2.7	4.2	9.6	22.7	39.4	54.9	62.1	79.8

*On day 3, all infants are included regardless of antenatal steroids and transfusions up to that time. Thereafter, infants who did not receive erythropoietin were studied regardless of the use of antibiotics and steroids.

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TABLE B.34 Cord Serum Ferritin Concentration for Low-Risk Term and Preterm Infants

	Cord Serum Ferritin Concentration (µg/L), Percentile				
	5th	25th	50th	75th	95th
Term (≥37 weeks), n = 308	40	84	134	200	309
Preterm (<37 weeks), n = 149	35	80	115	170	267

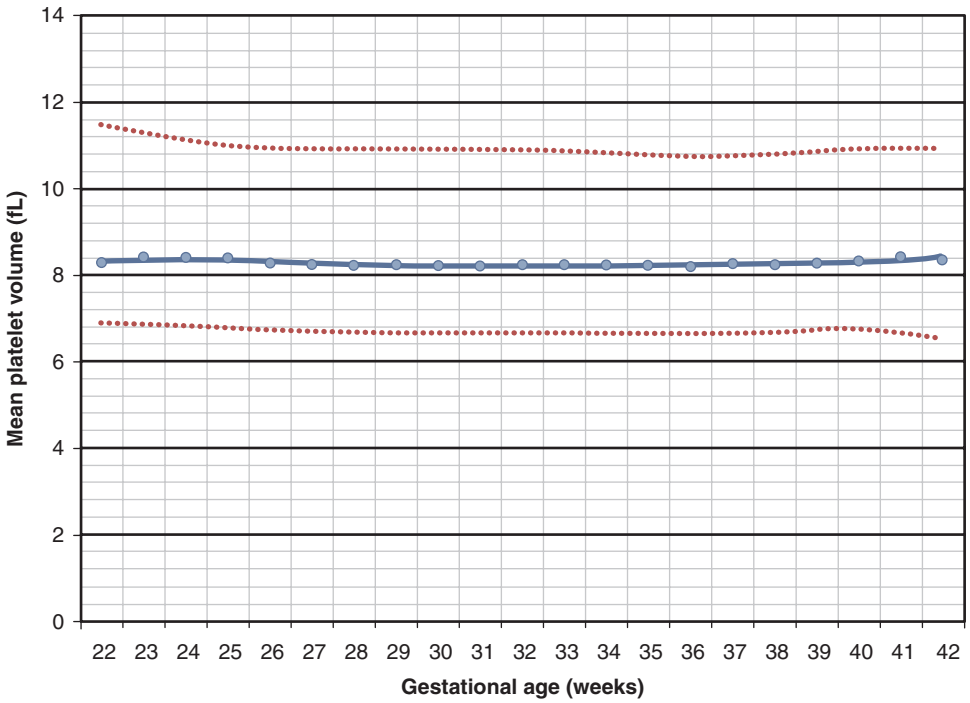
From Siddappa AM, et al. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. *Neonatology*. 2007;92(2):78. Copyright © 2007 Karger Publishers, Basel, Switzerland.

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TABLE B.35 Reference Ranges of Reticulocyte Hemoglobin Content (Ret-He) in Venous Blood Samples Shortly after Birth

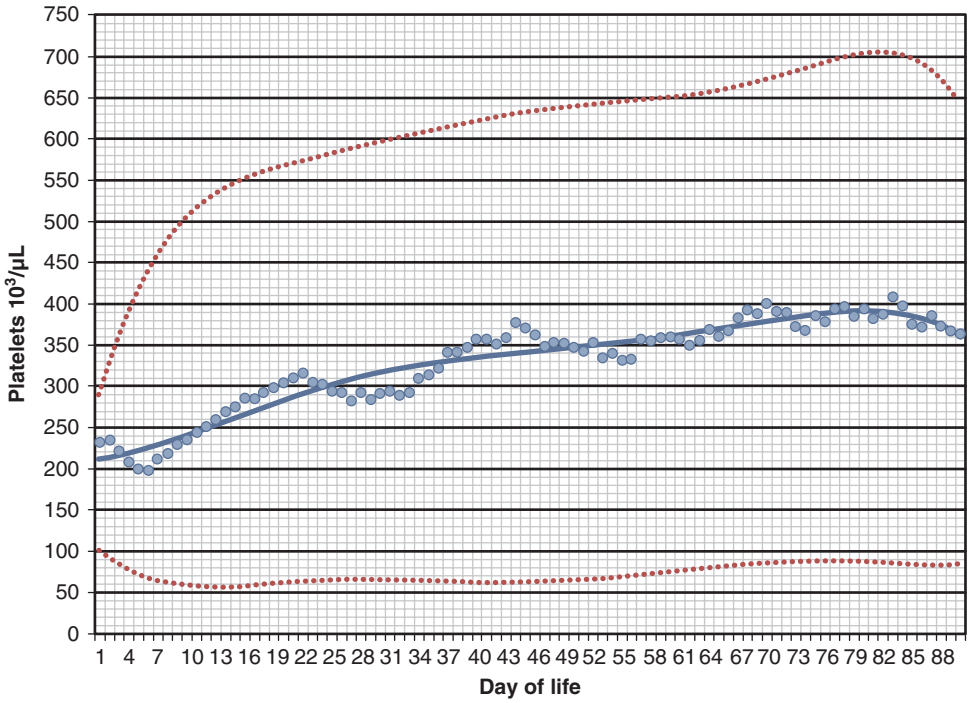
Gestational Age (weeks)	*n*	Ret-He (pg) by Percentile						
		2.5th	10th	25th	50th	75th	90th	97.5th
24-29	55	21.1	27.2	29	31.2	32.6	33.5	36.8
30-36	241	25.1	27.9	29.7	31.4	32.9	34.2	36.1
37-42	216	25.5	27.3	29.9	32.4	34.4	35.8	37.6
24-42 (all)	512	25.2	27.5	29.8	31.7	33.5	35.2	37

From Lorenz L et al. Reference ranges of reticulocyte haemoglobin content in preterm and term infants: a retrospective analysis. *Neonatology*. 2017;111:191. Copyright © 2017 Karger Publishers, Basel, Switzerland.

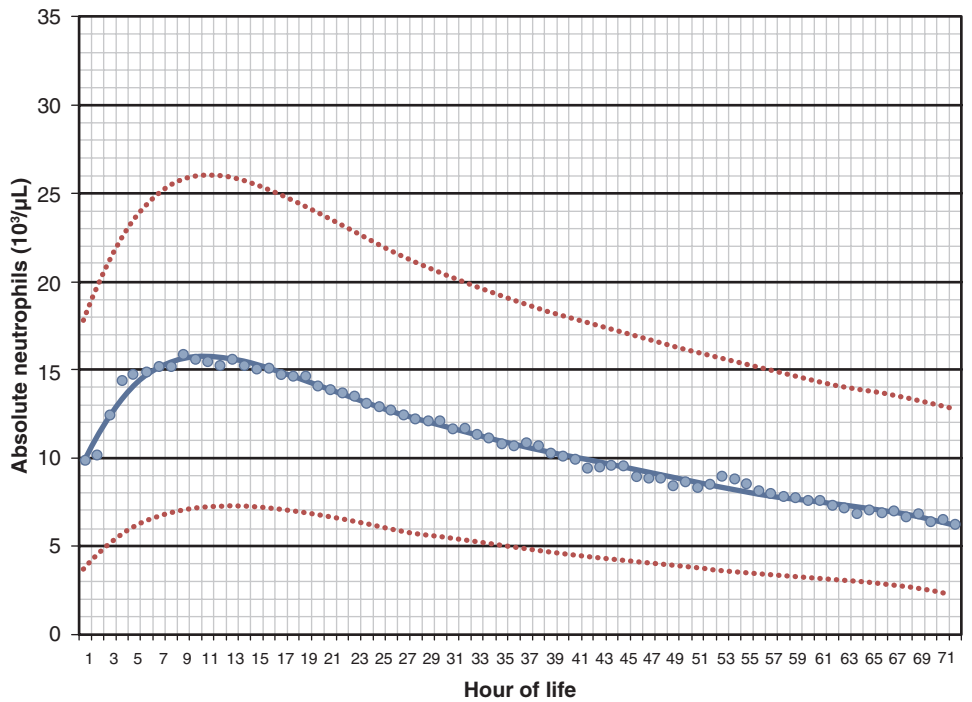


• **Fig. B.28** Platelet counts on the day of birth according to gestational age. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:490.)

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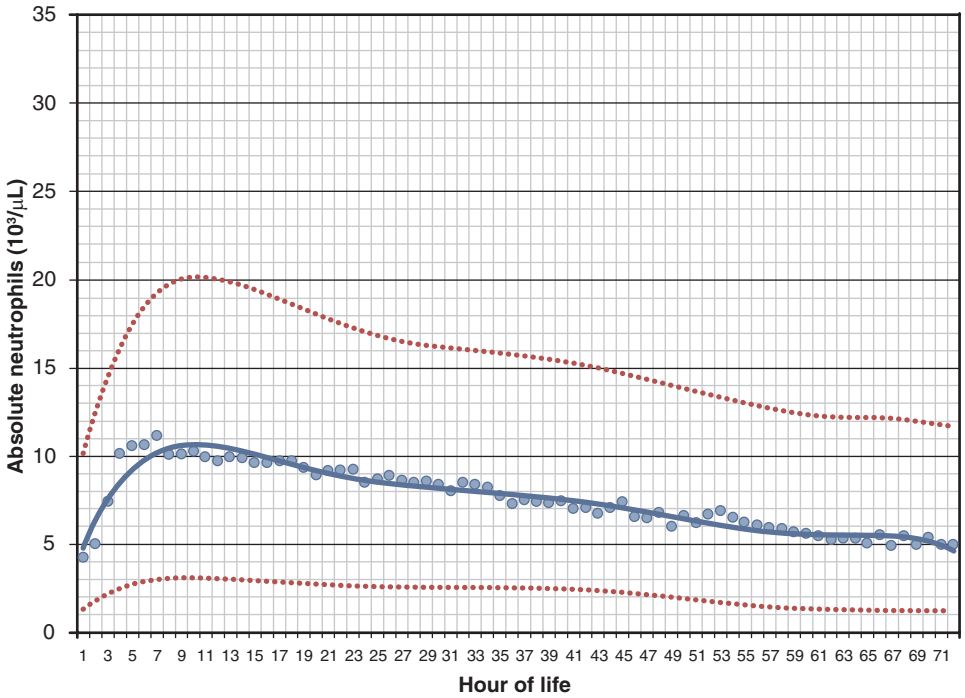


• **Fig. B.29** Platelet counts during the first 90 days of life. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:490.)

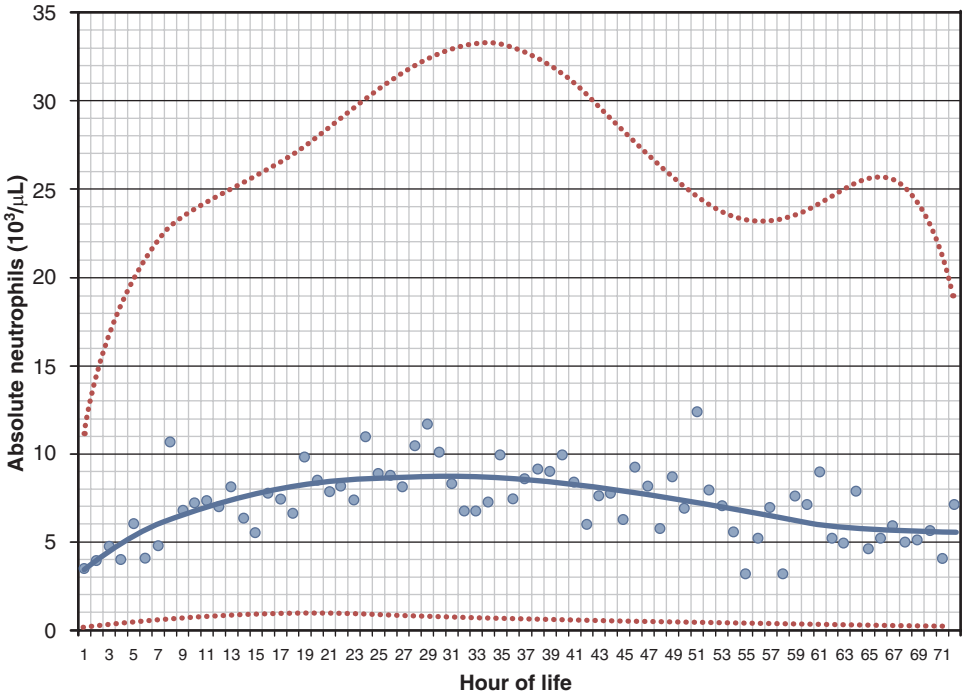


• **Fig. B.30** Neutrophil levels of neonates ≥36 weeks' gestation during the first 72 hours of life. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:492.)

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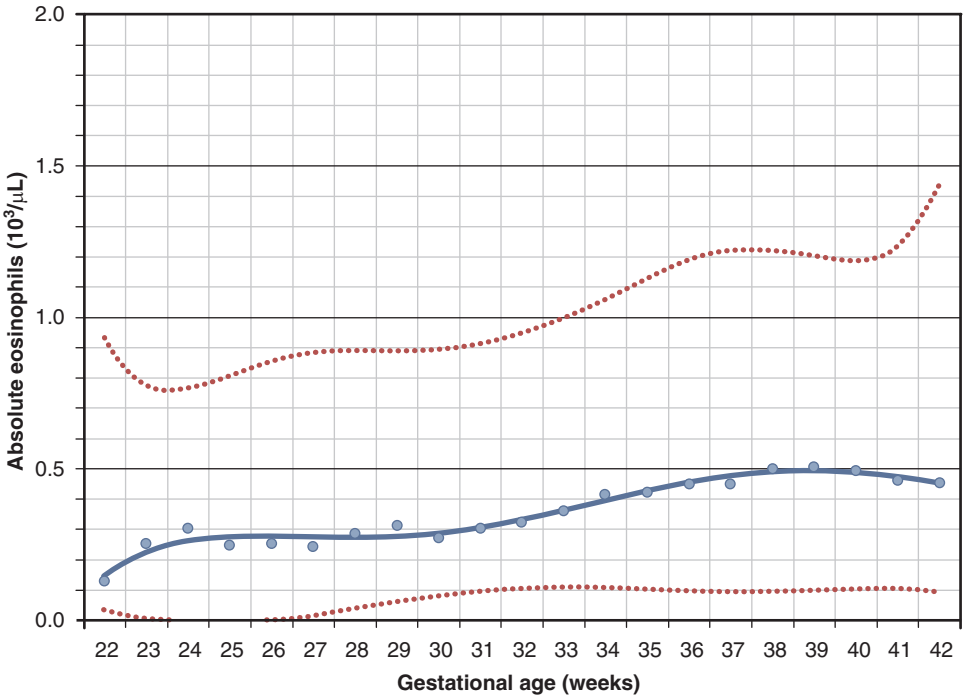


• **Fig. B.31** Neutrophil levels of neonates 28-36 weeks' gestation during the first 72 hours of life. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:492.)

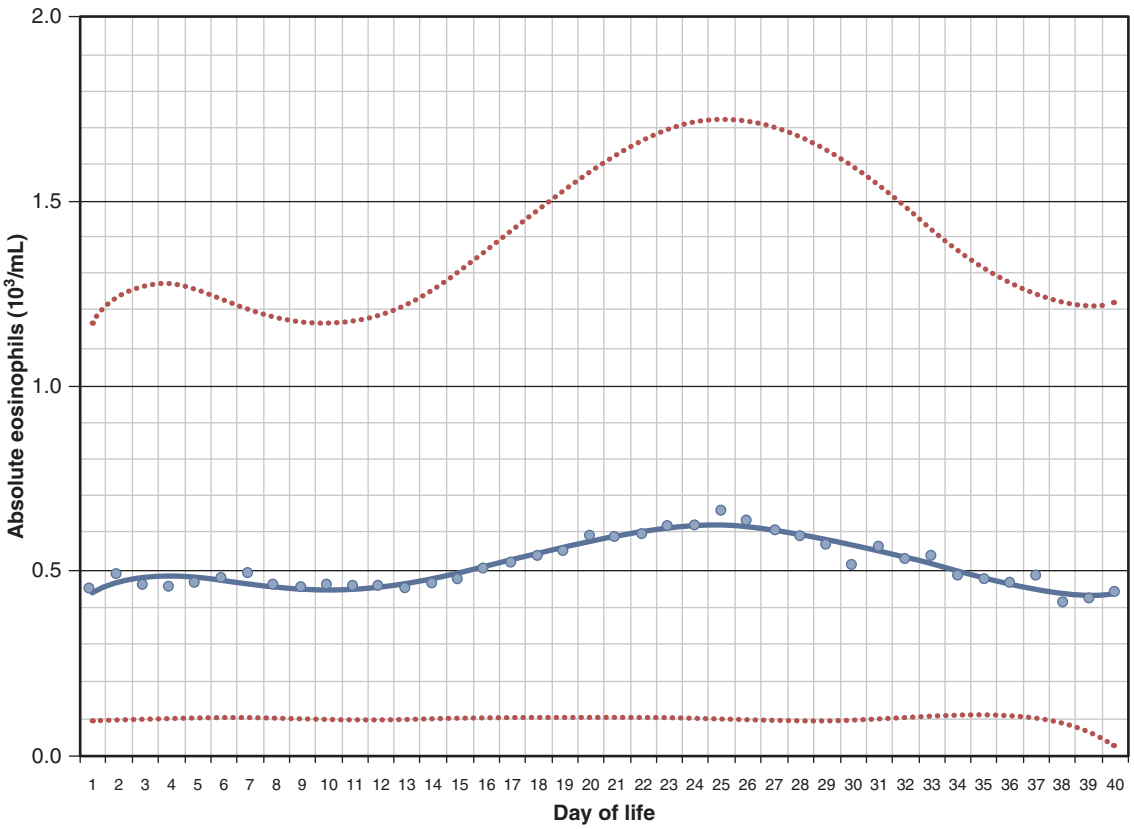


• **Fig. B.32** Neutrophil levels of neonates <28 weeks' gestation during the first 72 hours of life. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:493.)

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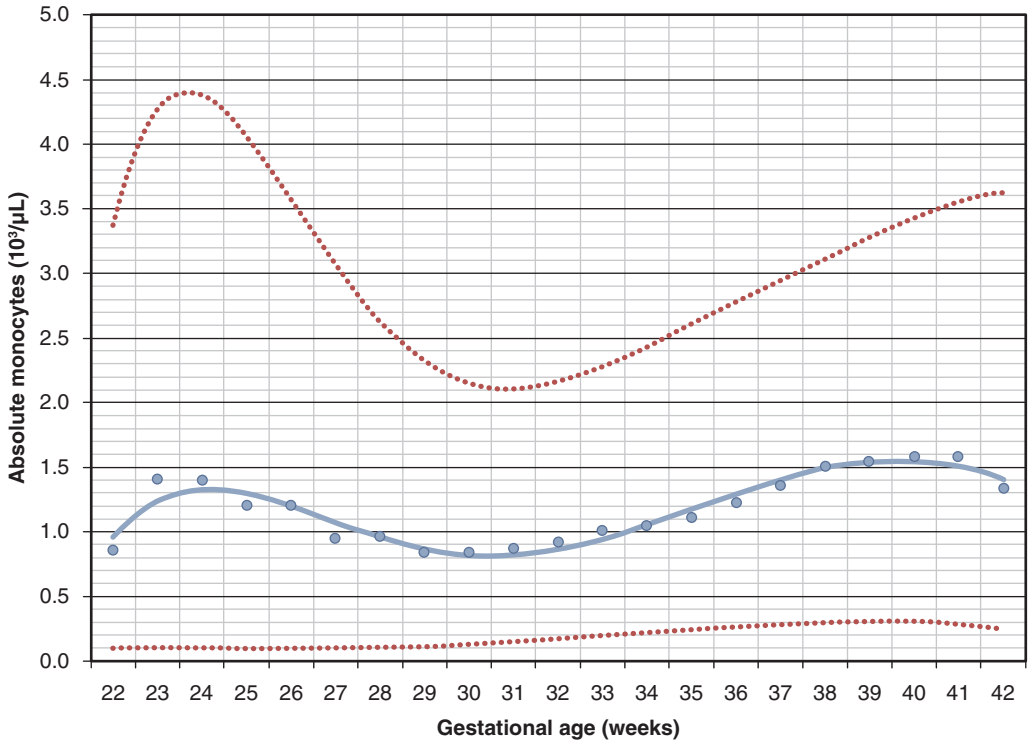


• **Fig. B.33** Eosinophil levels on the day of birth according to gestational age. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:493.)

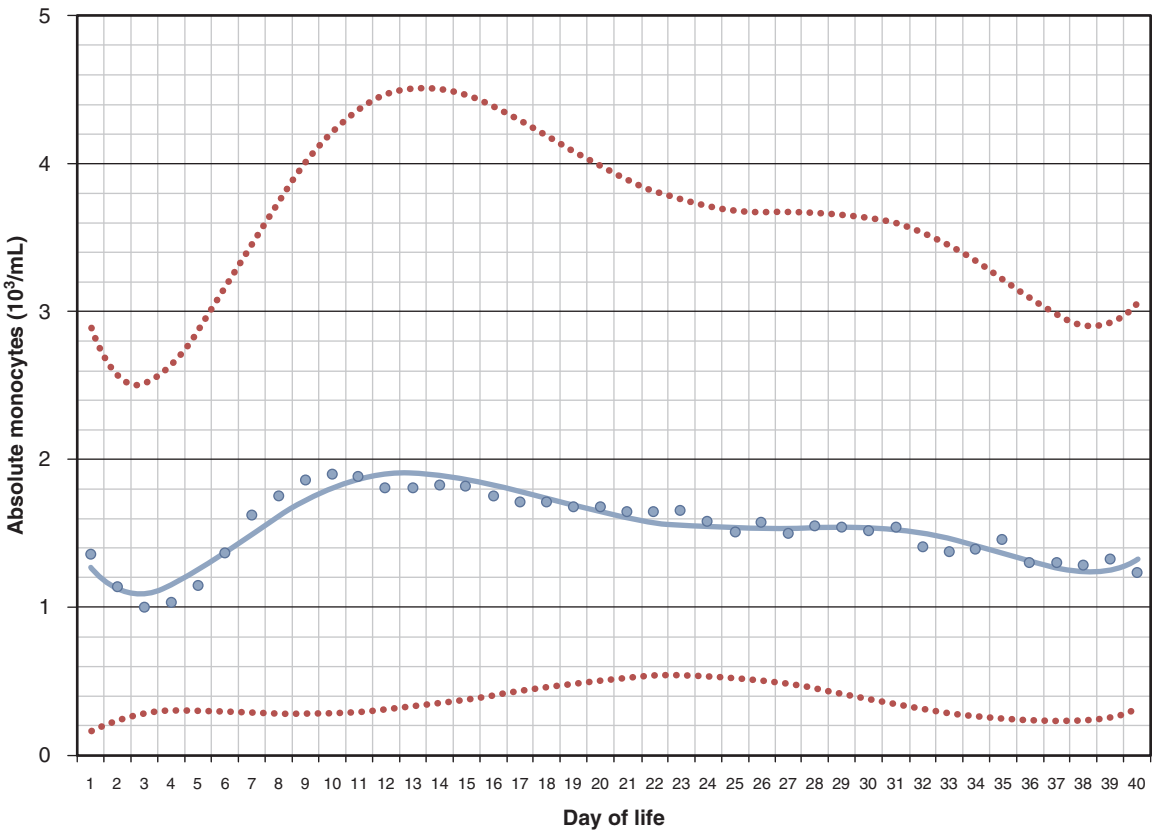


• **Fig. B.34** Eosinophil levels during the first 40 days of life. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:494.)

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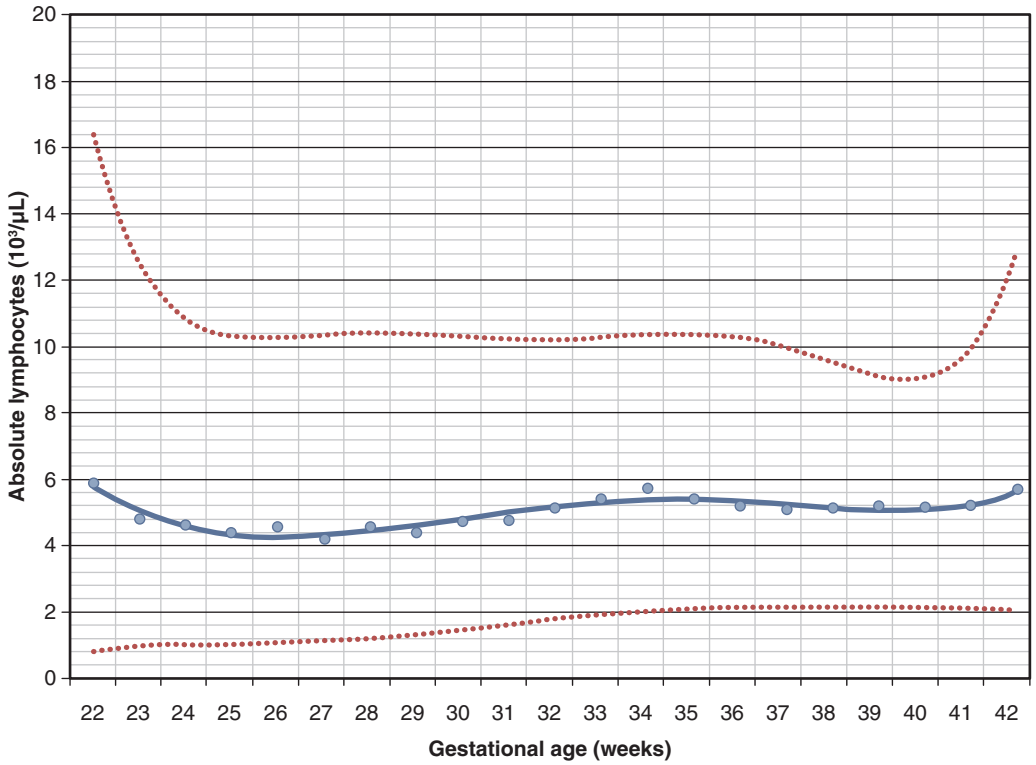


• **Fig. B.35** Monocyte levels on the day of birth according to gestational age. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:494.)

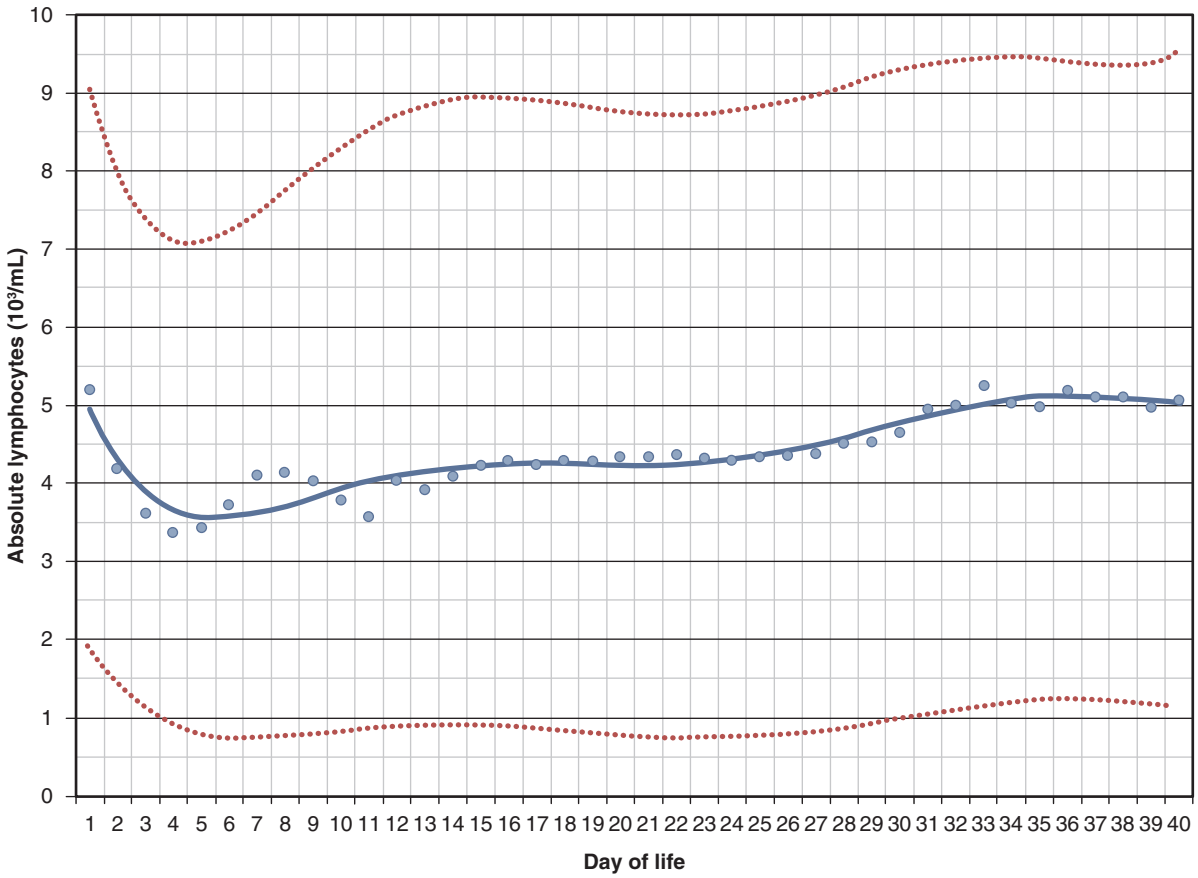


• **Fig. B.36** Monocyte levels during the first 40 days of life. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol.* 2015;42:495.)

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• **Fig. B.37** Lymphocyte levels on the day of birth according to gestational age. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:495.)



• **Fig. B.38** Lymphocyte levels during the first 40 days of life. The lower dotted line is the 5th percentile, the solid middle line is the mean, and the upper dotted line is the 95th percentile. (From Henry E, Christensen RD. Reference intervals in neonatal hematology. *Clin Perinatol*. 2015;42:496.)

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TABLE B.36 Reference Intervals for Measurements of "Left Shift"

	First 48 Hours after Birth $n = 4808$			Beyond 48 Hours of Life $n = 1654$		
Measurement	Median ± SD	5th Percentile	95th Percentile	Median ± SD	5th Percentile	95th Percentile
IG%	1.99 ± 1.7	0.5	6.2	1.62 ± 0.7	0.2	4.2
I/T	0.09 ± 0.08	0	0.29	0.12 ± 0.05	0	0.31
IG (cells per µl)	539 ± 270	50	1460	308 ± 70	10	613
Bands (cells per µl)	1303 ± 680	0	3710	702 ± 160	0	1785

IG, Immature granulocytes; I/T, immature to total neutrophil ratio.
From MacQueen BC, et al. Comparing automated vs manual leukocyte differential counts for quantifying the 'left shift' in the blood of neonates. *J Perinatol.* 2016;36:845.

Conversion Tables

Standard International Unit

TABLE B.37 Conversion Table to Standard International Units

Component	Conventional Unit	Conversion Factor (Multiply by)	SI Unit
Adrenocorticotropic hormone (ACTH)	pg/ml	0.22	pmol/L
Alanine aminotransferase (ALT)	U/L	0.0167	µkat/L
Albumin	g/dL	10	g/L
Aldosterone	ng/dL	27.74	pmol/L
Alkaline phosphatase	U/L	0.0167	µkat/L
Ammonia	µg/dL	0.714	µmol/L
Amylase	U/L	0.0167	µkat/L
Androstenedione	ng/dL	0.0349	nmol/L
Antidiuretic hormone	pg/mL	0.923	pmol/L
Alpha1-antitrypsin	mg/dL	0.184	µmol/L
Aspartate aminotransferase (AST)	U/L	0.0167	µkat/L
Bicarbonate	mEq/L	1	mmol/L
Bilirubin	mg/dL	17.104	µmol/L
Blood gases			
Carbon dioxide (P_{CO_2})	mmHg	0.133	kPa
Oxygen (P_{O_2})	mmHg	0.133	kPa
Brain-type natriuretic peptide (BNP)	pg/mL	1	ng/L
C-reactive protein (CRP)	mg/L	9.524	nmol/L
Caffeine	µg/L	0.515	µmol/L
Calcium, ionized	mg/dL	0.25	mmol/L
Calcium, total	mg/dL	0.50	mmol/L
Chloride	mEq/L	1	mmol/L
Copper	µg/dL	0.157	µmol/L
Cortisol	µg/dL	27.59	nmol/L

Continued

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TABLE B.37 Conversion Table to Standard International Units—cont'd

Component	Conventional Unit	Conversion Factor (Multiply by)	SI Unit
Creatinine	mg/dL	88.4	µmol/L
D-Dimer	µg/mL	5.476	nmol/L
Dehydroepiandrosterone (DHEA)	ng/mL	3.47	nmol/L
Dehydroepiandrosterone sulfate (DHEAS)	µg/dL	0.027	µmol/L
Digoxin	ng/mL	1.281	nmol/L
Estradiol	pg/mL	3.671	pmol/L
Ferritin	ng/mL	2.247	pmol/L
Fibrinogen	mg/dL	0.0294	µmol/L
Follicle-stimulating hormone (FSH)	mIU/mL	1	IU/L
Gamma-glutamyltransferase (GGT)	U/L	0.01667	µkat/L
Gentamicin	µg/mL	20.9	µmol/L
Glucose	mg/dL	0.0555	mmol/L
Glucose-6-phosphate dehydrogenase	U/g hemoglobin	0.0167	nkat/g hemoglobin
Growth hormone (GH)	ng/mL	1	µg/L
hematocrit	%	0.01	Proportion of 1.0
Hemoglobin	g/dL	10	g/L
Insulin	µIU/mL	6.945	pmol/L
Iron	µg/dL	0.179	µmol/L
Iron-binding capacity	µg/dL	0.179	µmol/L
Lactate	mg/dL	0.111	mmol/L
Lactate dehydrogenase (LDH)	U/L	0.0167	µkat/L
Lead	µg/dL	0.0483	µmol/L
Lipase	U/L	0.1667	µkat/L
Luteinizing hormone (LH)	mIU/mL	1	IU/L
Magnesium	mEq/L	0.5	mmol/L
Methemoglobin	g/dL % of total hemoglobin	155 0.01	µmol/L Proportion of total hemoglobin
Osmolality	mOsm/kg	1	mmol/kg
Phenobarbital	µg/mL	4.31	µmol/L
Phenytoin	mg/L	3.968	µmol/L
Phosphate	mg/dL	0.323	mmol/L
Platelet count	$x10^3/\mu L$	1	$x10^9/L$
Potassium	mEq/L	1	mmol/L
Prealbumin	mg/dL	10	mg/L
Progesterone	ng/mL	3.18	nmol/L
Pyruvate	mg/dL	113.56	µmol/L
Red blood cell count	$x10^6/\mu L$	1	$x10^{12}/L$
Reticulocyte count	$x10^3/\mu L$ % of red blood cells	1 0.01	$x10^9/L$ Proportion of red blood cells

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TABLE B.37 Conversion Table to Standard International Units—cont'd

Component	Conventional Unit	Conversion Factor (Multiply by)	SI Unit
Sodium	mEq/L	1	mmol/L
Testosterone	ng/dL	0.347	nmol/L
Theophylline	µg/mL	5.55	µmol/L
Thyroglobulin	ng/mL	1	µg/L
Thyroid-stimulating hormone (TSH)	mIU/L	1	mIU/L
Thyroxine, free (FT_4)	ng/dL	12.871	pmol/L
Thyroxine, total (T_4)	µg/dL	12.871	nmol/L
Thyroxine-binding globulin	µg/mL	17.094	nmol/L
Triglycerides	mg/dL	0.0113	mmol/L
Triiodothyronine, free (FT_3)	pg/mL	0.0154	pmol/L
Triiodothyronine, total (T_3)	ng/dL	0.0154	nmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
Vancomycin	µg/mL	0.69	µmol/L
Vitamin A (retinol)	µg/dL	0.349	µmol/L
Vitamin B_1 (thiamine)	µg/dL	29.6	nmol/L
Vitamin B_2 (riboflavin)	µg/dL	26.6	nmol/L
Vitamin B_3	µg/mL	4.56	µmol/L
Vitamin B_6 (pyridoxine)	ng/mL	4.046	nmol/L
Vitamin B_{12}	pg/mL	0.7378	pmol/L
Vitamin C (ascorbic Acid)	mg/dL	56.78	µmol/L
Vitamin D (1,25 dihydroxyvitamin D)	pg/dL	2.6	pmol/L
Vitamin D (25 dihydroxyvitamin D)	ng/mL	2.496	nmol/L
Vitamin E (alpha-tocopherol)	µg/mL	23.22	µmol/L
Vitamin K	ng/mL	2.22	nmol/L
White blood cell (WBC) count	/µL	0.001	$x10^9$/L
WBC differential count			
Neutrophils, segmented	/µL	0.001	$x10^9$/L
Neutrophils, bands	/µL	0.001	$x10^9$/L
Lymphocytes	/µL	0.001	$x10^9$/L
Monocytes	/µL	0.001	$x10^9$/L
Eosinophils	/µL	0.001	$x10^9$/L
Basophils	/µL	0.001	$x10^9$/L
WBC differential count (number fraction)			
Neutrophils, segmented	%	0.01	Proportion of 1.0
Neutrophils, bands	%	0.01	Proportion of 1.0
Lymphocytes	%	0.01	Proportion of 1.0
Monocytes	%	0.01	Proportion of 1.0
Eosinophils	%	0.01	Proportion of 1.0
Basophils	%	0.01	Proportion of 1.0
Zinc	µg/dL	0.153	µmol/L

Modified from Iverson C, et al. Table 2. Selected laboratory tests, with reference ranges and conversion factors. In *AMA manual of style: a guide for authors and editors*. 10th ed. New York: Oxford University Press; 2007.

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Metric Units

TABLE B.38 Conversion Tables for Metric Units

A. Metric System Weights

1 kilogram (kg)	=	1000 grams (g)
1 milligram (mg)	=	0.001 gram (g)
1 microgram (μg)	=	10^{-6} g or μ
1 nanogram (ng)	=	10^{-9} g or mμ
1 picogram (pg)	=	10^{-12} g or μμ
1 femtogram (fg)	=	10^{-15} g or mμμ

B. Metric and Avoirdupois Systems of Volume (Fluid)

1 liter (L)	=	1000 milliliters (mL)
1 milliliter (mL)	=	1000 microliters (μL)
1 deciliter (dL)	=	100 mL

C. Standard Prefixes

Less than 1			More than 1		
atto	10^{-18}	A	deka	10^{1}	da
femto	10^{-15}	F	hector	10^{2}	h
pico	10^{-12}	P	Kilo	10^{3}	k
nano	10^{-9}	N	mega	10^{6}	M
micro	10^{-6}	M	Giga	10^{9}	G
milli	10^{-3}	M			
centi	10^{-2}	C			
deci	10^{-1}	D			

D. Conversion Factors

1 kg	=	2.2 pounds
1 pound	=	0.45 kilogram
1 ounce	=	28 grams
1 L	=	1.06 quarts
1 fluid ounce	=	30 mL
1 inch	=	2.54 cm
1 cm	=	0.394 inch
Degrees Celsius	=	(°F – 32) x 5/9
Degrees Fahrenheit	=	(°C x 9/5) + 32

Parts per million (ppm) to percent:

1 ppm	=	0.0001%
10 ppm	=	0.001%
100 ppm	=	0.01%
1000 ppm	=	0.1%

Atomic Weight and Valence

TABLE B.39 Atomic Weight and Valence for Common Elements

Element	Atomic Weight	Valence
Calcium	40	2
Sodium	23	1
Potassium	39	1
Chlorine	35.5	1
Magnesium	24.3	2
Phosphorus	31	*

Conversion of Common Elements from Milligrams (mg) to Milliequivalents (mEq)

To convert mg to mEq:

$$\frac{\text{mg} \times \text{valence}}{\text{atomic weight}} = \text{mEq}$$

To convert mEq to mg:

$$\frac{\text{mEq} \times \text{atomic weight}}{\text{valence}} = \text{mg}$$

*The valence of phosphorus varies. For nutritional purposes, it is convenient to express quantities in moles.

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Appendix C

Schedule for Immunization of Preterm Infants

Jill E. Baley

All Preterm Infants[1]

- Vaccine doses should not be reduced for preterm infants.
- Use thimerosal-free vaccines.
- Intramuscular injections to preterm infants might require a shorter needle than the standard 5/8 to 1" needle.
- Immunizations may be given during corticosteroid administration.
- Palivizumab (synagis) should be given according to the respiratory syncytial virus policy.
- Preterm infants should receive a full dose of diphtheria and tetanus toxoids and acellular pertussis (DTaP), *Haemophilus influenza* type B (Hib) conjugate, inactivated poliovirus (IPV), hepatitis B (Hep B), and pneumococcal conjugate (PCV13) at 60 days' chronologic age, regardless of birth weight and gestational age, as long as they are medically stable and consistently gaining weight. These should be repeated in another 60 days.
- Immunizations for preterm infants may be given over 2 or 3 days to minimize the number of injections at a single time.
- Hospitalized infants with birth weight lower than 1000 g should be observed for apnea for 72 hours after the primary series of immunizations. The CBC may show a left shift and the CRP may be elevated.
- Breastfeeding by a mother who is positive for hepatitis B surface antigen (HBsAg) poses no additional risk for acquisition of hepatitis B virus (HBV) infection by the infant.
- Infants with chronic respiratory tract disease should receive the influenza inactivated trivalent or quadrivalent immunization annually, before or during the influenza season, when they are 6 months' postnatal age or older:
  - Infants who are 6 months to 8 years of age who have not previously received two doses of the influenza vaccine should receive two doses of vaccine at least 28 days apart.
  - Family and other caregivers should also receive the inactivated trivalent or quadrivalent influenza vaccine annually in the fall to protect the infant from exposure.
- The American Academy of Pediatrics recommends routine immunization of infants in the United States with rotavirus vaccine. There is no preference for either the live oral human-bovine reassortant vaccine (RV5) or the live oral, human attenuated rotavirus vaccine (RV1).
- Preterm infants who are clinically stable should be immunized for rotavirus on the same schedule and with the same precautions as term infants. The infant's postnatal age must be between 6 weeks and 14 weeks, 6 days postnatal age. Rotarix is a two-dose series, at 2 and 4 months of age. RotaTeq is a three-dose series, at 2, 4, and 6 months of age. If any dose is RotaTeq or an unknown product, three doses should be given.
- Preterm infants who are in the NICU or nursery may be immunized at the time of discharge if they are clinically stable and age-eligible for the vaccine. The AAP believes that the risk of shedding vaccine virus in the stool, and theoretically transmitting vaccine virus to another acutely ill or non-age-eligible infant, if the infant is readmitted, is less than the benefit of immunizing eligible infants.
- Any rotavirus vaccine-immunized infant who requires readmission to the NICU or nursery within 2 weeks of vaccination should remain under contact precautions for 2-3 weeks after vaccine administration.

Hepatitis B Vaccine at Birth[2]

1. Examine the original maternal lab report to verify the correct maternal serology for hepatitis B during this pregnancy.
2. Repeat the maternal hepatitis B serology at birth if the mother is high risk:
   a. Greater than one sexual partner in the last 6 months
   b. Evaluated or treated for a sexually transmitted disease
   c. Recent or current injection drug use
   d. HBsAg-positive partner
   e. Clinical hepatitis since last testing
3. Hepatitis B preventive measures depend on the maternal serology and the birth weight of the infant, as follows:

Hepatitis BsAg–Negative Mother

- Give the mother a hepatitis B vaccine information statement and obtain verbal consent prior to immunization.

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Keywords

immunizations
hepatitis B vaccine

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- If the infant is ≥2000 g birth weight, administer a single-antigen, pediatric, 0.5 mL, intramuscular vaccine into the anterolateral thigh within 24 hours of birth or at discharge, whichever is sooner.
- If the infant is <2000 g birth weight, administer the vaccine at 1 month of age or at hospital discharge, whichever is sooner.
- Document vaccine administration or refusal in the chart. Give the parent a record of the vaccination.

Hepatitis BsAg–Positive Mother

- Give the mother a hepatitis B vaccine information statement and obtain verbal consent prior to immunization.
- Notify Child Protective Services if the mother continues to refuse vaccination after discussion with the physician.
- Administer hepatitis B immune globulin (HBIG) 0.5 mL, IM, in the anterolateral thigh in the delivery room or as soon as possible within 12 hours of birth to all infants, regardless of the birth weight.
- Administer the single antigen hepatitis B vaccine, pediatric, 0.5 mL, into the opposite anterolateral thigh as soon as possible within 12 hours of birth to all infants, regardless of birth weight.
- Document both doses within the chart and give the parent a copy of the record.
- Notify the State Health Department of the positive maternal screen.
- Notify the primary care provider of the administration of HBIG and hepatitis B vaccine, and the need for additional, on-time doses. Infants with birth weights <2000 g need four doses of the vaccine as the birth dose is not counted.
- The infant should be tested for HBsAg and anti-HBs 1-2 months after completing the vaccine series, but no earlier than 8-12 months of age.
- The infant may breastfeed.

Hepatitis B Surface Antigen–Unknown Mother

- Give the mother a hepatitis B vaccine information statement and obtain verbal consent prior to immunization.
- Administer the single antigen hepatitis B vaccine, pediatric, 0.5 mL, IM, into the anterolateral thigh within 12 hours of birth, to all infants, regardless of birth weight.
- Administer hepatitis B immune globulin (HBIG), 0.5 mL, IM, within 12 hours of birth, if the infant weighs <2000 g at birth unless the maternal serology is confirmed to be negative by that time.
- Administer hepatitis B immune globulin (HBIG), 0.5 mL, IM, within 7 days of birth to all infants with a birth weight ≥2000 g if the maternal serology is confirmed to be negative. If the maternal serology remains unknown, administer HBIG by 7 days of life or at hospital discharge, whichever comes first.
- Document all doses in the chart and give the parent a copy of the immunizations.
- Notify the primary care provider of the immunizations and the need for follow-up.

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1. Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red book: 2015 report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.
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